PROF. DIETER WOLKE (Orcid ID : 0000-0003-0304-268X)

Article type : Main research article

Small for Gestational Age - Cognitive Performance from Infancy to Adulthood: An Observational Study

Robert EVES [1], Marina MENDONÇA[1], Peter BARTMANN,[2] and Dieter WOLKE[1].

[1]Department of Psychology, Lifespan Health and Wellbeing Group, University of Warwick, University Road, Coventry, CV4 7AL, United Kingdom

[2]Department of Neonatology, University Hospital Bonn, Bonn, Germany

Corresponding Author: Dieter Wolke; University of Warwick, Coventry, CV4 7AL, UK

D.Wolke@warwick.ac.uk

Running head: Longitudinal IQ performance of adults born SGA

Abstract

Objective: To determine whether cognitive performance from infancy to adulthood is affected by being born SGA, and if this depends on the SGA reference used. Furthermore, to determine SGA's effect while considering the effects of very preterm/very low birth weight (VP/VLBW), socioeconomic status (SES), and parent-infant relationship.

Design, setting and population: 414 participants (197 Term-Born, 217 VP/VLBW) of the Bavarian Longitudinal Study

Methods: SGA was classified using neonatal or fetal growth references. SES and the parent-infant relationship were assessed before 5 months old.

Main outcome measures: Developmental (DQ) and IQ tests assessed cognitive performance on 6 occasions, from 5-months to 26-years old.

Results: The fetal reference classified more infants as SGA (<10th percentile) than the neonatal reference (N=138, 33% Vs N=75,18%). Using linear mixed models, SGA was associated with IQ -8 points lower than AGA, regardless of reference used (CI [-13.66, -0.64] and [-13.75,-1.98]). This difference narrowed minimally into adulthood. Being VP/VLBW was associated with IQ -16 [CI -21.01,-10.04, -] points lower than term-born participants. Low SES was associated with IQ -14 [CI -18.55, -9.06] points lower than high SES. A poor parent-infant relationship was associated with IQ -10 points lower than those with a good relationship [CI -13.91,-6.47]

Conclusions: SGA is associated with lower IQ throughout development, independent of VP/VLBW birth, low SES or poor parent-child relationship. Social factors have comparable effects on IQ than SGA and should be considered for interventions.

Funding: All authors are supported by EU horizon 2020 grant (RECAP-preterm; www.recap-preterm.eu) under agreement number 733280.

Key Words: Cognition, Cognitive development, growth restriction, IQ, SGA, Small for gestational age, Term, Very preterm

Tweetable abstract: Small for gestational age is associated with lower cognitive performance from infancy to adulthood.

Introduction

Small for Gestational Age (SGA, birthweight <10% for gestation) has been consistently associated with lower cognitive performance in childhood, as demonstrated by lower scores on developmental and intelligence tests (DQ and IQ).[1] However, there are contradictory findings of long-term effects of SGA on IQ,[2–4] suggesting diminishing cognitive differences between SGA and Appropriate for Gestational Age (AGA) adults. To investigate this, studies assessing cognitive performance throughout development are needed, from infancy to adulthood. This contrasts to previous studies that have reported on different individuals and their DQ/IQ scores cross-sectionally.

Additionally, it has been hypothesised that SGA's effects on IQ differ depending on whether one is born at term or preterm, with SGA's effects being disproportionately larger for those born very preterm.[5] However, the few very preterm/very low birthweight (VP/VLBW; <32 weeks gestation and/or <1500g) cohorts that have tested whether the factors interact have not found significant interactions.[4,6] Rather, results suggest that SGA has an independent adverse effect[1,6] or no effect on IQ for VP/VLBW groups.[3,4]

Determining SGA's effect on IQ is complicated due to no universally accepted reference for classifying SGA. Longitudinal cohorts have traditionally used SGA references based on large datasets of neonates.[7] However, as preterm infants are more likely to be growth restricted[7], neonatal references classifying only the lowest 10% as SGA may underdiagnose the true rates of growth restriction in the VP/VLBW population.[7] Alternatively, references comparing birthweight to estimated fetal weight can be used. Fetal references are prone to measurement error[8] but have been found to be superior in predicting infant mortality, especially for VP/VLBW infants.[9] For predicting cognitive outcomes, fetal references may have superior sensitivity than neonatal references[10], however this has not been further supported.[11]

Finally, socio-environmental factors that influence cognitive performance must also be considered.[12] Low familial socioeconomic status (SES) has been consistently associated with

lower IQ.[13] However, the mechanisms of how SES affects IQ scores are not well understood and are likely multifactorial. One pivotal factor may be the parent-infant relationship,[12] as it has been found to predict long-term cognitive outcomes.[14]

The primary objective of this study was to determine whether the IQ of SGA and AGA participants differed over time, classified using either fetal or neonatal references. The second objective was to determine whether SGA's effects were disproportionately larger for participants born VP/VLBW than at term. Finally, to consider whether SGA's effects persisted once socio-environmental risk factors were controlled for.

Methods

Participants

The BLS is a geographically defined prospective whole population sample of VP/VLBW(<32 weeks gestation and/or <1500g) and term-born children born in Southern Bavaria (Germany) between January 1985 and March 1986. The VP/VLBW group were admitted to one of 17 children's hospitals within the first 10 days after birth[15]. Of the initial 682 VP/VLBW, 411 were alive and eligible for the 26-year follow-up assessment with 260 (63%) VP/VLBW participants participating. 203 undertook IQ testing in adulthood while a further 14 participants had severe impairments and were unable to undertake adult assessment and were given a proxy IQ score at 26 years of age.[4] This resulted in 217 (53%) VP/VLBW participants included. Infants who were born at term in the same obstetric hospitals were recruited as controls. Of the initial 916 term-born controls alive at 6 years, 350 were randomly selected within the stratification variables of sex and family SES as to be comparable to the VP/VLBW sample. Of these, 308 were eligible for the 26-year follow-up assessment, 229 participated (74%) with 197 (64%) completing cognitive assessments in adulthood. A full flow chart can be found in Figure S1.

Ethical approval for this study was granted by the Ethical Board of the University Hospital Bonn (date of approval: 19th august 2009, reference 159/09). Informed consent was provided by parents and adult participants. The BLS was supported by grants PKE24, JUG14, 01EP9504 and 01ER0801 from the German Federal Ministry of Education and Science, which underwent peer review but did not involve public involvement, see Table S3 for the completed GRIPP2 form. The funders had no role in the study design, data collection, data analysis, data interpretation, or

writing of the report. While the BLS has measured other outcomes of interest (behavioural outcomes, mental health etc.), cognitive outcomes were the sole focus of the current study.

Gestational age and birth weight

Gestational age was determined from maternal dates of the last menstrual period and serial ultrasounds during pregnancy. . Where gestational age estimates from these methods differed by less than 2 weeks, maternal dates were used[16]; . Birth weight was documented from birth records.

Small for Gestational Age classification

Two references were used to classify SGA, a neonatal reference (SGA_N) and a fetal reference (SGA_F). SGA_N used Voigt's data from 2.3 million live and still singleton births in Germany from 1995 – 2000 with a gestational age from 20 – 43 weeks,[17] allowing for sex-specific weight percentiles to be calculated. SGA_F instead compared the birthweight of our participants to the expected fetal weight of healthy developing fetuses using Mikolajczyk et al's model.[7] This method is based on Hadlock's growth equation which used ultrasound measurements to calculate weight percentiles from 10- 41 weeks gestation.[18] A key aspect of Hadlock's equation is that a healthy developing fetus should reach a final weight of 3705g at 40.5 weeks gestation, however this uses USA data and is non-sex specific.[18] Mikolajczyk et al. adjusts Hadlock's equation from 3705g to a country specific average birthweight at 40 weeks. We therefore took the 50th percentile for a German infant at 40 weeks from Voigt's data as reference, while also doing this separately for males (3624g) and females (3473g) so that both SGA references were country and sex specific. For both references, SGA/AGA status was determined if the respective weight percentile was below or above the 10th percentile (SD = -1.282).

Cognitive assessments

The cognitive assessments used in the BLS have been previously reported.[19]

The Griffiths Mental Development Scale measures DQ at 5 and 20 months old, age corrected for prematurity. It assesses 5 dimensions of development: locomotor, personal-social development, hearing and speech, hand and eye coordination, and performance [19].

IQ at 4 years was assessed through a composite of cognitive tasks: the Columbia Mental Maturity Scale, the Active Vocabulary Test, and the Beery-Buktenica Developmental Test of Visual-Motor Integration.[19] Using confirmatory factor analysis a composite score was constructed using the standardized scores from all participants who undertook cognitive testing at 4 years of age, for more information see Appendix S1 and Table S4.

IQ at 6 and 8 years was assessed with the German version of the Kaufmann Assessment Battery for Children. A total IQ score was calculated from the sequential (3 subtests) and simultaneous (5 subtests) processing scales.[19]

IQ at 26 years was assessed with a German version of the Wechsler Adult Intelligence Scale. The 6 subtests were vocabulary, similarities, letter number-sequence, block design, matrix reasoning, and digit symbol coding. Cognitive functioning scores of the subtests were converted into a Full-Scale IQ score.[19]

For brevity, all differences in DQ and IQ scores will be simply referred to as differences in IQ scores. IQ scores were standardized at each time point based upon the mean and standard deviation of the most optimal birth group, participants who were born both at term and AGA. Therefore, while the term and AGA group would demonstrate a flat cognitive group score (i.e. mean IQ scores equal to 100 and a standard deviation of 15 at each time point), scores for all other participants reflect catch up or deterioration in relation to the most optimal birth group over time.

Socio-environmental Factors

Family SES data was obtained by standard interviews with the infants' parents in the first 10 days of life. SES was computed as a weighted composite score of maternal highest educational qualification, paternal highest educational qualification, and occupation of the head of family and grouped as low, middle or high.[20]

The Parent-Infants Relationship Index (PIRI) is an 8-item based scale derived from concerns regarding the mother and infant or father and infant relationship.[14] 5 items were derived from questions during an interview with the parents in the neonatal ward or at 5 months of age. The final 3 items were assessed by the study nurse in the neonatal ward. Items were coded as 0=No concern or 1= Concern. Final scores on the PIRI were dichotomized into good parent-infant

relationship (0, all items= 0) or poor parent-infant relationship (1, at least one item=1), see Appendix S2 for more detail on the PIRI.

Data Analyses

Participants with IQ scores at 26 years of age were included for analysis. The missing datapoints from IQ tests (4.8%) in childhood were imputed using the R package mice.[21] Mixed modelling was used to investigate IQ trajectories from infancy to adulthood, using maximum likelihood for parameter estimation. Advantages of the mixed modelling method is the use of a structure that allows multiple assessments across time to be nested within a single individual, with variation between individuals treated as a random effect. This method then allows for trajectories of IQ scores to be predicted as a linear function of fixed effects, such as SGA or VP/VLBW status.

Analyses using either SGA_N or SGA_F references were performed separately. Initial unadjusted mixed models (Model 1- SGA_N and Model 1 - SGA_F) added two fixed effects based on birth group: an SGA or AGA group variable and a VP/VLBW or term-born group variable. Additionally, interactions between these variables and age (measured in years) were considered as to determine if being VP/VLBW interacted with the effect of SGA or if their effects changed over time. Secondly, models were adjusted for sex and SES, both as fixed effects (Model 2- SGA_N and Model 2 - SGA_F). Thirdly, the effect of the parent-infant relationship measured with the PIRI was considered as another fixed effect (Model 3- SGA_N and Model 3 - SGA_F). In regard to random effects, all models allowed for the intercept and slope of IQ trajectories to vary by individual. In total, this resulted in 3 models for each SGA classification reference and therefore 6 models altogether.

Results

Participants

Baseline characteristics of SGA and AGA participants according to SGA_N and SGA_F are shown in in Table 1. The SGA_N reference classified 61 (28%) VP/VLBW and 14 (7%) term-born participants as SGA. In contrast, the SGA_F reference classified 116 (53%) VP/VLBW and 22 (11%) term-born participants as SGA. Further perinatal information can be found in Table S1.

IQ trajectories by SGA_N status and VP/VLBW status

Observed and predicted group trajectories are shown in Figure 1 while the results of the mixed models are displayed in Table 2. In the initial unadjusted model utilizing the SGA_N it was found that in comparison to AGA participants, being born SGA resulted in an initial -7.89 IQ points decrease (95% CI [-14.62, -1.17]), (see Model 1- SGA_N). The effect of being VP/VLBW resulted in scores -21 IQ points [CI -25.98, -16.28] lower than being term-born. The interaction between being term-born and SGA was not significant, indicating that the effect of being born SGA was similarly detrimental on IQ for both term and VP/VLBW participants[CI -12.14,15.98]. Trajectories were found to be relatively stable with age and similar across the birth groups. However, there was a trend indicating SGA participants caught up in comparison to AGA participants, at approximately 0.23 IQ points [CI -0.02,0.48] per year, meaning Model 1- SGA_N estimated the difference between SGA and AGA participants to reduce from 7.89 to just 2.01 IQ points by 26 years old.

IQ trajectories by SGA_F status and VP/VLBW status

Observed and predicted group trajectories are shown in Figure 2 while the results of the mixed models are displayed in Table 2. In the unadjusted model utilizing SGA_F, it was found that the effect of being born SGA resulted in an initial -8.38 IQ points [CI -14.46,-2.29] decrease in comparison to being born AGA, (see Model 1- SGA_F). The effect of being VP/VLBW resulted in a decrease in -19 IQ points [CI -13.46, -24.63] in comparison to being born at term. The interaction between being term-born and SGA was not significant, indicating that the effect of being born SGA was similar regardless of VP/VLBW status [CI -7.98,15.62]. Trajectories were found to be stable with age and similar across the birth groups. A minimal trend indicated SGA participants demonstrated an approximate 0.18 IQ points [CI -0.04,0.41] per year catch-up in comparison to AGA participants. Thus, Model 1- SGA_F estimated the difference between SGA and AGA participants to reduce from 8.38 to 3.78 IQ points by 26 years old. In regard to rates of minor (IQ<85) and major (IQ<70) impairment, the percentage at each time point for both SGA references are provided in Table S2.

Effects of sex, socioeconomic status and the parent-infant relationship on IQ trajectories

The addition of sex did not have a significant effect in either of the adjusted models (Model 2- SGA_N, CI [-5.60,1.63]; Model 2 – SGA_F, CI [-5.37,1.92]). SES was found to be significantly associated with IQ scores in both models, with those born into a low SES family having on

average -14 IQ points less than those from a high SES family (Model 2- SGA_N CI [-19.17,-9.41], Model 2- SGA_F CI [-19.16, -9.36]). Finally, the effect of having a poor parent-infant relationship (PIRI) was found to have a large effect of approximately -10 IQ points in both final models (Model 3- SGA_N CI [-13.80, -6.39]; Model 3- SGA_F CI [-13.91,-6.47]). The inclusion of sex, SES and PIRI did not significantly change the effects of VP/VLBW status or SGA status on IQ scores in either final model. Additionally all models demonstrated evidence of individual differences in intercept and slope, as demonstrated by the random effects. On average, intercepts had a standard deviation of approximately 20 IQ points and slopes varied with a standard deviation of 0.31 IQ points per years. See Table 2 for all models.

Discussion

Main Findings

In this longitudinal study, regardless of the SGA reference used, SGA was associated with lower IQ scores that had not fully diminished into adulthood. This was found despite the fact that the fetal SGA reference classified more participants as SGA than the neonatal reference, with almost double the number of VP/VLBW participants classified as SGA, We found the effect of SGA was additive but not interactive with VP/VLBW, indicating that both factors are important for cognitive development. We also found large effects of early socio-environmental factors. Being born into a low SES family and having a poor parent-infant relationship were both strong and independent risk factors, associated with lower IQ scores throughout development.

Strengths and Limitations

Our study has several strengths. It assessed cognitive performance 6 times, from infancy to adulthood. We controlled for important covariates such as SES and the parent-infant relationship and assessed their independent effects on IQ. Limitations are that we were unable to differentiate between SGA participants with intrauterine growth restriction and those who are constitutionally small; future research should address this potential measurement error. Finally, there was a lack of moderately/late preterm participants while the number of participants born both SGA and at term was small. This limited the ability to determine whether SGA has a disproportionately larger effect on the VP/VLBW or preterms generally.

Interpretation

Past cross-sectional research has found larger effects of SGA on IQ in childhood than in adulthood.[1–4] This resulted in our hypothesis that SGA participants may demonstrate cognitive catch up in comparison to AGA participants. Our longitudinal study found SGA participants continued to have lower IQ scores in adulthood, however, the difference with AGA participants had diminished from approximately 8 IQ points to 2.01 or 3.78 IQ points depending on the SGA reference used. Rather than between childhood and adulthood, it was between infancy and childhood that the largest temporal change in cognitive performance was seen, between the DQ assessment at 20 months and IQ at 4 years. This may in part be due to the difference in tasks, such as the greater reliance on sensorimotor skill for DQ assessments.[22] The neurological mechanism that underpins the relationship between SGA and continued lower IQ is unclear. As IQ is a general measure of intelligence, it may not be linked to any specific cortical or subcortical deficit[2] but instead global differences between the brains of SGA and AGA participants, such as reduced cortical thickness or lower brain volume.[2,23]

We also found that the effect of VP/VLBW on IQ was stable across lifespan, in concordance with past research of cognitive trajectories of preterm individuals.[19,24] Our hypothesis that the effect of SGA on IQ would be disproportionately larger for the VP/VLBW participants was not supported, with the interaction term failing to reach significance. Despite the fact that VP/VLBW infants are also more likely to be growth restricted,[9] the current research suggests that both SGA and VP/VLBW have significant, independent effects on IQ.

The use of neonatal references to classify SGA in longitudinal cohorts has been debated, especially for VP/VLBW participants.[10] However, we did not find large differences between references for their subsequent effects on IQ. This may be surprising considering the fetal reference almost doubled the number of participants classified as SGA. Charkaluk et al. (2012) suggested that if fetal SGA references simply lower the threshold to be classified as SGA then the inclusion of less at-risk individuals should reduce the effect of SGA on IQ.[11] Instead, in both the current and Charkaluk's study, those classified as SGA using the fetal SGA reference have a similar risk as those classified using the neonatal SGA reference.[11] Future research should investigate how references differ on birthweight percentiles as well as the binary SGA vs AGA cut-offs used here, as the relationship between birthweight percentile and IQ is likely continuous[25] . Additionally, other anthropological measurements, such as head circumference, may provide better utility in predicting long term cognitive outcomes[26].

Our study also considered the effect of socio-environmental measures on IQ, finding both to be significant factors on IQ. Low familial SES was associated with IQ scores 14 points lower than those born into high SES, a considerably larger effect than SGA. However, SES is a multifactorial construct with the specific mechanisms that influence IQ needing to be elucidated.[12] Parenting behaviour has been previously linked to SES.[12] However, the parent-infant relationship measure also had a significant independent effect on IQ, with a slightly larger effect than SGA. As the effect of socio-environmental factors on IQ appear to be of similar magnitude but have less measurement error than the effect of SGA, more focus should be spent on optimizing these potentially modifiable factors through intervention.

Conclusion

To conclude, SGA is associated with lower IQ into adulthood, regardless of how SGA is determined. The effect of SGA on IQ is similar regardless of whether the infant is born at term or very preterm, or after controlling for socio-environmental factors. Familial SES and the parent-infant relationship have similar but potentially more modifiable effects on IQ than SGA, suggesting interventions in parent-infant relationship in the perinatal period may be beneficial.

ACKNOWLEDGMENTS

The authors thank all current and former Bavarian Longitudinal Study group members, paediatricians, psychologists, and research nurses. They also thank those who contributed to study organization, recruitment, data collection, and management at the 26-year assessment: Barbara Busch, Stephan Czeschka, Claudia Gruenzinger, Christian Koch, Diana Kurze, Sonja Perk, Andrea Schreier, Antje Strasser, Julia Trummer, and Eva van Rossum. Special thanks are due to the study participants and their families. Finally, they also thank Professor Ulrich Gembruch for reading a draft copy of the manuscript prior to submission.

DISCLOSURE OF INTERESTS

All authors declare no conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

CONTRIBUTION TO AUTHORSHIP

RE: coordinated data preparation, analysed and interpreted the data, drafted and revised the manuscript, and approved the final manuscript as submitted.

MM: aided in the interpretation of the results, critically reviewed the manuscript, and approved the final manuscript as submitted.

PB designed and conceptualized the adult assessment of the Bavarian Longitudinal Study, critically reviewed the manuscript, and approved the final manuscript as submitted.

DW: designed, conceptualized, and supervised the Bavarian Longitudinal Study, participated in analyses and interpretation of data, revised the manuscript, and approved the final manuscript as submitted.

DETAILS OF ETHICS APPROVAL

Ethical approval for this study was granted by the Ethical Board of the University Hospital Bonn (date of approval: 19th august 2009, reference 159/09).

FUNDING

The Bavarian longitudinal study was supported by grants PKE24, JUG14, 01EP9504, and 01ER0801 from the German Federal Ministry of Education and Science. All authors are supported by an EU horizon 2020 grant, agreement number 733280, which enabled the writing of this manuscript.

REFERENCES

1. Bie HMA de, Oostrom KJ, Waal HAD de. Brain Development, Intelligence and Cognitive Outcome in Children Born Small for Gestational Age. HRP. 2010;73(1):6–14.

2. Østgård HF, Løhaugen GCC, Bjuland KJ, Rimol LM, Brubakk A-M, Martinussen M, et al. Brain Morphometry and Cognition in Young Adults Born Small for Gestational Age at Term. The Journal of Pediatrics. 2014 Nov 1;165(5):921-927.e1.

3. Pyhala R, Lahti J, Heinonen K, Pesonen A-K, Strang-Karlsson S, Hovi P, et al. Neurocognitive abilities in young adults with very low birth weight. Neurology. 2011 Dec;77(23):2052–60.

4. Eryigit Madzwamuse S, Baumann N, Jaekel J, Bartmann P, Wolke D. Neuro-cognitive performance of very preterm or very low birth weight adults at 26 years. Journal of Child Psychology and Psychiatry. 2015 Aug;56(8):857–64.

5. Shah P, Kingdom J. Long-term neurocognitive outcomes of SGA/IUGR infants. Obstetrics, Gynaecology & Reproductive Medicine. 2011 May 1;21(5):142–6.

6. McCarton CM, Wallace IF, Divon M, Vaughan HG. Cognitive and Neurologic Development of the Premature, Small for Gestational Age Infant Through Age 6: Comparison by Birth Weight and Gestational Age. Pediatrics. 1996 Dec 1;98(6):1167–78.

7. Mikolajczyk RT, Zhang J, Betran AP, Souza JP, Mori R, Gülmezoglu AM, et al. A global reference for fetal-weight and birthweight percentiles. The Lancet. 2011 May 28;377(9780):1855–61.

8. Mayer C, Joseph KS. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. Ultrasound in Obstetrics & Gynecology. 2013 Feb 1;41(2):136–45.

9. Ding G, Tian Y, Zhang Y, Pang Y, Zhang J, Zhang J. Application of *A global reference for fetal-weight and birthweight percentiles* in predicting infant mortality. BJOG: An International Journal of Obstetrics & Gynaecology. 2013 Dec;120(13):1613–21.

10. Neta G, Grewal J, Mikolajczyk R, Klebanoff M, Zhang J. Does the individualized reference outperform a simple ultrasound-based reference applied to birth weight in predicting child neurodevelopment? Ultrasound in Obstetrics & Gynecology. 2011 Jul;38(1):62–6.

11. Charkaluk M-L, Marchand-Martin L, Ego A, Zeitlin J, Arnaud C, Burguet A, et al. The Influence of Fetal Growth Reference Standards on Assessment of Cognitive and Academic Outcomes of Very Preterm Children. The Journal of Pediatrics. 2012 Dec 1;161(6):1053-1058.e1.

12. Wolke D. Is Social Inequality in Cognitive Outcomes Increased by Preterm Birth–Related Complications? JAMA Netw Open. 2019 May 3;2(5):e192902–e192902.

13. Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Prognostic Factors for Poor Cognitive Development in Children Born Very Preterm or With Very Low Birth Weight: A Systematic Review. JAMA Pediatr. 2015 Dec;169(12):1162–72.

14. Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D. Neonatal predictors of cognitive ability in adults born very preterm: a prospective cohort study. Developmental Medicine & Child Neurology. 2017;59(5):477–83.

15. Wolke D, Schmid G, Schreier A, Meyer R. Crying and Feeding Problems in Infancy and Cognitive Outcome in Preschool Children Born at Risk: A Prospective Population Study. Journal of Developmental & Behavioral Pediatrics. 2009 Jun;30(3):226.

16. Riegel K, Betke KF. Die Entwicklung gefährdet geborener Kinder bis zum fünften Lebensjahr: die Arvo-Ylppö-Neugeborenen-Nachfolgestudie in Südbayern und Südfinnland;[Prof. Dr. Dr. hc Klaus Betke zum 80. Geburtstag]. Enke; 1995.

17. Voigt M, Fusch C, Olbertz D, Hartmann K, Rochow N, Renken C, et al. Analyse des Neugeborenenkollektivs der Bundesrepublik Deutschland. Geburtshilfe und Frauenheilkunde. 2006 Oct;66(10):956–70.

18. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology. 1991 Oct 1;181(1):129–33.

19. Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D. Preterm Cognitive Function Into Adulthood. Pediatrics. 2015 Sep 1;136(3):415–23.

20. Bauer A. Ein Verfahren zur Messung des für das Bildungsverhalten relevanten Status (BRSS) [A procedure for the measurement of social status related to educational behaviour (BRSS)]. Frankfurt: Deutsches Institut für Internationale Pädagogische Forschung. 1988;

21. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software. 2011 Dec 12;45(1):1–67.

22. Aylward GP. Developmental Screening and Assessment: What Are We Thinking? Journal of Developmental. 2009 Apr;30(2):169–73.

23. De Bie HMA, Oostrom KJ, Boersma M, Veltman DJ, Barkhof F, Delemarre-van de Waal HA, et al. Global and regional differences in brain anatomy of young children born small for gestational age. PLoS ONE. 2011;6(9):e24116.

24. Linsell L, Johnson S, Wolke D, O'Reilly H, Morris JK, Kurinczuk JJ, et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. Archives of Disease in Childhood. 2018 Apr 1;103(4):363–70.

25. McEwen EC, Guthridge SL, He VYF, McKenzie JW, Boulton TJ, Smith R. What birthweight percentile is associated with optimal perinatal mortality and childhood education outcomes? American Journal of Obstetrics and Gynecology. 2018 Feb 1;218(2, Supplement):S712–24.

26. Jaekel J, Sorg C, Baeuml J, Bartmann P, Wolke D. Head Growth and Intelligence from Birth to Adulthood in Very Preterm and Term Born Individuals. J Int Neuropsychol Soc. 2019;25(1):48–56.

	SGA using Neonatal Reference				SGA using Fetal Reference			
	AGA_N + VP/VLBW (n=156)	**SGA_N + VP/VLBW (n=61)**	**AGA_N + Term-Born (n=183)**	**SGA_N + Term-Born (n=14)**	**AGA_F + VP/VLBW (n=101)**	**SGA_F + VP/VLBW (n=116)**	**AGA_F + Term-Born (n=175)**	**SGA_F + Term-Born (n=22)**
Birthweight (g)								
Mean (SD)	1390 (313)	1110 (239)	3430 (398)	2540 (235)	1490 (325)	1150 (219)	3460 (395)	2700 (292)
Gestational Age (weeks)								
Mean (SD)	29.7 (1.49)	32.0 (2.40)	39.7 (1.13)	38.8 (1.25)	29.6 (1.56)	31.0 (2.17)	39.7 (1.14)	39.6 (1.40)
Sex								
Male	86 (55.1%)	28 (45.9%)	86 (47.0%)	8 (57.1%)	60 (59.4%)	54 (46.6%)	83 (47.4%)	11 (50.0%)
Female	70 (44.9%)	33 (54.1%)	97 (53.0%)	6 (42.9%)	41 (40.6%)	62 (53.4%)	92 (52.6%)	11 (50.0%)
Socioeconomic Status								
High	34 (21.8%)	14 (23.0%)	64 (35.0%)	5 (35.7%)	23 (22.8%)	25 (21.6%)	61 (34.9%)	8 (36.4%)

Middle	75 (48.1%)	27 (44.3%)	77 (42.1%)	6 (42.9%)	47 (46.5%)	55 (47.4%)	74 (42.3%)	9 (40.9%)
Low	47 (30.1%)	20 (32.8%)	42 (23.0%)	3 (21.4%)	31 (30.7%)	36 (31.0%)	40 (22.9%)	5 (22.7%)
Parent Infant Relationship								
Poor	73 (46.8%)	29 (47.5%)	50 (27.3%)	3 (21.4%)	48 (47.5%)	54 (46.6%)	47 (26.9%)	6 (27.3%)
Good	78 (50.0%)	28 (45.9%)	133 (72.7%)	11 (78.6%)	49 (48.5%)	57 (49.1%)	128 (73.1%)	16 (72.7%)
Missing	5 (3.2%)	4 (6.6%)	0 (0%)	0 (0%)	4 (4.0%)	5 (4.3%)	0 (0%)	0 (0%)

Table 1. Baseline characteristics of adults born SGA and AGA according to the Neonatal based reference (SGA_N) or Fetal Reference (SGA_F).

Table 2. Estimated mean differences in cognitive test scores from linear mixed model analyses using either Neonatal (SGA_N) or Fetal(SGA_F) references for SGA classification.

Parameters	**SGA_N Model 1**		**SGA_N Model 2**		**SGA_N Model 3**		**SGA_F Model 1**		**SGA_F Model 2**		**SGA_F Model 3**	
Fixed effects	*Est*	*CI*	*Est*	*CI*	*Est*	*CI*	*Est*	*CI*	*Est*	*CI*	*Est*	*CI*
(Intercept)	78.87	**[75.32,82.43]**	90.53	**[83.40,97.65]**	93.15	**[86.18,100.13]**	80.95	**[76.51,85.39]**	92.03	**[84.52,99.53]**	94.70	**[87.36,102.04]**
SGA(AGA=0, SGA=1)	-7.89	**[-14.62,-1.17]**	-7.68	**[-14.38,-0.99]**	-7.14	**[-13.64,-0.64]**	-8.38	**[-14.46,-2.29]**	-8.02	**[-14.09,-1.96]**	-7.86	**[-13.75,-1.98]**
Control(VP/VLBW=0, Term = 1)	21.13	**[16.28,25.98]**	19.71	**[14.84,24.57]**	17.61	**[12.83,22.39]**	19.05	**[13.46,24.64]**	17.75	**[12.15,23.34]**	15.52	**[10.04,21.01]**
Age	0.10	[-0.04,0.23]	0.10	[-0.04,0.23]	0.10	[-0.04,0.23]	0.06	[-0.11,0.23]	0.06	[-0.11,0.23]	0.06	[-0.11,0.23]

SGA*Age	0.23	[-0.02,0.48]	0.23	[-0.02,0.49]	0.23	[-0.02,0.49]	0.18	[-0.05,0.42]	0.18	[-0.05,0.42]	0.18	[-0.05,0.42]
SGA*Control	1.92	[-12.14,15.98]	1.36	[-12.63,15.36]	0.36	[-13.23,13.95]	3.82	[-7.98,15.62]	3.28	[-8.47,15.03]	3.20	[-8.19,14.59]
Control*Age	-0.10	[-0.28,0.09]	-0.10	[-0.28,0.09]	-0.10	[-0.28,0.09]	-0.06	[-0.27,0.15]	-0.06	[-0.28,0.15]	-0.06	[-0.28,0.15]
Control*SGA*Age	-0.05	[-0.58,0.48]	-0.05	[-0.59,0.48]	-0.05	[-0.59,0.48]	-0.09	[-0.54,0.36]	-0.09	[-0.54,0.37]	-0.09	[-0.54,0.37]
Sex(Male=1,Female = 2)	-	-	-1.98	[-5.60,1.63]	-0.65	[-4.18,2.88]	-	-	-1.72	[-5.37,1.92]	-0.35	[-3.90,3.21]
Middle SES at birth (High- as reference)	-	-	-9.31	**[-13.66,-4.95]**	-9.10	**[-13.32,-4.89]**	-	-	-9.19	**[-13.56,-4.81]**	-8.97	**[-13.21,-4.74]**
Low SES at birth (High as reference)	-	-	-14.29	**[-19.17,-9.41]**	-13.86	**[-18.58,-9.14]**	-	-	-14.26	**[-19.16,-9.36]**	-13.81	**[-18.55,-9.06]**
PIRI (0= No Concern, 1 = Concern)	-	-	-	-	-10.10	**[-13.80,-6.39]**	-	-	-	-	-10.19	**[-13.91,-6.47]**
Random Effects												
sd(Intercept)	20.65	[19.03,22.42]	20.52	[18.90,22.28]	19.79	[18.20,21.53]	20.66	[19.01,22.45]	20.53	[18.90,22.30]	19.78	[18.17,21.53]
sd(Age)	0.29	[0.21,0.40]	0.31	[0.24,0.42]	0.32	[0.24,0.42]	0.29	[0.21,0.40]	0.33	[0.25,0.43]	0.32	[0.24,0.43]
cor(Intercept, Age)	-0.83	[-0.94,-0.55]	-0.90	[-0.97,-0.67]	-0.90	[-0.97,-0.67]	-0.85	[-0.95,-0.55]	-0.90	[-0.97,-0.68]	-0.89	[-0.97,-0.66]
BIC	22071		22059		22039		22160		22150		22130	

Note P <0.05 signified in bold, BIC (Bayesian Information Criterion), PIRI (Parent-Infant Relationship Index), Est (Estimate from linear mixed model), CI (95% confidence interval).

Table/Figure Caption List

Table 1. Baseline characteristics of adults born SGA and AGA according to the Neonatal based reference (SGA_N) or Fetal Reference ($SGA_{F)}$

Table 2. Estimated mean differences in cognitive test scores from linear mixed model analyses using either Neonatal (SGA_N) or Fetal(SGA_F) references for SGA classification.

Figure 1. Observed and predicted (Model 3- SGA_N) cognitive trajectories stratified by small for gestational age (SGA) status and very preterm/very low birthweight (VP/VLBW) status.

Figure 2. Observed and predicted cognitive trajectories (Model 3- SGA_F) stratified by small for gestational age (SGA) status and very preterm/very low birthweight(VP/VLBW) status.

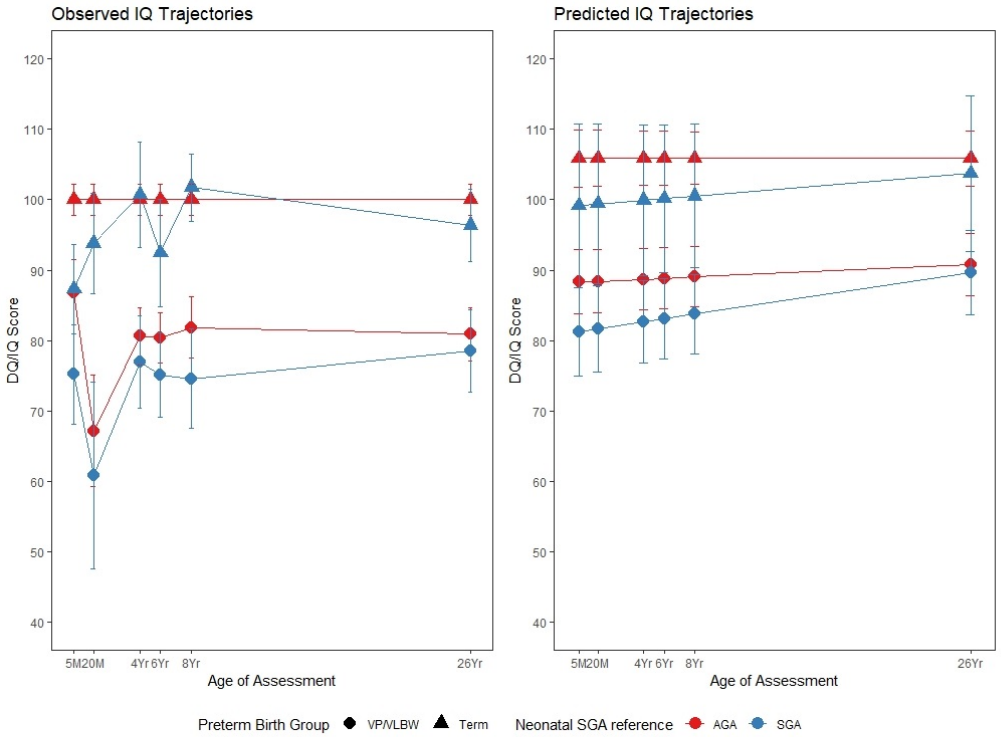

Figure 1. Observed and predicted (Model 3- SGA_N) cognitive trajectories stratified by small for gestational age (SGA) status and very preterm/very low birthweight (VP/VLBW) status.

bjo_16341_f1.jpg

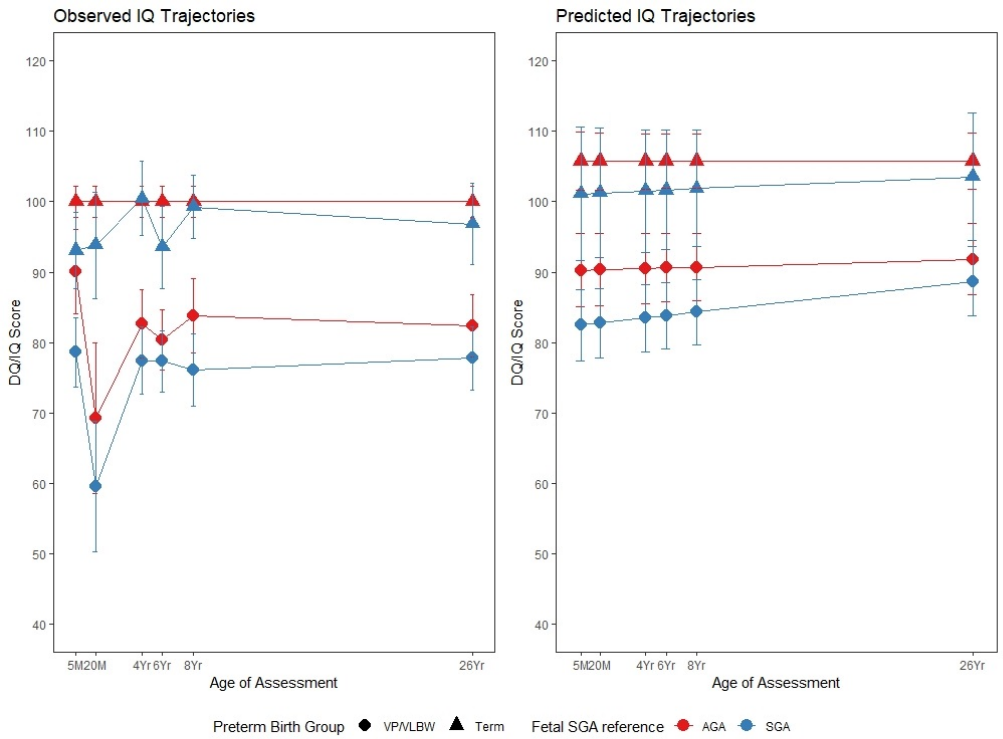

Figure 2. Observed and predicted cognitive trajectories (Model 3 - SGA_F) stratified by small for gestational age (SGA) status and very preterm/very low birthweight(VP/VLBW) status.

bjo_16341_f2.jpg