Differentiating the Preterm Phenotype: Distinct Profiles of Cognitive and Behavioral Development Following Late and Moderately Preterm Birth

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Objectives To explore patterns of comorbidity in cognitive and behavioral outcomes at 2 years' corrected age among children born late or moderately preterm (LMPT) and to identify predictors of different patterns of comorbidity.

Study design Geographical, prospective population-based cohort study of 1139 infants born LMPT ($32^{0/7}$ to $36^{6/7}$ weeks' gestation) and 1255 infants born at term ($37^{0/7}$ to $42^{6/7}$ weeks' gestation). Parent questionnaires were obtained to identify impaired cognitive and language development, behavioral problems, delayed social–emotional competence, autistic features, and clinically significant eating difficulties at 24 months corrected age for 638 (57%) children born LMPT and 765 (62%) children born at term.

Results Latent class analysis revealed 2 profiles of development among the term group: optimal (84%) and a profile of social, emotional, and behavioral impairments termed "nonoptimal" (16%). These 2 profiles were also identified among the LMPT group (optimal: 67%; nonoptimal: 26%). In the LMPT group, a third profile was identified (7%) that was similar to the phenotype previously identified in infants born very preterm. Nonwhite ethnicity, socioeconomic risk, and not receiving breast milk at hospital discharge were risk factors for nonoptimal outcomes in both groups. Male sex, greater gestational age, and pre-eclampsia were only associated with the preterm phenotype.

Conclusions Among children born LMPT with parent-reported cognitive or behavioral impairments, most had problems similar to the profile of difficulties observed in children born at term. A smaller proportion of children born LMPT had impairments consistent with the "very preterm phenotype" which are likely to have arisen through a preterm pathway. These results suggest that prematurity may affect development through several etiologic pathways in the late and moderately preterm population. *(J Pediatr 2017;■■:■■-■■).*

Globally, 15 million babies are born preterm (<$37^{0/7}$ weeks' gestation) each year.[1] Prematurity places infants at increased risk for neurodevelopmental sequelae and the need for special educational support.[2] Studies of children who were born very preterm (VP, <$32^{0/7}$ weeks of gestation) have revealed a phenotype or profile of disorders in multiple developmental domains. Relative to children born at term, children born VP are at increased risk for cognitive impairments, attention deficits and social–emotional problems, however, there is an absence of increased risk for disruptive or oppositional behavioral problems.[3,4] There is remarkable consistency in outcomes over time and between countries, cultures, and healthcare systems providing evidence for a universal "preterm phenotype" that is associated with the neurodevelopmental immaturity conferred by VP birth.[3,5,6]

However, adverse outcomes are not confined to children born VP. Compared with peers born at term, children born late and moderately preterm (LMPT; $32^{0/7}$ to $36^{6/7}$ weeks' gestation) are also at increased risk for cognitive, language, social–emotional, and eating difficulties at 2 years of age,[7-9] as well as 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 etiology 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 subgroup of babies at high clinical risk? (2) Do the cognitive and behavioral 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? To address these questions, the objectives of the study were to

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BIC*	Bayesian Information Criterion using an adjusted sample size calculation
BITSEA	Brief Infant and Toddler Social Emotional Assessment
CAIC	Consistent Akaike Information Criterion
LCA	Latent class analysis
LMPT	Late and moderately preterm
M-CHAT	Modified Checklist for Autism in Toddlers
SGA	Small for gestational age
VP	Very preterm

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

Methods

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.[13] During the same time period and region, a random sample of babies born at $37^{0/7}$ to $42^{6/7}$ weeks' gestation was recruited to a term-born control group. All multiples born at term also were 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).

At 24 months' corrected age, parents completed a questionnaire that comprised validated scales to identify children with cognitive impairment,[14] language delay,[14] behavioral problems,[8] delayed socioemotional 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. Subscale scores for nonverbal 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 (nonverbal scores <22) and/or language delay (language scores <9). The Parent Report of Children's Abilities–Revised 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 behaviors and a competence scale to assess socioemotional 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 behavioral 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. 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 autism spectrum disorders. The M-CHAT is used widely to identify young children with autism spectrum symptoms.[23-25]

A 17-item validated eating behavior questionnaire[26] was used to assess the presence of eating difficulties, including refusal/picky eating, oral–motor problems, oral hypersensitivity, and eating behavior 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 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 less than the third percentile using customized antenatal growth charts[27]), receipt of any breast milk at discharge (irrespective of method of feeding), maternal ethnicity, pre-eclampsia, and smoking during pregnancy (at least 1 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 socioeconomic status was derived that used indices of mothers' occupational status, highest educational qualification, social support, income, and wealth from which a total socioeconomic status 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 Johnson et al[14]).

Statistical Analyses

Latent class analysis (LCA) was used to identify profiles of cognitive and behavioral outcomes within the LMPT and term-born groups using dichotomous variables for cognitive impairment, language delay, behavioral problems, delayed socioemotional competence, positive autism screen, and eating difficulties. LCA was carried out with Stata Plugin, version 1.2 (Release 64-1.3.2; StataCorp LLC, College Station, Texas) and the doLCA command to produce maximum likelihood estimates for model variables with 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 via 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. A total of 5000 iterations of each model were run via randomly generated seed values to ensure that the maximum likelihood solution was identified correctly. Two sets of variables 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 that show the association between the 6 outcome variables and the latent classes. Univariable multinomial regression was then used to explore predictors of class membership separately by group.

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