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Risk of developmental delay increases exponentially as gestational age of preterm infants decreases: a cohort study at age 4 years

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ABBREVIATIONS

ASQ Ages and Stages Questionnaire
Lollipop Longitudinal Preterm Outcome Project
PCHC Preventive child healthcare
SGA Small for gestational age

AIM The aim of the study was to assess the influence of decreasing gestational age on the risk of developmental delay in various domains at age 4 years among children born at a wide range of gestational ages.

METHOD In a community-based cohort, the parents of 1439 preterm-born children (24 0/7 to 35 6/7wks) and 544 term-born children (38 0/7 to 41 6/7wks') born in 2002 and 2003 completed the Ages and Stages Questionnaire (ASQ) when their child was 3 years 7 months to 4 years 1 month old. The prevalence rates of abnormal scores on the ASQ-total problems scale were compared in preterm and term-born children and the resulting odds ratios for gestational age groups were calculated and adjusted for social and biological covariates.

RESULTS The prevalence rates of abnormal scores on the ASQ-total problems scale increased with decreasing gestational age: from 4.2% among term-born children to 37.5% among children born at 24–25 weeks' gestation ($p < 0.001$). The risk of an abnormal ASQ-total score increased exponentially with decreasing gestational age compared with children born at term (odds ratio per week of gestation 1.14, 95% confidence interval 1.09–1.19). A similar exponential pattern was seen on all underlying ASQ domains, both before and after adjustment.

INTERPRETATION The risk of developmental delay increases exponentially with decreasing gestational age below 36 weeks' gestation on all developmental domains of the ASQ. Adjustment for covariates did not alter the pattern of exponential increase in developmental risk with decreasing gestational age. We speculate that both direct perinatal cerebral injuries and tropic and maturational brain disturbances are involved.

Two recent meta-analyses reported a pattern of continuously decreasing IQ scores with decreasing gestational age.^{1,2} By and large, in these meta-analyses the results for children born at between 32 and 36 weeks' gestation, that is moderately preterm children were arrived at by extrapolation, as relatively few studies on long-term development have been carried out in this particular group.^{3,4} Recently, we demonstrated that moderately preterm children are also at increased risk of developmental delay at school entry.⁵

Studies on the effect of decreasing gestational age on development in early childhood that cover the entire preterm gestational age range are few and inconclusive regarding the increased risk of developmental delay with decreasing gestational age.^{6,7} Further, most studies examining the association between decreasing gestational age and increasing developmental problems focus solely on global IQ scores or on rates of specific school problems such as difficulties in reading and mathematics, or failure to complete school at all.^{2,8,9} To our

knowledge, no study has addressed the effect of decreasing gestational age over the entire preterm gestational age range on the developmental domains that may underlie these problems at school entry.

Most studies included in meta-analyses of the relation between gestational age and development of children born below 32 weeks of gestation control only for a limited number of biological and social covariates.^{1,2} This may be an important limitation, since several studies have demonstrated that biological and social covariates influence the likelihood of both preterm birth and adverse long-term developmental outcomes.^{9,10} This is particularly true for the effect of socioeconomic status beyond the age of 2 years.¹¹

The aim of our study was, therefore, to assess the influence of decreasing gestational age on the risk of developmental delay in a variety of developmental domains at age 4 years. We compared a group of preterm children born at a wide range of gestational ages with term-born children. We

analysed crude data and data adjusted for biological and social covariates.

We hypothesized that the prevalence of developmental delay would show a pattern of continuous increase with decreasing gestational age in several developmental domains, independent of biological and social covariates.

METHOD

Participants

This study was part of the Dutch Longitudinal Preterm Outcome Project (Lollipop).^{5,12} From a community-based preventive child healthcare (PCHC) cohort of 45 455 children born in 2002 and 2003, we sampled all children with a gestational age of less than 36 weeks. For every second preterm child we sampled, we selected the next term-born child (38 0/7 to 41 6/7wks' gestation) from the same PCHC cohort as a comparison. The cohort was expanded with very preterm children (<32wks gestation) born in 2003 who had been admitted to any of five tertiary neonatal intensive care units that cater for all very preterm children in their region. These very preterm children accounted for 17.8% of the study cohort. The cohort size of the complete Lollipop sample was based on estimates of numbers needed to compile the growth charts for Dutch preterm-born children. This led to a planned inclusion of 1500 preterm children and 500 term-born comparison children.

The children were recruited during a routine visit to their local PCHC centre at the age of 43 to 49 months (inclusion period 2005–2007): 95% of all Dutch children are routinely seen at a PCHC centre at this age.¹³ Children with major congenital malformations, syndromes, and congenital infections were excluded. The study was approved by the Ethics Review Board of the University Medical Center Groningen. Written informed consent was obtained from all parents. In total, 79% of eligible children ($n=2517$) participated in the Lollipop study. We have previously published a detailed description of the Lollipop study design.^{5,12}

Measures: assessment of developmental delay

We used the Dutch 4 years version of the Ages and Stages Questionnaire (ASQ) to assess development.¹² The ASQ is a parent-completed, validated developmental screening instrument. It measures development in five domains: fine motor, gross motor, communication, problem-solving, and personal-social functioning.¹⁴ The scores of these five domains are summed to obtain an ASQ-total problems score. The original ASQ has proved to be a reliable and cost-effective screening instrument with excellent psychometric properties.¹⁴ Concurrent validity ranges from 76% to 88%.¹⁴ Overall sensitivity and specificity are 75% and 86%, respectively. ASQ scores were based on the children's uncorrected calendar age in accordance with the ASQ manual and the recommendations of the American Academy of Pediatrics.^{14,15} A score of more than 2SD below the mean score for the term-born children was considered abnormal.¹²

The ASQ was completed by the parents of 81.4% of the children who participated in the study ($n=2050$). The median

What this paper adds

- Among children born from 25 to 36 weeks of gestation, risk of developmental delay at age 4 increases exponentially with decreasing gestational age.
- This holds true for the domains of fine motor, gross motor, communication, problem-solving, and personal-social functioning of the ASQ.
- Adjustment for covariates did not alter the pattern of exponential risk.

age of the children for whom the ASQ was completed was 46 months. Ninety-seven per cent of the parents ($n=1983$) completed the ASQ within a time window of 46 months (SD 3mo). We based our analyses on this group, hereafter referred to as the participating children. In comparison with the participating children, the mothers of the non-participating children were more often of a lower socio-economic status (lower vocational level 40.4% vs 28.9%, non-Dutch 15.6% vs Dutch 5.4%, both $p<0.001$). The sex ratio and rate of small for gestational age (SGA) status were not significantly different in the participating and non-participating children.

Measures: gestational age, biological, and social covariates

We compared the data on gestational age provided by the PCHC physicians with the data supplied by the paediatricians, obstetricians, midwives, and parents. In the case of conflicting data, we retrieved the original data from the paediatricians' records. We expressed gestational age in completed weeks of gestation. The children's biological and social details, collected from the parental questionnaires, were cross-matched with the data from the medical sources. The biological covariates included the child's sex, multiple birth, and SGA. We defined SGA, as a proxy for intrauterine growth restriction, as birthweight below the 10th centile of the Dutch Kloosterman growth curves.¹⁶ The social covariates comprised the level of education of both parents, mother's age, and mother's country of birth.

Statistical analyses

We compared the prevalence of abnormal scores on the ASQ-total problems scale and on each of the ASQ domains for preterm children of each gestational week and term-born children (38 0/7 to 41 6/7wks' gestation). As there was only one child with a gestational age of 24 weeks, we included this child in the group of children born at 25 weeks' gestation. Next, we computed the crude odds ratios for abnormal scores on ASQ-total problems scales and ASQ domains for decreasing gestational age as a continuous variable (defined as 'number of weeks born too early', ranging from 5 to 15wks). We compared these scores with those for term-born comparison children (38 0/7 to 41 6/7wks), for whom gestational age was set at 'zero weeks too early'. Adding 'number of weeks too early' as a continuous variable to the model led to the assessment of an exponential association between risk of developmental delay and decreasing gestational age because of the statistical properties of the logistic model. Subsequently, in order to examine whether the model was truly exponential, we added the quadratic term ('number of weeks born too early' \times 'number of weeks born too early') to the model. We examined the goodness-of-fit for both models with the Hosmer–Lemeshow test.¹⁷

We repeated the analyses omitting the child born at 24 weeks of gestation. As there is considerable discussion about whether being born at 'early term gestational age' (i.e. 38–39wks gestation) might also have negative developmental consequences,¹⁸ we also repeated the analyses with the comparison group limited to the children born at 40 0/7 to 41 6/7wks' gestation. In this model, we categorized the children born at 38 and 39 weeks as born 1 and 2 weeks too early, respectively.

Finally, we performed a multivariable logistic regression analysis, with adjustment for all biological and social covariates that had a possible relation ($p < 0.20$) with developmental outcome for ASQ-total-problems in the univariate analyses in the model with all term-born comparison children (38 0/7 to 41 6/7wks') grouped together. The covariates we entered in the univariate analysis were sex, multiple birth, SGA, level of maternal and paternal education, mother's age and her country of birth.

We used SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) for all the analyses. All analyses were two-sided and p -values below 0.05 were considered statistically significant.

RESULTS

Prevalence of developmental delay

Demographic data of the participating children are presented in Table I. The children are grouped according to the dichotomous outcome of the ASQ-total problems score. The groups differed significantly on almost all covariates. In Figure 1 we present the prevalence rates of abnormal ASQ-total problems scores by week of gestation. The prevalence rate of abnormal ASQ-total problems scores increased with decreasing gestational age below 36 weeks ($p < 0.001$, χ^2 for trend test). Overall, the prevalence rate rose from 4.2% among term-born children to 37% among children born at 24 to 25 weeks' gestation. The same pattern of increasing prevalence of developmental delay with decreasing gestational age from 36 weeks was reflected in the scores on all ASQ domains (all p -values < 0.001 , χ^2 for trend test).

Odds ratios for the number of weeks born too early

Table II shows the crude and adjusted odds ratios (OR) for abnormal scores on the ASQ-total problems scale and on all the ASQ domains for decreasing gestational age measured as a continuous variable (number of weeks born too early). The odds ratio risk of preterm children having an abnormal score on the ASQ-total problems scale compared with term-born children increased by 1.14 for each week by which gestation was reduced (95% confidence interval [CI], 1.09–1.19; $p < 0.001$). This implies that the odds ratio for an abnormal ASQ-total problems score rises from 1.14⁵ (OR 1.93) for a child born 5 weeks too early to 1.14¹⁵ (OR 7.14) for a child born 15 weeks too early. Model fit, as tested with the Hosmer–Lemeshow statistic (HL test), was good (χ^2 7.25, degrees of freedom [df] 5, $p = 0.20$). Adding the weeks born too early as an additional quadratic term did not improve the fit of the model (HL-test: χ^2 7.36, df 5, $p = 0.20$), indicating that no deviations from the exponential association occurred.

Table I: Numbers and percentages of children (n [%]) with normal and abnormal ASQ-total problems scores for biological and social variables

	Abnormal ASQ score	Normal ASQ score	p
Sex			
Male	132 (12.9)	895 (87.1)	<0.001
Female	38 (4.3)	849 (95.7)	
Multiple birth			
Singleton	120 (8.1)	1361 (91.9)	0.027
Part of a multiple	50 (11.5)	383 (88.5)	
SGA ^a			
≥ 10 th centile	129 (7.6)	1566 (92.4)	<0.001
<10th centile	41 (18.7)	178 (81.3)	
Maternal education ^b			
Low	65 (12.3)	465 (87.7)	<0.001
Medium or high	104 (7.6)	1272 (92.4)	
Paternal education ^b			
Low	71 (12.2)	509 (87.8)	<0.001
Medium or high	89 (7.0)	1183 (93.0)	
Mother's age at birth of child			
>19y	168 (8.8)	1732 (91.2)	0.726
<20y	1 (12.5)	7 (87.5)	
Country of birth of mother			
Netherlands	156 (8.6)	1654 (91.4)	0.050
Non-Netherlands	14 (14.4)	83 (85.6)	
Age at completing ASQ			
43–46mo	156 (9.4)	1496 (90.6)	0.030
47–49mo	14 (5.3)	248 (94.7)	

^aSGA below 10th centile according to Dutch Kloosterman growth curve. ^bLow education equals primary school or less and/or low-level technical and vocational training. Medium level equals high school or medium-level technical and vocational training for 12–16 years. High level equals university or high-level technical and vocational training for more than 16 years. ASQ, Ages and Stages Questionnaire; SGA, small for gestational age.

As shown in Table II for separate ASQ domains, the odds ratios for 'number of weeks born too early' ranged from 1.10 to 1.14. This resulted in the odds ratios for children born 15 weeks too early varying between 4.17 (1.10¹⁵) and 7.14 (1.14¹⁵). These models for each of the five separate underlying ASQ domains also had a good fit. Adding the quadratic term 'number of weeks born too early' did not improve the fit on any of the ASQ domains.

Next, we repeated the analyses to assess whether we would obtain similar results if we were to make different choices in our models. In the model excluding the child born at 24 weeks' gestation and in the model with the control group restricted to children born at 40 0/7 to 41 6/7 weeks' gestation, the odds ratios for decreasing gestational age and model fit were very similar to those in our first set of models. Adding the quadratic term did not improve model fit in these models either.

As all covariates, except maternal age, had a significant or borderline association with developmental outcome on ASQ-total problems, all covariates, except maternal age, were added to the final multivariable logistic regression models. Adjustment for these covariates hardly affected the odds ratios for developmental risk by week born too early, for both ASQ-total problems and ASQ domains. Adjustment for age at completing the ASQ did not change our results (not shown).

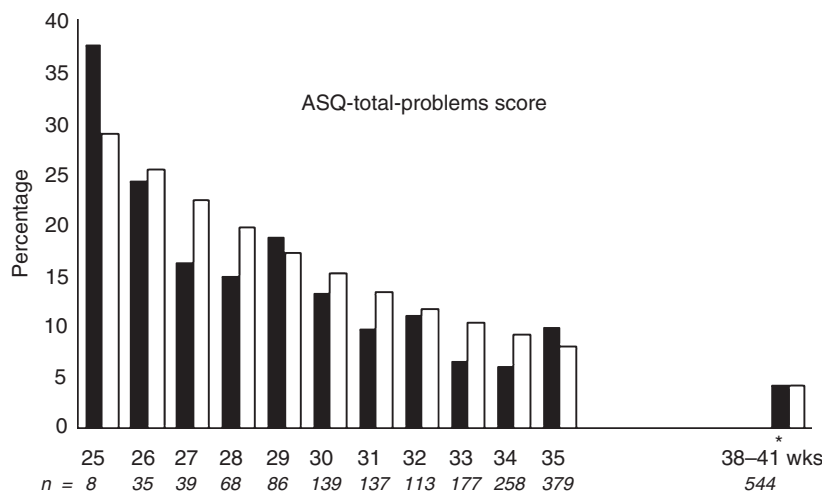


Figure 1: Percentages of children born at each gestational week with abnormal Ages and Stages Questionnaire (ASQ)-total problems scores at age 4 years. Black bars, percentages of children with abnormal ASQ-total-problems scores; open bars, percentages of children with expected abnormal ASQ-total-problems scores according to the exponential model; *n* total number of children per gestational age group. *The rate of term-born children with an abnormal ASQ-total-problems score was more than 2.3% because of a non-normal distribution of the ASQ scores.

Table II: Odds ratios, 95% confidence intervals, and *p*-values of univariate and multivariate logistic regression analyses for the gestational age of preterm infants as a continuous variable on ASQ-total problems and ASQ domains compared with term-born children^a

Domain	Univariate			Multivariate ^b		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i> -value
Total problems	1.14	1.09–1.19	<0.001	1.13	1.08–1.18	<0.001
Fine motor	1.12	1.07–1.17	<0.001	1.13	1.08–1.18	<0.001
Gross motor	1.14	1.09–1.19	<0.001	1.13	1.08–1.19	<0.001
Communication	1.10	1.06–1.14	<0.001	1.08	1.04–1.13	<0.001
Personal–social	1.14	1.08–1.19	<0.001	1.13	1.07–1.19	<0.001
Problem-solving	1.10	1.05–1.15	<0.001	1.10	1.05–1.16	<0.001

^aTerm-born children (38 + 0 to 41 + 6wks), defined as zero weeks too early. ^bAdjusted for sex, small for gestational age status, father's education, mother's education, mother's birth country, and multiple birth. OR, odds ratio; CI, confidence interval.

DISCUSSION

This study demonstrates that the risk of developmental delay increases exponentially as gestational age decreases in the range 25 to 36 weeks. This is demonstrated by abnormal scores on both the ASQ-total problems scale and all five underlying ASQ domains, that is fine motor, gross motor functioning, communication, problem-solving, and personal–social functioning. Adjustment for covariates did not alter the pattern of exponential increase in developmental risk with decreasing gestational age.

Our finding that the risk of developmental delay increased exponentially as the number of weeks born too early increased is in contrast with the findings of other studies on the association between increasing weeks too early and developmental outcome. Other authors studying the association in *very* preterm-born children found linear associations between decreas-

ing gestational age and global IQ measures.^{1,2} However, probably as a result of the limited range of gestational ages in their studies, they were unable to discriminate between a linear and an exponential association. Our study covered a much wider range of preterm gestational ages.

Several reviews on the outcomes of preterm birth have mentioned stepwise increases in developmental disabilities with decreasing gestational age in broad gestational age groups, but without providing data by week of gestational age.^{19,20} Two research groups that did study a wide range of preterm gestational ages per week gestational age did find non-linear associations between decreasing gestational age and global developmental outcome, but neither labelled the association exponential.^{6,7} Wolke et al.⁶ described a stepwise association between decreasing gestational age and global IQ score in a German cohort born between 27 and 42 weeks' gestation. Mathiasen et al.⁷ presented two straight regression lines with different slopes to model the association between decreasing gestational age and the risk of not finishing basic education for preterm-born Danish children, one for children born at 24 to 31 weeks' gestation and one for those born at 32 to 41 weeks' gestation.

We found only one recent study, by Mackay et al.²¹, showing results that could lead one to conclude that an exponential relation might exist between decreasing gestational age and special educational needs as a proxy for developmental problems. In a series of logistic regression analyses for each week of gestation between 24 and 43 weeks, Mackay et al. analysed the association between gestational age and the proportion of children with special educational needs. They presented their results on a logarithmic scale.

Our findings also deviated from those of other studies concerning the association between the risk of developmental delay and decreasing gestational age with regard to the measure used to assess development. Instead of looking at global IQ measures, or global school problems, we studied

specific developmental domains that might underlie these problems at the age of 4 years. We found exponential associations between decreasing gestational age and the risk of abnormal scores on all five of the developmental domains of the ASQ, with relatively small differences in effect sizes. This might well explain the wide variety of high-prevalence/low-severity developmental disabilities and educational problems found in preterm children at school age.²²

Adjusting for biological and social covariates did not alter the exponential increase in the developmental risk associated with decreasing gestational age, as measured by score on the ASQ-total problems scale and ASQ domains. In effect, differences in the odds ratios of scores on the ASQ-total problems scale and ASQ domains before and after adjustment were small. This shows that the exponential relationship is a real effect of gestational age, and not confounded by these factors. If social factors have an impact on this relationship, then this occurs in parallel with the effect of gestational age.

The explanation for the exponential association between the risk of developmental delay and the number of weeks born too early might be found in the rapid growth of the brain during the third trimester of pregnancy. Between 24 and 40 weeks of gestation, cortical volume increases fourfold. This corresponds with increasing synaptogenesis, neuronal and axonal growth, myelination, and focused apoptosis, all leading to exponentially increasing brain connectivity.²³ The conditions necessary for all the different maturational processes of the brain that lead to increased brain connectivity are more favourable in utero than after birth. Direct brain destruction caused by perinatal insults and maturational and trophic disturbances of normal brain development after preterm birth might be involved in the exponentially increasing risk of developmental delay.^{2,23}

Strengths and limitations

Our study has several strengths. Firstly, it is based on a large, prospective, community-based sample involving a wide range of preterm and term gestational ages. Secondly, gestational ages were determined by several methods, enhancing reliability. Finally, we excluded children with congenital malformations, syndromes, and congenital infections. Excluding these children, which usually is not possible in birth register cohorts, might be important as children with congenital malformations and syndromes are more often born preterm.

We also recognize limitations of our study. We measured developmental outcome with a parent-completed screening instrument rather than more extensive neuropsychological tests. Even so, developmental screens are considered to be reliable measures for identifying developmental problems in large high-risk populations.²⁴ Another limitation is that we did not include in our study design children born at 36 and 37 weeks' gestation. In the Netherlands, children born at 36 weeks are considered to be preterm and children born at 37 weeks are considered to be born at term. The fact that both our first model with term-born comparison children born between 38 0/7 and 41 6/7 weeks and the restricted model with term-born comparison children born between 40 0/7 and 41 6/7 weeks yielded similar results, including a good model fit,

confirms the hypothesis of an effect of decreasing gestational age below 40 weeks' gestation, even in the early term range.^{20,21} Thus, these findings are in line with those of other recent studies that found an effect of decreasing gestational age below 40 weeks of gestation.¹⁹⁻²¹ None of them, however, formally assessed its exponential nature.

Implications

Our study may have several implications. Firstly, it emphasizes that professionals (obstetricians, paediatricians) and parents should be aware that there is no clear preterm gestational threshold below which risk of developmental delay starts to increase. In fact, the increase is exponential. Evidence that the prevalence of developmental delay increases exponentially with decreasing gestational age, even in the moderately preterm age range, might influence the delicate balance between the advantages and disadvantages involved in planning a birth before term. Secondly, knowledge about specific developmental domains already affected at preschool age should lead to a closer link with prevention and early treatment. Finally, since we presume that problems in these developmental domains on entering school may be precursors to problems persisting into late childhood and adulthood, early, targeted intervention might also have long-lasting socio-economic implications for society.²⁵ Some studies have found that very preterm children seem to do better when entering adulthood.^{19,20} Whether the pattern of exponential increase of developmental disabilities with decreasing gestational age will persist into adulthood therefore deserves additional study.

CONCLUSION

With decreasing gestational age from 36 to 25 weeks, the prevalence of parent-reported developmental delay of preterm-born children at the age of 4 years increases exponentially in five domains: fine motor, gross motor, communication, problem-solving, and personal-social functioning.

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British Academy of Childhood Disability (BACD)

Annual Scientific Meeting

Monday 25 March 2013

Theme: Paediatric Brain Injury – time to intervene

The 2013 BACD Annual Scientific Meeting will take place at the University of Birmingham. It will focus on paediatric brain injury and how timely focused interventions can improve outcome. Dr Mary-Clare Waugh, head of brain injury rehabilitation at Westmead Children's Hospital, Sydney, will be delivering the Polani Lecture, giving an overview of brain injury in childhood and adolescence.

Mac Keith Poster Prize The BACD is calling for abstracts for Poster Presentations at the ASM. We are seeking posters that report innovative multi-disciplinary work for children with neurodisability and their families. The submission deadline is **18 January 2013**.

The Royal College of Paediatrics & Child Health and the **BACD** are calling for applications for the **Paul Polani Award** which supports research in paediatric neurodisability in the UK. The deadline to apply is Thursday **31 January 2013**.

For more information on all these visit the BACD website: www.bacids.org.uk