Infants Born Late/Moderately Preterm Are at Increased Risk for a Positive Autism Screen at 2 Years of Age

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Objectives To assess the prevalence of positive screens using the Modified Checklist for Autism in Toddlers (M-CHAT) questionnaire and follow-up interview in late and moderately preterm (LMPT; 32-36 weeks) infants and term-born controls.

Study design Population-based prospective cohort study of 1130 LMPT and 1255 term-born infants. Parents completed the M-CHAT questionnaire at 2-years corrected age. Parents of infants with positive questionnaire screens were followed up with a telephone interview to clarify failed items. The M-CHAT questionnaire was re-scored, and infants were classified as true or false positives. Neurosensory, cognitive, and behavioral outcomes were assessed using parent report.

Results Parents of 634 (57%) LMPT and 761 (62%) term-born infants completed the M-CHAT questionnaire. LMPT infants had significantly higher risk of a positive questionnaire screen compared with controls (14.5% vs 9.2%; relative risk [RR] 1.58; 95% CI 1.18, 2.11). After follow-up, significantly more LMPT infants than controls had a true positive screen (2.4% vs 0.5%; RR 4.52; 1.51, 13.56). This remained significant after excluding infants with neurosensory impairments (2.0% vs 0.5%; RR 3.67; 1.19, 11.3).

Conclusions LMPT infants are at significantly increased risk for positive autistic screen. An M-CHAT follow-up interview is essential as screening for autism spectrum disorders is especially confounded in preterm populations. Infants with false positive screens are at risk for cognitive and behavioral problems. *(J Pediatr 2015;166:269-75)*.

Preterm birth (<37 weeks) and low birthweight (<2500 g) have long been identified as risk factors for autism spectrum disorders (ASD).[1,2] Compared with a median prevalence of 0.6% in the general population,[3] an increased prevalence of ASD has been documented among 4%-8% of children born very preterm (<28 weeks),[4] extremely preterm (<26 weeks),[5] or with extremely low birthweight (<1000 g),[6] and among 1%-5% of children with low birthweight.[7-9] Although infants born late and moderately preterm (LMPT; 32-36 weeks) account for up to 84% of all preterm births,[10] the long-term outcomes of these children have only recently been studied. In particular, studies of the risk for ASD have produced conflicting results.[11-16]

The Modified Checklist for Autism in Toddlers (M-CHAT)[17] parent questionnaire is widely used to screen for autistic features in infancy. Up to 10% of toddlers in the general population have positive M-CHAT screens,[18] thus, it is recommended that a follow-up interview is performed to improve specificity.[17-19] These interviews were shown to reduce the rate of positive screens and substantially improve positive predictive values for ASD.[18,19] Despite this, recent preterm birth cohort studies that have used the M-CHAT have not included this measure.[20] In these studies, 26% of infants born <1500 g,[21] 21% of infants born <28 weeks,[22] and 41% of those born <26 weeks[23] had positive M-CHAT screens at 2 years of age using the questionnaire alone. False positive screens are purported to be especially common among preterm infants given the high prevalence of neurosensory impairments, which impair children from displaying the behaviors assessed.[22-25] As yet, no studies have used the M-CHAT questionnaire along with the follow-up interview to examine the false positive screen rate in preterm infants. Although adverse neurodevelopmental outcomes extend across the full spectrum of preterm birth,[12,26] the extent to which symptoms predictive of ASD are increased among LMPT infants is unknown.

The aim of the present study was to explore the prevalence of positive M-CHAT screens among LMPT infants. We hypothesized that there would be a significantly higher rate of positive M-CHAT screens among LMPT than term-born infants, that positive M-CHAT screens would remain significantly

ASD	Autism spectrum disorders
LMPT	Late and moderately preterm
M-CHAT	Modified Checklist for Autism in Toddlers
RR	Relative risk
SES	Socioeconomic score

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increased after application of the follow-up interview and after exclusion of children with neurosensory impairments, and that the rate of false positive screens would be significantly higher among LMPT than term-born infants.

Methods

Mothers of all babies born at 32-36 weeks of gestation from September 1, 2009 to December 31, 2010 within a large geographical region of the East Midlands (UK) were invited to participate in the Late and Moderate Preterm Birth Study. A randomly sampled control group of babies born at 37-42 weeks gestation was also recruited during the same period and geographical region. Eligible term births were identified based on random sampling of the dates and times of birth of babies in the same population during the previous year. Mothers of all term-born multiples were invited to participate. Babies with major congenital anomalies were recruited but were excluded from the study.

The study was approved by Derbyshire National Health Service Research Ethics Committee. Informed consent was obtained from mothers shortly after birth. Mothers were interviewed in hospital or at home shortly after discharge for information about social, demographic, lifestyle factors, and antenatal health. Information about obstetric factors was obtained from mothers' medical notes and data relating to neonatal course were from infants' notes at discharge. Follow-up questionnaires were completed by mothers at 6 and 12 months after birth. At 2 years corrected age, parents completed a questionnaire about their child's health and development including the M-CHAT. Follow-up telephone interviews were conducted by a study psychologist (A.G.).

The M-CHAT[17] is a 23-item parent questionnaire for the identification of early behaviors associated with ASD in children aged 16-30 months. Infants who fail ≥2 of 6 critical items (critical fail) or ≥3 items overall (noncritical fail) screen positive for the risk of ASD; critical fails predict the presence of ASD with greater specificity.[18] Where ≤3 questionnaire items were missing, these were coded as zero (passes) and the questionnaire was scored as usual. Data were excluded for children with >3 missing questions who screened negative on the completed items; infants with >3 missing items who screened positive on the completed questions were followed up. The recommended 2-stage screening process was adopted in which a structured M-CHAT follow-up telephone interview was conducted with the main caregiver of infants with positive questionnaire screens.[17] This was designed by the authors of the M-CHAT to ascertain more detailed information for each failed item to discriminate false positive item responses from those that are indicative of ASD and, thus, reduce the overall false positive screen rate. The interview takes approximately 5-15 minutes to complete and is free to use for educational, clinical, and research use.[27] After completing the interview, the M-CHAT was then re-scored and children with positive screens after follow-up were classified as 'true positives' and those with negative screens as "false positives."

Maternal demographic variables included age, ethnicity, and language. A composite socioeconomic score (SES) index was computed using 5 indices of mothers' socioeconomic status comprising highest educational qualification, socio-occupational status (coded using the UK national statistics socio-occupational classification system[28]), cohabiting status, car ownership, and home ownership. These were scored on a 4-point scale (2-point scale for dichotomous variables), and a total SES index score (range 0-12) was computed. Mothers were then classified into 3 risk categories using total SES index scores: low (scores 0-2), moderate (scores 3-5), and high socioeconomic risk (scores ≥6). Mothers were asked about feelings of anxiety and depression during pregnancy, which were dichotomized as none vs moderately or extremely anxious or depressed. Obstetric data collected included smoking, recreational drug use and infection during pregnancy, diabetes, preeclampsia, pre-labor rupture of membranes, antenatal corticosteroids, induction of labor, mode of delivery, and antenatal Doppler findings. Neonatal data items included sex, gestational age, multiple birth status, birthweight, small for gestational age (classified using customized antenatal growth charts[29]), respiratory support, jaundice requiring phototherapy, receipt of antibiotics, hypoglycaemia, cranial ultrasound, and magnetic resonance imaging findings and feeding at discharge.

The following data collected as part of the wider 2-year assessment were used to explore the characteristics of children with false positive screens. Infants' motor, communication, vision, and hearing were rated by parents from which moderate/severe impairment in each domain was classified using standard definitions.[30] Parents also completed the Parent Report of Children's Abilities-Revised to assess cognitive and language development from which total Parent Report Composite scores (range 0-158) were derived. Parent Report Composite scores <49 were used to identify cognitive impairment.[31] Parents also completed the Brief Infant Toddler Social Emotional Assessment, a parent report to assess behavior problems and socioemotional competence.[32] A total problem score (higher scores indicate greater problems) and total socioemotional score (lower scores indicate lower competence) were computed and compared with published norms to identify children with behavior problems (scores ≥75th percentile) and delayed competence (scores <15th percentile).[32]

Statistical Analyses

Analyses were undertaken using Stata v 12 (StataCorp, College Station, Texas). Associations between maternal and neonatal characteristics and nonresponse to 2-year follow-up were reported as relative risk (RR) with 95% CI.[33] The association between LMPT birth and the prevalence of positive M-CHAT screens was also reported using RR (95% CI). To explore risk factors for true positive screens and characteristics of infants with false positive screens, univariable associations with demographic, obstetric, and neonatal factors were quantified by RR (95% CI) for categorical variables and independent sample *t* tests were used to derive

mean difference (95% CI) for continuous variables. All *P* values were 2-tailed.

Results

During the study period, 1130 (84%) LMPT and 1255 (79%) term-born babies were recruited. At 2 years of age, questionnaires were received for 651 (58%) LMPT and 771 (62%) term-born infants. Nineteen infants with major congenital anomalies and 8 infants with missing M-CHAT questionnaire data were excluded. The final sample was comprised of 634 (57%) LMPT and 761 (62%) term-born infants (**Figure**; available at www.jpeds.com). Of LMPT infants, 86 (14%) were moderately preterm (32-33 weeks) and 548 (86%) late preterm (34-36 weeks). Mothers who did not complete the M-CHAT questionnaire were more likely to be <25 years, non-white, have poor general and mental health, and higher socioeconomic risk (**Tables I** and **II**; available at www.jpeds.com).

Prevalence of Positive M-CHAT Questionnaire Screens

M-CHAT questionnaires were completed at 24.6 months (range 23.3-33.3 months) for LMPT infants and 24.6 months (range 23.3-30.2 months) for controls ($P = .73$). On the questionnaire alone, a significantly higher proportion of LMPT infants had a positive screen compared with controls (14.5% vs 9.2%; **Table III**). Among the 92 LMPT infants with positive screens, 5 (5.4%) had motor impairment, 1 (1.1%) a vision impairment, and 3 (3.3%) a hearing impairment. Overall, 27 (4.3%) LMPT and 13 (1.7%) term-born controls had critical fails.

Ascertainment of Telephone Follow-Up Data

Of 162 infants with positive screens, the caregivers of 26 could not be contacted for a follow-up; one had a clinical diagnosis of ASD and was classified with a true positive screen. Follow-up data were, therefore, available for 79 (86%) LMPT and 58 (83%) controls (**Figure**). Interviews were conducted at a mean corrected age of 29.2 months (range 24.0-40.2 months) for LMPT infants and 29.2 months (range 24.2-41.7 months) for controls ($P = .93$). The mean difference in age between questionnaire completion and follow-up interview was 4.4 months (range 0.0-6.7 months) for LMPT infants and 4.6 months (range 0.2-17.7 months) for controls ($P = .77$). There was no significant group difference in the proportion of infants with positive questionnaire screens who were followed up (**Table III**).

Prevalence of True Positive Screens after Follow-Up

After follow-up, a significantly higher proportion of LMPT infants had true positive screens (LMPT n = 15 [2.4%] vs controls n = 4 [0.5%]; **Table III**). The rate of false positive screens was significantly higher among LMPT than term-born infants (10.3% vs 7.2%; **Table III**), and overall 12 (1.9%) LMPT and 3 (0.4%) term-born infants had critical fails. Of the 15 LMPT infants with true positive screens, none had vision or hearing impairments, but 3 (20.0%) had motor impairment. After excluding infants with neurosensory impairments, LMPT infants still had a significantly higher prevalence of true positive screens (2.0% vs 0.5%; **Table III**).

Risk Factors for True Positive Screens in LMPT Infants

Risk factors for true positive screens were explored in LMPT infants (**Table IV**). Given the small number with true positive screens (n = 15), the significance of associations with a number of variables could not be estimated. Although there were no significant associations with those factors examined, data are presented in **Table IV** for descriptive purposes. Notably, maternal age ≥35 years, poor mental health, and not giving breast milk at discharge were marginally associated with a true positive screen ($P < .1$).

Characteristics of Infants with False Positive Screens

The 2 groups were combined to assess the characteristics of infants with false positive screens (n = 118). Compared with infants with negative screens, those with false positive screens were significantly more likely to have moderate to severely impaired communication and motor function and poorer cognitive, behavioral, and socioemotional outcomes at 2 years (**Table V**; all $P < .01$).

Discussion

Consistent with our hypotheses, LMPT infants were at significantly increased risk for a positive M-CHAT questionnaire screen compared with term-born infants, and

Table III. Prevalence of positive M-CHAT screens for LMPT and term-born infants at 2 years corrected age

M-CHAT results	Moderately preterm (32-33 wk) (n = 86)	Late preterm (34-36 wk) (n = 548)	All LMPT (32-36 wk) (n = 634)	Term (37-42 wk) (n = 761)	Difference all LMPT vs term, RR (95% CI)	*P*
Positive screen	8/86 (9.3%)	84/548 (15.3%)	92/634 (14.5%)	70/761 (9.2%)	1.58 (1.18, 2.11)	<.01
Followed up	4/8 (50.0%)	75/84 (89.3%)	79/92 (85.9%)	58/70 (82.9%)	1.04 (0.91, 1.19)	.61
False positive*	3/82 (3.7%)	61/539 (11.3%)	64/621 (10.3%)	54/749 (7.2%)	1.43 (1.01, 2.02)	.04
True positive*	1/82 (1.2%)	14/539 (2.6%)	15/621 (2.4%)	4/749 (0.5%)	4.52 (1.51, 13.56)	<.01
True positive excluding infants with neurosensory impairment†	1/82 (1.2%)	11/529 (2.1%)	12/611 (2.0%)	4/747 (0.5%)	3.67 (1.19, 11.32)	.02

*Denominator excludes 25 infants (n = 13 LMPT; n = 12 term) who could not be contacted for follow-up as the final outcome could not be defined for these children.
†Denominator excludes a further 12 infants (n = 10 LMPT; n = 2 term) with neurosensory impairments.

Table IV. Demographic, obstetric, and neonatal risk factors for a true positive M-CHAT screen in infants born LMPT

Variables	Negative screen¶	True positive screen		
Obstetric factors	**(n = 558)**	**(n = 13)**	**RR (95% CI)**	***P***
Mothers age				
<25 y	99 (97.1)	3 (2.9)	2.10 (0.51, 8.65)	.30
25-34 y	352 (98.6)	5 (1.4)	Baseline	-
35+ y	106 (95.5)	5 (4.5)	3.22 (0.95, 10.92)	.06
SES index				
Low risk	251 (98.8)	3 (1.2)	Baseline	-
Medium risk	174 (97.2)	5 (2.8)	2.37 (0.57, 9.78)	.24
High risk	133 (96.4)	5 (3.6)	3.07 (0.74, 12.66)	.12
White ethnic group	442 (98.0)	9 (2.0)	Baseline	-
Non-white ethnic group	115 (96.6)	4 (3.4)	1.68 (0.53, 5.38)	.38
No diabetes	538 (97.8)	12 (2.2)	Baseline	-
Prepregnancy diagnosed diabetes	20 (95.2)	1 (4.8)	2.18 (0.30, 16.04)	.44
No gestational diabetes	536 (98.0)	11 (2.0)	Baseline	-
Gestational diabetes	20 (95.2)	1 (4.8)	2.37 (0.32, 17.53)	.40
Nonsmoker	442 (97.8)	10 (2.2)	Baseline	-
Smoked during pregnancy*	114 (97.4)	3 (2.6)	1.16 (0.32, 4.15)	.82
Nondrinker	167 (97.1)	5 (2.9)	Baseline	-
Alcohol drank during pregnancy†	260 (98.5)	4 (1.5)	0.52 (0.14, 1.92)	.33
No preeclampsia	479 (98.0)	10 (2.0)	Baseline	-
Preeclampsia	79 (96.3)	3 (3.7)	1.79 (0.50, 6.37)	.37
Rupture of membranes during labor	444 (97.4)	12 (2.6)	Baseline	-
Prelabor rupture of membranes >24 h	114 (99.1)	1 (0.9)	0.33 (0.04, 2.52)	.29
Antenatal corticosteroids not given	406 (97.4)	11 (2.6)	Baseline	-
Antenatal corticosteroids given	149 (99.3)	1 (0.7)	0.25 (0.03, 1.94)	.19
Normal vaginal delivery	295 (97.7)	7 (2.3)	Baseline	
Cesarean, breech, or instrumental delivery	263 (97.8)	6 (2.2)	0.96 (0.33, 2.83)	.94
Good mental health	490 (98.2)	9 (1.8)	Baseline	
Poor mental health‡	66 (94.3)	4 (5.7)	3.17 (1.00, 10.03)	.05
Neonatal factors	**(n = 606)**	**(n = 15)**		
Female	285 (98.6)	4 (1.4)	Baseline	
Male	321 (96.7)	11 (3.3)	2.39 (0.77, 7.44)	.13
Singleton	503 (97.7)	12 (2.3)	Baseline	-
Multiple birth	103 (97.2)	3 (2.8)	1.21 (0.35, 4.23)	.76
Appropriate growth for gestational age	464 (97.5)	12 (2.5)	Baseline	-
Fetal growth restriction* (<10th percentile)§	142 (97.9)	3 (2.1)	0.82 (0.23, 2.87)	.76
No resuscitation at birth	499 (97.5)	13 (2.5)	Baseline	-
Needed resuscitation at birth	107 (98.2)	2 (1.8)	0.72 (0.17, 3.16)	.67
No respiratory support received	525 (97.6)	13 (2.4)	Baseline	-
Any respiratory support received	81 (97.6)	2 (2.4)	1.00 (0.23, 4.35)	.98
No evidence of jaundice	518 (97.6)	13 (2.4)	Baseline	-
Jaundice requiring phototherapy	47 (97.9)	1 (2.1)	0.85 (0.11, 6.38)	.88
Antibiotics not given	398 (97.3)	11 (2.7)	Baseline	-
Antibiotics given	208 (98.1)	4 (1.9)	0.70 (0.23, 2.18)	.54
No hypoglycemia	531 (97.4)	14 (2.6)	Baseline	-
Hypoglycemia	75 (98.7)	1 (1.3)	0.51 (0.07, 3.85)	.52
No breast milk given at discharge	219 (96.1)	9 (3.9)	Baseline	
Any breast milk given at discharge§	387 (98.5)	6 (1.5)	0.39 (0.14, 1.07)	.07

*Smoked during pregnancy is classified as mothers who smoked at least 1 cigarette per day at any time during pregnancy vs <1 cigarette per day.
†Drank alcohol during pregnancy is classified as mothers who drank any alcohol at any time during pregnancy vs no alcohol.
‡Poor antenatal mental health is classified for mothers who reported feeling moderately or severely anxious or depressed.
§Fetal growth restriction is classified as birthweight <10th percentile using customized fetal growth charts.[31]
¶Includes infants with a negative screen before and after follow-up. Percentages are calculated across rows such that denominators represent the number of infants with each risk factor.

this remained significant after application of the follow-up interview and exclusion of infants with neurosensory impairments. There is growing interest in the sequelae of late and moderate prematurity, and recent studies have shown that adverse outcomes associated with very preterm birth extend across birth at 32-36 weeks of gestation.[16,26,34-37] Here we have shown that the spectrum of adversity extends to behavioral traits indicative of early risk for ASD: 2.4% of LMPT infants had a true positive screen compared with 0.5% of controls, equating to 4.5 times increased risk. Excluding infants with neurosensory impairments, LMPT birth was associated with a 3.7 times increased risk for a true positive screen.

As anticipated, this is markedly lower than the 21%-41% prevalence of positive M-CHAT questionnaire screens in previous studies of very preterm infants.[21-23] These studies did not include a term reference group to estimate RR, nor did they include the M-CHAT follow-up interview. M-CHAT items may be failed as a result of neurodevelopmental impairments commonly associated with preterm birth,[20,22,25,38] problems interpreting items by caregivers with poor command of English, or because of behaviors which trigger a fail, but are

Table V. Characteristics of LMPT and term-born infants with false positive M-CHAT screens at 2 years corrected age

Characteristics	Negative screen*	False positive screen		
Dichotomous variables, n (%)	**(n = 1233)**	**(n = 118)**	**RR (95% CI)**	***P***
Hearing impairment	0 (0.0)	3 (2.5)	-	-
Vision impairment	1 (0.08)	1 (0.9)	10.45 (0.66, 166.15)	.10
Communication impairment	7 (0.6)	6 (5.1)	8.96 (3.06, 26.22)	<.01
Motor impairment	1 (0.08)	3 (2.5)	31.35 (3.28, 299.24)	<.01
Cognitive impairment†	110 (9.1)	43 (37.4)	4.13 (3.07, 5.55)	<.01
BITSEA problem behaviors	192 (15.7)	53 (45.3)	2.89 (2.28, 3.67)	<.01
BITSEA delayed socioemotional competence	210 (17.1)	69 (59.5)	3.48 (2.87, 4.23)	<.01
Continuous variables, mean (SD)			**Mean difference (95% CI)**	***P***
PARCA-R composite score	95.7 (32.8)	65.5 (32.2)	−30.22 (−36.48, −23.96)	<.01
BITSEA total problem score	8.7 (5.7)	14.2 (8.8)	5.50 (4.36, 6.64)	<.01
BITSEA total competence score	17.4 (2.7)	13.8 (3.7)	−3.58 (−4.12, −3.05)	<.01

BITSEA, Brief Infant and Toddler Social and Emotional Assessment; *PARCA-R*, Parent Report of Children's Abilities-Revised.
*Includes infants with a negative screen before and after follow-up.
†Cognitive impairment is defined as PARCA-R Composite score <49.

indicative of developmental delay or are required in greater intensity or frequency to be symptomatic of ASD. The false positive screen rate has up to this point not been compared with that of a term reference group to corroborate these findings. Here, we have shown that the rate of false positive M-CHAT screens was significantly higher among LMPT infants than term-born controls and that the follow-up interview reduced the overall positive screen rate to a significantly greater extent in LMPT than term-born infants. These findings provide empirical evidence that screening for ASD is especially confounded in preterm populations. This effect is likely to be even greater with increasing immaturity at birth given the gestational age related gradient in neurodevelopmental outcomes. When using the M-CHAT questionnaire alone, results should be interpreted with caution and in light of other clinical information when assessing infants born preterm.

The long-term significance of positive M-CHAT screens for ASD diagnoses in preterm children is unknown. It is likely that predictive validity may be lower than in the general population as behaviors rated on the M-CHAT may represent developmental delays that are frequently associated with preterm birth, rather than the sociocommunicative impairments and repetitive/stereotyped behaviors that are characteristic of ASD.[39,40] However, we assessed the rate of true positive screens in which failed M-CHAT items were probed via a telephone interview in order to differentiate autistic features from other developmental problems. Thus, we believe that the increased rate of true positive screens identified here may be indicative of a true increase in the risk for ASD among infants born LMPT. Follow-up studies are needed to determine the predictive accuracy of infant screens for later diagnoses in children and adolescents born preterm, including those born at LMPT gestations.

The etiology of ASD in preterm children is poorly understood. Diagnoses are thought to have a neurodevelopmental origin arising as a result of aberrant brain development in very preterm children[5,14,15,21,41-44] and may also underlie ASD in LMPT children given reduced brain volume and intracranial injuries among neonates born at these gestations.[45] However, other factors associated with both LMPT birth and ASD may account for this relationship, including advanced maternal age, induction of labor, perinatal inflammation, and preeclampsia.[13,46,47] Given the small number of infants with true positive screens, we were unable to carry out multivariable analyses to adjust for factors that may confound the relationship between ASD and LMPT birth. Where we explored potential associations using univariate analyses, no factors were significantly associated with true positive screens. However, it is interesting to note that advanced maternal age (≥35 years), poor mental health, and not giving the baby breast milk at discharge were both marginally significant ($P < .1$) and have previously been associated with ASD in both preterm and community samples.[5,13,48] In particular, not receiving breast milk is an independent predictor of ASD symptoms in extremely preterm children, although the causal mechanisms by which this operates are not clear.[5]

The high rate of false positive screens does not negate the utility of screening for ASD in preterm populations. Similar to previous reports[39,49] we have shown that infants with false positive M-CHAT screens are likely to be a group at risk for cognitive and behavioral problems at 2 years of age. In particular, these children were 3 times more likely to have delayed socioemotional competence and behavior problems, outcomes which have been associated with the later onset of psychiatric disorders.[50] Screening for ASD in infancy may, thus, have clinical utility for identifying a group of children who are risk, not only for ASD, but for later learning difficulties and mental health sequelae.

The strengths of this study lie in the collection of data from a large, geographical prospective population-based cohort of LMPT infants and term-born controls. The inclusion of the M-CHAT follow-up interview was a particular strength of this study and significantly adds to the literature in this field. Detailed prospective data were collected about mothers' antenatal health, socioeconomic, and demographic characteristics and infants' neonatal course. However, limitations are as follows. The prevalence of positive screens in the

general population is low. As such, even having screened 634 LMPT and 761 term-born infants, there was still insufficient power to detect a dose response effect of gestation and, thus, to investigate within-group differences in the prevalence of positive screens among LMPT infants. Although we observed a lower rate of positive screens in moderately preterm compared with late preterm infants, there was insufficient power to establish whether this was a true difference or a chance finding. In addition, there was low power for evaluating risk factors for true positive screens. We were unable to include a diagnostic assessment in the present study and, therefore, were unable to ascertain caseness in those with true positive screens. Despite intensive efforts to maximize follow-up rates, M-CHAT questionnaires were received for 60% of infants recruited to the study. Mothers who were nonresponders had greater socioeconomic risk and poorer mental and general health. We have previously reported that mothers not recruited to the study lived in areas of greater socioeconomic deprivation. These factors may impact upon the observed prevalence of adverse outcomes.[51,52] As such, our findings may underestimate the true prevalence of positive ASD screens in this population. ■

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References

1. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta Obstetricia et Gynecologica Scandinavica 2012;91:287-300.
2. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Oleson AV, Agerbo E, et al. Risk factors for Autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol 2005;161:916-25.
3. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res 2012;5:160-79.
4. Treyvaud K, Ure A, Doyle LW, Lee KJ, Rogers CE, Kidokoro H, et al. Psychiatric outcomes at age seven for very preterm children: rates and predictors. J Child Psychol Psychiatry 2013;54:772-9.
5. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. J Pediatr 2010;156:525-31.e2.
6. Hack M, Taylor HG, Schlichter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. J Dev Behav Pediatr 2009;30:122-30.
7. Elgen I, Sommerfelt K, Markestad T. Population based, controlled study of behavioral problems and psychiatric disorders in low birthweight children at 11 years of age. Arch Dis Child Fetal Neonatal Ed 2002;87:F128-32.
8. Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. Pediatrics 2011;128:883-91.
9. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. Arch Dis Child 2004;89:F445-50.
10. Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. Semin Fetal Neonatal Med 2012;17:120-5.
11. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med 2008;359:262-73.
12. Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics 2008;121:1155-64.
13. Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparen P, Cnattingius S. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? Pediatrics 2009;124:e817-25.
14. Hwang YS, Weng SF, Cho CY, Tsai WH. Higher prevalence of autism in Taiwanese children born prematurely: a nationwide population-based study. Res Dev Disabil 2013;34:2462-8.
15. Kuzniewicz MW, Wi S, Qian Y, Walsh EM, Armstrong MA, Croen LA. Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants. J Pediatr 2014;164:20-5.
16. de Jong M, Verhoeven M, van Baar AL. School outcome, cognitive functioning, and behavior problems in moderate and late preterm children and adults: a review. Semin Fetal Neonatal Med 2012;17:163-9.
17. Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and prevasive developmental disorders. J Autism Dev Disord 2001;31:131-44.
18. Robins DL. Screening for autism spectrum disorders in primary care settings. Autism 2008;12:537-56.
19. Kleinman JM, Robins DL, Ventola PE, Pandey J, Boorstein HC, Esser EL, et al. The Modified Checklist for Autism in Toddlers: a follow-up study investigating the early detection of autism spectrum disorders. J Autism Dev Disord 2008;38:827-39.
20. Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. Pediatr Res 2011;69(5 Pt 2):11R-8R.
21. Limperopoulos C, Bassan H, Sullivan NR, Soul JS, Robertson RL, Moore M, et al. Positive screening for autism in ex-preterm infants: prevalence and risk factors. Pediatrics 2008;121:758-65.
22. Kuban KCK, O'Shea TM, Allred EN, Tager-Flusberg H, Goldstein DJ, Leviton A. Positive Screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. J Pediatr 2009;154:535-40.
23. Moore T, Johnson S, Hennessy E, Marlow N. Screening for autism in extremely preterm infants: problems in interpretation. Dev Med Child Neurol 2012;54:514-20.
24. Johnson S, Marlow N. Positive screening results on the modified checklist for autism in toddlers: implications for very preterm populations. J Pediatr 2009;154:478-80.
25. Luyster RJ, Kuban KCK, O'Shea TM, Paneth N, Allred EN, Leviton A, et al. The Modified Checklist for Autism in Toddlers in extremely low gestational age newborns: individual items associated with motor, cognitive, vision and hearing limitations. Paediatr Perinat Epidemiol 2011;25:366-76.
26. Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. Arch Dis Child Fetal Neonatal Ed 2012;97:F167-73.
27. Robins DL. Modified Checklist for Autism in Toddlers (M-CHAT) Follow-up Interview. 1999.
28. The Office for National Statistics. Standard Occupational Classification 2010. Volume 3. The National Statistics Socioeconomic Classification User Manual. London: Palgrave Macmillan; 2010.
29. Gardosi J, Francis A. Gestation Network. GROW version 5.16: Gestation Network 2013.
30. British Association of Perinatal Medicine. Report of a BAPM/RCPCH Working Group: Classification of health status at 2 years as a perinatal outcome. London: BAPM; 2008.
31. Johnson S, Marlow N, Wolke D, Davidson L, Marston L, O'Hare A, et al. Validation of a parent report measure of cognitive development in very preterm infants. Dev Med Child Neurol 2004;46:389-97.
32. Briggs-Gowan MJ, Carter AS. BITSEA Brief Infant-Toddler Social and Emotional Assessment. San Antonio, TX: Harcourt Assessment Inc; 2006.
33. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-6.
34. Gurka MJ, LoCasale-Crouch J, Blackman JA. Long-term cognition, achievement, socioemotional, and behavioral development of healthy late-preterm infants. Arch Pediatr Adolesc Med 2010;164:525-32.

35. Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. BMJ 2012;344:e896.
36. 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 2009;124:251-7.
37. 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. J Pediatr 2011;159:92-8.
38. Stephens BE, Bann CM, Watson VE, Sheinkopf SJ, Peralta-Carcelen M, Bodnar A, et al. Screening for autism spectrum disorders in extremely preterm infants. J Dev Behav Pediatr 2012;33:535-41.
39. Dereu M, Roeyers H, Raymaekers R, Meirsschaut M, Warreyn P. How useful are screening instruments for toddlers to predict outcome at age 4? General development, language skills, and symptom severity in children with a false positive screen for autism spectrum disorder. Eur Child Adolesc Psychiatry 2012;21:541-51.
40. Hofheimer JA, Sheinkopf SJ, Eyler LT. Autism risk in very preterm infants–new answers, more questions. J Pediatr 2014;164:6-8.
41. Indredavik MS, Skranes JS, Vok T, Heyerdahl S, Romundstad P, Myhr GE, et al. Low-birth-weight adolescents: Psychiatric symptoms and cerebral MRI abnormalities. Pediatr Neurol 2005;33:259-66.
42. Johnson S, Marlow N. Growing up after extremely preterm birth: lifespan mental health outcomes. Semin Fetal Neonatal Med 2014;19:97-104.
43. Healy E, Reichenberg A, Nam KW, Allin MP, Walshe M, Rifkin L, et al. Preterm birth and adolescent social functioning-alterations in emotion-processing brain areas. J Pediatr 2013;163:1596-604.
44. Movsas TZ, Pinto-Martin JA, Whitaker AH, Feldman JF, Lorenz JM, Korzeniewski SJ, et al. Autism spectrum disorder is associated with ventricular enlargement in a low birth weight population. J Pediatr 2013;163:73-8.
45. Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. Semin Perinatol 2006;30:81-8.
46. Meldrum SJ, Strunk T, Currie A, Prescott SL, Simmer K, Whitehouse AJ. Autism spectrum disorder in children born preterm-role of exposure to perinatal inflammation. Frontiers Neurosci 2013;7:123.
47. Gregory SG, Anthopolos R, Osgood CE, Grotegut CA, Miranda ML. Association of autism with induced or augmented childbirth in North Carolina Birth Record (1990-1998) and education research (1997-2007) databases. JAMA Pediatr 2013;167:959-66.
48. Parner ET, Baron-Cohen S, Lauritsen MB, Jorgensen M, Schieve LA, Yeargin-Allsopp M, et al. Parental age and autism spectrum disorders. Ann Epidemiol 2012;22:143-50.
49. Johnson S, Hollis C, Hennessy E, Kochhar P, Wolke D, Marlow N. Screening for autism in preterm children: diagnostic utility of the Social Communication Questionnaire. Arch Dis Child 2011;96:73-7.
50. Briggs-Gowan MJ, Carter AS. Social-emotional screening status in early childhood predicts elementary school outcomes. Pediatrics 2008;121:957-62.
51. Wolke D, Sohne B, Ohrt B, Riegel K. Follow-up of preterm children: important to document dropouts. Lancet 1995;345:447.
52. Kramer MS, Wilkins R, Goulet L, Seguin L, Lydon J, Kahn SR, et al. Investigating socioeconomic disparities in preterm birth: evidence for selective study participation and selection bias. Paediatr Perinat Epidemiol 2009;23:301-9.

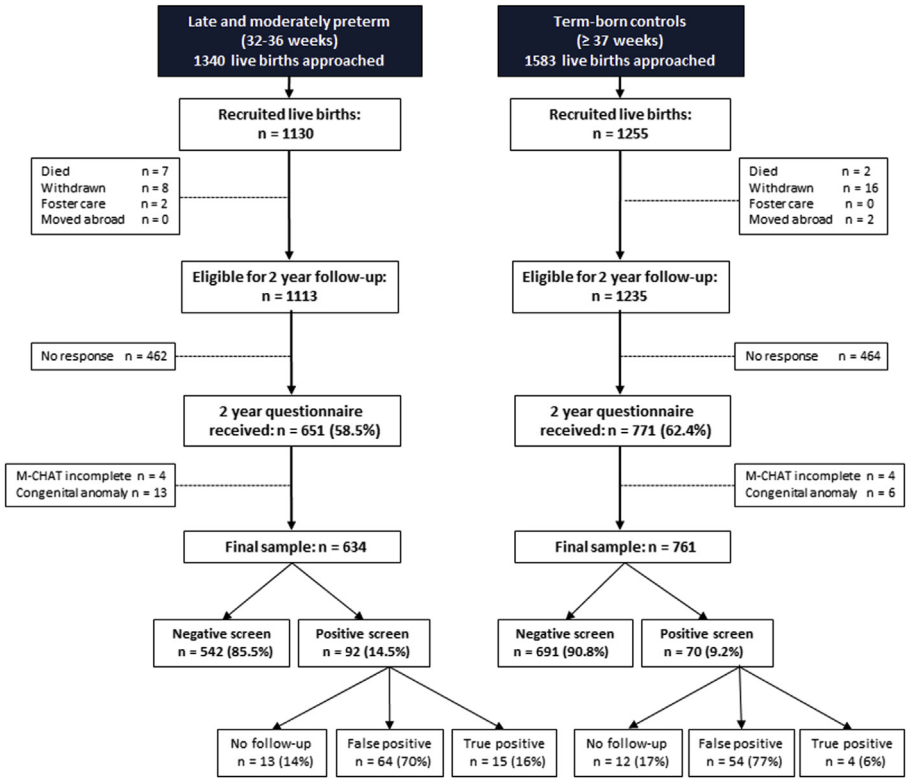

Figure. Recruitment, follow-up rates, and ascertainment of M-CHAT data for LMPT and term-born infants.

Table I. Demographic, obstetric, and neonatal characteristics of infants born LMPT (32-36 weeks gestation) for whom M-CHAT data were and were not obtained at 2 years corrected age

Characteristics	Responders	Nonresponders		
Mothers	**(n = 592)**	**(n = 428)**	**RR (95% CI)**	***P***
Age at baby's birth				
<20 y, n (%)	19 (31.2)	42 (68.8)	1.81 (1.45, 2.27)	<.01
20-24 y, n (%)	88 (45.4)	106 (54.6)	1.44 (1.18, 1.75)	<.01
25-29 y, n (%)	176 (62.0)	108 (38.0)	Baseline	-
30-34 y, n (%)	193 (63.9)	109 (36.1)	0.95 (0.77, 1.17)	.63
≥35 y, n (%)	115 (64.6)	63 (35.4)	0.93 (0.73, 1.19)	.57
Ethnic group				
White, n (%)	465 (62.6)	278 (37.4)	Baseline	-
Mixed, n (%)	12 (36.4)	21 (63.6)	1.70 (1.29, 2.24)	<.01
Asian or Asian British, n (%)	87 (49.2)	90 (50.9)	1.36 (1.14, 1.61)	<.01
Black or Black British, n (%)	22 (41.5)	31 (58.5)	1.56 (1.22, 2.00)	<.01
Chinese or other ethnic group, n (%)	5 (38.5)	8 (61.5)	1.64 (1.06, 2.56)	.03
SES index				
Low risk, n (%)	258 (79.6)	66 (20.4)	Baseline	-
Medium risk, n (%)	184 (63.0)	108 (37.0)	1.82 (1.40, 2.36)	<.01
High risk, n (%)	150 (37.1)	254 (62.9)	3.09 (2.46, 3.88)	<.01
English first language, n (%)	499 (59.6)	338 (40.4)	Baseline	-
English not first language, n (%)	78 (48.8)	82 (51.3)	1.27 (1.07, 1.51)	.01
Good mental health, n (%)	520 (59.3)	357 (40.7)	Baseline	-
Poor mental health*, n (%)	70 (50.0)	70 (50.0)	1.23 (1.02, 1.48)	.03
Good general health, n (%)	544 (59.4)	372 (40.6)	Baseline	-
Poor general health†, n (%)	48 (46.2)	56 (53.9)	1.33 (1.09, 1.61)	<.01
Infants	**(n = 647)**	**(n = 476)**		
Birthweight (kg), mean (SD)	2.43 (0.50)	2.42 (0.50)	0.98 (0.85, 1.12)	.77
No major congenital anomaly, n (%)	634 (57.5)	468 (42.5)	Baseline	-
Major congenital anomaly, n (%)	13 (61.9)	8 (38.1)	0.90 (0.52, 1.55)	.70
Appropriate fetal growth, n (%)	577 (58.5)	410 (41.5)	Baseline	-
Fetal growth restriction (<3rd centile)‡, n (%)	70 (51.5)	66 (48.5)	1.17 (0.97, 1.41)	.11
Singleton, n (%)	536 (58.5)	381 (41.5)	Baseline	-
Multiple birth, n (%)	111 (53.9)	95 (46.1)	1.11 (0.94, 1.31)	.22
No respiratory support, n (%)	556 (56.9)	421 (43.1)	Baseline	-
Any respiratory support§, n (%)	91 (62.3)	55 (37.7)	0.87 (0.70, 1.09)	.23
No intracranial abnormality, n (%)	640 (57.5)	473 (42.5)	Baseline	-
Intracranial abnormality¶, n (%)	7 (70.0)	3 (30.0)	0.71 (0.27, 1.82)	.47
No breast milk given at discharge, n (%)	241 (49.6)	245 (50.4)	Baseline	-
Any breast milk given at discharge**, n (%)	406 (63.7)	231 (36.3)	0.72 (0.63, 0.82)	<.01

RR is given for the probability of nonresponse.
*Mothers' mental health self-reported as moderately or extremely anxious or depressed.
†Mothers' health self-reported as poor or very poor (vs excellent, good, or fair).
‡Fetal growth restriction calculated using customized antenatal growth charts.
§Any respiratory support includes infants who were ventilated or received noninvasive respiratory support.
¶Intracranial abnormality includes grade III or IV intraventricular hemorrhage, periventricular leukomalacia, and grade II or III neonatal encephalopathy.
**Breast milk fed by any method.

Table II. Demographic, obstetric, and neonatal characteristics of term-born (≥37 weeks gestation) infants for whom M-CHAT data were and were not obtained at 2 years corrected age

Characteristics	Responders	Nonresponders		
Mothers	**(n = 691)**	**(n = 425)**	**RR (95% CI)**	***P***
Age at baby's birth				
<20 y, n (%)	17 (30.4)	39 (69.6)	1.78 (1.42, 2.23)	<.01
20-24 y, n (%)	95 (47.0)	107 (53.0)	1.35 (1.12, 1.64)	<.01
25-29 y, n (%)	182 (60.9)	117 (39.1)	Baseline	-
30-34 y, n (%)	210 (65.8)	109 (34.2)	0.87 (0.71, 1.08)	.20
≥35 y, n (%)	187 (78.2)	52 (21.8)	0.56 (0.42, 0.73)	<.01
Ethnic group				
White, n (%)	571 (66.2)	291 (33.8)	Baseline	-
Mixed, n (%)	8 (34.8)	15 (65.2)	1.93 (1.41, 2.64)	<.01
Asian or Asian British, n (%)	75 (47.2)	84 (52.8)	1.56 (1.31, 1.86)	<.01
Black or Black British, n (%)	30 (50.0)	30 (50.0)	1.48 (1.13, 1.94)	<.01
Chinese or other ethnic group, n (%)	7 (63.6)	4 (36.4)	1.08 (0.49, 2.37)	.85
SES index				
Low risk, n (%)	341 (78.2)	95 (21.8)	Baseline	-
Medium risk, n (%)	208 (63.2)	121 (36.8)	1.69 (1.34, 2.12)	<.01
High risk, n (%)	142 (40.5)	209 (59.5)	2.73 (2.24, 3.33)	<.01
English first language, n (%)	599 (64.4)	331 (35.6)	Baseline	-
English not first language, n (%)	85 (51.2)	81 (48.8)	1.37 (1.15, 1.64)	<.01
Good mental health, n (%)	620 (62.4)	373 (37.6)	Baseline	-
Poor mental health*, n (%)	69 (57.5)	51 (42.5)	1.13 (0.91, 1.41)	.28
Good general health, n (%)	659 (62.8)	391 (37.2)	Baseline	-
Poor general health†, n (%)	32 (48.5)	34 (51.5)	1.38 (1.08, 1.77)	.01
Infants	**(n = 767)**	**(n = 486)**		
Birthweight (kg), mean (SD)	3.3 (0.5)	3.2 (0.6)	0.80 (0.71, 0.91)	<.01
No major congenital anomaly, n (%)	762 (61.3)	482 (38.7)	Baseline	-
Major congenital anomaly, n (%)	5 (55.6)	4 (44.4)	1.15 (0.55, 2.39)	.71
Appropriate fetal growth, n (%)	717 (61.9)	441 (38.1)	Baseline	-
Fetal growth restriction (<3rd centile)‡, n (%)	50 (52.6)	45 (47.4)	1.24 (0.99, 1.56)	.06
Singleton, n (%)	616 (63.0)	362 (37.0)	Baseline	-
Multiple birth, n (%)	151 (54.9)	124 (45.1)	1.22 (1.04, 1.42)	.01
No respiratory support, n (%)	759 (61.1)	483 (38.9)	Baseline	-
Any respiratory support§, n (%)	8 (72.7)	3 (27.3)	0.70 (0.27, 1.85)	.47
No intracranial abnormality, n (%)	762 (61.3)	482 (38.8)	Baseline	-
Intracranial abnormality¶, n (%)	5 (55.6)	4 (44.4)	1.15 (0.55, 2.39)	.71
No breast milk given at discharge, n (%)	177 (47.8)	193 (52.2)	Baseline	-
Any breast milk given at discharge**, n (%)	590 (66.8)	293 (33.2)	0.64 (0.56, 0.73)	<.01

RR is given for the relative probability of nonresponse.
*Mothers' mental health self-reported as moderately or extremely anxious or depressed.
†Mothers' health self-reported as poor or very poor (vs excellent, good, or fair).
‡Fetal growth restriction calculated using customized antenatal growth charts.
§Any respiratory support includes infants who were ventilated or received noninvasive respiratory support.
¶Intracranial abnormality includes grade III or IV intraventricular hemorrhage, periventricular leukomalacia, and grade II or III neonatal encephalopathy.
**Breast milk fed by any method.