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Late Preterm Infants Have Worse 24-Month Neurodevelopmental Outcomes Than Term Infants

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Late Preterm Infants Have Worse 24-Month Neurodevelopmental Outcomes Than Term Infants

WHAT'S KNOWN ON THIS SUBJECT: Data suggest that late preterm infants have worse neurodevelopmental outcomes and academic performance at school age and require special education more frequently.

WHAT THIS STUDY ADDS: It is important to know whether late preterm infants with worse neurodevelopmental outcomes can be identified before school age, permitting them to have earlier interventions to limit the need for later special education.

abstract

BACKGROUND: Late preterm infants (34–37 weeks' gestation) are often perceived at similar risks for morbidity and mortality as term infants.

OBJECTIVE: To compare the neurodevelopmental outcomes of late preterm to term infants.

METHODS: Our study sample of 6300 term and 1200 late preterm infants came from the Early Childhood Longitudinal Study-Birth Cohort. We used general estimating equations to get weighted odds of having developmental delay, mental index scores (MDI) or psychomotor index scores (PDI) < 70, at 24 months of age.

RESULTS: Late preterm infants compared with term infants had lower MDI (85 vs 89) and PDI (88 vs 92), both $P < .0001$, respectively. A higher proportion of late preterm infants compared with term infants had an MDI <70 (21% vs 16%; $P < .0001$). An equal number had PDIs <70 (6.1% vs 6.5%). After controlling for statistically significant and clinically relevant descriptive characteristics, late preterm infants still had higher odds of mental (odds ratio: 1.52 [95% confidence interval: 1.26–1.82] $P < .0001$) or physical (odds ratio: 1.56 [95% confidence interval: 1.30–1.89] $P < .0001$) developmental delay.

CONCLUSIONS: Late preterm infants have poorer neurodevelopmental outcomes than term infants and have increased odds to have a mental and/or physical developmental delay. *Pediatrics* 2011;127:e622–e629

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KEY WORDS

infant, premature, infant, very low birth weight, developmental disabilities, postnatal development, cognition, follow-up studies

ABBREVIATIONS

ECLS-B—Early Childhood Longitudinal Study-Birth Cohort
BSF-R—Bayley Scales of Infant Development Short Form-Research Edition
MDI—mental developmental index
PDI—Psychomotor Developmental Index
BSID-II—Bayley Scales of Infant Development, Second Edition
CI—confidence interval

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Preterm births account for 12.8% of the 4.27 million annual births in the United States.[1] Since 1990, the late preterm infant (34–36 weeks' postmenstrual age) birth rate rose 25% (from 7.3% to 9.14% of all births).[1] A July 2005 Eunice Kennedy Shriver National Institute of Child Health and Human Development panel redefined infants born at 34 to 36 weeks' gestation from "near term" to "late preterm" to emphasize the increased risk and vulnerability of these infants.[2] Most of the increased risk assessed by this panel reflects acute neonatal complications. Currently, these infants have little or no developmental follow-up. Additional investigations are required to identify potential points for intervention to improve long-term outcomes.

Concerns about longer-term outcomes arise because significant brain development occurs between 34 and 36 weeks' gestation.[3–9] Economic disadvantage is a well characterized risk factor for preterm birth, and, independently, poorer cognitive and behavioral outcomes.[10–13] Late preterm infants also experience increased morbidity compared with term infants in the neonatal period.[14–16] Combined, these factors suggest that the late preterm infant is at increased risk for poorer neurodevelopmental outcomes from both biological and environmental factors.

Data suggest that late preterm infants have worse neurodevelopmental outcomes and academic performance at school age and require special education more frequently.[17–19] However, substantial data has accumulated that early educational intervention can prevent these adverse school-aged outcomes, and this group of infants may be likely to have sustained long-term benefits from such early programs.[20,21] Thus, it is important to know whether this group of infants can be identified before school age, permitting them to have earlier interventions to limit the need for later special education. To address this question, we compared neurodevelopmental outcomes for late preterm infants at 24 months with their term counterparts.

METHODS

Data Source: Early Childhood Longitudinal Study-Birth Cohort

We used the Early Childhood Longitudinal Study-Birth Cohort (ECLS-B), a prospective national longitudinal study focused on the early health care as well as developmentally influential in- and out-of-home child experiences from birth through kindergarten of children born in 2001 and their families. The ECLS-B oversampled racial/ethnic groups (American Indian, Asian, and Pacific Islander), low birth weight infants, and twins. Data collection included parent interviews and developmental assessments by trained personnel. The ECLS-B is sponsored by the US Department of Education's National Center for Education Statistics in the Institute of Education Sciences, in collaboration with several federal education and health policy agencies.

Study Population

We included infants with >34 weeks' completed gestation (including multiple gestations) who had complete developmental assessments at 24 months' chronological age. Developmental assessments were the Bayley Scales of Infant Development Short Form-Research Edition (BSF-R).[22] Other data came from birth certificates and parental interviews at 9 and 24 months. We excluded infants who either were not or were unable to be adequately assessed with the BSF-R because of a major congenital anomaly (Appendix 1) or blindness.

Variables

Outcome

The primary outcome measures were the mental developmental index (MDI) and psychomotor developmental index (PDI).[23] The BSF-R was derived from the Bayley Scales of Infant Development, Second Edition (BSID-II) to evaluate the development of children at 23 to 25 months. Similar to the BSID-II, the BSF-R has a core set of items that are administered to all children and the supplementary basal and ceiling item sets that can be administered. The BSID-II generates a raw score that is converted to the standardized MDI and PDI. Item response theory modeling was used to estimate the BSID-II raw scores from the BSF-R.

The BSF-R was tested extensively to ensure that the psychometric properties of the BSID-II were maintained and that it successfully measured children's abilities across the entire distribution. The overall reliability coefficients for the BSF-R mental and psychomotor scales were 0.98 and 0.97, respectively. A MDI and PDI score on the BSF-R (both have a mean of 100 and SD of 15) of <70 equates to significant developmental delay, 70 to 84 represents mild developmental delay, and ≥85 reflects normal development.

The BSF-R was administered in the child's home by trained personnel. Each administrator's testing and scoring abilities were validated through in-person quality control visits and also through videotaped interviews.[22]

Maternal and infant descriptive characteristics were obtained from birth certificates and maternal surveys.

Detailed Maternal and Home Descriptive Characteristics

Maternal race/ethnicity were characterized as white non-Hispanic, black non-Hispanic, or other/unknown. Adequacy of prenatal care was based on the Kotelchuck index (1994).[24,25] This previously validated index uses the week of pregnancy prenatal care was initiated, total number of prenatal visits, and length of gestation together in an algorithm in which prenatal care is characterized as "inadequate," "intermediate," "adequate," and "adequate plus."

Maternal depression was diagnosed using the Composite International Diagnostic Interview Short Form.[26] A score of 3 or more characterizes a person as being "depressed" on the basis of the diagnostic criteria of major depressive disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.[27]

Households were identified as primarily or not primarily English-speaking (Appendix 2). Total household income was in the following categories: \$20 000 or less; \$20 001 to \$30 000; \$30 001 to \$50 000; \$50 001 to \$75 000; and >\$75 000. When the household income-to-size ratio was such that it was below the 2002 Census poverty threshold, the household was labeled as "impoverished."

Detailed Child Descriptive Characteristics

Infants were characterized as either late preterm (34⁰⁄₇–36⁶⁄₇ weeks' completed gestation) or term (≥37⁰⁄₇ weeks' completed gestation). Birth weight in grams was in the following categories: <750; 750 to 1499; 1500 to 2499; 2500 to 2999; 3000 to 3499; 3500 to 3999; and ≥4000.

Adjusting for the child's gender and race/ethnicity as per Alexander et al,[28] we defined small for gestational age as less than the 10th percentile, and large for gestational age as >90th percentile birth weight for gestational age.

As part of the maternal questionnaire at 9 months of age, mothers were asked whether they ever fed breast milk to their child.

Statistical Analyses

All unweighted sample sizes included in this analysis were rounded to the nearest 50 to protect the confidentiality of respondents as specified in the restricted data license agreement.

We used the weights provided in the ECLS-B manual to adjust for survey design and allow for accurate population estimates of mild and severe developmental delay. We used these weights in the SURVEYFREQ analysis to make appropriate adjustments to the SEs.

The maternal, home, and child descriptive characteristics were compared in bivariate analysis using the *t* test for 2 sample comparison of continuous data, χ^2 analysis for multiple sample comparison of categorical data, and analysis of variance for continuous variable multiple sample comparisons. Maternal characteristics were compared after removing twin pairs so individual mothers were represented only once.

Because siblings share genetic, in utero, and environmental factors related to neurodevelopmental outcomes, they are correlated and represent clustered data. For multivariable analysis, we used generalized estimating equation models to generate odds ratios and 95% confidence intervals (CIs). Conceptually similar to logistic regression, generalized estimating equation models differ because they account for clustering of the data.

We calculated the relative contribution of each significant correlate of having a MDI or PDI < 70 by examining the marginal increase in the model log likelihood ratio accounted for by each correlate as it was added and removed from a model containing all the significant correlates.[29,30]

All statistical tests were 2-tailed, and the level of significance was set at α of 0.05. All the analyses used SAS 9.1 statistical software (SAS Institute Inc, Cary, NC).

Human Subjects

The institutional review boards of Beth Israel Deaconess Medical Center and National Center for Education Statistics in the Institute of Education Sciences approved this study.

RESULTS

A total of 9050 infants were included in our cohort at 24 months of age. Of these, 50 infants were excluded because of congenital anomaly (Appendix 1) or blindness, and another 1500 (1300 full preterm and 200 late preterm) were excluded because they lacked BSF-R assessments. Thus, we used 7500 (6300 term and 1200 late preterm) infants for analysis. Ninety percent of the children were assessed during the 23- to 25 month time period at home visits. A small percentage (1.6%; $n = 150$), were assessed before they were 23 months old. Another 8.4% ($n = 750$) were seen at 26 months or greater. The mean age at assessment was equivalent for the 2 groups, 24.4 (± 1.3) and 24.5 (±1.3) months for the late preterm and term groups, respectively.

Mothers with infants excluded because of missing BSF-R scores were more likely to have a high school level education, be impoverished, and have less prenatal care.

Maternal and Infant Characteristics

All maternal and infant descriptive characteristics are in Tables 1 and 2, respectively. Mothers of the late preterm infants, compared with mothers of term infants, were more likely to be black, at least high school educated, unmarried, depressed, and impoverished. These mothers were more likely to have complicated pregnancies evidenced by more prenatal care use and

TABLE 1 Maternal and Delivery Characteristics

Characteristics	Weighted Cohort	Weighted Late Preterm	Weighted Full Term	Weighted *P*
Age, mean (SD)	27.3	27.5 (6.9)	27.3 (7.9)	.2748
Race, %				
White	80.8	75.1	81.4	
Black	14.8	20.4	14.3	<.0001
Other	4.4	4.5	4.3	
Education, %				
< High school	5.7	4.8	5.7	
High school	46.9	52.5	46.4	.0229
College and beyond	47.4	42.7	47.9	
Marital status, %				
Married	67.5	61.8	68.2	.0018
Unmarried	32.5	38.2	31.8	
Depression, %	6.0	8.3	5.8	.0220
English is primary language, %	81.2	80.3	81.3	.7248
Household income, %				
20 000 or less	24.7	30.3	24.1	
20 001–30 000	14.8	15.4	14.6	.0026
30 001–50 000	21.6	21.9	21.7	
50 001–75 000	16.1	14.9	16.3	
≥75 001	22.7	17.5	23.3	
Impoverished, %	21.4	30.3	20.3	<.0001
Prenatal care use, %				
Inadequate	10.6	10.7	10.5	<.0001
Intermediate	14.8	5.4	15.8	
Adequate	44.1	12.8	47.2	
Adequate plus	30.4	71.1	26.6	
No tobacco use during pregnancy, %	87.5	85.6	87.8	.1837
No alcohol use during pregnancy, %	99.5	99.5	99.5	.9804
Delivery type, %				
Vaginal	74.6	67.0	75.4	<.0001
Cesarean delivery	25.4	33.0	24.6	

TABLE 2 Infant Characteristics

Characteristics	Weighted Cohort, %	Weighted Late Preterm, %	Weighted Full Term, %	Weighted *P*
Gender				
Male	51.4	52.6	51.4	.6041
Female	48.6	47.4	47.4	
Birth weight, g				
<750–1499	0.3	1.2	0.2	
1500–2499	4.7	29.3	2.7	
2500–2999	16.4	30.7	15.0	<.0001
3000–3499	38.4	21.2	39.8	
3500–3999	29.7	11.6	31.4	
≥4000	10.5	5.9	11.0	
Fetal growth				
<10% (SGA)	10.0	8.9	10.1	
20%–89%	79.1	78.7	79.1	0.4667
≥90% (LGA)	10.9	12.4	10.8	
Plurality				
Single	93.7	85.3	98.5	<.0001
Multiple	2.5	14.7	1.5	
Any breastfeeding				
Yes	69.7	61.0	70.6	<.0001
No	30.3	39.0	29.4	

SGA indicates small for gestational age; LGA, large for gestational age.

cesarean delivery. The late preterm infants were less likely to be the product of a singleton gestation or to receive any breast milk.

Developmental Test Results

For late preterm compared with term infants, the mean MDI (85 and 89, respectively; $P < .0001$) and PDI (88 and 92, respectively; $P < .0001$) were significantly lower (Table 3). Similarly, they were more likely to have scores < 70 on the MDI (21.2% vs 16.4%, respectively; $P = .007$), but not the PDI (Table 4).

When gestational age, plurality, maternal race, education, marital status, depression, prenatal care, primary language, infant gender, poverty level, delivery type, fetal growth, and any breast milk feeding were controlled for, the adjusted odds (95% CI) of a late preterm infant having more severe developmental delay (MDI score < 70) was 1.51 (95% CI: 1.26–1.82) and milder mental developmental delay (MDI score 70–84) was 1.43 (95% CI: 1.22–1.67) compared with a term infant. Late preterm infants also had increased odds of having more severe psychomotor developmental delay (PDI score < 70: 1.56 [95% CI: 1.29–1.88]) and milder psychomotor developmental delay (PDI score 70–84: 1.58 [95% CI: 1.37–1.83]).

On the basis of our data, social factors collectively had the largest relative contribution to the MDI score, with the most important social factor being language spoken at home. Individually, gender had the largest relative contribution to significant mental delay, with male gender having worse outcomes. In contrast, medical factors were the largest contributors to the PDI, with gestational age being the largest single contributor (34%) (Figs 1 and 2).

DISCUSSION

We found that late preterm infants have worse developmental outcomes

TABLE 3 Developmental Outcomes at 24 mo

BSF-R	Weighted Late Preterm	Weighted Full Term	Weighted *P*
Mental raw score, mean (± SD)	125.5 (10.3)	127.6 (10.4)	<.0001
Derived MDI	85	89	
Psychomotor raw score, mean (± SD)	81.1 (5.1)	81.9 (5.1)	<.0001
Derived PDI	88	92	

TABLE 4 MDI and PDI Score Comparison at 24 mo

BSF-R	Weighted Late Preterm (%)	Weighted Full Term (%)	Weighted *P*
Derived MDI			
<70	21.2	16.4	
70–84	28.6	25.3	.007
≥85	50.2	58.3	
Derived PDI			
<70	6.1	6.5	
70–84	33.3	23.4	.02
≥85	60.7	70.0	

than do term infants at 24 months of age. Compared with term infants, late preterm infants had increased odds of having more severe mental delay (52%), milder mental developmental delay (43%), severe psychomotor developmental delay (56%), and milder psychomotor developmental delay (58%). In our analyses, the most important single contributor to severe mental developmental delay was male gender, whereas the most significant contributor to severe psychomotor developmental delay was being a late preterm infant.

The observed increased risks to late preterm infants could be because of brain immaturity and its vulnerability to injury. At 34 weeks' gestation, the brain weighs 65% of term brain weight, leaving 35% more growth to achieve its term weight.[3] Quantitative MRI data indicate that total brain volume increases linearly with increasing gestational age.[3] In the last half of gestation are major organizational events in the development of neurons and glia at the cellular and molecular level.[4] The cerebellum is also actively growing and developing, with ~25% of its growth occurring after late preterm gestations.[5]

One could hypothesize that brain growth is altered or damaged by preterm delivery and/or complications known to adversely affect neurodevelopmental outcomes such as respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, and apnea.[14,31,32] Evidence from animal models reveals that these factors can promote or precipitate neuronal cell death in the immature brain.[33]

Our results reveal that mental delay is more closely associated with modifiable social factors (including socioeconomic factors) that could improve outcomes. Currently, late preterm infants do not routinely get referred to

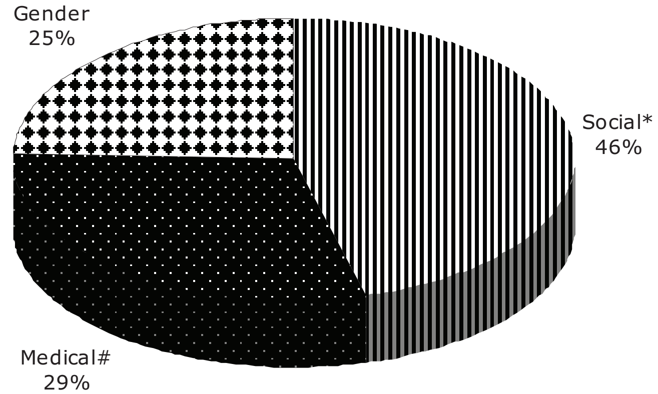

FIGURE 1
Relative contribution of gender, medical, and social factors to the MDI. *, social factors include maternal race, maternal education, marital status, depression, poverty, and primary language at home; #, medical factors include prenatal care, delivery type, whether the infant was ever breastfed, fetal growth, and gestational age.

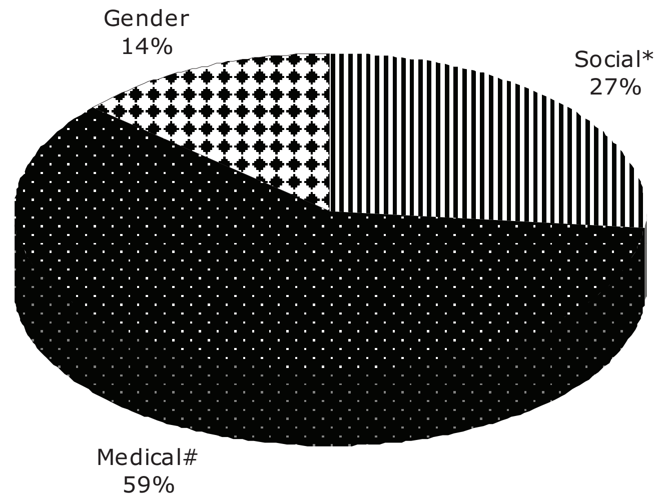

FIGURE 2
Relative contribution of gender, medical, and social factors to the PDI. *, social factors include maternal race, maternal education, marital status, depression, poverty, and primary language at home; #, medical factors include prenatal care, delivery type, whether the infant was ever breastfed, fetal growth, and gestational age.

early intervention, a program that helps prevent some disability and poor school performance.[34,20,21]

These results are consistent with recent reports that raised concerns about the neurodevelopmental outcomes of late preterm infants. Chyi et al[17] noted increased rates of learning difficulties in late preterm infants at school age. Morse et al[18] demonstrated increased risk for late preterm infants to have developmental delay or disability, and school suspension. Petrini et al[19] found that decreasing gestational age was associated with increased incidence of cerebral palsy and developmental delay/mental retardation for those born at 34 to 36 weeks' gestation. A group in the Netherlands found that preterm children born at 32 to 36 weeks' gestation have cognitive and emotional regulation difficulties that affected their functioning at school age, including slightly lower IQ scores and an increased incidence of attention, behavioral, and school problems when compared with term-born children.[35] This group also reported that twice as many moderately preterm born children attend special education schools compared with the general population.[35]

Our study expands the current literature in several ways. First, we focus on actual measures of the outcome as opposed to specific diagnoses, distinguishing us from Petrini et al.[19] This is an important difference because diagnoses can be affected by diagnostic practices in a way that administering a standardized assessment tool in a standardized way will not be. Second, unlike some other studies, our study is a nationally representative sample. Third, Chyi et al[17] also had a nationally representative sample and a similar study design, but they used school assessments and special education. Although these are important outcomes, the assessments across schools may not have been standardized nor was the criteria for special education likely to be consistent across all settings. Finally, the strength of our study is that assessment at 24 months allows for earlier identification of a problem and may permit prompt intervention potentially reducing the subsequent need for special education.

There are, however, limitations to our study. Data on birth events were obtained solely from the birth certificate.[36,37] Thus, we are unable to assess severity of illness at the time of birth, duration of neonatal hospitalization, or other neonatal complications and morbidities to further risk stratify our late preterm infant population. However, on the basis of other evidence, the prevalence of complications is likely to be low.[38]

A second limitation affects the interpretation of the significance of infant developmental testing. The parent instrument, the BSID-II, has been criticized as having limited predictive validity for future development.[39] However, designed to sample a wide array of emerging developmental abilities and inventory developmental milestone attainment, the BSID-II is meant to be a general indicator of functioning at the time of testing and remains a useful tool for relative comparisons between different populations within the same cohort.

In addition, the research form of the BSID-II used in this study characterizes ~6% to 20% of the infants in this cohort as having severe mental and psychomotor delays, a much higher proportion than would be expected on the basis of the BSID-II normative population.[23] There are several possible reasons for this difference. First, the BSID-II normative sample may be less representative than the ECLS-B. The former was born in 1988 and stratified according to the 1988 update of the US Census by race/ethnicity, parent education, and geographic region. It lacked other information on socioeconomic status and clinical cases or those with established lower function. The lack of clinical cases in the sample could lead to inflated mean scores and truncated norms when the test is applied to a more general population.[40] In addition, the BSID-II normative population was born in 1988, whereas the ECLS-B population was born in 2001. The proportion of children from various ethnic and racial backgrounds, as well as regions of the country, changed from 1988 to 2001, factors that could influence the test performance.[41] Second, although the BSF-R is derived from the BSID-II, substantial methodologic work has been done for the scoring, Thus, these scores would reflect the experience of the ECLS-B population. Andreassen and Fletcher[42] have noted mental and psychomotor scale scores nearly a SD below normal at the 24-month assessment. The implications of these scores for future performance thus remain to be established. However, these test considerations do not eliminate concerns about the poorer performance of late preterm infants compared with their term peers.

Our study has several major strengths, including the large numbers of participants, a nationally representative sample, impressive follow-up after 2 years (92%), and wide socioeconomic and racial backgrounds of the participants. This database also is rich with multiple data sources.

Although preterm infants born at <28 weeks' completed gestation are at highest risk for severe adverse outcomes, their numbers are relatively small and stable. Late preterm births constitute 9% of all live US births and account for >70% of all preterm births.[1] Because of the large number of potentially affected infants, a small derangement in neurodevelopmental outcome could put a larger strain on the educational and medical systems. For example, it has been shown that late preterm infants accumulate more health care costs throughout the birth hospitalization,[43] are rehospitalized more frequently,[16] and have more costs during the first year of life.[43]

Late preterm infants merit closer observation and developmental follow-up. These data support reorganization of services with more resource allocation to late preterm infants. The effectiveness of early educational intervention in this group indicates that earlier developmental delay detection with family support and child services could ameliorate later school problems. Also, antenatal counseling regarding delivery before 37 weeks' completed gestation should include potential developmental issues.

APPENDIX 1. CONGENITAL ANOMALIES FROM BIRTH CERTIFICATE DATA

Congenital anomalies from birth certificate data were anencephaly, spina bifida, hydrocephalus, microcephalus, other central nervous system anomaly, heart malformations, other circulatory/respiratory disorder, rectal atresia/stenosis, tracheo-esophageal fistula, omphalocele, gastroschesis, other gastrointestinal anomalies, malformed genitalia, renal agenesis, other urogenital anomalies, cleft lip/pal ate, plydactyly, syndactyly, adactyly, club foot, diaphragmatic hernia, other musculoskeletal anomaly, Down syndrome, other chromosomal anomaly, and other diagnosis without category.

APPENDIX 2. LANGUAGES SPOKEN

Languages spoken were English, Arabic, Chinese, Filipino, French, German, Greek, Italian, Japanese, Korean, Polish, Portuguese, Spanish, Vietnamese, African, East European, Native American, Sign Language, Middle Eastern, West European, Indian Subcontinent, Southeast Asian, Pacific Island, cannot chose, and some other language (specify).

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To compare short- and long-term neurodevelopmental outcomes at 3 years of corrected age of preterm infants cared for by 24-hour in-house staff neonatologists and those cared for by staff neonatologists during daytime only. Tweet. This is a preview of a remote PDF: https://academic.oup.com/pch/article-pdf/22/5/249/23830017/pxx051.pdf. Lodha, A., Brown, N., Soraisham, A., Amin, H., Tang, S., Singhal, N.. Twenty-four-hour in-house neonatologist coverage and long-term neurodevelopmental outcomes of preterm infants, Paediatrics & Child Health, 2017, 249-254, DOI: 10.1093/pch/pxx051. Home. Â· Abo 1 Long-term outcomes for late and moderately preterm (LMPT) infants remain poorly characterised although they account for up to 84% of all preterm births. 2 Compared with term-born peers, increasing numbers of reports indicate that children born at late and/or moderately preterm gestations are at increased risk for health and developmental sequelae, 3â€“5 cognitive deficits, 6â€“8 learning difficulties 9â€“13 and behaviour problems 8 , 14 at school age; however, some studies have reported no differences compared with term-born controls.Â . Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. Pediatrics2011;127:e622â€“9. doi:10.1542/peds.2009-3598. OpenUrl Abstract/FREE Full Text Google Scholar. School outcomes of late preterm infants: special needs and challenges for infants born at 32 to 36 weeks gestation. J Pediatr (2008) 153:25â€“31. doi:10.1016/j.jpeds.2008.01.027. PubMed Abstract | CrossRef Full Text | Google Scholar. 12. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. Pediatrics (2011) 127:e622â€“9. doi:10.1542/peds.2009-3598. PubMed Abstract | CrossRef Full Text | Google Scholar. 13. Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, et al. Early term and late preterm birth are associated wi