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REVIEW

Long-term neurodevelopmental outcomes of infants born late preterm: a systematic review

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Purpose: Late preterm (LPT) births constitute a large proportion of the preterm births in the USA. Over the last few decades, there has been an increase in research focusing on the neurodevelopment of infants born LPT. The purpose of this research was to systematically review the long-term neurodevelopmental outcomes in LPT infants.
Materials and methods: We identified studies by using PubMed, ERIC, CINAHL, and PsycINFO databases. The references of included papers were reviewed for additional papers that met the inclusion criteria. Included papers compared motor, cognitive, language development, or academic performance outcomes between individuals born LPT and a term control group assessed between 12 months and 18 years of age. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards for systematic reviews were utilized including a two-step, two-investigator review process.
Results: Of the 4,720 studies found in the initial search, 20 studies met the inclusion criteria. Approximately 75% of the 16 studies that assessed cognitive outcomes reported cognitive delay in the LPT group when compared to their full-term counterparts. More than 50% of the seven studies that assessed motor outcomes suggested a delay in motor development in the LPT group in comparison to full-term. Fewer papers assessed academic performance and language in children born LPT; however, the majority identified borderline differences when LPT infants were compared to those born full-term.
Conclusion: Evidence suggests that infants born LPT are at an increased risk of neurodevelopmental delay between 1 and 18 years of life when compared to those born at term. The delay is most evident in the cognitive domain of neurodevelopment. Children born LPT are also at a risk of delayed language development, motor development, and lower academic performance. The rate of developmental delay is reduced somewhat when controlling for social factors; however, group differences persist.
Keywords: late preterm infants, developmental outcomes, motor development, cognitive development, language development and school performance

Introduction

A preterm infant, as defined by the American Academy of Pediatrics and the American College of Obstetricians, is an infant born before the end of the 37th week (259th day) of pregnancy, counting from the first day of the last menstrual period.[1] Infants born prior to 37 weeks of gestation are often physiologically immature and show restricted compensatory responses to the extrauterine environment when compared to infants born full term.[1] Until 2005, infants born between 34 and 36 weeks of gestation were frequently referred to as "near term", giving a false impression of being similar to term infants in their risk of developing medical complications.[2] Near term infants were

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treated by parents, caregivers, and health care providers as being developmentally equivalent to their full term counterparts. The lack of understanding regarding developmental biology was reflected in an increased rate of elective delivery during the last month of gestation.[3] The National Institute of Child Health and Human Development (NICHD) held a workshop in which invited experts discussed the rising rate of preterm births, 70% of which was attributed to births between 34–37 weeks of gestation and the accompanying medical concerns.[2,4] Following the Optimizing Care and Outcome of the Near-Term Pregnancy and the Near-Term Newborn Infant workshop,[1] a recommendation was made to change the term near term to "late preterm" (LPT) in order to underscore the importance of regular screening of neurodevelopmental delay in this population. LPT infants are now defined as infants born between 34 weeks 0 days and 36 weeks 6 days of gestation.

LPT birth on its own is identified as an independent risk factor for neonatal mortality and morbidity.[5] The mortality rate for infants born LPT is three fold higher than for those infants born at term.[4] Infants born LPT are at an increased risk of respiratory distress, bronchopulmonary dysplasia, apnea, patent ductus arteriosus, feeding problems leading to compromised nutrition, hypoglycemia, hyperbilirubinemia, and hypothermia.[6] LPT births are thought to have a major impact on the cost of health care and are identified as an important factor contributing to an increase in the rate of hospital readmissions, thus making them a matter of major health concern.[4]

The nervous system in an embryo matures a great deal during the third trimester of pregnancy, including a three- to fourfold increase in brain volume in the form of increase in gyri, sulci, synapses, dendrites, axons, oligodendrocytes, astrocytes, and microglia.[1] Infants born preterm have an immature central nervous system with fewer gyri and sulci and a brain size of approximately two-thirds to the size of term infant's brain.[3] This central nervous system immaturity places infants born LPT at risk of neurodevelopmental disabilities.

Over the last decade, many researchers have broadened their focus from determining the neurodevelopmental outcomes in extremely premature infants (23–28 weeks of gestation) to include outcomes of LPT infants. A 2011 systematic review of early childhood development outcomes of LPT infants identified ten papers published prior to March 2010.[7] Their findings suggests that children born LPT are at an increased risk of adverse neurodevelopmental outcomes when compared to their full term counterparts between 1 and 7 years of age. While this review paper provided current evidence at its time, the purpose of our systematic review is to systematically review the long-term neurodevelopmental outcomes of infants born LPT, including the vast amount of new evidence published since the McGowan review in 2011[7] and including literature addressing developmental outcomes in older children who were born LPT.

Materials and methods

Search strategy

We identified studies by using MEDLINE®, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Education Resource Information System (ERIC), and PsycINFO databases, and the reference lists of the included papers. We identified literature published from January 1990 to January 2015. The comprehensive search was undertaken using following search terms: Late preterm infants; developmental outcomes; motor development; cognitive development; language development and school performance. The Supplementary materials section provides a detailed list of search terms and Medical Subject Headings (MeSH) used for each database.

Selection of eligible studies

The preferred reporting Items for systematic reviews and meta-analyses (PRISMA) standards for systematic reviews were utilized, including a two-step, two-investigator review process. Included studies compared motor, cognitive, language development, or school/academic performance between individuals born LPT and a term control group assessed between 12 months and 18 years of age. Studies were excluded if they met any of the following criteria: not published in English, no LPT infants group, studies not reporting a developmental outcome or not including a developmental assessment between 12 months of age and 18 years of age, and studies not comparing an LPT group with a full term control group. Studies that combined moderate/LPT subjects in one group were included if they examined a large cohort and the mean gestational age fell into the LPT range. During the screening step, the titles and abstracts of all papers identified in the search were reviewed and excluded only if they clearly did not meet the inclusion criteria. During the eligibility determination step, two reviewers used the inclusion and exclusion criteria to review the full text of all papers not eliminated in the screening step. Papers that met the inclusion criteria were included, and their references were reviewed to determine if any relevant papers were missed in the search.

Data extraction

For this study, we designed data extraction forms that included information regarding author name and location, objective/hypothesis, study sample and sample size, type of study, developmental domain assessed, and age of assessment, along with results of each domain assessed. These data were compiled for review and interpretation. Any disagreement between reviewers was resolved with discussion. A meta-analysis was not performed, given the wide variety of ages and outcomes included in the review.

Study quality assessment

The methodologic quality of the included studies was assessed by using the Critical Appraisal Skills Program (CASP) checklist for cohort studies. Only section A from the checklist was used for screening the quality of the study design (not analysis) of the studies included. Section A of the CASP checklist consists of eight questions, answers to which can range from "yes", "no", and "not clear", where "yes" is given a value of 1 and "no" and "not clear" are given a value of 0. For this study, the research team considered cohorts to be recruited in an acceptable way if they included all infants born in a hospital or a random selection of infants, and studies appeared to have limited selection bias. LPT birth needed to be documented in the medical records vs parental recall to be scored as having minimal bias. Outcome measures needed to be completed by reliable and blinded assessors to be considered unbiased. Subject follow-up of ≥30% was considered acceptable. Using these criteria and the CASP guidelines, each study received a score in the range of 0–8 points.[8]

Results

Included studies

The initial database searches retrieved 6,269 studies of which 1,549 were duplicates (Figure 1). Of 4,720 studies found in the initial search, 4,382 were excluded during the screening phase based on title and abstract review. Of 338 studies extracted during eligibility determination, 20 studies met the inclusion criteria (Table 1). A major proportion of the studies were excluded following full text review because the sample did not include an LPT group that was distinguished from other preterm groups, a full term control group was not included, results did not compare full term and LPT groups, or developmental assessments were completed prior to 12 months of age.

Description of included studies

Of the 20 included studies, ten studies focused solely on the LPT group and three studies included a subgroup of complicated LPT Infants who were identified with a history of neonatal intensive care unit (NICU) admission due to clinical instability

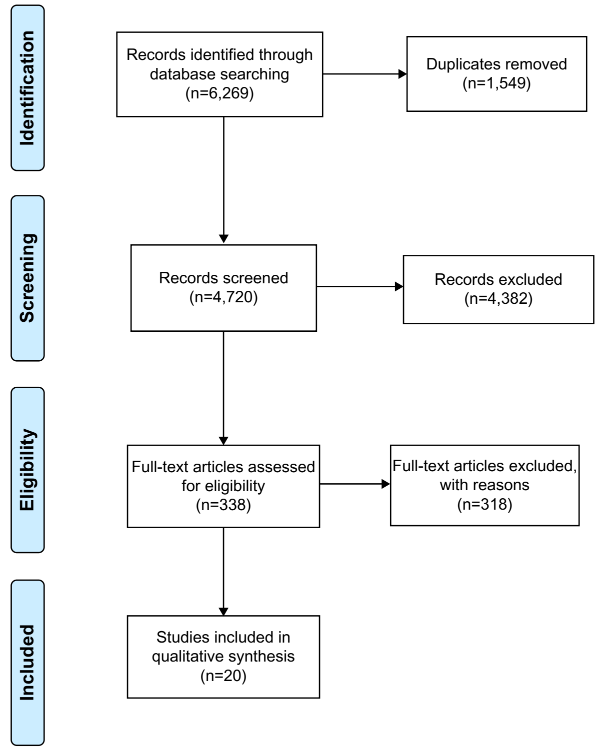

Figure 1 Flowchart of study selection process.
Abbreviation: n, number of studies included in the current review.

and/or birth weight <2 kg. All of the studies had been undertaken in past 13 years. Most studies were conducted in USA (ten studies),[9–18] followed by the UK (four studies),[19–22] Australia (two studies),[23,24] Italy (one study),[25] Spain (one study),[26] Israel (one study),[27] and Canada (one study),[28] indicating a large proportion of research had been carried out in developed nations. Six of the 21 studies had a retrospective cohort design. Seven studies included analysis of national datasets, three studies were part of the Early Childhood Longitudinal Survey, Birth cohort (ECLS-B),[11,12,18] two studies were part of the Avon Longitudinal Study of Parents and Children (ALSPAC) study group[20,21] one study was the Cohort Millennium Study,[22] and one study was the National Longitudinal Survey of Children and Youth (NLSYC).[28] The majority of papers measured outcomes at age 8 years or less. No studies assessed outcomes beyond 15 years of age (Table 1).

The Cognitive Studies, Motor Development Studies, Language Study, School/Academic performance studies section of the result provide an concise review of the findings while Table 2 provides details of the findings in of each study. The study results are described under the four key long-term neurodevelopmental outcomes measured: cognitive, motor, language, and school/academic performance. Many studies included outcomes in more than one of the four domains.

Table 1 Description of papers included in the current systematic review

Authors and location	Study design	Ages assessed	Study population	Control	Primary objective
Chyi et al[18] US	Secondary analysis of cohort study Early Childhood Longitudinal Study, Kindergarten cohort (ECLS-K) dataset	5–11 years	Moderate preterm; n=203 Late preterm; n=767*	Full term; n=13,671	To compare the rate of learning difficulties between late preterm and full term infants at school age
Baron et al[17] US	Retrospective cohort study	3–4 years	Complicated late preterm (cLPT); n=60*	Full term; n=35	To compare general cognition, attention, working memory, motor and visuomotor skills, and executive functions between infants born preterm and admitted to NICU, and full term infants as 3-year-olds
Gurka et al[16] US	Prospective cohort study	4–15 years	Late preterm; n=53	Full term; n=1,245	To compare a variety of cognitive, academic, socioemotional, and behavioral outcomes between healthy late preterm infants and full term infants from ages 4–15 years
Romeo et al[25] Italy	Secondary analysis of a prospective cohort study	12 and 18 months	Late preterm; n=61, and normal head ultrasound or Gr I IVH	Full term; n=60	To compare the neurodevelopmental performance of low-risk late preterm infants, at 12 and 18 months of corrected and uncorrected age, to those of full term infants
Talge et al[15] US	Secondary analysis of a prospective cohort study	6–7 years	Late preterm; n=168	Full term; n=168	To compare the risk of cognitive and socioemotional problems in middle childhoods of late preterm infants and full term infants
Baron et al[14] US	Retrospective cohort study	3.51–4.19 years	cLPT; n=9* Uncomplicated late preterm; n=28*	Full term; n=100	To compare the cognitive abilities (general conceptual ability, verbal cluster, nonverbal reasoning cluster, and spatial cluster) of children born late preterm and not admitted to NICU, and those born at full term
Lipkind et al[13] US	Retrospective cohort study Longitudinal Study of Early Development data warehouse	8–9 years	Preterm; n=2,332 Late preterm; n=13,207*	Full term; n=199,599	To compare school-age educational outcomes of late preterm infants compared to preterm and full term infants
Nepomnyaschy et al[12] US	Cohort study ECLS-B	2 and 4 years	Late preterm; n=400	Full term; n=5,050	To compare cognitive, motor, and behavioral outcomes of healthy late preterm and healthy full term singleton infants at 2 and 4 years of age
Quigley et al[19] UK	Retrospective cohort study	5 years	Born between 23–31 weeks; n=106 Born between 32–33 weeks; n=99 Born between 34–36 weeks; n=537* Born between 37–38 weeks; n=1,827	Full term; n=6,159	To compare school performance at age 5 years in children born at full term (39–41 weeks) with those born at early term (37–38 weeks), late preterm (34–36 weeks), moderately preterm (32–33 weeks), and very preterm (<32 weeks)
Woythaler et al[11] US	Prospective cohort study ECLS-B	24 months chronological age	Late preterm; n=1,200*	Full term; n=6,300	To compare neurodevelopmental outcomes for late preterm infants and full term infants at 24 months of age
Baron et al[10] US	Retrospective cohort study Fairfax Neonatal Associates PETIT (Prematurity's Effects on Toddlers, Infants and Teens) study	3 years 0 months to 3 years 11 months	23–33 weeks; n=52 34–36 weeks; n=196*	Full term; n=121	To compare executive functions of extremely low birth weight and late preterm infants to full term infants at preschool age

Odd et al[20] UK	Cohort study Avon Longitudinal Study of Parents and Children (ALSPAC)	8–11 years	Moderate/late preterm; n=741 Late preterm (34–36 weeks); n=6,905* Moderate preterm (32–33 weeks); n=6,655	Full term; n=13,102	To compare cognitive, memory, attention, or school outcomes in children born late preterm to full term infants
Pitcher et al[23] Australia	Cohort study PREMOCODE (Preterm Motor and Cognitive Development) study	12–13 years	Early preterm; n=40 Late preterm; n=65*	Full term; n=46	To determine if atypical excitability in the brain and cortical pathways assessed with transcranial magnetic stimulation and surface electromyography are related to decreased motor development in 10–13-year-old children born at 25–41 weeks gestational age
Morag et al[27] Israel	Prospective cohort	6 and 12 months of chronological age	Late preterm; n=124	Full term; n=33	To compare the developmental outcome of late preterm infants to full term infants from birth to the end of their first year of life
Odd et al[21] Bristol, UK	Cohort study ALSPAC	7 and 8 years	Moderate/late preterm (mean gestation =35 weeks); n=741	Full term; n=13,102	To compare the risk of being diagnosed with cerebral palsy or having poor motor performance between infants born at late or moderate preterm with infants born preterm
Poulsen et al[22] UK: England and Scotland	Cohort study Millennium cohort study	9 months, 3 years, 5 years, and 7 years	<32 weeks; n=225 32–33 weeks; n=192 34–36 weeks; n=1,107 * 37–38 weeks; n=3,655	Full term; n=12,540	To determine the relationship between gestational age and cognition in late preterm and early term groups
Baron et al[9] Virginia, US	Cohort study PETIT study, Fairfax Neonatal Associates' longitudinal study of the outcomes of preterm birth	3–4 years chronological age	cLPT (admitted to NICU); n=278* 34 weeks; n=132*	Full term; n=192	To compare a range of cognitive measures between late preterm infants admitted to NICU and full term infants at 3 years of age
Brown et al[28] Canada	Cohort study National Longitudinal Survey of Children and Youth (NLSCY)	2–3 years and 4–5 years	n=15,099 Late preterm; n=1,103* Early term; n=4,333 n=12,203 Late preterm; n=866* Early term; n=3,478	Full term; n=9,663 Full term; n=7,859	To study the role of gestational age in determining the risk associated with late preterm and early term births
Oros et al[26] Spain	Cross-sectional cohort study	6–8 years	Late preterm; n=6* Late SGA; n=11	Full term; n=96	To investigate the hypothesis that SGA births and late prematurity present a distinct pattern of structural changes with specific cognitive difficulties
Schneider et al[24] Australia	Retrospective cohort study	11–13 years	<32 weeks; early preterm; n=38 33–36 weeks; late preterm; n=63*	Full term; n=44	To investigate the influence of a range of prenatal and post-natal factors on cognitive development in preterm and term-born adolescents

Note: *The group of interest that was compared with the control group and was included in our interpretation of the results.
Abbreviations: n, the size of the sample included in the current study; NICU, neonatal intensive care unit; SGA, small-for-gestational age; Gr 1 IVH, grade 1 intraventricular haemorrhage; ECLS- B, Early Childhood Longitudinal Study-Birth Cohort; ALSPAC, Avon Longitudinal Study of Parents and Children.

Table 2 Summary of results comparison between infants born LPT and Full term of included studies

Outcome domain	Outcome: Definition/ Measurement	Group comparisons		Confounders adjusted for	Short synopsis
Cognition					
Chyi (2008)[18]	Early childhood longitudinal study-kindergarten assessment scores	Risk of poor outcome 34–36 weeks adjusted OR (95% CI)		Adjusted for sex, race, and maternal education level. Only including singletons	Children born LPT in the United states are at an increased risk of having a below average score in first grade even when controlling for social factors and multiple gestations
	Reading T score				
	Kindergarten	1.13 (0.97 to 1.33)			
	First grade	1.24 (1.06 to 1.45)*			
	Third grade	1.03 (0.86 to 1.23)			
	Fifth grade	1.03 (0.84 to 1.26)			
	Math T score				
	Kindergarten	1.15 (0.98 to 1.34)			
	First grade	1.22 (1.04 to 1.43)*			
	Third grade	0.98 (0.82 to 1.17)			
	Fifth grade	1.07 (0.88 to 1.31)			
Baron (2009)[17]		cLPT compared to term children		None	cLPT have lower cognitive and visual motor outcomes than infants born at term
	DAS-II – general conceptual ability	Student's *t*-test 2.16, *P*=0.033*			
	Spatial cluster	Student's *t*-test 2.88, *P*=0.005*			
	Pattern construction T score	Student's *t*-test 2.72, *P*=0.008*			
	Copying T score	Student's *t*-test 2.50, *P*=0.014*			
	Beery Visual Motor Integration	Student's *t*-test 2.57, *P*=0.012*			
	Animal fluency total	Student's *t*-test 2.41, *P*=0.018*			
	Action- verb fluency total	Student's *t*-test 2.27, *P*=0.026*			
Gurka (2010)[16]	Woodcock Johnson psycho educational battery revised	No difference in the cognitive and achievement scores through age 15 years		Adjusted for sex, race, maternal education, maternal age, delivery type, maternal health, home environment, maternal depression score, and maternal vocabulary	This study found no significant difference between the LPT and FT infants on cognitive or behavioral outcomes. This was a small sample of 53 LPT infants who were at very low medical and social risk
Romeo (2010)[25]	Development quotient at 12 and 18 months	12 months Mean ± SD	18 months Mean ± SD	None	This study found that LPI have "caught up" to their term peers by 12 or 18 months – meaning when using uncorrected ages they are still delayed
	Term	99.8±8.7	97.8±8.1		
	LPT corrected age	100.3±8.7	97.0±9.1		
	LPT uncorrected age	91.9±9.3	87.9±9.9		
	Developmental quotients comparison	Mann Whitney U results			
	Full term vs LPT	$P<0.01$*	$P<0.01$*		
	LPT corrected age vs LPT uncorrected age	$P<0.01$*	$P<0.01$*		

Talge (2010)[15]	Wechsler Intelligence scale for children		Adjusted for residential setting, maternal IQ, maternal education, marital status, and child sex	LPT infants (unknown of health status) are more likely to have a full scale and performance IQ which is 1 SD below the mean than those who were born FT, even though their full scale IQ and verbal IQ were similar to the term infants even after adjusting for social and maternal education factor
	Mean group differences, (95% CI), *P*-value			
	Full scale IQ	1.31, (1.67 to 4.29), Ns		
	Verbal IQ	0.15, (2.91 to 3.21), Ns		
	Performance IQ	2.49, (0.53 to 5.51), $P<0.10$*		
	Odds of having a delay, (95% CI), *P*-value			
	Full scale IQ	aOR =2.35, (1.20 to 4.61), $P<0.05$*		
	Verbal IQ	aOR =1.52, (0.78 to 2.95), Ns		
	Performance IQ	aOR =2.04, (1.09 to 3.82), $P<0.05$*		
Baron (2011)[14]	Mean DAS-II standard score		None	Mean DAS-II General conceptual ability non-verbal reasoning, and spatial clusters of cLPT, but not uLPT, are lower than that of term infants. However, all groups had a mean score within the average range Rate of impairment (being more than 1 SD below the mean) in nonverbal reasoning and spatial cluster was higher in the cLPT, but not uLPT. However there was no difference in general cognitive impairments or composite verbal scores
	General conceptual ability	cLPT < full term: $P=0.006$*		
	Composite verbal score-	Ns differences		
	Nonverbal score	cLPT < full term: $P=0.022$*		
	Spatial score	cLPT < full term: $P=0.005$*		
	Rate of Impairment (standard score <85) on DAS-II			
	General conceptual ability	Ns differences		
	Composite verbal score	Ns differences		
	Nonverbal score	cLPT vs full term: RR 7.22 (95% CI; 1.68 to 31.13)*		
	Spatial score	cLPT vs full term: RR 5.56 (95% CI; 1.25 to 24.68)*		
Woythaler (2011)[11]	BSF-R Derived MDI	Adjusted odds ratio (95% CI) MDI score <70 1.51(1.26 to 1.82)* MDI score 70–84 1.43 (1.22 to 1.67)*	Adjusted for gestational age, plurality, maternal race, education, marital status, depression, prenatal care, primary language, infant sex, poverty level, delivery type, fetal growth, and any breast milk feeding	Infant born late preterm had lower mental abilities at 24 months even when adjusting for prematurity and maternal factors So the LPT infants have not caught up resulting in statistically significant differences at 24 months
Baron (2012)[10]	DAS-II general conceptual ability	$t(366) = -2.96$, $P<0.01$*	Mother's educational level Age	LPT group had reduced cognitive scores on the DAS and had lower executive function scores on 3 out of 8 measures used. Thus only a minor difference in executive function and lower general cognitive scores
	Executive function			
	Preschool Continuous Performance Test			
		F-test, *P*-value		
	Commission	$F_{(2,354)}$ =5.93, Ns		
	Omission	$F_{(2,354)}$ =17.57, $P<0.01$*		
	Reaction time	$F_{(2,354)}$ =0.74, Ns		
	Go/No-Go test			
	Comissions	$F_{(2,354)}$ =11.92, Ns		
	Omission	$F_{(2,354)}$ =10.38, $P<0.01$*		
	Reaction time	$F_{(2,354)}$ =3.85, Ns		
	Boy-Girl stroop test			
	Correct	$F_{(2,354)}$ =1.63, Ns		
	Time	$F_{(2,354)}$ =19.32, Ns		

(*Continued*)

Table 2 (*Continued*)

Outcome domain	Outcome: Definition/ Measurement	Group comparisons	Confounders adjusted for	Short synopsis
	Jack's boxes test			
	Within-error	$F_{(2,354)}$ =3.15, Ns		
	Between error	$F_{(2,354)}$ =6.14, $P<0.01$*		
	Digit repetition	$F_{(2,354)}$ =3.83, Ns		
Nepomnyaschy (2012)[12]	Association between late preterm birth and developmental outcomes at ages 2 and 4 years		Adjusted for race/ethnicity, age, education, marital birth, father co-residence, household below poverty, and complications of labor and delivery	The LPT group showed significant differences in math ability at 4 years of age when compared to the full term group Literacy and vocabulary are the only impairments seen in this national sample of LPT infants at 2 and 4 years when controlling for social and labor and delivers complications
	At 4 year outcome	Adjusted ordinary least squares, (95% CI), *P*-value		
	Math ability	–0.99, (–1.78 to –0.19), $P<0.05$*		
	Score >1 SD below sample means			
	Math ability	1.18, (0.85 to 1.65), Ns		
	At 2 year outcomes			
	Bayley mental score	–0.35, (–1.53 to 0.83), Ns		
	Vocabulary	–0.72,(–2.24 to 0.79), Ns		
	Language use	–0.25, (–0.47 to –0.03), $P<0.05$*		
	At 4 years			
	Literacy	–1.05, (–1.75 to –0.35), $P<0.01$*		
	Receptive language	–0.17, (–0.37 to 0.03), Ns		
	Expressive language	–0.05, (–0.15 to 0.06), Ns		
	Color knowledge	–0.15, (–0.41 to 0.12), Ns		
	Vocabulary	0.56, (–1.33 to 0.21), Ns		
	Language use	0.04, (–0.36 to 0.44), Ns		
	Receptive language	–0.17, (–0.37 to 0.03), $P<0.10$*		
	Expressive language	–0.05, (–0.15 to 0.06), Ns		
	Odds ratio of having a score > 1 SD below sample means, (95% CI), *P*-value			
	At 2 year outcomes			
	Bayley mental score	1.07, (0.76 to 1.50), Ns		
	Vocabulary	1.22, (0.85 to 1.74), Ns		
	Language use	1.17, (0.85 to 1.60), Ns		
	At 4 years			
	Literacy	0.89, (0.59 to 1.32), Ns		
	Receptive language	0.98, (0.67 to 1.44), Ns		
	Expressive language	1.04, (0.68 to 1.57), Ns		
	Color knowledge	1.15, (0.83 to 1.61), Ns		
	Vocabulary	1.33, (1.00 to 1.77), $P<0.05$*		
	Language use	1.03, (0.73 to 1.43), Ns		
	Receptive language	0.98, (0.67 to 1.44), Ns		
	Expressive Language	1.04,(0.68 to 1.57), Ns		

Odd (2012)[20]	Wechsler scale for moderate/LP compared with term infants. Adjusted difference in mean, (95% CI), *P*-value				Adjusted for ethnicity, housing, crowding, maternal education, socio-economic group, car ownership, age, sex, weight, length and head circumference at birth, mode of delivery, and maternal hypertension and pyrexia	As a group moderate and late preterm (mean age 35 weeks) infants combined together are at higher risk of mild cognitive issues. When controlling for social and medical risk factors these infants still show mild difficulty in reading accuracy, but in other areas are less significant. They also get more special education support in school but this could be related to a higher rate of identification in infants born preterm compared to the FT with cognitive issues
	Verbal subtest					
	Information	–0.29, (–0.63 to 0.04), Ns				
	Arithmetic	–0.22, (–0.67 to 0.24), Ns				
	Vocabulary	–0.04, (–0.50 to 0.42), Ns				
	Comprehension	0.13, (–0.28 to 0.54), Ns				
	Similarities	0.18, (–0.25 to 0.61), Ns				
	Performance subtest					
	Picture completion	0.26, (–0.14 to 0.67), Ns				
	Coding	–0.22, (0.55 to 0.10), Ns				
	Picture arrangement	0.00, (0.53 to 0.53), Ns				
	Block design	–0.03, (–0.45 to 0.38), Ns				
	Object assembly	–0.12, (–0.55 to 0.31), Ns				
	Summary scores					
	Verbal IQ	–0.33, (–2.06 to 1.40), Ns				
	Performance IQ	–0.12, (–1.96 to 1.73), Ns				
	Summary IQ	0.18, (–1.88 to 1.52), Ns				
	Linear regression difference for moderate/Late preterm compared with term infants					
		Fully adjusted mean difference, (95% CI), *P*-value				
	Test of memory					
	No word repetition	1.55, (–3.18 to 0.09), Ns				
	Span score	1.04, (–2.77 to 0.68), Ns				
	Test of attention					
	Sky search Attention	1.29, (–3.00 to 0.42), Ns				
	Dual Attention Score	1.12, (–3.03 to 0.79), Ns				
	Test of reading					
	Accuracy	1.97, (–3.61 to –0.32), *P*=0.019*				
	Read per minute	1.18, (–2.84 to 0.47), Ns				
	Comprehension	0.98, (–2.58 to 0.61), Ns				
Morag (2013)[27]	Griffith mental development scale - at 12 month chronological age				Adjusted to corrected Age	Similar to the Romeo study this study suggests that the LPT infant are not "catching up" by 12 months of age and appear delayed if tested without correction. But with correction are similar to full term infants
		LPT Mean (SD)	Control Mean (SD)	*P*-value		
	Personal-Social	112 (10)	117 (8)	0.001*		
	Performance	84 (10)	95 (19)	0.001*		
	Griffith mental development scale - at 12 month adjusted age					
		LPT Mean (SD)	Control Mean (SD)	*P*-value		
	Personal-Social	123 (11)	117 (8)	Ns		
	Performance	95 (12)	95 (19)	Ns		

(*Continued*)

Table 2 (*Continued*)

Outcome domain	Outcome: Definition/ Measurement	Group comparisons	Confounders adjusted for	Short synopsis
Poulsen (2013)[22]	Mean differences LPT vs term; Adjusted z score (95% CI)		Adjusted for mother's education, mother's SES based on occupation, mother's age at birth, mother's marital status, first-born status, child's ethnic group, smoking and alcohol use during pregnancy	Infant born LPT have lower mean scores and are at higher risk of having a mild cognitive delays in some cognitive domains between 3 and 7 years of age even when controlling for maternal and social risk factors
	British ability scale II			
	Naming vocabulary subscale	At age 3 yr: –0.1 (–0.2 to 0.01)		
		At age 5 yr: 0.03 (–0.05 to 0.1)		
	Picture similarities subscale	At age 5 yr: –0.02 (–0.1 to 0.1)		
	Pattern construction measures	At age 5 yr: –0.1 (–0.2 to –0.1)*		
		At age 7 yr: –0.1 (–0.2 to 0.02)		
	Word reading subscale	At age 7 yr: –0.1 (–0.2 to –0.03)*		
	Bracken school readiness assessment	At age 3 yr, –0.1 (–0.2 to –0.04)*		
	Mathematics assessment numeracy skills	At age 7 yr, –0.04 (–0.1 to 0.04)		
	Risk ratio of scoring > 1 SD below the mean (95% CI)			
	British ability scale II			
	Naming vocabulary subscale	At age 3 yr-aRR =1.1 (0.9 to 1.3)		
	Picture similarities subscale	At age 5 yr-aRR =1.0 (0.8 to 1.2)		
	Pattern construction measures	At age 5 yr-aRR =1.2 (1.0 to 1.3)*		
	Word reading subscale	At age 5 yr-aRR =1.4 (1.1 to 1.6)*		
		At age 7 yr-aRR =1.05 (0.8 to 1.3)		
	Bracken School readiness assessment	At age 7 yr-aRR =1.4 (1.2 to 1.6)*		
	Mathematics assessment numeracy skills	At age 3 yr, aRR =1.3 (1.1 to 1.5)*		
		At age 7 yr, aRR =1.05 (0.8 to 1.3)		
Brown (2014)[28]	Motor and social development scale developed by the US National Center for Health Statistics	Adjusted Risk Ratio (95% CI) 1.06 (0.79 to 1.43) 1.13 (0.90 to 1.42)	Adjusted for perinatal variables (smoking during pregnancy, alcohol use during pregnancy, placental ischemia and other hypoxia [maternal hypertension, small for gestational age], other biological determinants of preterm family resources (family income adequacy, maternal education, maternal age, maternal health, maternal mental health), and family functioning and other covariates (child sex)	Motor/Social development is decreased in infants born LPT (compared to term infants). However, this decrease disappears when you control of social factors, lower maternal education level, financial instability, negative style or inconsistent parenting. Vocabulary is not delayed in infants born LPT, and continues to be unrelated to LPT birth status when you control for social factors

Baron (2014)[9]	At 3–4 years	ANOVA results cLPT < Term Cohen's d, *P*-value	 uLPT < Term Cohen's d, *P*-value	Adjusted for medical variables and demographic variables (sex, maternal education)	This study suggests that both cLPT and cLPT infant have cognitive impairments at preschool age when adjusting for medical and social factors
	General conceptual ability	–0.511, $P<0.05$*	–0.452, $P<0.05$*		
	Verbal cluster	–0.302, $P<0.05$*	–0.329, $P<0.05$*		
	Non verbal	–0.386, $P<0.05$*	–0.325, $P<0.05$*		
	Spatial cluster	–0.491, $P<0.05$*	–0.395, $P<0.05$*		
	Picture similarities	–0.279, $P<0.05$*	–0.311, $P<0.05$*		
	Pattern construction	–0.418, $P<0.05$*	–0.271, Ns		
	Copying	–0.422, $P<0.05$*	–0.422, $P<0.05$*		
	Beery Visual Motor Integration	–0.398, $P<0.05$*	–0.319, Ns		
	BASC- 2 adaptability	–0.352, $P<0.05$*	–0.417, $P<0.05$*		
Oros (2014)[26]	Abnormal Children's Bender Visual Motor Gestalt Test	Proportion of LPT and FT 16.7% and 6.2% (P=0.32)		None	There was no difference between LPT and FT controls on percent of children with abnormal visual motor function
Schneider (2014)[24]	Woodcock Johnson III Tests of cognitive abilities Verbal ability Thinking ability Cognitive efficiency Auditory processing Phonemic awareness Working memory Global intelligence composite score	There was not significant difference between the LPT and FT group on any cognitive domain (no specific data provided to support this statement)		Head circumference, body length at birth, Apgar score, multiple birth, parity, maternal age, maternal BMI, child height, weight and % of body fat, and laterality quotient	This study compares the cognitive abilities of Early preterm, late preterm, and full term infants between groups and others factors which may contribute to cognitive development. No data is presented on the comparison on LPT to term other than a statement the models were not significant
School/Academic performance					
Chyi (2008)[18]	Teacher academic rating scales, 34–36 weeks adjusted OR (95% CI)			Adjusted for sex, race, and maternal education level, and only including singletons	Significant differences were found in the school based outcomes between late preterms and full terms where late preterms had lower scores in reading abilities at K grade. The teacher assessment scale showed that LPT infants were less proficient in reading and math abilities than FT. Late preterms are at a higher need for individualized education program than FT. However, these risk decreased by 3-5 grade
	Math				
	Kindergarten	1.30 (1.07 to 1.59)*			
	First grade	1.28 (1.06 to 1.54)*			
	Third grade	1.28 (1.01 to 1.61)*			
	Fifth grade	1.31 (1.05 to 1.65)*			
	Reading				
	Kindergarten	1.25 (1.05 to 1.49)*			
	First grade	1.19 (0.99 to 1.43)			
	Third grade	1.18 (0.86 to 1.62)			
	Fifth grade	0.99 (0.71 to 1.37)			

(*Continued*)

Table 2 (*Continued*)

Outcome domain	Outcome: Definition/ Measurement	Group comparisons	Confounders adjusted for	Short synopsis
	Individualized Education Program			
	Kindergarten	2.10 (1.47 to 3.00)*		
	First grade	1.56 (1.10 to 2.21)*		
	Third grade	1.27 (0.92 to 1.74)		
	Fifth grade	1.29 (0.92 to 1.82)		
		34–36 weeks adjusted OR (95% CI)		
	Special education			
	Kindergarten	1.38 (1.00 to 1.89)*		
	First grade	1.44 (1.08 to 1.91)*		
	Third grade	1.13 (0.85 to 1.49)		
	Fifth grade	1.10 (0.80 to 1.50)		
	Individualized Education Program			
	Kindergarten	2.13 (1.56 to 2.90)*		
	First grade	1.44 (1.04 to 1.98)*		
	Third grade	1.22 (0.92 to 1.63)*		
	Fifth grade	1.28 (0.95 to 1.74)*		
Quigley (2011)[19]	Foundation Stage profile	Adjusted Risk Ratios for not working securely in foundation stage profile scales (95% CI)	Adjusted for multiple birth, child's sex, ethnicity, whether first born, breastfeeding duration, month of birth (age within the school year) and mother's age, marital status, education, social class, and whether languages other than English were spoken at home	The findings suggests that there was a 12% increased risk of poorer academic achievement in late preterm children compared to full term infants
	Not good level of overall achievement	1.12, (1.04 to 1.22)*		
	Not working securely in all three scales of personal, social, and emotional development	1.14, (0.99 to 1.32)		
	Not work securely in all scales of communication, language, and literacy	1.16, (1.00 to 1.34)*		
	Not working securely in the knowledge and understanding of the world scale	1.30, (1.08 to 1.56)*		
	Not working securely in the physical development scale	1.27, (0.92 to 1.74)		
	Not working securely in the creative development	1.46, (0.94 to 2.27)		
Odd (2012)[20]	Teacher completed questionnaire: 'Has this child ever been recognized as having special educational needs?'	Fully adjusted odds ratio, (95% CI), *P*-value 1.56, (1.18 to 2.07), 0.002*	Adjusted for ethnicity, housing, crowding, maternal education, socio-economic group, car ownership, age, sex, parity, weight, length and head circumference at birth, mode of delivery, and maternal hypertension and pyrexia	While this study found that there was little cognitive difference between groups, moderate to late preterm infants required more special education services than full term infants

Lipkind (2013)[13]		Adjusted SD%, (95% CI), *P*-value			Adjusted for child sex, maternal age, maternal race/ethnicity, insurance status, parity, low Apgar score, medical risk factors, complications of pregnancy, neonatal intensive care admission, days absent in third grade, and small for gestational age <10th percentile	LPT infants in 3rd grade in New York city demonstrated impaired language arts and math performance on standardized school assessment and received more special education services even when the risks are controlled by social factors and medical risk factors. This was a fairly sick group of LPT infants while the analysis should have controlled for this It is possible that some factors related to the medical fragility could have not been adjusted and impacted the outcomes
	Standard 3rd grade English Language Arts Assessments	4.0%, (–5.7 to –2.3), $P<0.001$*				
	Standardized 3rd grade Math Assessment	6.7%, (–8.4 to –5.1), $P<0.001$*				
		Adjusted OR (95% CI)				
	Individualized Education Program	1.34, (1.29 to 1.40)*				
Language						
Morag (2013)[27]	Hearing and Language	LPI Mean ± SD	Control Mean ± SD	*P*-value	Adjusted for corrected age	This study found significant difference in the means of the hearing and language scores at 12 months of chronological age between LPT and FT group. No differences were seen between the groups when corrected age was used
	At 12 month chronological age	87±14	96±14	0.001*		
	At 12 month corrected age	96±15	96±14	Ns		
Motor development						
Woythaler (2011)[11]	BSF-R Derived PDI	Adjusted odds ratio of PDI score <70 (95% CI) 1.56 (1.29 to 1.88)* Adjusted odds ratio PDI score 70–84 (95% CI) 1.58 (1.37 to 1.83)*			Gestational age, plurality, maternal race, education, marital status, depression, prenatal care, primary language, infant sex, poverty level, delivery type, fetal growth, and any breast milk feeding	Infants born late preterm have an increased risk of motor delays at 24 months even when adjusted for prematurity and social factors
Nepomnyaschy (2012)[12]	Adjusted Ordinary Least Squares (95% CI)				Adjusted for race/ethnicity, age, education, marital birth, father co-residence, household below poverty, and complications of labor and delivery	Infants born LPT are similar to infant born full in their motor development in the first 2-4 years of life
	At 2 years					
	Derived Bayley Motor score	–0.33, (–1.58 to 0.91)*				
	At 4 years					
	Gross motor ability	–0.10, (–0.39 to 0.18), Ns				
	Fine motor ability-copying forms	0.13, (–0.33 to 0.07), Ns				
	Fine motor-building w/blocks	–0.02, (–0.11 to 0.07), Ns				
	Adjusted ordinary least squares of having a score > 1 SD below sample mean (95% CI), *P*-value					
	At 2 years					
	Bayley motor score	1.00, (0.71 to 1.42), Ns				
	At 4 years					
	Gross motor ability	1.08, (0.73 to 1.58), Ns				
	Fine motor ability-copying forms	1.18, (0.75 to 1.87), Ns				
	Fine motor-building w/blocks	1.23, (0.87 to 1.73), Ns				

(*Continued*)

Table 2 (*Continued*)

Outcome domain	Outcome: Definition/ Measurement	Group comparisons			Confounders adjusted for	Short synopsis
Pitcher (2012)[23]		Mean percentile score for MABC ± SD			Adjusted for sex, GA, BW %, and corticomotor excitability	The study suggests there are no groups differences in the motor abilities of children about 12 months when assessed on the M-ABC
		LPT	Term	*P*-value		
	Manual dexterity					
	Males	34.4±22.3	41.6±24.3	Ns		
	Females	53.1±27.4	42.0±25.5	Ns		
	Aiming and catching					
	Males	74.5±23.8	70.5±28.2	Ns		
	Females	60.0±27.1	63.4±28.3	Ns		
	Balance					
	Males	45.5±30.6	62.7±26.7	Ns		
	Females	67.6±31.2	71.4±28.5	Ns		
	Total Score					
	Males	50.4±26.0	59.8±23.8	Ns		
	Females	59.4±29.9	60.8±26.8	Ns		
	Total score	54.3±27.9	60.2±25.0	Ns		
Baron(2014)[9]	Purdue dominant hand, raw	cLPT < Term Cohen's d, *P*-value –0.294 , *P*<0.05*	uLPT< Term Cohen's d, *P*-value –0.451, *P*<0.05*		Adjusted for medical variables and demographic variables (sex, maternal education)	At 3 years of age, children who were born LPT as a groups have some fine motor delays regardless of their medical course at birth
Morag (2013)[27]	Griffiths Mental Development Scales				Adjusted for corrected age	Infant born LPT have a not "caught up" from their PT birth by 12 months, but with correction for prematuritiy their motor skills are appropriate at 12 months
		LPT Mean ± SD	Control Mean ± SD	*P*-value		
	At 12 month chronologic age					
	Locomotor	90±11	97±12	0.001*		
	Eye hand Coordination	97±8	104±11	0.001*		
	At 12 month corrected age					
	Locomotor	100±12	97±12	Ns		
	Eye hand Coordination	107±9	104±11	Ns		
Odd (2013)[21]	Avon Longitudinal Study of Parents and Children coordination test	Association between moderate/late preterm gestation and risk of poor movements scores/outcomes Fully adjusted differences, (95% CI), *P*-value			Adjusted for ethnicity, housing, crowding, and maternal education, socio-economic group, car ownership, and age Sex, parity, weight, length and head circumference at birth Mode of delivery, maternal hypertension, pyrexia, and need for resuscitation at birth	Infant born moderate/late preterm have an increased risk of fine motor impairments as well as movement impairments and CP. However, it is unclear how much of this risk is associated with the moderately preterm vs the late preterm.
	Heel-to-toe score	1.27, (0.98 to 1.63), Ns				
	Bean-bag score	1.17, (0.91 to 1.50), Ns				
	Peg score	1.40, (1.08 to 1.81), 0.011*				
	Summary score	1.39, (1.12 to 1.72), 0.003*				
	Movement disorders					
	Cerebral palsy	6.38, (2.28 to 17.76), *P*<0.001*				
	Poor coordination score or cerebral palsy	1.56, (1.01 to 2.42), 0.045*				

Brown (2014)[28]	Motor and Social Development Scale developed by the US National Center for Health Statistics	Adjusted risk ratio, (95% CI) 1.13; (0.90 to 1.42)	Adjusted for perinatal variables (smoking during pregnancy, alcohol use during pregnancy, placental ischemia and other hypoxia [maternal hypertension, small for gestational age], other biological determinants of preterm birth [maternal diabetes, other medical conditions during pregnancy], delivery mode); social context as described in terms of family structure (maternal partnership status, number of siblings), family resources (family income adequacy, maternal education, maternal age, maternal health, maternal mental health), and family functioning and other covariates (child sex)	Children born LPT are at an elevated risk for developmental delay when compared to those born full term when not adjusted for any of the medical and social factors. However, non significant group differences were seen once adjusted for medical and social factors.

Notes: All results presented are adjusted if presented by the authors as adjusted for confounders. * results which were statistically significant $P<0.05$ or RR did not include 1 or OR did not include 0.
Abbreviations: LPT, late preterm; cLPT, complicated late preterm; FT, full term; SD, Standard deviation; CI, confidence interval; Ns, not statistically significant; RR, risk ratio; OR, odds ratio; aRR, adjusted relative risks; DAS-II, Differential Ability Scale; GCA, General Conceptual ability; BSF-R, Bayley Short Form-Research Edition; BASC-2, Behavior Assessment System for Children – Second Edition; MDI, Mental Development Index; PDI, Psychomotor Developmental Index; MABC, Movement Assessment Battery for Children; yr, year; uLPT, uncomplicated late preterms; aOR, adjusted odds ratio; GA, gestational age; BW, body weight; CP, Cerebral Palsy; SES, socioeconomic status.

Cognitive studies

Sixteen studies analyzed for the current review included cognitive development as one of the outcome measures.[9–12,14–18,20,22,24–28] Under cognition, the subdomains commonly measured are: general conceptual ability, executive function, vocabulary, verbal ability, attention, and memory. The scales commonly used are the Bayley scales of infant development, second edition (Bayley-II), the differential ability scales, second edition (DAS-II), the Griffiths mental development scales (GMDS), and the Woodcock–Johnson III test of cognitive abilities. The Wechsler intelligence scale for children and British ability scale are also commonly used.

Seventy-five percent of the 16 studies that assessed cognitive outcomes suggested that as a group, infants born LPT are at increased risk of having cognitive scores that are lower than full term infants, or lower than the average range in at least one of the cognitive domains assessed.

Eight of the 16 studies assessed at least one of the following cognitive abilities: verbal ability, vocabulary, language use, receptive and expressive language, and literacy at ages ranging from 2 to 13 years.[9,12,14,15,17,20,22,24] Significant differences between LPT and full term groups were seen in language use at age 2 years,[12] and significant differences were also seen in the domains of literacy and receptive language at age 4 years.[12] Similarly, significant differences were seen in verbal cluster ability at ages 3–4 years when complicated and uncomplicated LPTs were compared with their full term counterparts.[9] At ages 6–11 years, no differences were seen in verbal ability.[15,24]

Four of the 16 studies measured reading and mathematical abilities at ages ranging from 3 to 11 years, and researchers found LPT groups had lower scores in at least one domain at ages 3–6 years when compared to their full term counterparts.[12,18,20,22] Only one study found significant difference in the reading at >7 years of age.[20] The risk of having a mathematics score more than one standard deviation below sample means was not significant at 4 years of age.[12]

Four of the 16 studies measured intelligence quotient (IQ) or mental abilities by using the Bayley and Wechsler intelligence scales for children.[11,12,15,20] Two studies suggested significant differences in performance IQ scores at 6–7 years of age ($P<0.05$) and a higher odds of having a lower Mental Developmental Index (MDI) score and poor IQ when compared to their full term counterparts at 24 months of chronological age and 6–7 years of age, respectively.[11,15]

Two of the 16 studies measured visuomotor function in complicated LPT infants.[9,17] The studies found significant

Table 3 Summary of Critical Appraisal Skills Program (CASP) results

Reference	Did the study address a clearly focused issue?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimize bias?	Was the outcome accurately measured to minimize bias?	Have the authors identified all important confounding factors?	Have the authors taken into account the confounding factors in the design and/or analysis	Was the follow-up of subjects complete enough?	Was the follow-up of subjects long enough?
Chyi et al[18]	Yes	Yes	No	Not clear	No	Yes	Yes	Yes
Baron et al[17]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Gurka et al[16]	Yes	Yes	No	Not clear	Yes	Yes	Yes	Yes
Romeo et al[25]	Yes	Yes	Yes	Not clear	Not clear	Yes	Not clear	Yes
Talge et al[15]	Yes	Yes	Not clear	Not clear	No	Yes	Yes	Yes
Baron et al[14]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Lipkind et al[13]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Nepomnyaschy et al[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quigley et al[19]	Yes	Yes	No	Yes	No	Yes	No	Yes
Woythaler et al[11]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Baron et al[10]	Yes	Yes	Yes	No	Yes	No	Not clear	No
Odd et al[20]	Yes	Yes	Yes	Not clear	Yes	Yes	No	Yes
Pitcher et al[23]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
Morag et al[27]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
Odd et al[21]	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	Yes
Poulsen et al[22]	Yes	Yes	No	Not clear	No	Yes	Yes	Yes
Baron et al[9]	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
Brown et al[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oros et al[26]	Yes	Yes	Yes	Not clear	No	Yes	Yes	Yes
Schneider et al[24]	Yes	Yes	Yes	Yes	No	Yes	No	Yes

differences in the visuomotor score of LPT infants when compared to those born full term at 3–4 years of age. The differences persisted in both studies even after adjusting for medical and demographic variables.[9,17]

Five studies measured spatial cluster, pattern construction, picture completion, and picture similarities as one of their outcome measures, of which four studies found significant differences between the LPT group and full term group when the groups were assessed at 3–5 years of age.[9,14,17,20,22] Three of these studies compared the full terms against complicated LPTs and found significant differences at less than 7 years of age.[9,14,17] Only one[22] of the two studies[20,22] that compared a broad group of LPT and full term infants on these domains found a significant result.

Four of the 16 studies did not find statistically significant results in any of the cognitive measures, suggesting no difference between the LPT and full term group.[16,24,26,28] The cognitive measures used were the Woodcock–Johnson III tests of cognitive abilities, the Abnormal Children's Bender Visual Motor Gestalt Test, and the motor and social development (MSD) scale. One paper had no details of the analysis results;[24] one paper had a small sample, which may have reduced the power to find significant differences;[16] and one paper only compared a proportion of children with visual motor abnormalities, limiting the depth of the cognitive domains assessed.[26] As described in detail in Table 2, studies often had a mixture of significant and non significant findings in different assessment subtests.

Motor development studies

Seven studies included measures of motor development as one of their outcomes.[9,11,12,21,23,27,28] Gross motor development, fine motor development, and coordination were the outcomes commonly assessed using the GMDS, Bayley-II, Bayley short form, research edition (BSF-R), Movement assessment battery for children (MABC), the ALSPAC coordination test, and the MSD scale developed by the US National Center for Health Statistics.

More than 50% of the included papers which compared the motor development of LPT and full term infants reported motor delays in the LPT cohort.[9,11,21,27] LPT and full term groups differed in gross motor abilities until 3 years of age. Only one study reported a difference in fine motor abilities at the age of 7 years.[21] However, the LPT and moderately preterm (34–35 weeks of gestation) groups were combined and were analyzed together, which may have increased the likelihood of finding significant differences.[21] The only study that compared motor development differences of complicated and uncomplicated LPT infants against full terms at 3–4 years of age found a significant difference in manual dexterity between both LPT groups and the full term infants.[9]

School/academic performance studies

Four studies included school/academic performance as one of their developmental outcomes.[13,18–20] The subjects' ages at assessment ranged from 5 to 11 years of age. Teacher-completed questionnaires, academic rating scales, and the need for individualized education plans were the measures commonly used.

All four papers identified reduced academic performance or an increased need for special education services in the infants born LPT. Chyi et al[18] found lower academic ratings in mathematical ability until fifth grade in children born LPT when compared to their full term counterparts. Quigley et al[19] suggested a 12% increase in the risk of poorer academic achievement in children born LPT compared to those born at term. Studies assessing the need for special education and individualized education programs have found that children born LPT have an increased need and require more special educational services compared to their full term counterparts.[13,18,20]

Language study

Only one study compared hearing and language in LPT and full term infants.[27] The authors reported statistically significant differences ($P=0.001$) when comparing the full term group with the LPT group at 12 months of chronological age. However, there was no difference when comparing the full term group with the LPT group if the LPT scores were calculated using the infants' adjusted age.[27]

Quality of the papers

The quality of the methods included in the 20 papers included in the current systematic review was fair overall (Table 3). Some common limitations were observed, including small sample sizes in the studies that followed infants with the most detailed assessments and those with complicated preterm infants. A lack of clarity or precision in measuring gestational age was another common limitation.[15,16,18,19,22] In 12 studies, it was unclear whether blinding techniques were used, or there was no blinding of the outcome measures.[9,15,16,18,20–23,25–28] While confounding factors such as maternal education level, race, and poverty status were often documented and in some cases adjusted for in the analyses, few studies included information on the medical status of the infants in the study. This was particularly true of the largest studies using national datasets, where information on medical status or the length of hospital stay at birth may not have been present.

Discussion

The findings of the present systematic review suggest that infants born LPT, as a group, are at an increased risk of having neurodevelopmental outcomes that are worse than infants born full term even, when social and medical risk factors are controlled for. Although the lower outcomes are not present in all domains and appear to improve over time in most areas, the findings are consistent with a previous systemic review.[7] The most evidence is available on the outcomes of infants born LPT in the cognitive domain. However, for all domains, the age of assessment, use of corrected vs chronological age, and medical fragility must be considered in interpreting the results, in addition to controlling for social factors that are known to increase the rate of developmental delays. In addition, the relationship between cognitive scores and academic performance is of great importance. The following three "Outcomes" sections discuss the results by age group, along with the special considerations that are most relevant to each age group.

Outcomes from 1 to 2 years of age

At 24 months of age, there were conflicting outcomes regarding the cognitive and motor outcomes of LPT infants evident in the literature. Woythaler et al[11] and Nepomnyaschy et al[12] completed their research using the same database, the ECLS-B, yet they found conflicting results. This disparity could be explained by the differences in their interpretation of the data and their use of statistical analyses. Woythaler et al[11] compared their data using standardized scores and found significant group differences in cognitive abilities at 24 months. In contrast, Nepomnyaschy et al[12] converted the cognitive and motor scores to percentiles prior to analysis, which may have reduced the ability to detect group differences due to the limitations of using percentiles in statistical analysis.

While it is common practice to use corrected or adjusted age (chronological age minus weeks' preterm) during developmental assessments on an extremely premature infants, this practice is less commonly used with infants born LPT. In five papers, four cognitive outcome measures[11,12,25,27] and one language outcome measure[27] were assessed in infants at $<$2 years of age, and outcomes showed significant group differences when scored using the infants' chronological age, rather than adjusting the age for prematurity. However, when each infant's corrected age was used to score the outcome measures, the groups appeared similar in their outcome measures.[25,27] This comparison suggests that LPT infants are not "catching up" developmentally with those born at full term by 1–1.5 years of age. No study included in the current review used a corrected age at or after 2 years of age, or compared the scores on corrected vs chronological age, limiting our ability to identify when and if the infants born LPT "catch up" with their full term peers. In addition, clinical differences in the use of corrected ages may alter if a child is identified as having a delay. Based on the papers included in the present systematic review, children at 1–1.5 years of age have lower cognitive and language scores when scored using a chronological age than infants born full term. There were no papers that assessed motor outcomes or school readiness between 1 and 2 years of age.

Outcomes from 3 to 5 years of age

At 3–5 years of age, cognitive, motor, and language assessments are more detailed, and assessments are divided between more conceptual areas. While the wide variety of assessments and lack of consistency on the conceptual areas measured makes interpretation challenging, deficits in the cognitive areas of literacy, general conceptual ability, vocabulary, and mathematics are noted in this age range. Brown et al[28] and Nepomnyaschy et al[12] assessed cognition at 3–5 years of age. Their findings were inconsistent, as Nepomnyaschy et al[12] found significant group differences in vocabulary, literacy, receptive language, and mathematical ability, while Brown et al[28] found no group differences. The inconsistency can be explained by the difference in the cognitive measures used in the outcome assessment. Nepomnyaschy et al[12] focused on more detailed conceptual constructs of cognition; Brown et al[28] used a general measure, ie, the MSD scale. This suggests that with a general measure, the infants born LPT and full term may score similarly, possibly because scores on some items inflate the overall score, thus reducing the likelihood of detecting more subtle deficits in conceptual areas. In contrast, the more detailed assessment of specific conceptual constructs allows the examiner to determine an understanding of strengths and weaknesses within the broader cognitive domain.

No significant group differences were seen between the LPT and full term groups in the motor domain at 3–5 years of age. Several studies[9,10,12,14,16,17,22,28] compared the motor and cognitive outcomes of 3–5-year-old children born LPT, with and without medical complications. The findings of these studies suggest that infants with medical complications requiring a prolonged hospitalization or stay in a neonatal intensive care unit are at higher risk than infants born LPT who did not have medical complications. However, three studies that compared medically complicated and uncomplicated LPT infants were completed in one medical center, limiting the generalizability of these results. In addition, there are no studies of the outcomes of these infants at school age or older.

Outcomes from 6 years of age and older

The findings of the included studies assessing cognition in children 6 years of age and older identified poor performance, lower IQ, and lower scores in reading and mathematics when compared with the full term group.[15,18,22] It is noteworthy that group differences are attenuated and become less or even nonsignificant with an increase in the age of assessment, ie, assessment performed at 11–15 years of age.[16,18,20] In addition, in multiple studies, there is a difference in the cognitive scores between groups; however, the scores of both groups are in the average range for the assessment utilized.[25,27] This result suggests that as a group, LPT infants have lower cognitive function in later years, but possibly not to the level of cognitive impairment in the early school years.

While many studies found that cognitive scores were only different on a few measures by school age, the number of children who were under-performing in school or who required special education was different between groups.[13,18,20] This fact suggests that while the infants born LPT may only have small gaps in their cognitive capacity, the gaps, combined with the other issues such as sensory processing or attention (which were not reviewed in this paper), may be resulting in reduced academic performance and a greater need for special education support in the school.

The present systematic review has some limitations that may have influenced the identification of papers or interpretation of our results. First, our key search terms restricted our search to four domains of neurodevelopment: the cognitive, motor, language, and school/academic performance domains. Thus, we did not include studies discussing social, emotional, or behavioral outcomes, or the diagnosis of specific conditions. Thus, we cannot comment on the presence of other impairments in the populations or their impact on the neurodevelopmental outcomes we assessed. Second, we focused on the outcomes, which in most cases had been statistically adjusted for social and medical factors. Thus, the results are likely a significant under-representation of the neurodevelopmental impairments in the entire population of children born LPT. This confounding factor may also account for some of the differences in cognitive and school outcomes. Infants born LPT who have mild cognitive impairment, but have access to highly qualified teachers, tutors, and educated parents may be able to compensate for their impairments, while children without these resources are less successful in school. Additional analysis of the outcomes, using both adjusted and non adjusted values, is required to begin to address this issue. Lastly, we have only discussed the design aspect of the included studies, and we did not weigh analysis quality of the included studies in our interpretation of results.

Further research is needed to fill in some gaps in the literature and to expand our understanding of the developmental outcomes of infants born LPT. Researchers aiming to work on the neurodevelopment of LPT infants should include a control/full term group in their study design along with confounding neonatal medical variables in order to determine post-birth fragility status. The inclusion of a healthy and a medically complex group of LPT infants would also add considerable value to all future studies. It is essential to note that recruiting the LPT group based on parental reports of gestational age raises questions about the accuracy of the exposure measured. A consistent use of outcome measures between studies would also greatly increase comparison power between future studies. Lastly, researchers and clinicians need to consider the chronological age and corrected age of infants born LPT until at least 2 years of age, and furthermore, they should document outcomes for both chronological and corrected ages until we have a better understanding of when and if infants born LPT do catch up to their peers.

Conclusion

In conclusion, infants born LPT are at a risk of having reduced long-term neurodevelopmental outcomes, with cognition being at the highest risk and persisting the longest. Physicians, early intervention, and early childhood education programs, policies makers, parents, therapists, and teachers need to be aware of the long-term neurodevelopmental risks associated with LPT birth. While the risks maybe be lower for LPT births than for extremely preterm infants, systematic follow-up and/or assessment at school entry be beneficial to improve the outcomes of infants born LPT.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Search terms

PubMed database

Keywords: (((“late preterm infants”) OR ((“Premature Birth”[Mesh]) OR “Infant, Premature”[Mesh]))) AND ((“Child Development”[Mesh]) OR “developmental outcomes” OR “Motor” OR “Cognitive” OR “Language” OR “School performance” OR “Skill”).

((“Child Development”[Mesh] OR “motor development” OR “cognitive development” OR “language development” OR “school performance” OR “developmental outcomes”)) AND ((“Infant, Premature”[Mesh]) OR “Premature Birth”[Mesh] OR (“late preterm infants”) OR (“premature infants”)).

CINAHL database

Search terms: (MM “Child Development”) OR (MH “Infant Development”) OR (MH “Language Development”) OR (MH “Child Development: 12 Months (Iowa NOC)”) OR (MH “Child Development: 2 Years (Iowa NOC)”) OR (MH “Child Development: 3 Years (Iowa NOC)”) OR (MH “Child Development: 4 Years (Iowa NOC)”) OR (MH “Child Development: 5 Years (Iowa NOC)”) OR (MH “Child Development: Middle Childhood (6–11 Years) (Iowa NOC)”) OR (MH “Child Development: Adolescence (12–17 Years) (Iowa NOC)”) OR (MH “Cognition”) OR (MH “Perception”) OR “Cognitive development” OR (MH “Psychomotor Performance”) OR (MH “Learning”) OR (MH “Mental Processes”) OR “Motor development” OR (MH “Academic Performance”) And (MH “Infant, Premature”).

PsycINFO database

{Cognitive Development} OR {Fine Motor Skill Learning} OR {Gross Motor Skill Learning} OR {Infant Development} OR {Language Development} OR {Motor Development} OR {Motor Performance} OR {Motor Skills} OR {Perceptual Motor Learning} OR {Skill Learning} And Premature Infant.

ERIC database

(Child development OR Motor development OR Cognitive development OR Language development OR School performance OR Skill AND late preterm OR preterm infant OR premature infant OR premature birth) AND (late preterm OR premature birth) OR (preterm infant OR premature infant).