

Early emergence of delayed social competence in infants born late and moderately preterm: A prospective population-based cohort study

Running head: Social competence in late/moderately preterm infants

Authors: Samantha Johnson¹, PhD, CPsychol, AFBPsS; Ruth Matthews¹, MSc; Elizabeth S Draper¹, PhD; David J Field¹, DM; Bradley N Manktelow¹, PhD; Neil Marlow², DM FMedSci; Lucy K Smith¹, PhD; Elaine M Boyle¹, MD PhD.

Affiliations: ¹Department of Health Sciences, University of Leicester, Leicester UK; ²Department of Academic Neonatology, Institute for Women's Health, University College London, London, UK.

Corresponding author (address for reprints): Dr Samantha Johnson, Department of Health Sciences, University of Leicester, 22-28 Princess Road West, Leicester, LE1 6TP, UK. Tel: 0116 252 5798. Fax: 0116 252 3272. Email: sjj19@le.ac.uk.

Conflicts of interest: The authors have no conflicts of interest to disclose.

Source of funding: This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research (PGfAR) Programme (Grant Reference Number RP-PG-0407-10029). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Neil Marlow receives a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme at UCLH/UCL.

Manuscript word count: 3207

Number of figures and tables: 4

Abbreviations: ADHD Attention Deficit/Hyperactivity Disorder; ASD Autism Spectrum Disorders; BITSEA Brief Infant and Toddler Social Emotional Assessment; LAMBS Late and Moderately Preterm Birth Study; LMPT Late and moderately preterm (birth at 32-36 weeks gestation); PARCA-R Parent Report of Children's Abilities Revised; SES Socio-economic status; SGA Small for gestational age.

Abstract

Objective. To assess behavioural outcomes and social competence at 2 years of age in infants born late and moderately preterm (LMPT; 32-36 weeks gestation).

Method. 1130 LMPT infants and 1255 term-born (≥ 37 weeks) controls were recruited at birth to a prospective geographical population-based study. Parents completed the Brief Infant and Toddler Social Emotional Assessment (BITSEA) at 2 years corrected age to assess infants' behaviour problems and social competence. Cognitive development was assessed using the Parent Report of Children's Abilities-Revised (PARCA-R). Parent questionnaires at 2 years were completed for 638 (57%) LMPT and 765 (62%) term-born infants. Group differences in the prevalence of behaviour problems and delayed social competence between LMPT infants and term-born controls were adjusted for age, sex, small-for-gestational-age, socio-economic status and cognitive impairment.

Results. LMPT infants were at significantly increased risk of delayed social competence compared with term-born controls (26.4% vs. 18.4%; adjusted-RR 1.28; 95% CI 1.03 to 1.58), but there was no significant group difference in the prevalence of behaviour problems (21.0% vs. 17.6%; adjusted-RR 1.13; 0.89 to 1.42). Non-white ethnicity (RR 1.68; 1.26 to 2.24), medium (RR 1.60; 1.14 to 2.24) and high (RR 1.98; 1.41 to 2.75) socio-economic risk and recreational drug use during pregnancy (RR: 1.70; 1.03 to 2.82) were significant independent predictors of delayed social competence in LMPT infants.

Conclusion. Birth at 32-36 weeks of gestation confers a specific risk for delayed social competence at two years of age. This may be indicative of an increased risk for psychiatric disorders later in childhood.

Keywords: Preterm; outcomes; behaviour problems; social competence; infant.

It is well documented that very preterm birth, before 32 weeks of gestation, is associated with lifelong neurodevelopmental sequelae. There is increasing interest in the development of psychopathology in preterm populations and growing evidence of a significant excess of behaviour problems and psychiatric disorders among very preterm survivors compared with their term born peers. The preterm behavioural phenotype is characterised by inattention, anxiety and socio-communicative problems which manifest in an increased risk for attention deficit/hyperactivity disorders, emotional disorders and autism spectrum disorders in childhood.¹ Signs of future disorders are evident in infancy and persist throughout childhood and adolescence.

Over recent years there has been growing interest in the outcomes of children born late (34-36 weeks) and moderately (32-33 weeks) preterm. Although historically considered low risk, accumulating evidence shows that infants born at these gestations are at increased risk for neurodevelopmental delay, cognitive deficits and learning difficulties compared with term-born peers. To date, the few studies of behavioural outcomes in this population have produced conflicting results and there is a paucity of prospective population-based studies. Whilst a number of authors have reported an increased risk of socio-emotional and attention problems in school-aged children born late and/or moderately preterm, the prevalence of externalising problems typically shows no difference from term-born controls.²⁻⁶ However, the authors of one study have reported an increased risk of problems in all behavioural domains in pre-schoolers born moderately preterm⁷ whilst others have reported no significant differences from term-born controls.⁸ Several authors have therefore stressed the need for large, prospective population-based studies of outcomes following late and moderately preterm birth^{9,10}, particularly as this population comprises up to 84% of the 15 million babies who are born preterm each year worldwide.¹¹ As such, even small increases in adverse outcomes in this population may confer a significant public health burden.

The presence of behaviour problems (aggression, defiance, overactivity, anxiety and withdrawal) and poor social competence (delayed development of social-emotional abilities such as empathy, prosocial behaviour and compliance) in the first two years of life have been shown to predict psychopathology later in childhood^{12,13}, and early detection and management of behaviour, social and emotional

problems can improve children's outcomes in the long term.¹⁴ Despite the importance of early identification, no studies have assessed behavioural outcomes at two years of age in infants born late and/or moderately preterm. In particular, it has recently been asserted that evaluations of early childhood outcomes are needed in this population.¹⁰

This paper reports the results of a large, prospective population-based cohort study of infants born late and moderately preterm (LMPT; 32-36 weeks) and a similar sized control group of infants born at term (≥ 37 weeks). The aims of the study were to assess the impact of LMPT birth on the risk for behaviour problems and delayed social competence at two years of age and to identify neonatal predictors of adverse outcomes.

METHOD

Population

Mothers of all babies born LMPT (32⁺⁰-36⁺⁶ weeks) from 1st September 2009 to 31st December 2010 within a geographically defined region of the East Midlands of England were invited to participate in the Late And Moderately preterm Birth Study (LAMBS). Births within this region were derived from four large maternity hospitals, a midwifery-led birthing unit and home births during the study period. A random sample of babies born at term (37⁺⁰-42⁺⁶ weeks) was also recruited over the same time period based on random sampling of the dates and times of birth of babies born in the same geographical area during the previous year. In addition, mothers of all term-born multiples were invited to participate given the high rate of multiple births in the LMPT population. Research midwives obtained informed consent for participation from mothers shortly after discharge. Infants with major structural or chromosomal congenital anomalies were recruited but were excluded from the present analyses. The study was approved by Derbyshire NHS Research Ethics Committee (Ref 09/H0401/25).

Obstetric and Neonatal Data Collection

Data about obstetric factors and pre-pregnancy health conditions were collected by research midwives from mothers' medical notes, and data relating to infants' neonatal course were obtained from their medical notes at discharge from hospital using standard clinical record forms and following a study data extraction manual. All forms were checked by a consultant neonatologist (EB) and any missing data or queries verified against the medical notes and amended as necessary. Obstetric data collected included whether the mother had pre-pregnancy diagnosed diabetes or hypertension; smoked, used recreational drugs or drank alcohol during pregnancy; preeclampsia, gestational diabetes or infection (positive culture) during pregnancy; pre-labour rupture of membranes; received antenatal corticosteroids; induced labour; mode of delivery; raised C-Reactive protein (CRP) during delivery and the results of any antenatal umbilical Doppler studies. Neonatal data items included sex, gestation and birthweight; small for gestational age status (SGA; fetal weight <3rd percentile for sex and gestation with customised antenatal growth charts using the GROW methodology¹⁵); temperature and need for resuscitation at birth; respiratory support; hypoglycaemia (blood glucose <2mmol/l); jaundice requiring phototherapy; antibiotic administration; any abnormal cranial ultrasound and MRI findings (defined as Grade III/IV intraventricular haemorrhage, periventricular leukomalacia or Grade II/II neonatal encephalopathy); method of feeding at discharge.

Maternal Socio-Demographic Data Collection

Mothers participated in a semi-structured interview after birth to obtain socio-demographic data. To quantify socio-economic status (SES), a composite SES-Index score was computed using five variables that measured mothers' (1) occupational status (using the UK Office for National Statistics Socio-Occupational Classification system), (2) highest educational qualification, (3) social support (co-habiting status during pregnancy), (4) income (car ownership) and (5) wealth (home ownership). These were scored on a 4-point scale (occupational status and educational qualification) or 2-point scale for dichotomous variables (social support, income and wealth) and a total SES-Index score was computed (range 0-12) with higher scores indicating greater socio-economic risk. SES-Index scores

were used to classify mothers into three risk categories: low (scores 0-2), moderate (scores 3-5) and high (scores ≥ 6) socio-economic risk. This classification system has been described in detail previously.¹⁶

Outcome Measures at Two Years

At two years corrected age, parents were asked to complete a study questionnaire. This was mailed to parents approximately seven to ten days before the child turned two years corrected age with instructions to return it to the study centre in the freepost envelope provided. Parents were contacted by telephone when the child reached two years corrected age to remind them to complete the questionnaire if they had not yet responded. For parents who could not be contacted by telephone, a second questionnaire was mailed and a reminder sent by email or text message where contact details were available. Parents who did not respond to the postal questionnaire were offered the option to complete it via a telephone interview or electronically in order to maximise response rates.

The study questionnaire comprised a series of parent report measures to assess children's developmental and behavioural outcomes. To assess behavioural outcomes, parents completed the Brief Infant Toddler Social Emotional Assessment (BITSEA).¹⁷ This 42 item questionnaire comprises two scales to assess behaviour problems and social competence and has previously been shown to have excellent test-retest reliability, inter-rater reliability and predictive validity for psychiatric disorders at school age in both term and preterm populations.^{12,17,18} The BITSEA 'problem scale' comprises 31 items that assess behavioural problems in the areas of externalising problems, internalising difficulties, dysregulation, maladaptive behaviours and atypical behaviours. Individual item scores are summed to provide a total problem scale score with higher scores indicating greater problems. Using the published age- and sex-specific norm-referenced cut-offs, infants were identified as having behaviour problems if they scored $>25^{\text{th}}$ percentile of the BITSEA standardisation sample.¹⁷ The BITSEA 'competence scale' comprises 11 items that assess areas of attention, compliance, mastery motivation, prosocial peer relations, empathy, imitation/play skills and social relatedness and is designed to identify children who have delays or deficits in the acquisition of social-emotional

competencies (irrespective of whether behaviour problems are present). Individual item scores were summed to provide a total competence score with lower scores indicating poorer social competence. Infants were identified as having delayed social competence if their total competence score was <15th percentile of children of the same age and sex in the BITSEA standardisation sample.¹⁷ Missing BITSEA items were scored 0 where there were ≤ 5 missing items on the problem scale and ≤ 2 missing items on the competence scale. Eighteen children with substantial missing data (>5 problem items or >2 competence items) were excluded from the analyses.

Cognitive development at two years corrected age was assessed using the Parent Report of Children's Abilities-Revised (PARCA-R), a parent questionnaire for assessing non-verbal cognitive and language development in preterm infants at 2 years of age.¹⁹ A total Parent Report Composite (PRC) score was derived (range 0-158) from which scores <2.5th percentile of the term-born control group (PRC <35) were used to identify children with moderate/severe delay.¹⁶ The PARCA-R has excellent test-retest reliability, concurrent validity and diagnostic utility in identifying preterm infants with cognitive impairment (scores <-2SD) measured by gold standard development tests.¹⁹

Statistical Analyses

All study data were double entered and verified prior to analysis. In all analyses, sampling weights were used to account for the over-sampling of multiple births among the term control group.

Demographic characteristics of LMPT and term-born infants were compared using t-tests for weighted means and chi-squared tests for weighted proportions. The prevalence of behaviour problems and delayed social competence was compared between LMPT and term-born infants using Poisson regression with differences quantified using relative risks (RR) with 95% confidence intervals (95% CI) in three consecutive models: (1) unadjusted; (2) adjusted for sex, age (month of corrected age), SES-Index category and small for gestational age (SGA) status; and (3) adding cognitive impairment at 2 years to Model 2. Cluster sandwich estimators were used in all models to obtain robust variance estimates in order to adjust for the correlation in outcomes within multiple births. To explore predictors of delayed social competence in LMPT infants, univariable associations were analysed

using Poisson regression. A multivariable model was constructed to identify independent risk factors. Variables that were significant ($P < 0.05$) in univariable analyses were all entered into the model. Variables that were not significant in this model were dropped in turn until only those variables significant at $P < 0.05$ were included in the final model. Variables that had been dropped were entered back into this final model one at a time to assess their significance. Infants were included if they had complete data for all the variables included. The final model was fitted for all those with complete data for the variables that were retained in this model. The final model was then fitted including sex and gestational age as these factors are well-documented to affect behavioural outcomes in preterm infants.

RESULTS

Population

In total, 1130 (84%) LMPT and 1255 (79%) term-born babies were recruited at birth during the study period. After excluding children with major congenital anomalies, 2-year questionnaires were received for 638 (57%) LMPT and 765 (62%) term-born infants, of which 625 (56%) and 760 (62%) respectively had complete BITSEA data (Figure 1). Demographic characteristics of the infants assessed at 2 years of age are shown in Table 1. Of the LMPT infants, 87 (14%) were moderately preterm and 551 (86%) late preterm. Compared with term born controls, LMPT infants were more likely to be born SGA and to be multiple births. LMPT infants were also more likely to have cognitive impairment at 2 years corrected age (Table 1). There were no significant between-group differences in infants' sex and age at assessment (Table 1).

We have previously reported that mothers of both LMPT and term-born infants who did not return a 2-year questionnaire were younger, more likely to be non-white, non-English speaking, a single parent, have lower occupational and educational status, to be struggling financially and have poorer health than responders.²⁰

<<FIGURE 1>> <<TABLE 1>>

Prevalence of Behaviour Problems and Delayed Social Competence

There was no significant difference in the prevalence of behaviour problems between groups (Table 2, Term 17.6%; LMPT 21.0%) in both unadjusted (RR 1.19; 95% CI 0.94 to 1.50) and adjusted analyses (RR 1.13; 95% CI 0.89 to 1.4). In contrast, LMPT infants were 1.4 (95% CI 1.15 to 1.78) times more likely to have delayed social competence than their term-born peers. This remained significant after adjustment for age, sex, SES and SGA (Model 2). Adding cognitive impairment at 2 years to the model (Model 3) reduced the RR to 1.28 (95% CI 1.03 to 1.58), but the difference remained statistically significant. After adjustment for confounders, there was no significant difference in the prevalence of term and LMPT infants with behaviour problems *and* delayed social competence (Term 7% vs. LMPT 10%; RR 1.34, 95% CI 0.91 to 1.97). However, there was a significant excess of infants with behaviour problems *or* delayed competence in the LMPT group (Term 29% vs. LMPT 37%; RR 1.17, 95% CI 1.00 to 1.38), reflecting the increased risk for poor social competence in this population. There was no significant difference in the prevalence of behaviour problems and delayed social competence between infants born moderately (32-33 weeks) and late preterm (34-36 weeks), though the number of moderately preterm infants was small for detecting such sub-group differences (Table 2).

Among LMPT infants, there was a higher rate of behaviour problems and delayed social competence among males than females but the differences were not significant (behaviour problems: 29.4% vs. 22.9%, RR 1.28, 95% CI 0.97 to 1.69; delayed social competence 22.3% vs. 19.4%, RR 1.14; 95% CI 0.83 to 1.57). There was a similar pattern of findings among male and female infants born at term (behaviour problems: 19.2% vs. 18.2 %, RR 1.06; 95% CI 0.78 to 1.43; delayed social competence: 22.3% vs. 19.4%, RR 1.14; 95% CI 0.83 to 1.57).

<<TABLE 2>>

Risk Factors for Delayed Social Competence in LMPT Infants

Demographic, obstetric and neonatal risk factors for delayed social competence in the LMPT group were explored to aid early identification of infants at risk (Table 3). Potential risk factors examined

were identified as clinically important because they are key neonatal morbidities or are known predictors of adverse outcomes following very preterm birth. In univariable analyses, infants of non-English speaking, non-white mothers of medium or high socio-economic risk were significantly more likely to have delayed social competence at two years corrected age. Infants whose mothers smoked or took recreational drugs during pregnancy were at greater risk of delayed competence than those of mothers who did not smoke or take recreational drugs. In addition, infants who were receiving breast milk at discharge were less likely to experience delayed social competence at two years of age (Table 3). In the final multivariable model (n=623), infants born to mothers of non-white ethnic origin (RR 1.68; 95% CI 1.26 to 2.24), with medium (RR 1.60; 95% CI 1.14 to 2.24) and high (RR 1.98; 95% CI 1.41 to 2.75) socio-economic risk and whose mothers took recreational drugs during pregnancy (RR 1.70; 95% CI: 1.03 to 2.82) were at significantly increased risk for delayed social competence at two years corrected age.

<<TABLE 3>>

DISCUSSION

The results of this large prospective population-based study provide evidence of the early emergence of deficits in social competence among infants born at 32-36 weeks of gestation. This is the first study to explore behavioural, social and emotional development in LMPT and term-born infants at two years of age and provides much needed evidence about early childhood outcomes in this population.¹⁰

Infants born LMPT were at 1.3 times increased risk for delayed social competence compared with their term-born peers. This remained significant after adjustment for a range of confounding factors including age, sex, SES, SGA status and cognitive impairment at two years. In contrast, there was no significant difference in the prevalence of behaviour problems between LMPT infants and term-born controls. Rather than providing evidence of a general risk for psychopathology, as is suggested in some studies⁷, our results are indicative of a specific risk for poor social competence following LMPT birth. These results are largely consistent with the findings from studies of school-aged children born

LMPT in which LMPT birth has been most consistently associated with an increased risk for socio-emotional and attention difficulties in childhood, typically in the absence of, or with weaker evidence for, externalising behaviour problems.^{2,3,5,7,8} The present results are also mirrored in population-based studies of the behavioural outcomes of two-year old children born very preterm. Using the Infant and Toddler Social Emotional Assessment (ITSEA), a closely related measure to that used in the present study, socio-emotional problems were more common among infants born <30 weeks gestation than difficulties in the other domains assessed.²¹

This pattern of findings reflects the preterm behavioural phenotype that has been characterised through studies of very preterm survivors¹ and suggests that the risk for this constellation of psychopathology extends across birth at all preterm gestations. Indeed, a continuum of adverse outcomes across the full spectrum of preterm birth has been evidenced in neurodevelopmental, behavioural and educational outcomes.²² This is unsurprising as interruption to brain development at any gestation prior to term confers an increased risk for structural immaturity, reduced brain volume and intra-cranial injuries.^{23,24}

Although studies have reported worse neurodevelopmental outcomes for LMPT boys²⁵, gender differences were not observed in the present study. A previous study of very preterm infants using the ITSEA also reported no significant gender differences at two years of age. The authors suggested that higher rates of problems among boys may emerge over the preschool years^{16,21} which may account for the gender differences observed in some studies of the behavioural outcomes of older children born LMPT.⁷ As the present analyses were adjusted for socio-economic adversity and cognitive deficits, the significant excess of delayed social competence cannot be fully accounted for by these factors. We also found that socio-demographic factors were the only significant independent predictors of delayed social competence in LMPT infants. The additive effect of low SES has previously been reported in this population^{25,26} and may represent a potential target for identifying LMPT children who may benefit from early intervention.

Although we did not observe an increased risk for behaviour problems, the early emergence of delayed social competencies in this population is of notable concern. Large Scandinavian register

studies have shown that LMPT birth confers an increased risk for psychiatric disorders in adulthood.²⁷ As poor social competence in early childhood is predictive of later psychiatric disorders in very preterm children and community populations^{12,13,28}, LMPT infants with delayed social competence at two years of age may be at risk for developing mental health disorders later in life. In very preterm infants, poor social competence has been frequently reported at two years and been shown to persist throughout childhood and adolescence.²⁹ Difficulties in relating to others and forming social relationships may impact on children's integration and performance at school and on their mental health and well-being in the long-term. Routine follow-up of LMPT infants, particularly those with high socio-economic risk, may be prudent to identify and ameliorate peer relationship difficulties from an early age. Early instigation of parenting interventions during the preschool years coupled with additional support in school may serve to enhance social competence in children born preterm²⁹, though their effectiveness in the LMPT population requires investigation.

The strengths of this study include the recruitment of a large geographic population-based cohort of LMPT infants, the inclusion of a similar-sized contemporaneous term control group and a prospective design with collection of comprehensive socio-demographic, obstetric and neonatal data. A well-validated measure of behavioural outcomes with good predictive validity for childhood psychiatric disorders was used and analyses were adjusted for key confounders. However, despite intensive efforts to minimise participant attrition, mothers of both LMPT and term-born infants who did not respond to two year follow-up invitations were of higher socio-economic and demographic risk and those not recruited to the study lived in areas of greater socio-economic deprivation.²⁰ As these factors are associated with poor neurodevelopmental and behavioural outcomes, the present results may underestimate the true prevalence of delayed social competence in this population. Given the size of the population to be assessed, outcome assessments were conducted using parent questionnaires alone as it was not feasible to carry out formal assessments. Future studies would benefit from the inclusion of direct observations and assessments of children's cognitive and behavioural outcomes. In addition, our data were derived from a cross-sectional analysis of outcomes at two years. Longer-term follow-up, including diagnostic psychiatric evaluations of childhood behavioural and emotional disorders, are

needed to determine the significance of these parent-reported delays in social competence at two years of age. Although children born at early term gestations (37-38 weeks) have been shown to be at a small but significantly increased risk of developmental disorders compared with those born at full term (39-40 weeks), these infants were included in the control group as the present study was initially powered to detect a difference in outcomes between two groups (LMPT vs. Term i.e. ≥ 37 weeks of gestation); again this means that the present results may underestimate the true prevalence of problems among LMPT infants when compared to infants born at 39-40 weeks of gestation. Given the small number of moderately preterm infants included, there was low power for assessing sub-group differences in outcomes and insufficient power to explore outcomes by individual week of gestation. Future studies are needed to assess early behavioural outcomes exploring the effects of gestational age as a continuum across the full gestation spectrum. In addition, future research should explore the mediating role of parenting and maternal mental health in the development of behavioural and emotional disorders in population. In particular, understanding the cognitive factors that contribute to the development of social competence following preterm birth is an important avenue for future investigation.^{30,31}

In conclusion, the present study provides evidence of a specific risk for delayed social competence following LMPT birth. LMPT infants born into families with low socio-economic status are at greatest risk for these early deficits. Longer term follow-up is needed to determine the prognostic significance of these parent-reported difficulties at two years of age and to ascertain how the LMPT behavioural phenotype manifests later in childhood.

Acknowledgements

The authors would like to thank the children and families that took part in the Late and Moderately preterm Birth Study (LAMBS).

References

1. Johnson S, Marlow N. Preterm Birth and Childhood Psychiatric Disorders. *Pediatric Research*. May 2011;69(5):11r-18r.
2. Talge NM, Holzman C, Wang J, Lucia V, Gardiner J, Breslau N. Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. *Pediatrics*. Dec 2010;126(6):1124-1131.
3. van Baar AL, Vermaas J, Knots E, de Kleine MJK, Soons P. Functioning at School Age of Moderately Preterm Children Born at 32 to 36 Weeks' Gestational Age. *Pediatrics*. July 1, 2009 2009;124(1):251-257.
4. Bul KC, van Baar AL. Behavior Problems in Relation to Sustained Selective Attention Skills of Moderately Preterm Children. *Journal of developmental and physical disabilities*. Apr 2012;24(2):111-123.
5. Loe IM, Lee ES, Luna B, Feldman HM. Behavior problems of 9-16 year old preterm children: biological, sociodemographic, and intellectual contributions. *Early Hum Dev*. Apr 2011;87(4):247-252.
6. Westrupp EM, Mensah FK, Giallo R, Cooklin A, Nicholson JM. Mental health in low-to-moderate risk preterm, low birth weight, and small for gestational age children at 4 to 5 years: the role of early maternal parenting. *J Am Acad Child Adolesc Psychiatry*. Mar 2012;51(3):313-323.
7. Potijk MR, de Winter AF, Bos AF, Kerstjens JM, Reijneveld SA. Higher rates of behavioural and emotional problems at preschool age in children born moderately preterm. *Arch Dis Child*. Feb 2012;97(2):112-117.
8. Gurka MJ, LoCasale-Crouch J, Blackman JA. Long-term cognition, achievement, socioemotional, and behavioral development of healthy late-preterm infants. *Archives of Pediatric and Adolescent Medicine*. 2010;164(6):525-532.
9. Samra HA, McGrath JM, Wehbe M. An integrated review of developmental outcomes and late-preterm birth. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG*. Jul-Aug 2011;40(4):399-411.

10. McGowan JE, Alerdice FA, Holmes VA, Johnston L. Early childhood development of late-preterm infants: A systematic review. *Pediatrics*. 2011;127(6):1111-1124.
11. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet*. Jun 9 2012;379(9832):2162-2172.
12. Briggs-Gowan MJ, Carter AS. Social-emotional screening status in early childhood predicts elementary school outcomes. *Pediatrics*. May 2008;121(5):957-962.
13. Treyvaud K, Doyle LW, Lee KJ, et al. Social-emotional difficulties in very preterm and term 2 year olds predict specific social-emotional problems at the age of 5 years. *Journal of pediatric psychology*. Aug 2012;37(7):779-785.
14. Thomas R, Zimmer-Gembeck MJ. Behavioral outcomes of Parent-Child Interaction Therapy and Triple P-Positive Parenting Program: a review and meta-analysis. *J Abnorm Child Psychol*. Jun 2007;35(3):475-495.
15. Gardosi J, Francis A. Gestation Network. GROW version 5.16. 2013; www.gestation.net. Accessed 15/07/2013, 2013.
16. Johnson S, Evans TA, Draper ES, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. *Archives of disease in childhood. Fetal and neonatal edition*. Apr 1 2015;100(4):F301-F308.
17. Briggs-Gowan MJ, Carter AS. *BITSEA Brief Infant-Toddler Social and Emotional Assessment*. San Antonio, TX: Harcourt Assessment Inc; 2006.
18. Briggs-Gowan MJ, Carter AS, Irwin JR, Wachtel K, Cicchetti DV. The Brief Infant-Toddler Social and Emotional Assessment: screening for social-emotional problems and delays in competence. *Journal of pediatric psychology*. Mar 2004;29(2):143-155.
19. Johnson S, Wolke D, Marlow N, Preterm Infant Parenting Study G. Developmental assessment of preterm infants at 2 years: validity of parent reports. *Dev Med Child Neurol*. Jan 2008;50(1):58-62.
20. Guy A, Seaton SE, Boyle EM, et al. Infants Born Late/Moderately Preterm Are at Increased Risk for a Positive Autism Screen at 2 Years of Age. *The Journal of pediatrics*. Dec 2 2014.

21. Spittle AJ, Treyvaud K, Doyle LW, et al. Early emergence of behavior and social-emotional problems in very preterm infants. *J Am Acad Child Adolesc Psychiatry*. Sep 2009;48(9):909-918.
22. MacKay DF, Smith GC, Dobbie R, Pell JP. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med*. 2010;7(6):e1000289.
23. Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. *Semin Perinatol*. Apr 2006;30(2):81-88.
24. Inder TE, Warfield SK, Wang H, Huppi P, Volpe J. Abnormal cerebral structure is present at term in premature infants. *Pediatrics*. 2005;115:286-294.
25. Kerstjens JM, de Winter AF, Bocca-Tjeertes IF, ten Vergert EM, Reijneveld SA, Bos AF. Developmental delay in moderately preterm-born children at school entry. *The Journal of pediatrics*. Jul 2011;159(1):92-98.
26. Potijk MR, de Winter AF, Bos AF, Kerstjens JM, Reijneveld SA. Behavioural and emotional problems in moderately preterm children with low socioeconomic status: a population-based study. *Eur Child Adolesc Psychiatry*. Oct 8 2014.
27. Lindstrom K, Lindblad F, Hjern A. Psychiatric Morbidity in Adolescents and Young Adults Born Preterm: A Swedish National Cohort Study. *Pediatrics*. January 1, 2009 2009;123(1):e47-53.
28. Treyvaud K, Ure A, Doyle LW, et al. Psychiatric outcomes at age seven for very preterm children: rates and predictors. *Journal of child psychology and psychiatry, and allied disciplines*. Jul 2013;54(7):772-779.
29. Ritchie K, Bora S, Woodward LJ. Social development of children born very preterm: A systematic review. *Dev Med Child Neurol*. 2015.
30. Johnson S. Understanding social development following very preterm birth. *Dev Med Child Neurol*. May 8 2015.

31. Campbell C, Horlin C, Reid C, et al. How do you think she feels? Vulnerability in empathy and the role of attention in school-aged children born extremely preterm. *The British journal of developmental psychology*. Jun 9 2015.

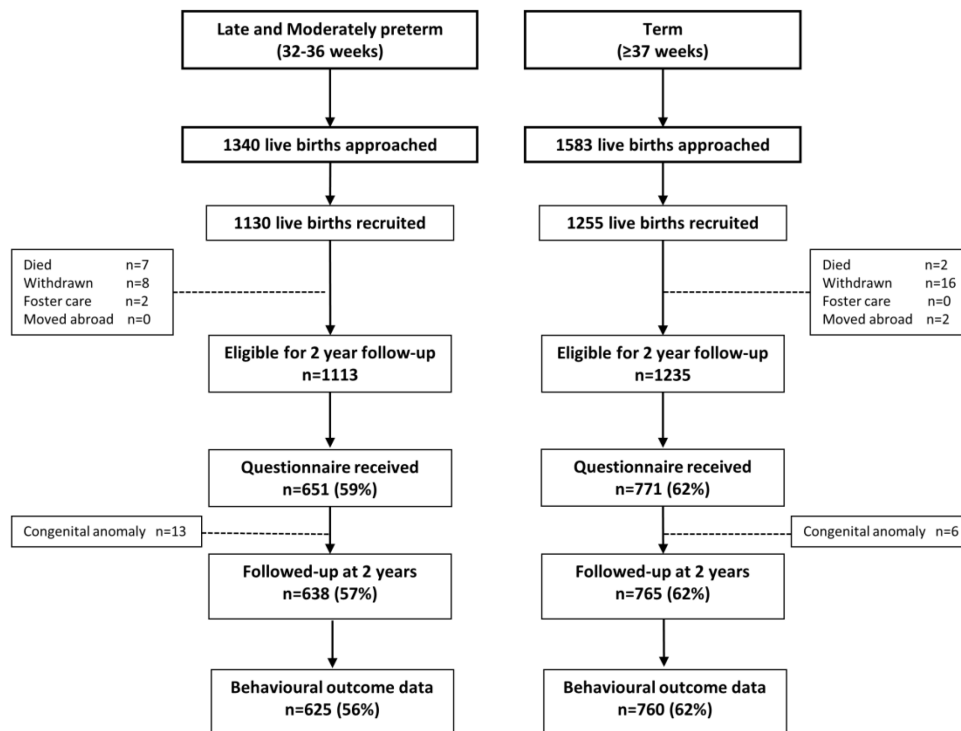


Figure 1. Recruitment and follow-up rates at 2 years corrected age in the geographic population-based Late and Moderately Preterm Birth Study (LAMBS).

Table 1. Demographic characteristics of late and moderately preterm and term-born infants assessed at 2 years corrected age.

Variable		Term	Term Weighted ^e	LMPT	p-value
INFANTS		n=765		n=638	
Gestational age (weeks)	Mean (SD)	39.3 (1.4)	39.7	34.9 (1.2)	-
	32-33 weeks, n (%)			87 (13.6)	-
	34-36 weeks, n (%)			551 (86.4)	-
	37-38 weeks, n (%)	241 (31.5)	(16.6)		-
	39-40 weeks, n (%)	357 (46.7)	(56.6)		-
	41-42 weeks, n (%)	167 (21.8)	(26.8)		-
Multiple birth	n (%)	151 (19.7)	(1.6)	107 (16.8)	<0.001
Birthweight (g)	Mean (SD)	3322.0 (534.9)	3446.5	2435.0 (502.1)	<0.001
SGA ^a	n (%)	48 (6.3)	(4.0)	67 (10.5)	<0.001
Male sex	n (%)	384 (50.2)	(49.6)	343 (53.8)	0.13
Corrected age (months)	Mean (SD)	24.6 (1.1)	24.6	24.6 (1.0)	0.53
Cognitive impairment ^b	n (%)	18 (2.4)	(2.8)	40 (6.3)	0.003
MOTHERS		N = 690		N = 587	
Mothers age ^c	Mean (SD)	31.0 (5.7)	30.8	30.3 (5.5)	0.13
Ethnic group	White, n (%)	569 (82.5)	(82.1)	461 (78.6)	0.28
	Mixed, n (%)	7 (1.0)	(1.0)	12 (2.0)	
	Asian or Asian British, n (%)	77 (11.2)	(11.7)	86 (14.7)	
	Black or Black British, n (%)	30 (4.4)	(4.1)	21 (3.6)	
	Chinese or other, n (%)	7 (1.0)	(1.1)	6 (1.0)	
	Unknown, n (%)	0 (0.0)	(0.0)	1 (0.2)	
English not first language	n (%)	86 (12.5)	(13.0)	82 (14.0)	0.55
SES-Index ^d	Low risk, n (%)	339 (49.1)	(47.4)	256 (43.6)	0.33
	Medium risk, n (%)	209 (30.3)	(30.8)	184 (31.4)	
	High Risk, n (%)	142 (20.6)	(21.9)	147 (25.0)	

^aSGA Small for gestational age classified using birthweight <3rd percentile for sex and gestation using customised antenatal growth charts.¹⁵

^bCognitive impairment is defined as a PARCA-R Parent Report Composite score < 2.5th percentile of the term reference group (PRC score <35)

^cMother's age missing for one LMPT infant ^dSES-Index refers to socio-economic risk category derived from a composite measure of 5 indices of socio-economic risk (see method section). ^eWeighted for over-sampling of multiple births in the term group.

Table 2. Prevalence of parent-reported behavioural problems and delayed social competence among late and moderately preterm (LMPT) and term-born infants at 2 years corrected age.

		Moderately preterm	Late preterm	All LMPT	Term (weighted) ^a	Difference LMPT vs. Term		
Behavioural outcomes		32-33 weeks n=84	34-36 weeks n=541	32-36 weeks n=625	≥37 weeks n=760	MODEL 1: Unadjusted RR (95% CI)	MODEL 2: Adjusted ^b RR (95% CI)	MODEL 3: Adjusted ^c RR (95% CI)
Behaviour problem	n (%)	17 (20.2)	114 (21.1)	131 (21.0)	132 (17.6)	1.19 (0.94 to 1.50)	1.15 (0.92 to 1.45)	1.13 (0.89 to 1.42)
Delayed competence	n (%)	23 (27.4)	142 (26.3)	165 (26.4)	138 (18.4)	1.43 (1.15 to 1.78)**	1.39 (1.12 to 1.72)**	1.28 (1.03 to 1.58)*
Problem <i>or</i> delay	n (%)	34 (40.5)	199 (36.8)	233 (37.3)	221 (29.5)	1.26 (1.07 to 1.49)**	1.23 (1.05 to 1.45)**	1.17 (1.00 to 1.38)*
Problem <i>and</i> delay	n (%)	6 (7.1)	57 (10.5)	63 (10.1)	49 (6.6)	1.53 (1.04 to 2.25)*	1.46 (0.99 to 2.15)	1.34 (0.91 to 1.97)

BITSEA: Brief Infant and Toddler Socio Emotional Assessment. ^aWeighted for over-sampling of multiple births in the term group. ^bModel 2: Adjusted for age, sex, SES-Index category and small for gestational age (SGA) status. ^cModel 3: Adjusted for age, sex, SES-Index category, SGA status and infant cognitive impairment (PARCA-R score <35). *p<0.05; **p<0.01.

Table 3. Demographic, obstetric and neonatal factors associated with delayed socio-emotional competence in infants born late and moderately preterm.

		Socio-emotional competence		Univariable analyses	Multivariable analyses
Obstetric factors ^a		Delayed (n=165)	Not delayed (n=460)	RR (95% CI)	RR (95% CI)
Mothers age (years)	Mean (SD)	30.2 (5.1)	30.5 (5.6)	0.99 (0.96 to 1.02)	-
Ethnicity	White	115 (23.0)	386 (77.1)	1	1
	Non white	48 (39.3)	74 (60.7)	1.71 (1.29 to 2.26)***	1.68 (1.26 to 2.24)***
Language spoken at home	English	130 (24.2)	407 (75.8)	1	-
	Non-English	34 (42.5)	46 (57.5)	1.76 (1.29 to 2.38)***	-
SES-Index	Low risk	51 (18.1)	231 (81.9)	1	1
	Medium risk	56 (29.2)	136 (70.8)	1.61 (1.14 to 2.27)**	1.60 (1.14 to 2.24)**
	High Risk	58 (38.4)	93 (61.6)	2.12 (1.52 to 2.96)***	1.98 (1.41 to 2.75)***
No diabetes		156 (25.9)	447 (74.1)	1	-
Pre pregnancy diagnosed diabetes		9 (40.9)	13 (59.1)	1.58 (0.93 to 2.67)	-
No hypertension		160 (26.2)	450 (73.8)	1	-
Pre pregnancy diagnosed hypertension		5 (33.3)	10 (66.7)	1.27 (0.61 to 2.64)	-
Non-smoker		120 (24.2)	376 (75.8)	1	-
Smoked during pregnancy ^b		44 (34.7)	83 (65.4)	1.43 (1.07 to 1.91)*	-
Non-drinker		107 (28.5)	269 (71.5)	1	-
Drank alcohol during pregnancy ^c		58 (23.6)	188 (76.4)	0.83 (0.62 to 1.10)	-
Non-drug user		159 (25.9)	454 (74.1)	1	1
Recreational drugs use during pregnancy ^d		6 (50.0)	6 (50.0)	1.93 (1.12 to 3.30)*	1.70 (1.03 to 2.82)*
No preeclampsia		141 (26.7)	388 (73.4)	1	-
Preeclampsia		23 (25.3)	68 (74.7)	0.95 (0.64 to 1.40)	-
No infection		145 (25.8)	418 (74.3)	1	-
Infection (+culture) during pregnancy		15 (33.3)	30 (66.7)	1.29 (0.84 to 1.99)	-
No gestational diabetes		156 (26.1)	442 (73.9)	1	-
Gestational diabetes		8 (33.3)	16 (66.7)	1.28 (0.70 to 2.32)	-
Rupture of membranes during labour		129 (25.9)	370 (74.2)	1	-
Pre-labour Rupture of Membranes >24h		35 (28.5)	88 (71.5)	1.10 (0.79 to 1.52)	-
Antenatal corticosteroids not given		124 (27.6)	326 (72.4)	1	-
Antenatal corticosteroids given		39 (22.8)	132 (77.2)	0.83 (0.60 to 1.14)	-
Labour not induced		130 (26.6)	359 (73.4)	1	-
Labour induced		35 (25.9)	100 (74.1)	0.98 (0.70 to 1.36)	-
CRP not raised		155 (26.9)	422 (73.1)	1	-
Raised CRP during labour (>5mg/l)		5 (20.8)	19 (79.2)	0.78 (0.37 to 1.61)	-
Normal vaginal delivery		89 (27.9)	230 (72.1)	1	-
C section, breech or instrumental delivery		76 (24.8)	230 (75.2)	0.89 (0.67 to 1.17)	-
No/normal antenatal doppler studies		156 (26.4)	435 (73.6)	1	-
Absent or reversed end diastolic flow		6 (23.1)	20 (76.9)	0.87 (0.43 to 1.76)	-
Neonatal factors					
Female		66 (22.9)	222 (77.1)	1	1

Male		99 (29.4)	238 (70.6)	1.28 (0.97 to 1.69)	1.27 (0.96 to 1.67)
Gestation (weeks)	36	76 (28.3)	193 (71.8)	1	1
	35	42 (25.6)	122 (74.4)	0.90 (0.65 to 1.27)	0.89 (0.64 to 1.23)
	34	24 (22.2)	84 (77.8)	0.79 (0.52 to 1.19)	0.80 (0.53 to 1.19)
	32-33	23 (27.4)	61 (72.6)	0.97 (0.65 to 1.44)	0.97 (0.65 to 1.45)
Singleton		143 (27.6)	376 (72.5)	1	-
Multiple birth		22 (20.8)	84 (79.3)	0.75 (0.48 to 1.18)	-
SGA ^e	>10th	141 (25.5)	413 (74.6)	1	-
	3 rd -10 th	11 (29.0)	27 (71.1)	1.14 (0.67 to 1.92)	-
	≤3 rd	13 (39.4)	20 (60.6)	1.55 (0.99 to 2.41)	-
No resuscitation		138 (26.9)	376 (73.2)	1	-
Resuscitated at birth		27 (24.3)	27 (24.3)	0.91 (0.63 to 1.29)	-
No respiratory support		150 (27.7)	392 (72.3)	1	-
Respiratory support received ^f		15 (18.1)	68 (81.9)	0.65 (0.40 to 1.06)	-
No intracranial abnormality		165 (26.6)	455 (73.4)		-
Intracranial abnormality ^g		0	5 (100)	-	-
No evidence of jaundice		131 (26.6)	361 (73.4)	1	-
Jaundice requiring phototherapy		34 (25.6)	99 (74.4)	0.96 (0.69 to 1.34)	-
No hypoglycaemia		157 (26.9)	426 (73.1)	1	-
Hypoglycaemia (<2 mmol/l)		8 (19.1)	34 (81.0)	0.71 (0.37 to 1.35)	-
Normal temperature		147(25.7)	425 (74.3)	1	-
Low temperature (<36°C)		18 (34.0)	35 (66.0)	1.32 (0.88 to 1.97)	-
No antibiotics		149 (25.8)	428 (74.2)	1	-
Antibiotics given		16 (33.3)	32 (66.7)	1.29 (0.83 to 2.00)	-
No breast milk at discharge		68 (31.5)	148 (68.5)	1	-
Any breast milk at discharge ^h		97 (23.7)	312 (76.3)	0.75 (0.57 to 0.99)*	-

^a Denominators vary due to missing data for some items ^b Classified as mothers who smoked at least one cigarette per day at any time during pregnancy vs. <1 cigarette per day; data were missing for 2 mothers. ^c Classified as mothers who drank any alcohol at any time during pregnancy vs. no alcohol during pregnancy. ^d Classified as 1 or more instances of recreational drug use at any time during pregnancy. ^e Fetal weight for sex and gestational age classified using customised fetal growth charts. ^f Any respiratory support includes infants who were ventilated or received any non-invasive respiratory support. ^g Intra-cranial abnormality includes Grade III or IV intra-ventricular haemorrhage (IVH), periventricular leukomalacia (PVL) and Grade II or III neonatal encephalopathy. ^h Includes breast milk fed by any method. *p<0.05; **p<0.01; ***p<0.001.