Early Childhood Development of Late-Preterm Infants: A Systematic Review

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KEY WORDS

late-preterm infants, neonatal admission, early childhood, developmental outcomes, neurodevelopment, cognitive, motor, language development, health, growth

ABBREVIATIONS

NIC—neonatal intensive care
LPI—late-preterm infant
ISPOR—International Society for Pharmacoeconomics and Outcomes Research
CP—cerebral palsy
ICD—*International Classification of Diseases*
CI—confidence interval

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abstract

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CONTEXT: Late-preterm infants (LPIs) born at 34 to 36 weeks' gestation are increasingly regarded as being at risk for adverse developmental outcomes. To date, the early childhood development of LPIs has not been systematically considered.

OBJECTIVE: To undertake a broad examination of literature relating to early childhood development at the ages of 1 to 7 years of LPIs born at 34 to 36 weeks' gestation.

METHODS: We conducted a systematic review of early childhood outcomes in LPIs by using 9 electronic databases (January 1980 to March 2010). Bibliographies were reviewed. After examination of abstracts, ineligible studies were excluded. A specifically designed data-extraction form was used. The methodologic quality of included studies was assessed by using well-documented quality-appraisal guidelines.

RESULTS: Of 4581 studies, 10 (3 prospective and 7 retrospective cohort) were included. Studies were heterogeneous, and poorer outcomes were reported among LPIs in relation to neurodevelopmental disabilities, educational ability, early-intervention requirements, medical disabilities, and physical growth in comparison to term-born children. No identified study used healthy nonadmitted LPIs as a comparison group for admitted LPIs.

CONCLUSIONS: Evidence suggests that LPIs are at increased risk of adverse developmental outcomes and academic difficulties up to 7 years of age in comparison to term infants. An infant control group matched for gestational age has not been used; thus, for LPIs, the effect of neonatal admission on longer-term outcomes has not been fully explored. Systematic measurement of early childhood outcomes is lacking, and focused long-term follow-up studies are needed to investigate early childhood development after late-preterm birth. *Pediatrics* 2011;127:1111–1124

Infants born preterm and admitted to neonatal intensive care (NIC) have unique and significant developmental concerns throughout early childhood.[1–3] Much of the research to date has focused on those infants born extremely premature (23–28 weeks' gestation) or at a very low (<1500 g) or extremely low (<1000 g) birth weight. However, even those infants admitted for NIC for only short periods of time or for less invasive care may still be at risk of negative neurodevelopmental outcomes.[4,5] Over recent years, there has been an increasing focus on the early outcomes of the late-preterm subgroup of premature infants. Late-preterm infants (LPIs) are defined as those born between 34⁰⁄₇ and 36⁶⁄₇ weeks' gestation[6,7] and account for up to 75% of all preterm births[8]; there was a reported 25% increase in late preterm births from 1990 to 2006.[9] Although some of these infants are not admitted for NIC but, rather, nursed with their mothers or in the special care setting only, the proportion of all infants admitted for NIC attributable to this late-preterm group is significant. Data relating to admission rates are not widely available, but sources have suggested that LPIs account for 20% to 25% of all NIC admissions.[10,11]

LPIs have unique and particular concerns in the neonatal period, including an increased risk of mortality in comparison to term infants.[12–15] Furthermore, compared with term infants, LPIs are at significant risk for increased morbidity including hypothermia, hypoglycemia, hyperbilirubinemia, respiratory distress, poor feeding, and nutritional compromise in the early neonatal period.[16–19] Disturbance of infant brain development during the third stage of pregnancy has also been reported.[20,21] Thus, it is plausible to propose that long-term morbidity may indeed be a reality and that general developmental immaturity may persist in LPIs.

Currently, clinical practice in the early care of LPIs is varied, and the long-term effect of neonatal care on this population of infants remains largely unknown. There is a dearth of research relating to the early childhood development of LPIs,[22,23] and further research has been called for in this infant group.[6]

To date, the number of studies on and the quality of information relating to the various facets of development of LPIs throughout early childhood has not been systematically considered. In light of this fact, we undertook a systematic review of the literature to explore current understanding of this significant group of NIC graduates.

The objective of this review was to examine studies of early childhood cognitive, motor, speech, and language development, health, and growth at the ages of 1 to 7 years of LPIs born at 34 to 36 weeks' gestation. Particular attention was given to the gestational age of the comparison groups used (whether healthy term-born infants or healthy, nonadmitted LPIs).

METHODS

Search Strategy

A comprehensive literature search was undertaken to identify literature from January 1980 through March 2010. The search strategy involved searching electronic databases, inspecting bibliographies of retrieved articles, and hand-searching the published literature.

We searched the Medline (from 1980), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (from 1982), Embase (from 1980), PsycINFO (from 1987), and Maternity and Infant Care (from 1980) databases. Searches were also undertaken of LILACS (from 1982) and the Science Citation Index (from 1980) via the ISI Web of Knowledge. Alongside this, CDSR (Cochrane Database of Systematic Reviews [from 1992]), CENTRAL (Cochrane Controlled Trial Register [from 1992]), and National Health Service Centre for Reviews and Dissemination (including DARE [Database of Abstracts of Reviews of Effects]) were searched via Wiley. Ongoing and current research was identified through the UK Clinical Research Network and the National Research Register Archive.

The search was undertaken by using the following search terms: late preterm; near term; 34 to 36 weeks; moderately preterm; preterm; premature; neonatal intensive care; child development; long-term outcome; neurodevelopment; early childhood; cognitive; motor; speech; language; health; and growth and development. Appendix 1 highlights a single electronic search strategy.

Selection of Eligible Studies

A range of study methodologies were reviewed, including randomized controlled trials (including follow-up of randomized controlled trials), prospective and retrospective cohort studies (including longitudinal studies), case-control studies, and case-series studies. A number of articles were excluded after an initial review of titles and abstracts. After this process, a study-selection panel (Ms McGowan and Drs Alderdice, Holmes, and Johnston) agreed on the inclusion of articles. Studies were deemed ineligible for inclusion if any of the following applied: data-collection dates were not reported; data were collected before 1980; the number of study participants was too small (<30 participants); participants did not meet specified criteria for gestation (34–36 weeks only) and age (1–7 years); infants were recorded by birth weight only; or the research methodology was not ade-

quately described. Only studies written in or translated into English were included. Full-text analysis was conducted for included studies. Authors of the early literature pertaining to preterm infant outcomes used birth weight as a measure of prematurity, which poses a well-recognized source of bias (potential inclusion of term intrauterine growth-retarded infants as "premature" and the potential for large-for-gestational-age infants to not be defined as preterm). In light of this potential, studies that solely used birth weight as the defining criterion were not included in this review.

Data Extraction

Data were extracted by using a specifically designed data-extraction form that included the authors and year of publication; study design; number, gestation, and admission status of study and comparison-group infants; exclusion criteria; age at assessment; and primary objective. Available summary results were then tabulated. The original search methodology was designed to examine 5 specific domains of childhood development: cognitive development; motor development; speech and language development; health; and physical growth. There are larger bodies of research relating to specific developmental domains for other premature infant groups; however, this review of developmental outcomes of LPIs has identified broad outcomes assessed using widely varying scales and measures. Therefore, a descriptive methodology was chosen and a narrative synthesis was undertaken.

Quality Assessment

Included studies investigated developmental outcomes of infants after late-preterm birth. There is limited consensus on how to appraise the quality of such "outcome" studies.[24] However, Hayden et al[25] provided a useful quality-assessment framework for appraising evidence relating to prognosis or health outcomes. Their framework appraises 6 areas of potential bias: study participation; study attrition; prognostic factor measurement; confounding measurement and account; outcome measurement; and analysis. Alongside this framework, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) retrospective database checklist[26] was used to assess the quality of data sources in those studies that used retrospective databases. Appendix 2 shows the adapted quality-assessment framework used. Published abstracts were not assessed for quality.

RESULTS

Included Studies

Ten studies considered the early childhood development of LPIs (see Table 1). The study-selection process is outlined in Fig 1. The combined initial database searches retrieved 4581 potentially relevant studies, of which 4192 were excluded on the basis of the title and abstract (including 46, which had not been translated into English). After a more detailed review, 222 did not meet all of the inclusion criteria and were excluded. In total, 167 articles were considered, and another 150 of them were excluded for the following main reasons: the studies included all preterm infants with no specific subgroup analysis of the defined late-preterm gestational age group, or the studies considered only short-term (up to 1-year) outcomes or considered developmental outcomes beyond the scope of the review (eg, behavior and attention). In total, 17 studies were considered by a panel of 4 investigators, and 10 were deemed eligible for detailed discussion in this review. Our stringent exclusion criteria excluded a number of studies on the basis of the "late-preterm" gestational age definition used (ie, not within the 34–36 weeks' gestational age group). Excluded studies that presented data relating to the wider group of infants born between 32 and 36 weeks' gestation have been detailed for reference (see Table 2).[27–35] For example, Darlow et al[27] considered 2-year outcomes in an entire preterm cohort, including a subgroup of infants who were born at 33 to 36 weeks' gestation; although excluded on the basis of gestational age, this study provided useful comparative data for the wider group.

Description of Included Studies

Included studies are summarized in Table 1. Of 10 studies that detailed infants born late preterm, 4 studies focused solely on the late-preterm group,[36–39] and 6 studies included a subgroup of infants born at 34 to 36 weeks' gestation within the infant population considered.[40–45] Most studies were conducted within developed nations: the United States (6),[36–39,42,45] France (1),[40] England (1),[44] Norway (1),[41] and Brazil (1).[43] All of the included studies had been undertaken within the past 10 years. Seven of the studies had a retrospective cohort design,[36,37,39,41,42,44,45] and 3 were prospective observational studies.[38,40,43] Reporting of neonatal comorbidities was limited in all studies; however, the neonatal admission status of infants studied were as follows: 3 studies considered LPIs admitted for NIC[37,39,40]; 4 studies were of birth cohorts that included all LPIs[41–44]; 2 included LPIs defined as "healthy"[36] or "without neonatal compromise that would qualify them for developmental follow-up"[45]; and admission status of the infants in 1 study were not reported.[38]

The results detailed in the following paragraphs are based on a narrative synthesis of studies identified in the existing literature relating to developmental outcomes of LPIs within 5 key areas: neurodevelopmental disabilities; educa-

TABLE 1 Description of Included Studies

Authors and Location	Study Design	Age Assessed	Description of Infants			Primary Objective
			Study	Control	Exclusions	
Baron et al[39] (2009), United States	Retrospective cohort	3 y	34–36 wk GA ($n = 60$)[a]	Term ($n = 35$)	Infants with genetic disorders, sensorineural loss, brain tumors, non–English-speaking	To examine general cognition, attention/working memory, language, manual coordination/motor dexterity, visuomotor, visuospatial, and executive function in NICU-admitted late-preterm preschool-aged children compared with term infants
Gyamfi[38] (2009), United States[b]	Prospective observational	32–64 mo	34–36 wk GA ($n = 130$)	≥39 wk ($n = 157$)	Infants with congenital abnormalities	To evaluate morbidity at birth and indicators of developmental delay for infants born at 34–36 wk GA compared with infants of ≥39 wk GA by using the Ages & Stages Questionnaire
Kalia et al[37] (2009), United States	Retrospective cohort	12 ± 2 mo	34–36 wk GA ($n = 50$)[a]	Very preterm (<32 wk) ($n = 77$)	Infants with congenital abnormalities that required surgery	To determine LPIs' requirement for therapeutic services compared with that of very preterm infants
Morse et al[36] (2009), United States	Retrospective cohort	Up to 5 y	34–36 wk GA ($n = 7152$)	Term ($n = 152\,661$)	Infants with length of stay > 3 d, major congenital abnormalities, multiple births, or transfer to other hospital	To compare prekindergarten and kindergarten outcomes among healthy LPIs (34–36 wk GA) with those of healthy singleton term infants
Petrini et al[42] (2009), United States	Retrospective cohort	Up to 5.5 y	>30 wk GA ($n = 141\,321$); subgroup: 34–36 wk GA ($n = 8341$)	Term ($n = 128\,955$)	None recorded	To assess the risks of moderate prematurity for CP, developmental delay/mental retardation, and seizure disorders in early childhood
Santos et al[43] (2009), Brazil	Prospective cohort	12 and 24 mo	All births ($n = 3285$); subgroup: 34–36 wk GA ($n = 371$)	Term ($n = 2149$)	Infants with weight for age < 10th centile	To assess the effect of late-preterm birth on growth outcomes, assessed at 12 and 24 mo
Chyi et al[45] (2008), United States	Retrospective cohort	5 –11 y	32–36 wk GA ($n = 970$); subgroup: 34–36 wk GA ($n = 767$)	Term ($n = 13\,671$)	Infants with anoxia/respiratory distress syndrome at birth	Comparison of school outcomes between moderate (32–33 wk GA), late-preterm (34–36 wk GA), and term infants
Moster et al[41] (2008), Norway	Retrospective cohort	Up to 5 y (including up to 36 y)	All preterm children ($n = 903\,402$); subgroup: 34–36 wk GA ($n = 32\,945$)	Term ($n = 858\,406$)	Infants with congenital abnormalities (excluding congenital hip dislocation)	Follow-up of all preterm infants in order to document medical disabilities and outcomes reflecting social performance
Marret et al[40] (2007), France	Prospective population-based	5 y	30–34 wk GA ($n = 1461$); subgroup: 34 wk GA ($n = 228$)[a]	None	None recorded	To evaluate inpatient deaths and neonatal outcomes and also 5 year outcomes of infants born at 30–34 wk GA
Huddy et al[44] (2001), United Kingdom	Retrospective cohort (nested case-control)	7 y	32–35 wk GA ($n = 176$); subgroups: 34 wk ($n = 38$) and 35 wk ($n = 45$) GA	None	Infants with known abnormality of chromosome 16	To identify incidence of school and behavior problems at 7 y of infants born between 32 and 35 wk GA

GA indicates gestational age.

[a] Infants admitted for NIC.

[b] Abstract only.

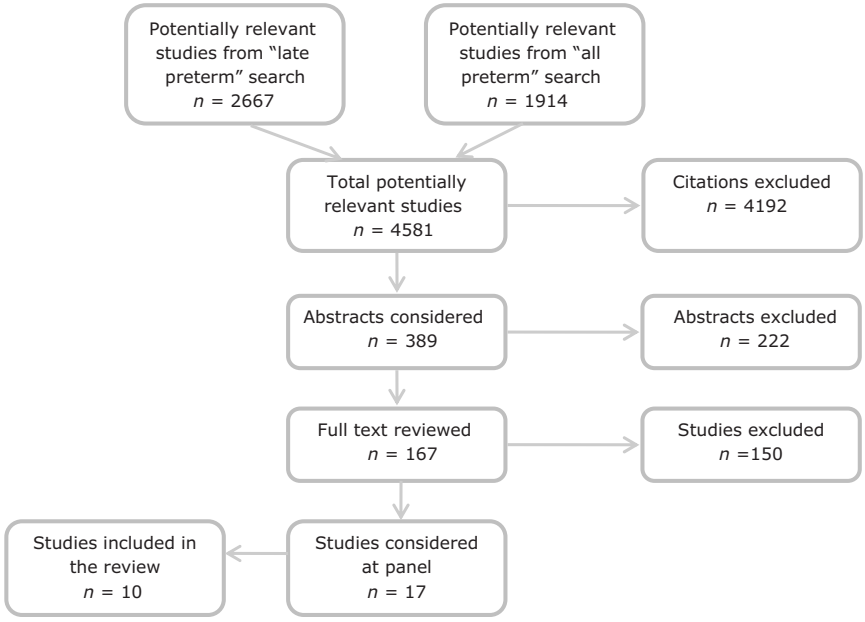

FIGURE 1
Flowchart of study selection.

tional ability; early-intervention requirement; medical disabilities; and physical growth. A summary of these results is shown in Table 3.

Early Childhood Outcomes

Neurodevelopmental Disabilities

Neurodevelopmental disabilities have been defined as "a group of heterogeneous conditions that share a disturbance in the acquisition of basic developmental skills in a chronologically appropriate manner."[46] This broad definition may include motor impairment such as cerebral palsy (CP), global developmental delay, intellectual disability, or developmental language impairments. Six studies considered neurodevelopmental disabilities in LPIs[38–42] (see Table 3). Three of these studies (2 prospective observational studies and 1 retrospective study) used standardized assessment tools.[38,39,40] Marret et al[40] examined infants born between 30 and 34 weeks' gestation and performed subgroup analysis of infants born at 34 weeks' gestation. Using the Kaufman-ABC assessment, they identified moderate cognitive impairment (Mental Processing Composite [MPC] scores of 70–84) in 18.6% of the infants born at 34 weeks' gestation and severe impairment (MPC scores of <70) in 5.3% of the infants. CP (according to the European CP Network definition) was noted in ~1% of those born at 34 weeks' gestation, which is 10-fold that in the general population. Gyamfi[38] assessed infants born late preterm at a mean age of 48 months (range: 32–64 months) by using the Ages & Stages Questionnaire to assess communication, gross motor, fine motor, problem-solving, and personal-social skills. This secondary analysis was undertaken with infants born after a randomized, placebo-controlled trial of 17 α-hydroxyprogesterone caproate, which was used to prevent preterm delivery. Contrary to other studies, the authors found similar Ages & Stages Questionnaire scores in both LPIs and term infants despite increased composite neonatal morbidity scores in LPIs. Baron et al[39] conducted a retrospective cohort study considering neuropsychological outcomes of LPIs when compared with term infants at 3 years of age using the Differential Ability Scales (2nd ed) and a range of neuropsychological tests; relative deficits were observed in comparison with term infants in 2 aspects: visuospatial ability and verbal fluency. Deficits in attention/working memory, language, nonverbal reasoning, and manual coordination/dexterity were not found between the groups.

Three further retrospective cohort studies used linked data sets to analyze neurodevelopmental disabilities, 2 according to *International Classification of Disease* (ICD) codes[41,42] and 1 according to database definitions[36] (see Table 3). Moster et al[41] reported data from a large cohort of premature infants in Norway, including data from a late-preterm subgroup, by using compulsory national registries to document medical disabilities and developmental outcomes. Significant increased risk ratios for CP (2.7 [95% confidence interval (CI): 2.2–3.3]) and developmental delay (1.6 [95% CI: 1.4–1.8]) were reported when compared with healthy term-born infants. Across this cohort of preterm infants, a continuous relationship between decreasing gestational age at birth and increased adverse outcomes without an obvious threshold was observed. Petrini et al[42] reported the rate of developmental delay among LPIs as 12.2 per 1000 children and an adjusted hazard ratio of 1.25 (95% CI: 1.01–1.54) compared with those of the healthy term-born reference group. The adjusted hazard ratio for CP in this study was 3.39 (95% CI: 2.54–4.52) compared with that of term infants. Morse et al[36] reported "developmental delay/disability" based on the requirement for early-intervention services up to 36 months; enrollment in such a program stipulates that an infant must attain a score of 1.5 SDs below the mean on a standardized developmental assessment. This requirement was 36% higher for healthy LPIs (stay of <72 hours) than for

TABLE 2 Studies That Included 32 to 36 Weeks Gestation Infants (Not Included)

Authors and Location	Study Type	Age at Assessment	Sample Size		Primary Objective	Outcome Measures
			Study	Control		
Darlow et al[27] (2009), New Zealand	Prospective cohort	2 y	All preterm ($n = 276$); subgroup: 33–36 wk GA ($n = 112$)[a]	Term ($n = 94$)	To assess neurodevelopmental outcome at 2 y for NICU admissions compared with controls and to trial a parent-reporting scheme	Mental and psychomotor development, health and behavior, pediatric examination, parental questionnaire based on Griffiths, Bayley II PDI, and Bayley II MDI
Kerstjens et al[28] (2007), Netherlands[b]	Longitudinal follow-up	43–51 mo	32–36 wk ($n = 719$) and <32 wk ($n = 163$) GA	Term ($n = 377$)	To investigate if LPIs have a higher rate of neurodevelopmental delay compared with children born at normal GA and how they compare with infants <32 wk GA	Ages & Stages Questionnaire: behavior; communication; gross and fine motor; problem-solving; personal-social development
Pietz et al[29] (2004), Germany	Prospective cohort	20 mo and 7 y	LBW ($n = 70$); subgroup: 32–36 wk GA ($n = 53$)	Term ($n = 50$)	To examine growth and neurodevelopmental outcome of a low-risk population of LBW children up to 7 y	Physical growth, language development, visual perception, visual-motor integration, fine motor skills, Griffiths Scales and a neuropsychological test battery
Hediger et al[30] (2002), United States	Cross-sectional	2–47 mo	All preterm ($n = 4621$); subgroup: 33–36 wk GA ($n = 329$)	None	To examine the effects of birth weight and gestation on motor and social development in a nationally representative cross-sectional sample of infants aged 2–47 mo	Motor and Social Development score as developed for the study
Hemgren and Persson[31] (2002), Sweden	Longitudinal follow-up	3 y	All preterm ($n = 246$); subgroup: 32–36 wk GA ($n = 81$)[a]	Term ($n = 72$)	To compare motor performance and behavior at 3 y of age of very preterm, moderately preterm, and term infants who required NIC and neonatally healthy term children	Combined assessment of motor performance and behavior (CAMPB tool) and motor perceptual development
Jennische and Sedin[32,33] (2001), Sweden	Longitudinal follow-up	6.5 y	All preterm ($n = 245$); subgroup: 32–36 wk GA ($n = 81$)[a]	Term ($n = 72$)	To evaluate and describe spontaneous speech at 6.5 y in children who required NIC, comparing differences between groups of those and neonatally healthy children (born 1986–1989)	Speech and language skills: 8 aspects of spontaneous speech assessed by conversation; also, linguistic skills assessed (3 motor functions/10 linguistic)
Jennische and Sedin[34,35] (1998/1999), Sweden	Longitudinal follow-up	6.5 y	All preterm ($n = 310$); subgroup: 32–36 wk GA ($n = 132$)[a]	Term ($n = 40$)	To evaluate and describe spontaneous speech at 6.5 y in children who required NIC, comparing differences between groups of those and neonatally healthy children (born 1980–1985)	Speech and language skills: 8 aspects of spontaneous speech assessed by conversation; also, linguistic skills assessed (3 motor functions/10 linguistic)

GA indicates gestational age; LBW, low birth weight; PDI, Psychomotor Development Index; MDI, Mental Development Index.
[a] Admitted for NIC.
[b] Abstract only.

healthy term-born infants. An increased relative risk of disability in prekindergarten at 3 and 4 years was reported (adjusted relative risk: 1.13 and 1.10, respectively).

Educational Ability

A significant proportion of current literature relates to educational ability, including infant groups between the ages of 3 and 7 years. Within all of the age groups, LPIs showed poorer academic performance and greater difficulty with school-related activities. Two key areas were considered:

TABLE 3 Summary of Results of Included Studies

Outcome Domain	Age Assessed	Outcome: Definition/Measurement	Results	95% CI	*P*
Neurodevelopmental disability					
Petrini et al[42] (2009)	Up to 5.5 y	Developmental delay/mental retardation: ICD-9 315–315.9; ICD-9 317–319	aHR: 1.25	1.01–1.54	—
		CP: ICD-9 343–343.9	aHR: 3.39	2.54–4.52	—
Moster et al[41] (2008)	Up to 5 y[a]	Mental retardation: ICD-9 317–319; ICD-10 F70–F79	aRR: 1.6	1.4–1.8	<.001[b]
		Cerebral palsy: ICD-9 342–344; ICD-10 G80–G83	aRR: 2.7	2.2–3.3	<.001[b]
Marret et al[40] (2007)	5 y	Cognition: Kaufman ABC (Mental Processing Composite)	aOR: 0.4[c]	0.2–1.2	.29
		Cerebral Palsy: European CP Network definition	aOR: 0.08[c]	0.01–0.60	<.001
Morse et al[36] (2009)	0–3 y	Developmental delay/disability: Early Intervention Program participation up to 36 mo (stipulates a score of 1.5 SDs below the mean on a standardized assessment)	aRR: 1.36	1.29–1.43	—
	3 and 4 y	Disability in prekindergarten (3 y)	aRR: 1.13	1.08–1.19	—
		Disability in prekindergarten (4 y): participation in a program for children with diagnosis of a learning problem as a result of physical, motor, sensory, or behavioral impairment	aRR: 1.10	1.05–1.14	—
Baron et al[39] (2009)	3 y	General cognition: DAS-II GCA	Students *t* test: 2.16	—	.033
		DAS-II GCA: spatial cluster	Students *t* test: 2.88	—	.005
		Motor/visuomotor: Beery VMI standard score	Students *t* test: 2.57	—	.012
		Verbal fluency	Students *t* test: 2.41	—	.018
		Animal fluency total, action-verb fluency total	Students *t* test: 2.27	—	.026
Educational ability					
Academic performance					
Chyi et al[45] (2008)	5–7 y	Child assessments: test items adapted from Peabody revised tests, Primary Test of Cognitive Skills, Tests of Early Reading and Early Mathematics Ability, and Woodcock Johnson Tests of Achievement-Revised			
	5 y	Below-average *T* score: Reading	aOR: 1.13	0.97–1.33	—
		Below-average *T* score: Math	aOR: 1.15	0.98–1.34	—
		Below-average *T* score: Reading	aOR: 1.24	1.06–1.45	—
	7 y	Below-average *T* score: Math	aOR: 1.22	1.04–1.43	—
		Teacher academic ratings: scaled evaluations of reading and math ability compared with classmates			
	5 y	Below-average academic rating: Reading	aOR: 1.30	1.07–1.59	—
		Below-average academic rating: Math	aOR: 1.25	1.05–1.49	—
	7 y	Below-average academic rating: Reading	aOR: 1.28	1.06–1.54	—
		Below-average academic rating: Math	aOR: 1.19	0.99–1.43	—
Morse et al[36] (2009)	4 y	Not ready to start school: 16-point checklist undertaken by a teacher to assess preacademic skills	aRR: 1.04	1.00–1.09	—
	5 y	Retention in kindergarten: disciplinary code indicating temporary removal of a student from school, not exceeding 10 d	aRR: 1.11	1.07–1.15	—
		Suspension in kindergarten: student is retained in the same grade at the end of the school year for failing to meet required performance levels	aRR: 1.16	1.10–1.29	—
Special education requirement					
Chyi et al[45] (2008)	5 y	Individualized Education Program requirement	aOR: 1.38	1.00–1.89	—
		Special education enrollment	aOR: 2.13	1.56–2.90	—
	7 y	Individualized Education Program requirement	aOR: 1.44	1.08–1.91	—
		Special education enrollment	aOR: 1.44	1.04–1.98	—
Morse et al[36] (2009)	5 y	Exceptional student status: 16-point checklist 6 wk into the school year undertaken by a teacher to assess preacademic skills	aRR: 1.10	1.07–1.13	—

academic ability and special education requirement.

Three studies considered academic ability by using direct infant assessments and teacher ratings.[36,44,45] An early prospective cohort study by Huddy et al[44] encompassed infants born between 32 and 35 weeks' gestation and included 2 subgroups of infants born between 34 and 35 weeks' gestation. No comparison group was included. School problems in children

TABLE 3 Continued

Outcome Domain	Age Assessed	Outcome: Definition/Measurement	Results	95% CI	*P*
Early intervention					
Kalia et al[37] (2009)	12 ± 2 mo	Early intervention (enrollment in any of the following: physical therapy, occupational therapy, speech therapy, or special education)	aOR: 0.90[d]	0.20–4.00	—
		Physical therapy	aOR: 0.40	0.10–2.30	—
		Occupational therapy	aOR: 0.40	0.10–2.80	—
		Speech therapy	aOR: 0.60	0.10–4.80	—
		Special education	aOR: 0.50	0.00–6.80	—
Medical disability					
Marret et al[40] (2007)	5 y	Visual deficiency: visual acuity of <3/10 in 1 or both eyes	Percentage: 0.8	—	.31
		Hearing deficiency: loss of >70 dB/hearing aid use in 1 or both ears	Percentage: 1.5	—	.23
Moster et al[41] (2008)	5 y[a]	Other major disability including epilepsy (ICD-9 345 and ICD-10 G40–G41), blindness/low vision (ICD-9 369 and ICD-10 H54), hearing loss (ICD-9 389 and ICD-10 H90 and H91)	aRR: 1.50	1.20–1.80	<.001[b]
Petrini et al[42] (2009)	Up to 5 y	Seizure disorders: ICD-9 345.0–345.9; 780.39	aHR: 1.27	0.69–2.32	—
Growth					
Santos et al[43] (2009)	1 and 2 y	Growth indicators: *z* scores for weight for age (underweight), length for age (stunting), and weight for length (wasting)			
	1 y	Underweight	aOR: 2.57	1.27–5.23	.009
		Stunting	aOR: 2.35	1.49–3.70	<.001
		Wasting	aOR: 3.98	1.07–14.85	.04
	2 y	Underweight	aOR: 3.36	1.56–7.23	.002
		Stunting	aOR: 2.30	1.40–3.77	.001
		Wasting	aOR: 1.87	0.50–7.01	.351

Note that data from Gyamfi et al[38] (2009) and Huddy et al[44] (2001) are not included because of the absence of summary statistics. aHR indicates adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; GCA, General Conceptual Ability; VMI, Visual-Motor Integration.

[a] Study includes data up to 36 years.

[b] *P* value for trend.

[c] Compared with infants born at 30 weeks' gestation.

[d] Adjusted for comorbidities of prematurity with a reference group of infants born at <32 weeks' gestation.

were defined in 1 aspect of this study as those who had a score of >3 in a skill area using a 5-point scale of difficulty in completing tasks, as assessed by teachers. Children born between 34 and 35 weeks' gestation showed poor performance (with a score of >3) in writing/composition (34% and 33%, respectively), fine motor skills (29% and 33%), mathematics (29% and 31%), speaking/listening (18%), reading (21% and 22%), and physical education (8% and 9%). Morse et al[36] evaluated 4 school outcomes between healthy late-preterm and term infants: not ready to start school; retention in kindergarten; suspension in kindergarten; and special educational status (see Table 3). They reported statistically significant differences between LPIs and term infants in 3 of the outcomes considered, and results of additional analysis indicated that infants born at 34 weeks' gestation were more likely to be "not ready for school" than infants born at 35 or 36 weeks' gestation. Chyi et al[45] compared learning difficulties between groups of infants born at 32 to 33 and 34 to 36 weeks' gestation and term infants from kindergarten through to fifth grade (only data for children up to 7 years old are reported here) by using the Early Childhood Longitudinal Study-Kindergarten Cohort data set. An adapted assessment including Peabody, Woodcock, Kaufman, and primary tests of cognition, reading, and math ability revealed that LPIs had lower reading and math scores than term infants in kindergarten and first grade ($P < .05$). The risk of LPIs obtaining below-average academic rating scores remained elevated at first grade for reading and math in comparison to that of term infants.

The second reported measure of school performance is that of a special education requirement. Chyi et al[45] considered the presence of an Individualized Education Program or special education services as an indicator of learning difficulties. They concluded that, although the results were nonsignificant, more LPIs were enrolled in the Individualized Education Program than term infants both in kindergarten (8.04% vs 6.18%) and first grade (10.54% vs 7.48%); special education services enrollment was also greater

in kindergarten and first grade. Huddy et al[44] also noted that support from a "nonteaching" assistant at school was required by 24% of children who were born at 34 to 35 weeks' gestation; however, no comparison group was available. Furthermore, Morse et al[36] reported that LPIs were at increased risk of being assigned "exceptional student status" in comparison to term infants.

Early-Intervention Requirement

In a retrospective cohort study, Kalia et al[37] considered the requirement for early intervention (therapeutic services) by using a unique comparison group of very preterm infants (<32 weeks' gestation). Overall, the percentage uptake of early-intervention services was lower for LPIs when compared with those in the very preterm group. However, after controlling for neonatal comorbidities, including 5-minute Apgar scores, receipt of caffeine for apnea of prematurity, bronchopulmonary dysplasia, respiratory distress syndrome, and length of stay, in the very preterm infant group, there was no significant difference in enrollment in early-intervention services between the late-preterm and very preterm infants.

Medical Disabilities

Medical disabilities were not reported extensively within the late-preterm outcomes literature. However, the authors of 3 studies did report sensory impairment: visual impairment/blindness; hearing impairment/deafness; and seizure disorders.[40–42] Moster et al[41] recorded medical disability as the occurrence of a single ICD code (see Table 3) denoting any of the above-listed conditions and reported a rate of 0.3% in the 34- to 36-weeks' gestation group (adjusted relative risk: 1.5 [95% CI: 1.2–1.8]; $P < .001$) compared with term infants. This analysis excluded ~2.3% of late-preterm children who died before their fifth birthday. Visual (0.8%) and hearing (1.5%) impairment were also reported by Marret et al[40] and did not vary significantly from infants born at 30 to 33 weeks. Seizure disorders were reported by Petrini et al[42] with an adjusted hazard ratio of 1.27 (95% CI: 0.69–2.32) at 34 to 36 weeks compared with term infants. The general health status of LPIs beyond 1 year was not identified in any of the studies.

Physical Growth

Physical growth was considered a primary outcome in 1 population-based cohort of all births during 1 year from a middle-income country: the 2004 Pelotas Cohort (southern Brazil).[43] The authors reported rates of underweight, stunting, and wasting in a late-preterm subgroup of all preterm infants in comparison with term infants. LPIs were at increased risk of underweight and stunting at 12 and 24 months of age (adjusted OR: 3.36 [95% CI: 1.56]7.23] and 2.30 [95% CI: 1.40–3.77], respectively). Wasting was significantly different between the groups in the first year of life; only a small number of the infants were reported to have wasting at both 12 and 24 months. Gyamfi[38] also considered height and weight in LPIs in comparison with term infants at 48 months (range: 32–64 months) as a secondary outcome, and no significant difference between the 2 groups was reported.

Quality Assessment of Studies

Our quality assessment of studies using the ISPOR Retrospective Database Checklist[26] and guidelines for assessing quality in prognostic studies[25] is summarized in Table 4 and identified the following methodologic concerns. First, regarding study design and sample size, 5 retrospective cohort studies used existing data sets,[36,37,41,42,45] and only 1 of these studies fully outlined the quality assessment of the original data sources.[42] In addition, outcomes were defined on the basis of existing data rather than being purposefully selected as measures of infant development. Although loss to follow-up and missing data are inherent concerns in longitudinal cohort studies, 8 of 9 of the included studies did account to some degree for missing data or loss to follow-up.[36,37,40–45] Prospective and observational studies also tended to be limited by small sample sizes, and 2 studies lacked a comparison group.[40,44] Second, the use of nonstandardized outcome measurements such as neurologic examination, caregiver report, and early-intervention uptake increases the risk of measurement bias and makes comparability between studies difficult. Indeed, although standardized ICD codes were used for defined outcomes in 2 studies,[41,42] the authors highlighted the subjective nature of diagnosis and the potential for missing data. Finally, although adjustment for previously reported potentially confounding perinatal, maternal, and socioeconomic factors was noted across the included studies, neonatal and childhood comorbidities were not considered at length.

DISCUSSION

LPIs constitute an epidemiologically significant group of preterm infants and NIC graduates, yet the extent of adverse developmental outcomes in their early years remains largely underresearched. In this comprehensive review of the literature, 10 studies relating to early childhood development up to the age of 7 years were identified. Only 4 of these studies focused solely on LPIs, which highlights a paucity of focused research on this particular group of infants. However, the authors of all but 1 of the included studies reported similar trends of adverse early childhood developmental outcomes in the late-preterm group as a whole.

TABLE 4 Summary of Quality Assessment

Potential Bias and Domains Addressed	Baron et al[39]	Kalia et al[37]	Morse et al[36]	Petrini et al[42]	Moster et al[41]	Santos et al[43]	Chyi et al[45]	Marret et al[40]	Huddy et al[44]
Data source[a]									
1. Rationale for using data source defined	NR	~	~	+	~	NR	~	NR	NR
2. Reliability/validity described									
3. Linkages between sources detailed									
Study participation[b]									
4. Source population clearly defined	−	+	+	~	+	+	+	+	+
5. Study population described									
6. Study population represents source population or population of interest									
Study attrition[b]									
7. Completeness of follow-up described	−	~	~	+	~	+	+	~	~
8. Completeness of follow-up adequate									
Prognostic factor measurement[b]									
9. Prognostic factors defined	~	~	+	+	+	+	+	+	+
10. Prognostic factors measured appropriately									
Outcome measurement[b]									
11. Outcome defined	+	+	~	~	~	+	~	~	~
12. Outcome measured appropriately									
Confounding measurement and account[b]									
13. Confounders defined and measured	~	~	+	~	+	+	~	+	−
14. Confounding accounted for									
Analysis[b]									
15. Analysis described	~	+	+	+	+	~	+	+	−
16. Analysis appropriate									
17. Analysis provides sufficient presentation of data									

Adapted from the ISPOR retrospective database checklist (Motheral et al[26]) and guidelines for assessing quality in prognostic studies (Hayden et al[25]). + indicates yes; −, no; ~, partly; NR, not relevant.

[a] ISPOR checklist for retrospective database studies.

[b] Guidelines for assessing quality in prognostic studies.

LPIs were at increased risk of neurodevelopmental disabilities up to 7 years, poorer performance on standardized testing, and increased diagnoses of developmental delay in comparison to term infants. Significant development of the infant brain takes place during the last 4 to 6 weeks of pregnancy; there is a fourfold increase in cortical volume during the third trimester[20] and an accrual of 35% of brain weight during the last 6 weeks of gestation.[21] Preterm delivery as an interruption of these processes may contribute to adverse neurodevelopmental outcomes experienced by LPIs. In addition, complex medical problems in the early neonatal period may further compound the negative effect of early birth and associated neonatal admission. It is interesting that 1 included study, which reported a requirement for early intervention, noted a similar uptake of services between LPIs and very preterm infants (<32 weeks) after adjustment for neonatal comorbidities,[37] which further highlights the influence of morbidity experienced in the early neonatal period on later childhood development. Despite this observation, only 3 studies specifically reported the NIC admission status of infants. It is of particular note that the neonatal admission status of infants and comorbidities experienced within the late-preterm group and their relationship to ensuing developmental outcomes have not been well addressed. At the time of this review, no identified study had used healthy nonadmitted LPIs as a comparison group for complicated, admitted LPIs.

A consistent observation throughout the review is that LPIs have more favorable outcomes than very preterm infants but less favorable outcomes than term infants. There seems to be a continuous relationship between decreasing gestational age and increasing risk of adverse outcomes such as neurodevelopmental disabilities and academic performance. This "scale" of prematurity identifies an important aspect of LPI development with an emphasis not on severe disability but potentially more and multiple subtle developmental concerns. Winders-Davis[47] highlighted the complexity of identifying these milder disabilities and the adverse effect they have on global development and noted that if undetected by school age, these milder disabilities may have a negative cumulative effect on development. This effect was apparent in those studies relating to school performance and academic ability, in which LPIs performed less well than their term-born peers and required more special education or academic support.[36,45] Developmental follow-up of infants born at late-preterm gesta-

tions during preschool years may help identify and alleviate subtle difficulties and potential learning problems encountered at school age.[48] As the number of LPIs delivered each year continues to rise,[9] the requirement for early intervention and early educational input becomes increasingly significant both in clinical follow-up and educational policy and planning.

The overarching aim of this review was to gain an understanding of early childhood development in the LPI population. Although LPIs were previously considered similar to term infants, emerging evidence suggests that significant adverse developmental outcomes do exist among LPIs, which further indicates that longer-term outcomes of prematurity remain a concern even for those infants born at the more optimistic late-preterm stages of pregnancy.

CONCLUSIONS

In recent years, LPIs have increasingly been regarded as "at-risk" rather than "low-risk" infants. They are born developmentally immature and with increased neonatal health concerns compared with term infants. The impact of early neonatal care on longer-term outcomes has not yet been well considered; comorbidities, neonatal admission, and surrounding factors have not been fully explored. Systematic measurement of early childhood outcomes, such as those already considered for extremely preterm infant groups, is lacking in the late-preterm population. There is a real need for focused long-term follow-up studies to investigate early childhood development after late-preterm birth.

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APPENDIX 1 Single Electronic Search Strategy for Ovid Medline: Key-Word Search for Late-Preterm Infants and Single Specified Outcome (Motor Development)

1. (late ADJ[a] preterm ADJ infant$1[b]). mp[c]. [mp=ti, ab, tx, ct, sh, de]
2. (near ADJ term ADJ infant$1).mp.
3. (late ADJ preterm ADJ birth).mp.
4. (near ADJ term ADJ birth).mp.
5. (moderate$ ADJ preterm ADJ infant$1).mp.
6. (moderate$ ADJ prematur[a] ADJ infant$1).mp.
7. (moderate$ ADJ preterm ADJ birth$1).mp.
8. (moderate$ ADJ prematur[a] ADJ birth).mp.
9. (low ADJ risk ADJ infant$1).mp.
10. (low ADJ risk ADJ birth).mp.
11. neonatal ADJ intensive ADJ care ADJ admission
12. neonatal ADJ admission
13. neonatal ADJ2 admi$
14. special ADJ care
15. high ADJ dependency ADJ care
16. or/1–15
17. motor.mp.
18. (motor ADJ development).mp.
19. (motor ADJ function).mp.
20. development.mp.
21. neuromotor.mp.
22. locomotor.mp.
23. movement.mp.
24. outcome$1.mp.
25. or/17–24
26. 16 and 23

[a] ADJ: the adjacent operator retrieves records with search terms next to each other.

[b] $n: limited truncation specifies a maximum number of characters that may follow the root word or phrase.

[c] [mp=ti, ab, tx, ct, sh, de] includes searching of the title, abstract, full text, controlled term, subject heading, and descriptors.

APPENDIX 2 Quality-Assessment Guidelines

Potential Bias	Items to Be Considered for Assessment
Data source: there is sufficient detail on the data source to limit selection and measurement bias (yes, partly, no, or unsure)[a]	Relevance: have the data attributes been described in sufficient detail for decision-makers to determine whether there was a good rationale for using the data source, the data source's overall generalizability, and how the findings can be interpreted in the context of their own organization? Reliability and validity: have the reliability and validity of the data been described, including any data quality checks and data-cleaning procedures? Linkages: have the necessary linkages among data sources and/or different care sites been carried out appropriately taking into account differences in coding and reporting across sources? Eligibility: have the authors described the type of data used to determine member eligibility?
Study participation: the study sample represents the population of interest on key characteristics sufficient to limit potential bias to the results (yes, partly, no, or unsure)[b]	The source population or population of interest is adequately described for key characteristics. The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used [eg, referral patterns in health care]), period of recruitment, and place of recruitment (setting and geographic location). Inclusion and exclusion criteria are adequately described (eg, including explicit diagnostic criteria or "zero-time" description). There is adequate participation in the study by eligible subjects.
Study attrition: loss to follow-up (from sample to study population) is not associated with key characteristics (ie, the study data adequately represent the sample), sufficient to limit potential bias (yes, partly, no, or unsure)[b]	Response rate (ie, proportion of study sample completing the study and providing outcome data) is adequate. Attempts to collect information on participants who dropped out of the study are described. Reasons for loss to follow-up are provided. Participants lost to follow-up are adequately described for key characteristics. There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Prognostic factor measurement: the prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (yes, partly, no, or unsure)[b]	A clear definition or description of the prognostic factor measured is provided (eg, including dose, level, duration of exposure, and clear specification of the method of measurement). Continuous variables are reported or appropriate (ie, not data-dependent), and cut points are used. An adequate proportion of the study sample has complete data for prognostic factors. The method and setting of measurement are the same for all study participants. Appropriate methods are used if imputation is used for missing prognostic factor data.
Outcome measurement: the outcome of interest is adequately measured in study participants to sufficiently limit potential (yes, partly, no, or unsure)[b]	A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct. The outcome measure and method used are adequately valid and reliable to limit misclassification bias (eg, may include relevant outside sources of information on measurement properties, and may include characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).
Confounding measurement and account: important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (yes, partly, no, or unsure)[b]	All important confounders, including treatments (key variables in conceptual model), are measured. Clear definitions of the important confounders measured are provided (eg, including dose, level, and duration of exposures). Measurement of all important confounders is adequately valid and reliable (eg, may include relevant outside sources of information on measurement properties, and may include characteristics, such as blind measurement and limited reliance on recall).
Analysis: the statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (partly, no, or unsure)[b]	There is sufficient presentation of data to assess the adequacy of the analysis. The strategy for model-building (ie, inclusion of variables) is appropriate and is based on a conceptual framework or model. The selected model is adequate for the design of the study. There is no selective reporting of results.

Adapted from the ISPOR Retrospective Database Checklist (Motheral et al[26]) and guidelines for assessing quality in prognostic studies (Hayden et al[25]).

[a] ISPOR checklist for retrospective database studies.

[b] Guidelines for Assessing Quality in Prognostic Studies.

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