Differentiating the preterm phenotype: Distinct profiles of cognitive and behavioural development following late and moderately preterm birth.

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CHAT Modified Checklist for Autism in Toddlers; PARCA-R Parent Report of Children's Abilities-Revised; SGA small for gestational age; VP: very preterm ($< 32^{+0}$ weeks of gestation).

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Abstract

Objectives: To explore patterns of comorbidity in cognitive and behavioural outcomes at two years corrected age among children born late and moderately preterm (LMPT) and to identify predictors of different patterns of comorbidity in this population.

Study design: Geographical prospective population-based cohort study of 1139 LMPT (32^{+0} to 36^{+6} weeks' gestation) and 1255 term-born (37^{+0} to 42^{+6} weeks' gestation) babies. Parent questionnaires were used to identify impaired cognitive and language development, behaviour problems, delayed social-emotional competence, autistic features and clinically-significant eating difficulties at 24 months corrected age for 638 (57%) LMPT and 765 (62%) term-born children.

Results: Latent Class Analysis revealed two classes of outcomes among the term group: optimal outcome (Class I: 84%) and non-optimal outcome (Class 2: 16%). In contrast, three classes were identified in the LMPT group: optimal outcome (Class 1: 67%), non-optimal outcome (Class 2: 26%), and an additional preterm phenotype (Class 3: 7%). Non-white ethnicity, socio-economic risk and not receiving breast milk at hospital discharge were risk factors for non-optimal outcome in both groups. Male sex, higher gestational age and preeclampsia were only associated with the preterm phenotype.

Conclusions: Only a small proportion of LMPT born children have cognitive and behavioural problems that are consistent with the very preterm phenotype and which are likely to have arisen through a preterm pathway. A larger proportion have a profile of problems that correspond with those observed in children born at term. This study advances understanding of the long term risks attached to birth at late and moderately preterm gestations.

Globally, 15 million babies are born preterm ($<37^{+0}$ weeks' gestation) each year.(1) Prematurity places infants at high risk for neurodevelopmental sequelae, often requiring long term healthcare provision or special educational support.(2) Studies of very preterm (VP; $<32^{+0}$ weeks' gestation) cohorts have revealed a phenotype that is characterised by a profile of disorders that span multiple developmental domains. Relative to term-born controls, VP survivors are at increased risk for cognitive impairment and attention, social and emotional problems, alongside an absence of increased risk for disruptive or oppositional behaviour problems.(3, 4) There is remarkable consistency in outcomes over time and between countries, cultures and healthcare systems providing evidence for a universal phenotype that is associated with the neurodevelopmental immaturity conferred by VP birth.(3, 5, 6)

However, adverse outcomes are not confined just to those born VP. Compared with term-born peers, babies born late and moderately preterm (LMPT; 32^{+0}-36^{+6} weeks' gestation) are also at increased risk for cognitive, language, social-emotional and eating difficulties at 2 years of age(7-9), and an increased risk for cognitive, attention and social-emotional problems at school age.(10-12) Although these outcomes appear to mirror the VP phenotype, key questions remain unanswered in relation to the aetiology of developmental disorders in this population: (1) Does preterm interruption to the developing brain have an adverse impact on outcomes in the total LMPT population, or among a sub-group of babies at high clinical risk? (2) Do the cognitive and behavioural sequelae associated with LMPT birth represent an extension of the VP phenotype, or, given the proximity to term, more closely resemble a profile of problems observed in the term-born population? Previous studies have focused almost entirely on investigating the risk for adverse outcomes in LMPT born children compared with their term-born peers, and there is a paucity of research exploring patterns of comorbidity in long term outcomes within the LMPT population. In order to address these questions, the objectives of the study were to explore patterns of comorbidity in cognitive and

behavioural outcomes at 2 years of age among LMPT born children and to identify predictors of different profiles of comorbidity in this population.

METHODS

Participants

From September 2009 to December 2010, the mothers of all babies born LMPT within a geographically defined region of the East Midlands of England were invited to participate in the Late and Moderately Preterm Birth Study (LAMBS).[13] During the same time period and region, a random sample of babies born at 37^{+0} to 42^{+6} weeks' gestation was recruited to a term-born control group. All term-born multiples were additionally invited to participate given the high rate of multiple births among the LMPT population. Infants with congenital anomalies were excluded from the present analyses. Research midwives obtained informed consent from mothers and information about antenatal and neonatal course was collected from medical notes. Demographic information was collected via a maternal interview. The study was approved by the Derbyshire National Health Service Research Ethics Committee (Ref 09/H0401/25).

Measures

At 24 months corrected age parents completed a questionnaire that comprised validated scales to identify children with cognitive impairment[14], language delay[14], behaviour problems[8], delayed socio-emotional competence[8], autism spectrum symptoms[15] and eating difficulties.[9]

The Parent Report of Children's Abilities-Revised (PARCA-R)[16] was used to assess cognitive and language development. Sub-scale scores for non-verbal cognition (range 0-34) and language (range 0-124) were derived. Children with scores <2.5th percentile of the

control group were classified as having cognitive impairment (non-verbal scores <22) and/or language delay (language scores <9). The PARCA-R has excellent diagnostic utility for identifying infants with developmental delay as measured using diagnostic tests.(16-19)

The Brief Infant and Toddler Social-Emotional Assessment (BITSEA)(20) is a 42-item questionnaire comprising a problem scale to assess externalizing problems, internalizing difficulties, dysregulation, and maladaptive and atypical behaviours, and a competence scale to assess socio-emotional competence including delays in attention, compliance, peer relations, empathy and social relatedness. Total scores for each scale were compared with norm-referenced cut-offs for identifying children with clinically significant behaviour problems (problem scores >25th percentile) and delayed social-emotional competence (competence scores <15th percentile).(20) The BITSEA has excellent reliability and predictive validity for later psychiatric disorders.(21, 22)

The Modified Checklist for Autism in Toddlers (M-CHAT)(23) was used to identify children at high risk for autism spectrum disorders (ASD). The M-CHAT comprises 23 items of which children who fail ≥ 2 of 6 critical items or ≥ 3 items overall screen positive for the risk of ASD. The M-CHAT is widely used to identify young children with autism spectrum symptoms.(23-25)

A 17-item validated eating behaviour questionnaire(26) was used to assess the presence of eating difficulties including refusal/picky eating, oral-motor problems, oral hypersensitivity and eating behaviour problems. A total eating difficulties score (range 0-34) was computed and children with scores >90th percentile of the control group (scores >12) were classified with clinically significant difficulties. The questionnaire has good internal consistency (Cronbach's alpha 0.83) and has been used to assess eating difficulties in children born preterm.(26)

Infants' sex, gestational age, small for gestational age (SGA; estimated fetal weight <3rd percentile using customised antenatal growth charts(27)), receipt of any breast milk at discharge (irrespective of method of feeding), maternal ethnicity, preeclampsia and smoking during pregnancy (at least one cigarette at any time during pregnancy) were explored as potential risk factors given their clinical importance and association with neurodevelopmental outcomes in this population.(8, 14) A composite variable for socio-economic status (SES) was derived using indices of mothers' occupational status, highest educational qualification, social support, income and wealth from which a total SES Index score was computed (range 0-12). This was used to classify mothers into 3 risk groups: low (0-2), medium (3-5) or high (≥6) risk (for a detailed description of this classification system see (14)).

Statistical analyses

Latent Class Analysis (LCA) was used to identify profiles of neurodevelopmental outcome within the LMPT and term-born groups using dichotomous variables for cognitive impairment, language delay, behaviour problems, delayed socio-emotional competence, positive autism screen and eating difficulties. LCA was carried out using Stata Plugin version 1.2 (Release 64-1.3.2) and the doLCA command to produce maximum likelihood estimates for model parameters using the EM algorithm.(28) Missing data were assumed to be missing at random. A series of LCA models were fitted separately for each group. The optimal number of classes for each group was assessed by statistical goodness of fit using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Bayesian Information Criterion using an adjusted sample size calculation (BIC*) and Consistent Akaike Information Criterion (CAIC).(29) Lower AIC, BIC, BIC* and CAIC values indicate a better model fit. The optimal number of latent classes to include in the final models were selected based on the goodness of fit criteria as well as interpretability of the estimates findings in a

given model. 5000 iterations of each model were run using randomly generated seed values to ensure that the maximum likelihood solution was correctly identified. Two sets of parameters were estimated in a model: a vector of class membership probabilities, from which individual children were assigned to the different classes based on these probabilities, and a matrix of item-response probabilities which show the association between the six outcome variables and the latent classes. Univariable multinomial regression was then used to explore predictors of class membership separately by group.

RESULTS

Cohort characteristics

A total of 1139 LMPT and 1255 term-born controls were recruited. After excluding babies with major congenital anomalies, the parents of 638 (57%) LMPT and 765 (62%) term-born children returned a questionnaire at 2 years corrected age. Key characteristics of the children assessed are shown in Table 1. LMPT children were more likely to be SGA and to have mothers with preeclampsia, high socio-economic risk or who smoked during pregnancy than controls, and were less likely to be receiving breast milk at discharge from hospital.(13) There was no significant difference between groups in terms of sex or age at follow-up. LMPT children were at significantly greater risk for cognitive impairment, delayed language development, delayed social-emotional competence, positive autism screen and eating difficulties than controls, but there was no significant difference in the proportion with behaviour problems (Table 1).(8, 9, 14, 15)

<<TABLE 1>>

Dropout analyses conducted previously revealed that non-responders were more likely to be younger mothers, of non-white ethnicity, non-English speaking, single parents and to have lower occupational status and educational qualifications than responders.(30)

Latent classes

Goodness of fit statistics for the latent class models are shown in Table 2 (online). For the term group, although the lower AIC suggested that the four class model was a good fit, the BIC, BIC* and CAIC were all lower for the two class model. As this model had better parameter estimates and greater parsimony it was selected as optimal for this group. For the LMPT group, the lower AIC for the four class model again suggested that this was superior. However, the BIC, BIC* and CAIC were lower for the three class model indicating a better fit. This was therefore selected as the optimal model as it had greater parsimony.

<<TABLE 2 (ONLINE)>>

The probabilities of having problems across the six domains within each class are shown in Table 3 (online) and in Figure 1. In the term group, the largest class (Class 1) comprised 84% of children who had low probabilities of adverse outcomes. The remaining 16% (Class 2) had high probabilities of having behaviour problems (0.59) and delayed social-emotional competence (0.57). The risk for a positive autism screen and eating difficulties were moderately elevated (0.46 and 0.31 respectively), and the probabilities of having cognitive impairment and delayed language were very low (Figure 1a).

<<TABLE 3 (ONLINE)>>   <<FIGURE 1>>

In the LMPT group, Class 1 comprised 67% of children in whom the response probabilities across all outcomes were low and very similar to that of Class 1 among the term group (Figure 1b). Class 2 comprised 26% of LMPT children and was similar to that of Class 2 in the term group: LMPT children in this class were at high risk for behaviour problems (0.51) and delayed social-emotional competence (0.46). The risk for feeding difficulties (0.38) and a positive autism screen (0.24) was also similar to Class 2 in the term group, and there was a similarly low risk for cognitive impairment (0.03) and language delay (0.00). This profile of comorbidity was therefore consistent with Class 2 in the term group (Figure 1b). A third class

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- Class 3- was also identified which comprised 7% of children. In contrast to Class 2, this class was characterised by a high risk for delayed social-emotional competence (0.92), cognitive impairment (0.72), autistic features (0.71) and delayed language development (0.52). Moreover, behaviour problems and eating difficulties were not further increased relative to children in Class 2.

Predictors of latent class membership

Table 4 shows the characteristics of LMPT and term-born children by class membership. The association of obstetric and neonatal variables with class membership was explored separately by group with Class 1 as the reference (Table 5). In the term group, those in Class 2 were significantly less likely to receive breast milk at discharge and were more likely to have a mother who smoked during pregnancy, non-white ethnicity and medium or high socio-economic risk than those with a healthy outcome. The greatest risk was among children with non-white mothers (OR 5.68, 95% CI 3.33, 9.68) and high socio-economic risk (OR 9.77, 95% CI 5.29, 18.02). Gestational age, SGA, sex and preeclampsia were not associated with membership of Class 2.

<<TABLE 4>>   <<TABLE 5>>

In the LMPT group, predictors of Class 2 membership were similar to those observed in the term group. That is, LMPT children in Class 2 were significantly less likely to receive breast milk at hospital discharge and were more likely to have a non-white mother and socio-economic risk. Effect sizes for these predictors were similar between groups and, as in the term group, the greatest risk was among children with non-white mothers (OR 4.87, 95% CI 2.59, 9.13) and high socio-economic risk (OR 5.30, 95% CI 2.84, 9.90). Smoking during pregnancy was marginally significant (OR 1.82, 95% CI 0.99, 3.37). As in the term group,

gestational age, SGA, sex and preeclampsia were not significantly associated with Class 2 membership.

In contrast, significant predictors of membership of Class 3 revealed a different pattern of associations. Not receiving breast milk at hospital discharge and having a non-white mother who smoked during pregnancy or had socio-economic risk continued to be significant predictors. However, there was also a significant association with male sex (OR 5.36; 95% CI 1.90, 15.12) and preeclampsia (OR 3.67; 95% CI 1.58, 8.51), and a small but statistically significant association with higher gestational age (OR 1.57; 95% CI 1.02, 2.40).

DISCUSSION

Latent class analyses carried out using data from 1403 children revealed both common and distinct profiles of development among the term and LMPT populations at 24 months of age. The majority of children in both groups were in Class 1; these children had no cognitive or behavioural problems and were classified with an "optimal outcome". Class 2 was also common to both groups. This class was characterised by an increased risk for behaviour problems and delayed social-emotional competence, and a moderately increased risk for autism spectrum symptoms and eating difficulties alongside no problems related to cognitive and language development. Both term-born and LMPT children in Class 2 had a "non-optimal outcome".

In contrast to the term-born group, a third class was identified among the LMPT group. This Class 3 was characterised by impaired cognitive and language development, social-emotional problems and autism spectrum symptoms, but no increased risk for behaviour problems and eating difficulties relative to children in Class 2. This profile of outcomes is similar to the VP phenotype which is characterised by cognitive and language delays in early childhood and a pattern of cognitive, attention, social and emotional problems and autism spectrum symptoms

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later in childhood.(3, 31) The striking difference to the pattern of outcomes observed among children with a non-optimal outcome in Class 2 was the high risk for non-verbal cognitive impairment and delayed-social emotional competence in the absence of increased risk for behaviour problems, which are the defining features of the VP phenotype.(31) As such, children in Class 3 could be classified as having the "preterm phenotype".

It is likely that the neurodevelopmental problems of children with the preterm phenotype (Class 3) have a different aetiology to the problems of other LMPT and term-born children with a non-optimal outcome (Class 2). In addition to the socio-economic risk factors that were associated with a non-optimal outcome, predictors of the preterm phenotype included factors related to biological or clinical risk, namely male sex and preeclampsia. The male disadvantage in neurodevelopmental outcomes is well documented in VP cohorts and there is often an interaction effect whereby there is no significant difference in outcomes observed in the term-born population. There was also a significant association between increasing week of gestation and risk for the preterm phenotype. However, this is likely to be a spurious finding given the small number of children in this class (n=44), especially at the moderately preterm gestations (n=5). The study was not powered to detect a difference in outcomes by week of gestation and we have previously found no evidence of a relationship between neurodevelopmental outcomes and gestational age in this cohort.(8, 14) The association of latent class membership with gestational age therefore requires investigation in larger, adequately powered studies. Previous reports also suggest that SGA is associated with increased risk for adverse outcomes following LMPT birth(32), but this was not observed in the present study. This may be due to low statistical power when examining sub-groups of LMPT children; however SGA was not significantly associated with adverse cognitive or behavioural outcomes in the whole LMPT cohort.(8, 14)

The task of identifying LMPT babies at risk of adverse long term outcome remains a challenge. This study investigated some key factors that may be considered, but future work should explore a wider range of risk factors including indices of neonatal morbidity and brain development, and using multivariable models to identify independent predictors. This was not possible in the present study given the sample size and low rate of severe neonatal morbidities and neurological abnormalities in this population.(13) Larger studies are also needed to explore outcomes by week of gestation in order to determine at which point the preterm phenotype is no longer observed. Longer term outcomes by class membership could also be examined to determine how these developmental profiles manifest later in childhood.

To answer the questions posed in the introduction. First, prematurity does not affect all LMPT babies to a greater or lesser extent. Rather, preterm birth per se appears to have an adverse effect on development only among a small sub-group of the LMPT population. Second, the pattern of adverse outcomes in this sub-group is similar to the VP phenotype. For the remaining LMPT children with non-optimal outcomes, these are consistent with the profile of problems observed in the term population and may be indicative of a different developmental pathway.

As LMPT babies comprise 84% of all preterm births(1), efforts to reduce the rates of adverse outcomes may have a significant public health impact. Reducing rates of LMPT birth may be advantageous in reducing the absolute number of children with cognitive or behavioural problems. An emphasis on prevention may also focus on reducing the rates of smoking in pregnancy and increasing breast feeding rates, the latter of which are lower among mothers of LMPT babies.(13) As noted above, further research to elucidate the range of risk factors for adverse outcomes may aid in identifying strategies to reduce developmental sequelae in this population.

The strengths of this study include the recruitment of a large geographical population-based birth cohort that was representative of the total population of births from which it was drawn.(13) Limitations include the follow-up rate at two years of age and the selective dropout of mothers in both groups. Although this is unlikely to have affected the current analyses, this may have underestimated the total proportion of children with poor outcomes. The size of the study also necessitated follow-up using parent questionnaires. Although measures with proven validity and diagnostic utility were used, such tools are inferior to diagnostic assessments in identifying children with developmental problems and disorders, and the present results may also be specific to the variables used. Moreover, the screening tests used may not differentiate sufficiently between distinct domains of behavioural outcomes to determine fully whether Class 3 represents the preterm phenotype. For example, the BITSEA problem scale contains items to asses both internalising and externalising problems and there may be overlap between this scale and the feeding scale in terms of behavioural problems during mealtimes. As such, these analyses should be replicated in other cohorts in which data from diagnostic measures are available that can reliably differentiate specific behavioural domains in order to determine the validity of these findings. Finally, the term-born reference group for this study comprised babies born at 37-42 weeks of gestation. Recent reports suggest that birth even at early term might be associated with increased risk for adverse outcomes.(33) Future studies may therefore investigate whether similar profiles of outcomes are observed among children born at early term (37-38 weeks) and full term (40-41 weeks) gestations.

Conclusions

There are distinct profiles of development among the LMPT population. Among LMPT children with cognitive and behavioural problems, most of these exhibit a profile of problems that is shared with term-born children with a non-optimal outcome and that is associated with

socio-economic risk. Only a small proportion of LMPT children have a profile of problems

that is similar to the VP phenotype and thus that appears to be due to preterm birth. Further

research is needed to replicate these findings using data derived from diagnostic tests.

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Figure legend

Figure 1. Profiles of neurodevelopmental outcomes among term (37^{+0} to 42^{+6} week's gestation; Figure 1a) and late and moderately preterm (32^{+0} to 36^{+6} weeks' gestation; Figure 1b) born children at 2 years corrected age using item response probabilities for the latent classes.

Table 1: Key characteristics of the late and moderately preterm (LMPT) and term-born children assessed at 24 months corrected age.

	Term n = 765	LMPT n = 638	p value
Obstetric and neonatal variables			
Gestational age (mean, SD)	39.29 (1.4)	34.93 (1.2)	0.001
Female sex (n, %)	381 (49.8)	295 (46.2)	0.183
Small for gestational age (n, %)			
>10th percentile	71 (9.3)	78 (12.2)	0.037
3rd – 10th percentile	646 (84.4)	493 (77.3)	-
<3rd percentile	48 (6.3)	67 (10.5)	0.002
Non-white ethnicity (n, %)	132 (17.3)	131 (20.6)	0.111
Socio-economic risk (n, %)			
Low risk	388 (50.7)	285 (44.7)	-
Medium risk	229 (29.9)	196 (30.7)	0.220
High risk	148 (19.4)	157 (24.6)	0.008
Smoked during pregnancy (n, %)	105 (13.7)	128 (20.1)	0.001
Pre-eclampsia (n, %)	35 (4.6)	94 (14.9)	0.001
Received breast milk at discharge (n, %)	594 (77.7)	418 (65.5)	0.001
Neurodevelopmental outcomes at 2 years corrected age			
Corrected age at assessment, months (mean, SD)	24.6 (1.1)	24.6 (1.0)	0.414
Non-verbal cognitive impairment (n, %)	13 (1.7)	39 (6.1)	0.001
Delayed language development (n, %)	14 (1.8)	31 (4.9)	0.002
Behaviour problems (n, %)	139 (18.3)	132 (21.0)	0.202
Delayed social-emotional competence (n, %)	142 (18.6)	167 (26.5)	0.001
Positive autism screen (n, %)	70 (9.2)	92 (14.5)	0.002
Clinically significant eating difficulties (n, %)	70 (9.6)	92 (15.2)	0.002

(ONLINE ONLY)

Table 2: Latent Class Analysis of neurodevelopmental outcomes at 2 years corrected age in late and moderately preterm and term born children: Indices of model fit.

	Term				Late and moderately preterm			
	2 classes	3 classes	4 classes	5 classes	2 classes	3 classes	4 classes	5 classes
AIC	65.9	96.5	90.2	94.2	129.2	85.9	83.5	93.9
CAIC	169.3	208.2	242.5	285.9	200.1	195.1	230.9	279.5
BIC	156.3	188.2	215.5	251.9	187.1	175.1	203.9	245.4
BIC*	114.9	124.7	129.7	143.9	145.8	111.6	118.2	137.5
d.f.	50	43	36	29	50	43	36	29
Log likelihood	-1237.9	-1231.1	-1222.7	-1222.4	-1338.2	-1309.6	-1301.4	-1299.9

AIC Akaike Information Criterion; BIC Bayesian Information Criterion; BIC* Bayesian Information Criterion using an adjusted sample size calculation; CAIC Consistent Akaike Information Criterion.

(ONLINE ONLY)

Table 3: Item-response probabilities and percent of children in each latent class.

	Term		Late and moderately preterm		
	CLASS 1: Healthy outcome	**CLASS 2: Term-born phenotype**	**CLASS 1: Healthy outcome**	**CLASS 2: Term-born phenotype**	**CLASS 3: Preterm phenotype**
Cognitive impairment	0.00	0.07	0.00	0.03	0.65
Delayed language development	0.01	0.05	0.01	0.00	0.52
Behaviour problems	0.09	0.59	0.05	0.51	0.45
Delayed social-emotional competence	0.10	0.57	0.09	0.46	0.95
Positive autism screen	0.01	0.46	0.04	0.24	0.71
Clinically significant eating difficulties	0.05	0.31	0.03	0.38	0.34
Percent of children in class	**84%**	**16%**	**67%**	**26%**	**7%**

Table 4. Characteristics of term-born and late and moderately preterm born children by latent class membership.

		TERM			
		Class 1: **n=641** **(84%)**	**Class 2:** **n=124** **(16%)**	**Class 3:** **n=0** **(0%)**	**Total** **n=765**
Obstetric and neonatal variables					
Gestational age				-	
	37 weeks	83 (12.9%)	15 (12.1%)	-	98 (12.8%)
	38 weeks	111 (17.3%)	32 (25.8%)	-	143 (18.7%)
	39 weeks	137 (21.4%)	25 (20.2%)	-	162 (21.2%)
	40 weeks	163 (25.4%)	32 (25.8%)	-	195 (25.5%)
	41 weeks	121 (18.9%)	15 (12.1%)	-	136 (17.8%)
	42 weeks	26 (4.1%)	5 (4.0%)	-	31 (4.1%)
Sex				-	
	Female	322 (50.2%)	59 (47.6%)	-	381 (49.8%)
	Male	319 (49.8%)	65 (52.4%)	-	384 (50.2%)
Small for gestational age				-	
	>10th percentile	58 (9.0%)	13 (10.5%)	-	71 (9.3%)
	<3rd percentile	38 (5.9%)	10 (8.1%)	-	48 (6.3%)
	3rd – 10th percentile	545 (85.0%)	101 (81.5%)	-	646 (84.4%)
Non-white ethnicity		88 (13.7%)	44 (35.5%)	-	132 (17.3%)
Socio-economic risk				-	
	Low risk	349 (54.5%)	39 (31.5%)	-	388 (50.7%)
	Medium risk	198 (30.9%)	31 (25.0%)	-	229 (29.9%)
	High risk	94 (14.7%)	54 (43.6%)	-	148 (19.4%)
Smoked during pregnancy		83 (12.9%)	22 (17.7%)	-	105 (13.7%)
Pre-eclampsia		31 (4.9%)	4 (3.3%)	-	35 (4.6%)
Breast milk at discharge		507 (79.1%)	87 (70.2%)	-	594 (77.7%)
Neurodevelopmental outcomes at 2 years corrected age					
Cognitive impairment		3 (0.5%)	10 (8.1%)	-	13 (1.7%)
Delayed language development		5 (0.8%)	9 (7.3%)	-	14 (1.8%)
Behaviour problems		57 (8.9%)	82 (66.1%)	-	139 (18.3%)
Delayed social-emotional competence		65 (10.2%)	77 (62.1%)	-	142 (18.6%)
Positive autism screen		0 (0%)	70 (56.5%)	-	70 (9.2%)
Eating difficulties		25 (4.1%)	45 (37.8%)	-	70 (9.6%)

LATE AND MODERATELY PRETERM

		Class 1: **n=425** **(67%)**	**Class 2:** **n=169** **(26%)**	**Class 3:** **n=44** **(7%)**	**Total** **n=638**
Obstetric and neonatal variables					
Gestational age					
	32 weeks	28 (6.6%)	10 (5.9%)	0 (0%)	38 (6.0%)
	33 weeks	32 (7.5%)	12 (7.1%)	5 (11.4%)	49 (7.7%)
	34 weeks	74 (17.4%)	28 (16.6%)	8 (18.2%)	110 (17.2%)
	35 weeks	112 (26.4%)	48 (28.4%)	6 (13.6%)	166 (26.0%)
	36 weeks	179 (42.1%)	71 (42.0)	25 (56.8%)	275 (43.1%)
Sex					
	Female	212 (49.9%)	74 (43.8%)	9 (20.5%)	295 (46.2%)
	Male	213 (50.1%)	95 (56.2%)	35 (79.5%)	343 (53.8%)

	Class 1: n=425 (67%)	Class 2: n=169 (26%)	Class 3: n=44 (7%)	Total n=638
Obstetric and neonatal variables				
Small for gestational age[a]				
>10th percentile	54 (12.7%)	16 (9.5%)	8 (18.2%)	78 (12.2%)
<3rd percentile	41 (9.7%)	20 (11.8%)	6 (13.6%)	67 (10.5%)
3rd – 10th percentile	330 (77.7%)	133 (78.7%)	30 (68.2%)	493 (77.3%)
Non-white ethnicity	59 (13.9%)	58 (34.7%)	14 (31.8%)	131 (20.6%)
Socio-economic risk status				
Low risk	219 (51.5%)	56 (33.1%)	10 (22.7%)	285 (44.7%)
Medium risk	122 (28.7%)	54 (31.9%)	20 (45.5%)	196 (30.7%)
High risk	84 (19.8%)	59 (34.9%)	14 (31.8%)	157 (24.6%)
Smoked during pregnancy[b]	76 (17.9%)	39 (23.2%)	13 (29.6%)	128 (20.1%)
Pre-eclampsia	60 (14.2%)	22 (13.1%)	12 (27.9%)	94 (14.9%)
Breast milk at discharge	294 (69.2%)	101 (59.8%)	23 (52.3%)	418 (65.5%)
Neurodevelopmental outcomes at 2 years corrected age				
Cognitive impairment	2 (0.5%)	1 (0.6%)	36 (81.8%)	39 (6.1%)
Delayed language development	6 (1.4%)	0 (0%)	25 (56.8%)	31 (4.9%)
Behaviour problems	1 (0.2%)	113 (69.3%)	18 (40.9%)	132 (21.0%)
Delayed social-emotional competence	52 (12.3%)	73 (44.5%)	42 (95.5%)	167 (26.5%)
Positive autism screen	18 (4.3%)	45 (26.9%)	29 (65.9%)	92 (14.5%)
Eating difficulties	0 (0%)	77 (48.7%)	15 (34.1%)	92 (15.2%)

[a]Fetal weight for sex and gestation classified using customised fetal growth charts [b]Smoked during pregnancy classified for mothers who smoked at least one cigarette per day at any time during pregnancy vs. <1 cigarette per day.

Table 5: Predictors of latent class membership among children born LMPT and at term.

Predictor variable	Term CLASS 2: (vs. Term Class 1)	Late and moderately preterm (LMPT) CLASS 2: (vs. LMPT Class 1)	CLASS 3: (vs. LMPT Class 1)
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Gestational age (per week increase)	0.86 (0.73, 1.02)	0.90 (0.72, 1.13)	1.57 (1.02, 2.40)
Male sex[a]	1.13 (0.71, 1.81)	1.44 (0.88, 2.35)	5.36 (1.90, 15.12)
Non-white ethnicity[b]	5.68 (3.33, 9.68)	4.87 (2.59, 9.13)	4.19 (1.97, 8.89)
Socio-economic risk[c]			
Medium risk SES	2.68 (1.51, 4.77)	1.98 (1.07, 3.68)	5.32 (2.07, 13.69)
High risk SES	9.77 (5.29, 18.02)	5.30 (2.84, 9.90)	5.11 (1.32, 19.85)
Small for gestational age[d] (<3rd centile)	0.87 (0.23, 3.31)	0.93 (0.29, 2.95)	1.91 (0.46, 7.83)
Breast milk at discharge	0.46 (0.27, 0.77)	0.55 (0.31, 0.96)	0.41 (0.21, 0.81)
Pre-eclampsia	0.59 (0.14, 2.49)	0.61 (0.27, 1.39)	3.67 (1.58, 8.51)
Smoked during pregnancy[e]	1.92 (1.01, 3.64)	1.82 (0.99, 3.37)	2.16 (1.02, 4.59)

[a]Reference: female; [b]Reference: white; [c]Reference: low risk; [d]Reference: weight 3rd-10th percentile for gestational age; fetal weight for sex and gestation classified using customised fetal growth charts. [e]Smoked during pregnancy classified for mothers who smoked at least one cigarette per day at any time during pregnancy vs. <1 cigarette per day.