ADHD and Learning Disabilities in Former Late Preterm Infants: A Population-Based Birth Cohort

WHAT'S KNOWN ON THIS SUBJECT: Previous studies have reported that former late preterm infants are at increased risk for future learning and behavioral problems; thus it has been suggested that their development be closely monitored.

WHAT THIS STUDY ADDS: This population-based study indicates that the risk for attention deficit/hyperactivity disorder and learning disabilities may not be higher in former late preterm infants, and therefore intensive neurodevelopmental follow-up may not be required for all late preterm infants.

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KEY WORDS

prematurity, neurodevelopmental outcome, late preterm, ADHD, learning disability, reading disorder, written language disorder, mathematics disorder

ABBREVIATIONS

ADHD—attention deficit/hyperactivity disorder

HR—hazard ratio

LD—learning disability

Dr Harris conceptualized and designed the study and drafted the initial manuscript; Drs Voigt, Barbaresi, Voge, Colby, Carey, and Katusic conceptualized and designed the study and reviewed and revised the manuscript; Ms Killian and Ms Weaver carried out the initial analyses and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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abstract

BACKGROUND AND OBJECTIVE: Previous studies suggest that former late preterm infants are at increased risk for learning and behavioral problems compared with term infants. These studies have primarily used referred clinical samples of children followed only until early school age. Our objective was to determine the cumulative incidence of attention deficit/hyperactivity disorder (ADHD) and learning disabilities (LD) in former late preterm versus term infants in a population-based birth cohort.

METHODS: Subjects included all children born 1976 to 1982 in Rochester, MN who remained in the community after 5 years. This study focused on the comparison of subjects in 2 subgroups, late preterm (34 to <37 weeks) and term (37 to <42 weeks). School and medical records were available to identify individuals who met research criteria for ADHD and LD in reading, written language, and math. The Kaplan-Meier method was used to estimate the cumulative incidence of each condition by 19 years of age. Cox models were fit to evaluate the association between gestational age group and condition, after adjusting for maternal education and perinatal complications.

RESULTS: We found no statistically significant differences in the cumulative incidence of ADHD or LD between the late preterm ($N = 256$) versus term ($N = 4419$) groups: ADHD (cumulative incidence by age 19 years, 7.7% vs 7.2%; $P = .84$); reading LD (14.2% vs 13.1%; $P = .57$); written language LD (13.5% vs 15.7%; $P = .36$), and math LD (16.1% vs 15.5%; $P = .89$).

CONCLUSIONS: These data from a population-based birth cohort indicate that former late preterm infants have similar rates of LD and ADHD as term infants. *Pediatrics* 2013;132:e630–e636

Until recently, most research concerning neurodevelopmental outcomes in high-risk neonates has focused on preterm infants born at less than 34 weeks gestational age. These infants have been found to have increased short-term medical morbidity and long-term neurodevelopmental morbidity compared with those born at term (37–41 weeks gestational age),^{1–4} with the bulk of the neurodevelopmental morbidity involving adverse school-age developmental outcomes, such as attention-deficit/hyperactivity disorder (ADHD) and learning disabilities (LD).^{5–7} It is therefore recommended that former preterm infants have their development closely monitored.⁸ Late preterm (34 0/7 to 36 6/7 weeks gestational age) infants are often healthy enough to be placed in the well-baby nursery and have previously been believed not to be at increased risk for neurodevelopmental morbidity. However, there has been a recent focus on outcomes of late preterm populations, as these infants have been reported to have increased short-term morbidity,^{9–11} as well as higher rates of health care utilization in the first year of life.¹² These findings, in turn, raise concern that former late preterm infants may also have increased long-term neurodevelopmental morbidity.^{9,13–16} Because of these concerns, it has been recommended that late preterm infants should be monitored closely before hospital discharge and have close follow-up on discharge.¹³

Despite this increased level of concern, recent studies have provided conflicting findings on the rates of neurodevelopmental, learning, and behavioral problems in former late preterm infants compared with former term infants.^{17–21} However, these studies have been limited primarily by the use of clinic-referred samples. Given this limitation and the importance of determining whether children born late preterm

require closer longitudinal developmental monitoring, our study was designed to test the hypothesis that former late preterm infants have increased rates of ADHD and LD compared with term infants using a population-based birth cohort.

METHODS

The capacity for population-based epidemiologic research is the result of a unique set of circumstances. First, Rochester is relatively isolated in southeastern Minnesota and, as a result, virtually all medical care is provided locally by Mayo Clinic and Olmsted Medical Center. Second, under a contractual research agreement between Independent School District 535 and Mayo Clinic, permission was obtained to access the richly documented cumulative school records of all birth-cohort members registered at any of the 41 public, parochial, or private schools, including those who had moved from the school district, were home-schooled, had died, or had graduated. Third, through the Rochester Epidemiology Project, all diagnoses and surgical procedures recorded at local affiliated medical facilities are indexed continuously for automated retrieval.^{22–25} Finally, under 2 additional research agreements, permission was obtained to access the resources of the only private community psychiatric practice in the area and the Reading Center/Dyslexia Institute of Minnesota, the only private tutoring agency in existence in the community during the school years of our birth-cohort members. In addition to the Rochester Epidemiology Project and school resources, birth certificate information (provided by the Minnesota Department of Health) was used to identify all 8548 children born in Rochester from 1976 to 1982 whose mothers were residents of the communities in Olmsted County comprising

Independent School District 535 (primarily the city of Rochester). Of the 8548 children, 5718 children still resided in Rochester at the age of 5 years, and of those, 1509 had been identified as having concerns for learning or behavioral problems in the school setting, including 19 with severe mental retardation. School and medical records were reviewed and information regarding all Individualized Education Program plans indicating special educational intervention and results of all individually administered psychometric tests for these children was abstracted. This information was placed in an established research folder for each potential LD/ADHD case. Children were identified as having LDs in reading, written language, and/or mathematics as previously described.^{26–29} Briefly, LDs were identified through the use of any 1 of 3 psychometric formulas, a discrepancy-based formula, a regression-based discrepancy formula, and a low achievement formula. The 2 discrepancy formulas diagnosed LDs in reading, written language, and mathematics based on defined discrepancies between individually-administered intelligence and academic achievement test scores. The low achievement formula is a more contemporary approach to identify children who have LDs, differing from the other 2 methods in that it is not dependent on a discrepancy between cognitive and academic achievement measures.^{26–29} Subjects were defined as research-identified ADHD incidence cases if their school and/or medical records included combinations of the following 3 categories of information: (1) met DSM-IV criteria for ADHD, (2) had positive ADHD questionnaire results, and (3) had clinical diagnoses of ADHD documented or made by a psychiatrist, psychologist, or pediatrician (Table 1). This method of retrospectively diagnosing ADHD has been validated in previous work by this group.^{28,30,31}

TABLE 1 Research Criteria for ADHD Case Status

ADHD cases	Meets DSM-IV Criteria for ADHD ^a	ADHD Questionnaire Results	Clinical Diagnoses of ADHD	Number of Subjects		
Research-identified	+	+	+	170	228	379
ADHD cases	+	+	—	41		
	+	—	+	17		
	—	+	+	122	151	
	—	—	+	29		

^a All DSM-IV criteria were met; only age criteria were not used.

The 5699 subjects were divided into early preterm (<34 weeks), late preterm (34 to <37 weeks), term (37 to <42 weeks), and post-term (≥42 weeks) groups based on gestational age available from birth certificates, and the analyses herein focus on the late preterm and term groups. Birth certificate characteristics were compared between the 2 groups by using the χ^2 test for categorical variables, the 2-sample *t* test for maternal age and birth weight, and the Wilcoxon rank sum test for Apgar scores. Separate analyses were performed for each of the 4 outcomes of interest: ADHD, reading LD, math LD, and written language LD. For each subject, duration of follow-up was calculated from the date of birth until the date the subject met the research criteria for a particular outcome. The duration of follow-up for subjects who did not meet the research criteria for a particular outcome was censored on the initial occurrence of migration from the community, death, last follow-up date, or at 19 years of age. The Kaplan-Meier method was used to estimate the cumulative incidence of each outcome. Cox proportional hazard models were fit to evaluate the association between gestational age category and each outcome, both with and without adjustment for potential confounders of maternal education category and presence of any perinatal complication.^{32,33} Hazard ratios (HR) and corresponding 95% confidence intervals were calculated from the regression coefficients and standard errors estimated in the Cox models

using the term gestational group as the referent group. All calculated *P* values were 2-sided and *P* values <0.05 were considered statistically significant. Statistical analysis was performed by using the SAS version 9.2 software package (SAS Institute, Inc.; Cary, NC).

RESULTS

Among the 5699 children who still resided within the community after age 5 years and who did not have severe intellectual disability, 81 infants (1.4%) were born <34 0/7 weeks' gestation, 256 infants (4.5%) were born between 34 0/7 and 36 6/7 weeks' gestation (the late preterm group), 4419 infants (77.5%) were born between 37 0/7 and 41 6/7 weeks' gestation (the term group), 728 infants (12.8%) were born at or >42 0/7 weeks' gestation, and 215 (3.8%) had undocumented gestational age. The birth characteristics of late preterm and term infants in this cohort are given in Table 2. Of note, the gestational ages are well distributed across late preterm and term categories. Apgar scores were statistically significant between groups but with no clinically significant difference.

Among the 256 late preterm subjects, 7 met the ADHD criteria only, 35 met the LD criteria only, and 10 met both; of the remaining 204 late preterm subjects, 155 (76.0%) were followed through completion of school or 19 years of age. Among the 4419 term gestational age subjects, 83 met the ADHD criteria only, 573 met the LD criteria only, and 189 met both; of the remaining 3574 term

subjects, 2610 (73.0%) were followed through completion of school or 19 years of age. The cumulative incidence of each outcome is graphically displayed in Fig 1, with each "step" denoting the age at which a subject met the outcome. Among the late preterm and term groups, the cumulative incidence of ADHD by 19 years of age was 7.7% and 7.2%, respectively. However, there was no significant difference in the cumulative incidence of ADHD in the late preterm group compared with the term group (*P* = .76 unadjusted; *P* = .84 adjusted for maternal education and perinatal complications; Table 3). The cumulative incidence of an LD in reading by 19 years of age was 14.2% and 13.1%, respectively, among the late preterm and term groups. However, this difference was not statistically significant (*P* = .62 unadjusted; *P* = .57 adjusted; Table 3). Likewise the cumulative incidence of an LD in written language or math, respectively, was not significantly different between the late preterm and term groups (Table 3).

DISCUSSION

It is well recognized that former preterm infants (those born at gestational age <34 weeks) are at significantly increased risk for a spectrum of neurodevelopmental, learning, and behavioral problems. These problems range from lower prevalence, higher morbidity conditions, such as cerebral palsy, intellectual disabilities, and autism spectrum disorders, to higher prevalence, lower morbidity conditions, such as developmental coordination disorders, speech disorders, LDs, ADHD, and other emotional and behavioral problems.^{8,34–36} It is presumed that this increased incidence of neurodevelopmental disability results from medical complications of prematurity that negatively impact on brain development. Late preterm infants

TABLE 2 Characteristics of Late Preterm and Term Infants in Cohort

Characteristic	Late Preterm (n = 256)	Term (n = 4419)	P value ^a
Gender, n (%)			
Female	129 (50.4)	2119 (48.0)	0.45
Race, n (%)			0.34
Caucasian	253 (98.8)	4305 (97.4)	
Non-Caucasian	3 (1.2)	111 (2.5)	
Not reported	0	3 (0.1)	
Maternal age (yr), mean (SD)	26.2 (4.9)	26.8 (4.7)	0.054
Maternal education, n (%)			0.30
<High school	20 (7.8)	244 (5.5)	
High school graduate	82 (32.0)	1351 (30.6)	
Some college	76 (29.7)	1337 (30.3)	
College graduate	53 (20.7)	1113 (25.2)	
Unknown	25 (9.8)	374 (8.5)	
Birth weight (g), mean (SD)	2751 (521)	3501 (486)	<0.001
Gestational age (wk), n (%)			—
34 to <35	52 (20.3)	— ^b	
35 to <36	85 (33.2)	—	
36 to <37	119 (46.5)	—	
37 to <38	—	221 (5.0)	
38 to <39	—	495 (11.2)	
39 to <40	—	913 (20.7)	
40 to <41	—	1938 (43.9)	
41 to <42	—	852 (19.3)	
NICU (available only for 1980–1982), n (%)			<0.001
Yes	12/132 (9.1)	5/2136 (0.2)	
No	74/132 (56.1)	1501/2136 (70.3)	
Unknown	46/132 (34.8)	630/2136 (29.5)	
1-min Apgar (available only for 1980–1982)			<0.001
Mean (SD)	7.3 (1.3)	8.0 (1.3)	
Median (25th–75th)	8 (6–8)	8 (8–9)	
Range	4–9	1–10	
5-min Apgar (available only for 1980–1982)			<0.001
Mean (SD)	8.7 (0.8)	9.2 (0.7)	
Median (25th–75th)	9 (8–9)	9 (9–10)	
Range	6–10	4–10	
Congenital defect, n (%)	1 (0.4%)	31 (0.7%)	0.56
Perinatal complications, n (%)	25 (9.8%)	86 (2.0%)	<0.001
Birth trauma	3	30	
Hypoxia/asphyxia	0	9	
Aspiration	0	21	
Abnormal fetal size or duration of gestation	19	17	
Hypoglycemia	1	0	
Nuchal chord	0	1	
Newborn respiratory distress	3	7	
Other and unspecified hemolytic anemia	0	1	
Isoimmunization	1	0	
GI disorder	0	1	
Metabolic acidosis	0	1	
Other/unspecified	0	2	

^a Birth certificate characteristics were compared between the 2 groups using the χ^2 test or Fisher's Exact test for categorical variables, the 2-sample *t* test for maternal age and birth weight, and the Wilcoxon rank sum test for Apgar scores.

^b not applicable.

generally do not experience the range of medical complications experienced by preterm infants, but these infants do have more short-term morbidity^{9–11} and increased rates of health care utilization in the first year of life¹² compared with former term infants.

Given their increased morbidity compared with term infants, it can be hypothesized that former late preterm infants are at increased risk for mild neurodevelopmental disability. However, in the current study, we found that late preterm infants are not at

increased risk for ADHD or LDs in reading, written language, or math compared with former term infants. Given the number of subjects in the late preterm and term gestational age groups and the number of subjects with each outcome, the study had 80% power to detect an HR between 1.64 (based on 622 events, ie the number of subjects with LDs in math) and 2.07 (based on 289 events, ie the number of subjects with ADHD).³⁷ Therefore the study was powered to detect moderate effect sizes if they existed. On the contrary, the estimated adjusted HRs were all in the range of 0.84 to 1.11.

Previous studies of neurodevelopmental outcomes of former late preterm infants have involved primarily clinic-referred samples and have reported conflicting results. Romeo et al found that late preterm infants have lower mental development index scores on the Bayley Scales of Infant Development at 12 and 18 months using uncorrected age, but by 5 years of age, they have IQs within the normal range.^{18,19} Similarly, Gurka et al reported that late preterm infants did not have a higher risk for cognitive, achievement, behavioral/emotional, or social disability as compared with term children at 15 years of age.¹⁷ These findings contrast with those of Talge et al, who reported lower IQs in former late preterm infants at the age of 6 years, independent of maternal age and socioeconomic factors.²⁰ Likewise Baron et al found that former late preterm infants had a higher rate of visuospatial and verbal fluency deficits as compared with term infants but no difference in attention/working memory, receptive or expressive language, nonverbal reasoning, or manual dexterity/coordination.³⁸ Furthermore, in this study, the late preterm group selected all required admission to the NICU, suggesting a group at increased risk for neurodevelopmental morbidity.

FIGURE 1
Cumulative incidence of ADHD and LD in late preterm and term infants.

TABLE 3 Incidence of ADHD and LD in Late Preterm and Term Infants

Outcome Category	Late Preterm ^a (n = 256)		Term ^a (n = 4419)		Unadjusted HR ^b (95% CI); P value	Adjusted ^c HR (95% CI); P value
	No. with Outcome	Cumulative Incidence of Outcome by Age 19 yr (%) Rate (95% CI)	No. with Outcome	Cumulative Incidence of Outcome by Age 19 yr (%) Rate (95% CI)		
ADHD	17	7.7 (4.1–11.2)	272	7.2 (6.4–8.0)	1.08 (0.66–1.76); P = .76	1.05 (0.64–1.73); 0.84
Reading LD	32	14.2 (9.5–18.7)	499	13.1 (12.0–14.1)	1.09 (0.77–1.56); P = .62	1.11 (0.77–1.59); 0.57
Written language LD	30	13.5 (8.9–17.9)	590	15.7 (14.5–16.9)	0.86 (0.59–1.24); P = .41	0.84 (0.58–1.22); 0.36
Math LD	36	16.1 (11.1–20.8)	586	15.5 (14.3–16.7)	1.05 (0.75–1.47); P = .78	1.03 (0.73–1.45); 0.89

CI, confidence interval.

^a Late preterm infants were defined as infants born between 34 0/7 and 36 6/7 weeks' gestation, and term infants were defined as infants born between 37 0/7 and 41 6/7 weeks' gestation.

^b HR, hazard ratio for late preterm versus term, estimated based on fitting Cox proportional hazards regression models.

^c Adjusted HRs based on Cox models that included maternal education category and presence/absence of any perinatal complications.

With these conflicting data, informed recommendations cannot be made as to whether former late preterm infants require developmental follow-up similar to that of former preterm infants. Given the limited number of specialists in developmental pediatrics and the long waiting lists at specialized developmental evaluation centers, it is

important to determine whether late preterm infants truly experience increased rates of neurodevelopmental disability and require specialized longitudinal developmental follow-up. To address this issue, our group has provided data from a longitudinal population-based birth cohort comparing outcomes of former late

preterm and term infants. We found that late preterm infants do not have an increased risk for ADHD or LD compared with former term infants. Thus, our data would not support recommendations for universal enrollment of former late preterm infants into high-risk neonatal developmental follow-up programs.

It is important to note that this study does not indicate that being born between 34 and 37 weeks' of gestation is risk-free, as it has been shown that late preterm infants are at increased risk for complications that may negatively impact on neurodevelopmental outcome, such as hyperbilirubinemia, infection, and dehydration.^{2,3} However, our findings predict that in a child born late preterm with no major morbidity, the risk for adverse neurodevelopmental outcomes is similar to that of a child born at term.

There are several potential limitations to this study. First, this is a retrospective cohort study, and we did not evaluate every child in the cohort. Thus, it is possible that we missed some children who may have had LD or ADHD. However, the comprehensive systematic multi-stage process and multiple independent, complementary sources of data used for all members of the birth cohort suggest that it is unlikely that we missed many cases of ADHD and LD.^{26,27,29–31} A second potential limitation is related to emigration from the entire birth cohort. However, detailed comparison of children who left the community before age 5 years and those who stayed strongly indicate that the 5718 children included in the study are representative of the entire birth cohort.²³ Third, Rochester is primarily a white, middle class community, which may limit

generalization to other populations.³⁹ These data provide much needed baseline information for comparison with similar studies,^{40,41} although they may not be as applicable to populations that are more diverse or of lower socioeconomic status. In addition, a homogenous population minimizes confounding effects of ethnicity and race. Fourth, given changes in definitions of ADHD subtypes over time and the retrospective nature of this study, we were unable to specifically identify the ADHD subtype for our patients, thus we are unable to identify whether former late preterm infants are at higher risk for any specific subtype. However, a recent study has shown that ADHD subtypes are inherently unstable and change within individuals over time.⁴² Finally, the members of the birth cohort were born at a time when they would not have received neonatal care consistent with contemporary practices. However, this would be expected to have increased the risk for adverse neurodevelopmental outcome as compared with the infants of today.

Future opportunities for research in this area will involve separating out those late preterm infants who required extended hospitalization and evaluating their developmental outcomes compared with those without extended hospitalization. Previous studies have

shown that late preterm infants with comorbid conditions may have a higher risk for poor neurodevelopmental outcomes, so it would be helpful to understand what specific risk factors may be associated with adverse neurodevelopmental outcome in the late preterm population. It would also be useful to conduct a similar study using a cohort of children who have received contemporary neonatal care.

CONCLUSIONS

Despite recent concerns to the contrary raised by studies using clinic-referred samples, this longitudinal population-based birth cohort study indicates that former late preterm infants are not at increased risk for ADHD or LDs in math, reading, or written language compared with former term infants. Given limited subspecialty-level resources in developmental medicine, our data indicate that former late preterm infants may not require specialized developmental monitoring for ADHD and LDs beyond the longitudinal developmental surveillance that is a component of their routine health maintenance within their medical homes.

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