Neurodevelopmental outcome of late-preterm infants

A pragmatic review

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This article is the fifth in a series on paediatric health. Articles in this series aim to provide information about diagnosis and management of presentations in infants, toddlers and pre-schoolers in general practice.

Background
The number of late-preterm births ($34^{0/7}$ to $36^{6/7}$ weeks of gestation at birth) has steadily increased over recent years. Recent reports suggest that late-preterm infants are at an increased risk of developing neurodevelopmental abnormalities, compared with full-term infants.

Objectives
The aim of this paper is to carry out a pragmatic review of the current evidence regarding the neurodevelopmental risks of speech delay, cerebral palsy, cognitive delay, autism spectrum disorder and attention deficit hyperactivity disorder in late-preterm infants.

Discussion
Evidence from cohort studies indicates that late-preterm infants have a higher risk of speech delay in the first two years, and cognitive delay and attention problems in early childhood, compared with infants born at term. However, the results are inconsistent. Some reports indicate 'catch up' development with speech and cognition. Developmental surveillance through regular follow-up of high-risk late-preterm infants is necessary to identify risks at the earliest.

ACROSS THE GLOBE, approximately 15 million babies are born preterm, at <37 weeks of gestation each year.[1] Over recent years the number of preterm births, especially in the late-preterm gestation ($34^{0/7}$ to $36^{6/7}$ weeks) category, has increased.[2]

Infants born preterm are at an increased risk of neurodevelopmental abnormalities.[3] Therefore, most neonatal intensive care units provide routine follow-up of at-risk patients for ongoing developmental surveillance. Infants born very preterm at gestational age $<32^{0/7}$ weeks and those who had complications during the neonatal period are considered to be at high risk.[3] Despite recent evidence of higher developmental risks in late-preterm infants when compared with full-term infants, routine developmental surveillance is not generally offered.[4]

With limited hospital-based resources to monitor the development of late-preterm infants, the responsibility for follow-up shifts to child health nurses and general practitioners (GPs), who need to be aware of the increased neurodevelopmental and cognitive risks for these infants. The aim of this review is to provide an understanding of the current evidence on the long-term developmental risks for late-preterm infants, compared with term infants (born at ≥37 weeks of gestation).

Selection of literature

Electronic databases (Cochrane library, Medline, Ovid) were searched to identify studies that explored the association between late-preterm infants and their long-term developmental outcomes. Only studies that reported predefined outcomes of interest were included. Details of the search methodology are available as Appendix 1 (online only). The study selection log is presented in Figure 1 (online only), and details of included studies in Table 4 (online only). Excluded studies and the reason for their exclusion are presented as Appendix 2 (online only). Only relevant results for the late-preterm category are presented.

Late-preterm birth and speech delay

A total of five studies (n = 8479 late-preterm infants and 27,410 term controls) reported this outcome (Table 1).[5–9] Stene-Larsen et al reported that the risk of speech delay was higher by 1.74 times at 18 months and 1.36 times at 36 months in late-preterm infants, compared with term controls. Rabie et al and Nepomnyaschy et al reported that late-preterm infants had significant speech delay at two years of age.[6] By contrast, Gurkha et al observed that the need for speech therapy referrals for late-preterm infants and term infants was comparable.[5] Studies used different methods for speech evaluation at different ages. Stene-Larsen et al evaluated speech at 18 and 36 months, while Nepomnyaschy evaluated speech at two years and four years, using parent-completed questionnaires.[6,8] Rabie et al diagnosed speech delay using ICD-9 coding,[7] while Gurka et al identified referrals for speech therapy needs.[5] Brown et al used the Peabody picture vocabulary test at four to five years of age.[9]

Late-preterm birth and cognitive delay

A total of eight studies (n = 11,511 late-preterm infants and 153,661 term controls) reported on cognitive outcomes (Table 2).[4–6,10–14] Although cognitive delay, special education and need for early intervention may be different measures of the same outcome, only studies that reported a cognitive measure were included. Two studies, Marks et al and Ballantyne et al, used screening questionnaires and were excluded.[14,15] Studies used different methods to identify cognitive delay and performed cognitive tests at different chronological and corrected ages: Morag used the Griffith Mental Development Scales;[14] Gurkha et al used the Woodcock-Johnson Psycho-Education Battery–Revised test;[5] Baron et al used the General Conceptual Ability test;[10] Talge et al used the Weschler Intelligence Scale for Children;[12] and Wolthayer et al used the Bayley Scales of Infant Development.[13] Of the eight studies, half of them – Gurkha et al, Baron et al, Nepomnyaschy et al and Morag et al – found that the cognitive scores of late-preterm infants were comparable with those of term infants.[5,6,10,14] Morag et al reported that late-preterm infants 'caught up' with term controls at 12 months of corrected age and scored less than term controls at a chronological age of 12 months. Four studies – Petrini et al, Talge et al, Wolthayer et al and Morse et al – reported that late-preterm infants were more likely to show lower cognitive scores, compared with term infants.[11–13,16] Talge et al reported that, at the age of six years, late-preterm infants were twice as likely to have IQ scores of below 85, compared with term controls.

Late-preterm birth and motor delay

Some of the studies that reported cognitive scores also reported motor achievement scores. Nepomnyaschy et al reported that the risk of scoring >1 standard deviations (SD) below the mean for gross motor ability was comparable for late-preterm and full-term (>39 weeks of gestation) infants at two and four years of age.[6] Morag et al evaluated motor scores using the Alberta Infant Motor scale at six months and the Griffiths test at 12 months. The authors reported that late-preterm infants showed a mean (± SD) locomotor score of 90 (± 11), significantly lower than the full-term infant score of 97 (± 12).[14] However, late-preterm infants caught up with full-term infants at 12 months of corrected age (Morag et al). Wolthayer et al reported that the adjusted odds ratio (AOR) for psychomotor development index score of <70 (95% CI) was 1.56 (1.29, 1.88) at 24 months of age using Bailey's short test version. The risk of low scores remained even after adjusting for some clinically important risk factors that included fetal growth and mode of delivery.[13]

Late-preterm birth and cerebral palsy

Two studies (n = 48,273 late-preterm infants and 1,096,283 full-term controls) reported on the link between late-preterm birth and cerebral palsy. In a Finnish study, Hirvonen et al reported that late-preterm infants had a higher risk of cerebral palsy diagnosis, with an odds ratio (OR) of 2.35 (95% confidence interval [CI]: 1.99, 2.77), compared with full-term infants by the age of seven years.[17] Factors predictive of an increased risk of cerebral palsy in late-preterm groups included resuscitation at birth (OR 1.78; 95% CI: 1.09, 2.90), antibiotic

Table 1. Late preterm and speech delay

Author	Study characteristics	Results
Stene-Larsen et al[8]	Late preterm n = 1673, term n = 7,109 Speech and language skills at 18 and 36 months evaluated using parent questionnaires.	Adjusted odds ratio (95% confidence interval [CI]) was: • 1.74 (95% CI: 1.41, 2.14) at 18 months • 1.37 (95% CI: 1.09, 1.73) at 36 months.
Rabie et al[7]	Late preterm n = 3270, term n = 11,527 Speech and language delay between three and five years using data from Medicaid claims based on ICD-9 coding.	Adjust hazard ratio was 1.36 (95% CI: 1.23, 1.50).
Nepomnyaschy et al[6]	Late preterm n = 400, full term n = 5050 Speech outcomes at two and four years using parent reports.	Late-preterm children scored lower than full-term children on language use at two years and receptive language at four years.
Gurka et al[5]	Late preterm n = 53, full term n = 1245 Speech outcomes assessed based on referral for speech and language services from grade 0 to 8.	4.7% late-preterm infants and 17.5% of full-term infants were referred for speech and language services. However, the adjust risk ratio of 0.27 (95% CI: 0.07, 1.04) was not statistically significant.
Brown et al[9]	Late preterm n = 3083, full term n = 2479 Peabody Picture Vocabulary test at five years of age.	Rate of receptive vocabulary delay in children aged four to five years was 13.1% in late-preterm infants and 12.7% in full-term infants. Adjusted risk ratio for late-preterm infants was 1.06 (95% CI: 0.79, 1.43).

treatment during the first hospitalisation (1.67; 95% CI: 1.13, 2.44), low one-minute Apgar score (1.80; 95% CI: 1.21, 2.67) and intracranial haemorrhage (12.8; 95% CI: 5.58, 29.2).[17] By the age of seven years, 0.6% late-preterm infants and 0.1% full-term infants were diagnosed with cerebral palsy.[17] Petrini et al evaluated the risk of cerebral palsy by five years of age.[11] Children born late preterm were more than three times as likely to be diagnosed with cerebral palsy when compared with full-term infants, with a hazard ratio of 3.39 (95% CI: 2.54, 4.52). However, results were not controlled for various clinical parameters, and the exact ages at diagnosis of cerebral palsy were variable.[11]

Table 2. Late preterm and cognitive delay

Author	Study characteristics	Key results and comments
Gurka et al[5]	Late preterm n = 53, term n = 1245. Cognitive outcomes at 4–15 years using the Woodcock-Johnson Psycho-Educational Battery–Revised. The subtests chosen included picture vocabulary, passage comprehension, and applied problem-solving skills.	Healthy late-preterm infants were comparable with full-term infants in all the domains. Longitudinal examination of the cognitive and achievement scores revealed no differences between groups.
Baron et al[10]	Late preterm n = 118 (complicated late preterm = 90, uncomplicated =28), term n = 100. Cognitive test using differential ability score at 3.5–4.1 years was performed in a blinded fashion.	Late-preterm infants were comparable with full-term infants with ARR 2.54 (95% CI: 0.77, 8.59). Complicated late-preterm infants scored less than term infants in the general conceptual ability scores (105.9 versus 112.3), in nonverbal reasoning and spatial clusters domains of the test.
Petrini et al[11]	Late preterm n = 8341, term n = 131,059. Developmental delay established using ICD-9 codes on the linked data.	Risk of developmental delay was 12.2 versus 9.2 per 1000 live births. Overall, AOR for risk of developmental delay was 1.36 (95% CI: 1.11, 1.66) when compared with full-term infants. However, age at assessment was unclear. Analysis was adjusted for maternal race/ethnicity, infant sex, multiple gestation, small and large for gestational age status.
Talge et al[12]	Late preterm n = 168, full term n = 168. Full scale and performance IQ and teacher-reported Wechsler Intelligence Scale for Children – Revised were performed at six years of age.	AOR for the risk of IQ scores below 85 for full scale IQ and performance scores were 2.35 (95% CI: 1.20, 4.61) and 2.04 (95% CI: 1.09, 3.82) respectively.
Woythaler et al[13]	Late preterm n = 1200, full term n = 6300. Developmental delay, Mental Development Index scores (MDI) or Psychomotor Index scores (PDI), at 24 months of age using Bailey Scale of Infant Development.	Late-preterm infants compared with full-term infants had lower MDI (85 versus 89) and PDI (88 versus 92) both P <0.0001 respectively. A higher proportion of late preterm infants compared with term infants had an MDI <70 (21% versus 16%; P <0.0001) and PDI <70 (6.1% versus 6.5). AOR for developmental delay was 1.52 (95% CI: 1.26, 1.82).
Nepomnyaschy et al[6]	Late preterm n = 400, full term n = 5050. Mental ability using The Bayley Short Form–Research Edition (BSF-R) was performed at two years of age.	AOR of having scores of >1 SD below the sample mean was 1.07 (95% CI: 0.76, 1.50).
Morag et al[14]	Late preterm n = 124, full term n = 33. Griffiths Mental Development Scale at 12 months of chronological and corrected age.	Mean (SD) developmental quotient scores for performance subscale was 84 (10) vs 95 (19), P <0.001 for late-preterm infants versus full-term infants. At corrected age of 12 months, the scores were comparable at 95 (12) versus 95 (19).
Poulsen et al[4]	Late preterm n = 1107, full term n = 9706. British ability scores at three and five years of age.	The ARR of scoring 1 SD below the mean for picture vocabulary was 1.1 (95% CI: 0.9, 1.3), at five years was 1.0 (95% CI: 0.8, 1.2). At the age of seven years, the ARR for pattern construction subset was 1.05 (95% CI: 0.8, 1.3).

AOR, adjusted odds ratio; ARR, adjusted relative risk; AHR, adjusted hazard ratio; SD, standard deviation.

Late-preterm birth and attention deficit hyperactivity disorder

Four studies (n = 60,328 late-preterm infants versus 101,638 full-term controls) reported on attention deficit hyperactivity disorder (ADHD; Table 3).[7,18–20] The studies used various methods for the diagnosis of ADHD. Talge et al used the Connors parent and teacher questionnaire,[18] Harris et al used diagnostic and statistical manual IV criteria,[19] Lindstrom used the need for stimulant medication as the basis for diagnosis,[20] while Rabie et al used International Classification of Diseases, ninth revision codes for the diagnosis.[7] Rabie et al studied a subgroup of late-preterm infants who were induced because of a medical reason and termed them 'medically indicated late-preterm infants'. They reported that medically indicated late-preterm patients had a higher risk of hyperactivity and high global index scores for ADHD. When all late-preterm infants were combined, the authors did not observe any increase in the risk of ADHD symptoms.[7] Talge et al reported that after adjustment for parity, sociodemographics, child age, and maternal symptoms of depression and serious mental illness during pregnancy and at the child survey, only medically indicated late-preterm was associated with higher hyperactivity and global index scores (mean difference of 3.8 [95% CI: 0.5, 7.0] and 3.1 [95% CI: 0.0, 6.2]).[18] The rate of ADHD also varied among the cohorts.

Late-preterm birth and autism

Only one study, by Guy et al, reported on the risk of autism spectrum disorder (ASD) in late-preterm infants at two years of corrected age using the modified checklist for autism questionnaire. In their population-based prospective cohort study of 548 late-preterm infants and 761 term-born infants, the authors reported that a total of 14.5% late-preterm infants versus 9.3% term controls scored above the clinical cut-off for ASD at two years of age.[21] The risk of true positive failure rate was 2.5% versus 0.5% for late-preterm versus full-term infants on follow-up interview. However, age at follow-up testing was variable. Moreover, information on the neonatal complications were not available and were not controlled for. On further analysis, late-preterm infants with sensory issues, developmental delay, and speech and language issues were more likely to receive a high score on screening tests for ASD.

Discussion

This literature review identifies that at various stages of early childhood, some late-preterm infants are at an increased risk of developmental abnormalities, compared with term infants.

The literature reviewed suggest that most late-preterm infants had typical neurodevelopment comparable with term infants. Some late-preterm infants showed 'catch up' growth with gross motor,[14] speech milestones,[6] cognitive scores[12,13] by early childhood. It appears that a subset of late-preterm infants have persistent problems. Although studies have tried to identify the truly 'at-risk' late-preterm infant, more targeted research is needed to identify this subset of infants.

The results of this review need to be interpreted with caution. It is possible that broadening the search criteria might have resulted in the identification of a greater number of eligible studies. Studies that reported on the cognitive assessment results may have also reported on speech, motor and behavioural outcomes that were

Table 3. Late-preterm birth and risk of attention deficit hyperactivity disorder

Author	Study characteristics	Results
Rabie N Z et al[7]	Late preterm n = 3270, full term n = 11,527. ADHD diagnosis based on ICD-9 codes and Medicaid eligibility.	The rate of ADHD was 2.8% for full-term infants and 3.6% for late-preterm infants. Adjusted hazard ratio was 1.21 (95% CI: 0.98, 1.49).
Harris et al[19]	Late preterm n = 256, full term n = 4419. ADHD and learning disability at school age using DSM-IV criteria and questionnaires. Outcome assessed at 19 years.	ADHD diagnosis for late-preterm versus full-term controls was 7.7% versus 7.2%, P = 0.84 for the overall cohort.
Talge et al[18]	Late preterm n = 152, full term n = 610. ADHD diagnosis was based on parent-reported Connors questionnaire.	Late-preterm birth was associated with higher hyperactivity and global index scores. Mean difference from full-term birth were 3.8 (95% CI: 0.5, 7.0) and 3.1 (95% CI: 0.0, 6.2) respectively.
Lindstorm et al[20]	Late preterm n = 56,650, full term n = 85,082. Diagnosis of ADHD was based on those needing medications identified through the national drug register.	AOR for ADHD was 1.3 (95% CI: 1.1–1.4). Results were adjusted for year of birth, gender, country of residence, birth order, maternal age, education, single parenthood, smoking, low Apgar scores, small for gestational age, parental addictive/psychiatric disorders.

ADHD, attention deficit hyperactivity disorder; AOR; adjusted odds ratio; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edn; ICD-9, International Classification of Diseases, ninth revision

not included in the review. Therefore, selection bias could not be eliminated.

Although many studies in this review were grouped under one clinical outcome, significant clinical heterogeneity between studies was observed. Ages at speech, motor and IQ assessments, as well as diagnosis of cerebral palsy, varied between each study. Some studies performed clinical assessments at chronological age while some studies used corrected age. Only some studies provided the information on other confounding variables such as Apgar scores at birth, growth status of the infant, maternal medical conditions, and need for admission to the neonatal intensive care unit. Each of these confounders can potentially affect the neurodevelopmental outcome of the infant. Therefore, the results of the review lack generalisability. Significant variation in the selection of comparison group was also observed across studies. This varied from full term (>39 weeks of gestation) to term (>37 weeks of gestation), thereby affecting the results of assessments.[5,21] The quality of each study was not evaluated. Therefore, one needs to be careful when drawing strong conclusions from this review.

Nevertheless, the review highlights that late-preterm infants are at increased risk of various developmental abnormalities and would benefit from ongoing developmental surveillance. National Institute for Health and Care Excellence guidelines recommend that late-preterm infants with risk factors such as moderate or severe hypoxic ischaemic encephalopathy, bacterial meningitis, herpes encephalitis or brain lesions identified on magnetic resonance imaging be followed up in the first two years of life.[3] For such patients, a minimum of two clinic visits in the first year between three and five months and at 12 months of corrected age and a developmental assessment at 24 months of corrected age are recommended.[3] Since there is no endpoint to the long-term follow-up of late-preterm infants, follow-up should continue with varying degrees of surveillance reflecting individual patient needs beyond the first two to three years.

The economic costs associated with late-preterm birth are significant. Using data from the National Health Service, UK, Khan et al reported on the cost of late-preterm births over the first two years of life.[22] The authors estimated that the mean societal cost of late-preterm infants was £5823 (AU$10,542), compared with £2056 (AU$3722) for children born at term. In view of medical complications as well as economic costs of late-preterm births, every attempt should be made to minimise delivery at late-preterm gestation. However, minimising the number of infants delivered in the late-preterm gestation may not be straightforward. Maternal conditions, such as gestational diabetes and preeclampsia, may prompt preterm induction of labour to minimise maternal and fetal complications. Fetuses with congenital anomalies or growth restriction may be spontaneously delivered early.[23] Such fetuses, irrespective of the time of gestation at birth, are more likely to have morbidities in infancy and childhood. While efforts to minimise late-preterm birth are ongoing, providing care to this large group of infants is paramount.

Conclusion

This review identifies that late-preterm infants are at an increased risk of developmental abnormalities in early childhood, compared with term infants. The review also identifies that the results are not consistently observed, and some late-preterm infants 'catch up' with speech, motor and cognitive outcomes. Some late-preterm infants show persistence of neurodevelopmental problems in early childhood. More research is needed in this complex area of paediatrics to understand the underlying risk factors for neurodevelopmental impairment in late-preterm infants.[24]

GPs should be more vigilant about the increased risk of neurodevelopmental complications in late-preterm infants. While it is desirable to follow up all late-preterm infants for developmental surveillance, this is not feasible. Therefore, a targeted approach is needed. When infants undergo developmental assessment in the first 2–2.5 years, corrected age (ie age from the due date) should be used for all preterm infants born at <37 weeks of gestation.[25] At least two visits in the first year of life and a review at two years to discuss development are necessary for at-risk late-preterm infants.[3]

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Table 4. Characteristics of included studies

Author/year	Study design	Outcomes	Analysis adjusted for
Baron et al[10]	Retrospective cohort study from 2004 to 2006 Washington DC, USA	Cognitive outcomes using differential conceptual ability scores performed at the age of 3.5–4.1 years of age	Maternal education, medical conditions during pregnancy, infant's sex
Brown et al[9]	Cohort study from Canada	Motor development scales evaluated using tools developed by the US National Center for Health Statistics. Peabody Picture Vocabulary test was performed at age five years	Maternal smoking, alcohol during pregnancy, maternal age, education, income, hypertension, infant's sex
Gurka et al[5]	Prospective cohort study from the National Institute of Child Health and Development Study of Early Child Care and Youth Development observed children from 10 US sites from birth through to age 15 years. Families were recruited at hospital visits after the birth of the child in 1991.	Eleven standard outcomes measuring cognition, achievement, social skills and behavioural/emotional problems using the Woodcock-Johnson Psycho-Educational Battery–Revised and the Child Behaviour Checklist, administered repeatedly through age 15 years	Sex, race, mode of delivery, maternal age, education and certain aspects of maternal health
Guy et al[21]	Prospective cohort study from 1 September 2009 to 31 December 2010 in East Midlands, UK. Mothers of all babies born at 32–36 weeks of gestation were invited to participate.	Autism screen using Modified Checklist for Autism questionnaire completed at two years of age. Brief Infant Toddler Social Emotional Assessment questionnaire was also completed.	Unclear
Harris et al[19]	Retrospective cohort study. Subjects included all children born from 1976 to 1982 in Rochester, USA who remained in the community after five years.	School and medical records were used to identify individuals who met criteria for attention deficit hyperactivity disorder (ADHD).	Maternal education, perinatal complications
Hirvonen et al[17]	Cohort study of live-born infants in Finland from 1991 to 2008	Cerebral palsy. The diagnosis of cerebral palsy was based on medical history, ultrasound and magnetic resonance imaging data, and multidisciplinary evaluations by paediatric neurology units. Hospital discharge summary and ICD-9 and 10 codes were used for ascertainment of the diagnosis.	Unclear
Lindstrom et al[20]	Swedish national cohort of 1,180,616 children born between 1987 and 2000	ADHD. Data linkage with ADHD drug notification system. Patients were followed-up for ADHD medication in 2006 at the age of 6–19 years.	Year of birth, gender, country of residence, birth order, maternal age, education, single parenthood, smoking, low Apgar scores, small for gestational age, parental addictive/psychiatric disorders
Morag et al[14]	Case control study form Israel	Alberta Infant Motor Scale at six months and Griffith Mental Development scales at 12 months of chronological age	Gestational age
Nepomnyaschy et al[6]	Cohort study of over 10,000 children born in USA in 2001. Data was obtained from vital statistics records.	Eighteen developmental outcomes that included cognitive ability, motor ability, and socioemotional skills at both two and four years of age	Ethnicity, maternal age, education, poverty level, father's co-residence status, complications at birth

Table 4. Characteristics of included studies (cont'd)

Author/year	Study design	Outcomes	Analysis adjusted for
Petrini et al[11]	Retrospective cohort study of 141,321 children born at >30 weeks' gestation between January and June 2000. Follow-up at five years of age. Data from inpatient and outpatient databases categorised as per gestational age	Cerebral palsy, developmental delay/ mental retardation was based on International Classification of Diseases, Ninth Revision (ICD 9) codes	Adjusted for maternal race/ ethnicity, infant sex, multiple gestation, small and large for gestational age status
Poulsen et al[4]	Cohort study from England and Wales of all infants born between 2000 and 2001 in Scotland and between 2000 and 2002 in Northern Ireland who were alive and living in the UK at age nine months. Part of the UK millennium prospective cohort study	Cognitive development was assessed using Bracken School Readiness Assessment at age three years, British Ability Scales II at ages three, five and seven years and Progress in Mathematics at age seven years	Maternal age, marital status, education, socio economic status, ethnicity, smoking and alcohol use in pregnancy
Rabie et al[7]	Retrospective cohort study from South Carolina, USA. Data from Medicaid claims and vital records databases based on ICD-9 codes from 2000 to 2003	ADHD, speech and language delay	Unclear
Stene-Larsen et al[8]	Cohort study from Norway – a part of Norwegian Mother and Child cohort study	Speech and language skills at 18 and 36 months using parent questionnaires	Maternal medical conditions, small for gestational age growth status, emergency caesarean section
Talge et al[18]	Prospective cohort study of infants born in Michigan, USA	Attention problems in childhood. Connors' Parent Rating Scales – Short Form: Revised was used for evaluation of attention at school age	Maternal IQ, education, marital status, residential setting and infant's gender
Talge et al[12]	Case control study of randomly selected low-weight and normal-weight births born between 1983 and 1985 in Michigan. Cases were matched for Z score for weight.	Cognitive testing. Child behaviour. Psychologist-administered Welscher's Intelligence scales. Behavioural problems assessed using Child Behaviour Checklists	Maternal IQ, education, marital status and residential setting
Wolthayer et al[13]	A longitudinal cohort of patients born in USA	Bayley Scales of Infant Development Short Form – Research Edition (BSF-R) was used. Cognitive scores that included Mental developmental index and psychomotor developmental index at 24 months of age	Maternal marital status, age, education, maternal depression scores, poverty level and prenatal care. Neonatal gestational age at birth, pleurality, fetal growth status, type of feeding

Appendix 1. Characteristics of excluded studies

Author	Reasons for exclusion
McGowan et al	No full-term controls
Odd et al (three studies)	Moderate-preterm and late-preterm infants were combined together in all three studies
Voigt et al	Moderate-preterm and late-preterm infants were combined together
Protijik et al	Moderate-preterm infants in both the studies
Berry et al	Only in-vitro fertilisation patients selected
Kerstijens et al	Moderate-preterm infants
Cserjesi et al	Moderate-preterm infants
Curry et al	No term controls
Barros et al	Studied infants of adolescent mothers only
Samra et al	Outcome not of interest (visuospatial outcomes)
Tomashek et al	Outcome not of interest (neonatal mortality)
Coletti et al	No full-term controls
Braumbah et al	Outcome not of interest
Baron et al	Outcome not of interest
Shah et at	No full-term controls
Peacock et al	Outcome not of interest
Romeo et al	Included infants born at 33 weeks
Morse et al	The mode of testing was not clear
Marks et al	Results not in required format
Lipkind	Results not in required format

Appendix 2. Literature search methodology

Methods

Study question: Are there differences in long-term neurodevelopmental outcomes among late-preterm infants compared with term infants (born at ≥37 weeks of gestation)?

Criteria for considering studies for this review: Randomised controlled studies, observational cohort studies, cross sectional studies and case control studies that explored the association between late-preterm infants and developmental outcomes were included in this review. Studies published as abstracts, reports from national or local vital statistics not published as peer-reviewed articles were excluded.

Assessment of exposure: Studies that ascertained gestation from parent reports, dating ultrasound, hospital birth certificates, discharge summaries, vital statistics data and national databases were included.

Types of outcome measures: Studies reporting data on speech delay, gross motor delay, cerebral palsy, cognitive delay, autism spectrum disorder, attention deficit hyperactivity disorder were included.

Search strategy for identification of studies: Electronic databases (Cochrane library, Medline, Ovid) were searched on 4 February 2018 and 10 June for published studies in English language. MeSH words 'late preterm' OR 'premature' AND 'developmental outcome' OR 'outcome', 'early intervention', 'cerebral palsy', 'gross motor delay', 'speech delay', 'autism', 'inattention', 'hyperactivity', 'ADHD', alone and in different combinations were used. Alternative terminologies 'neonate', 'infant', 'newborn' were used to identify additional articles. The reference lists of the identified articles were searched for additional eligible studies. The articles were meticulously scanned on the basis of titles and abstracts. Selected articles were retrieved in full and were assessed for eligibility.

Only studies that reported the outcome of interest in late-preterm infants were included. If the study population included gestational age <32 weeks, or a group of 32–36 weeks, or no term comparison group, they were excluded. Given the nature of existing publications, statistical and clinical heterogeneity was expected. Hence descriptive review was planned.

Results

The results of study log is presented in Figure 1. The literature search did not identify any randomised controlled trials. Since this is not intended to be a systematic review, quality assessment or meta-analysis of the studies were not carried out. Excluded studies and the reason for their exclusion are presented as Appendix 1 and clinical characteristics of included studies are summarised in Table 1. Only relevant results for late-preterm category are presented.

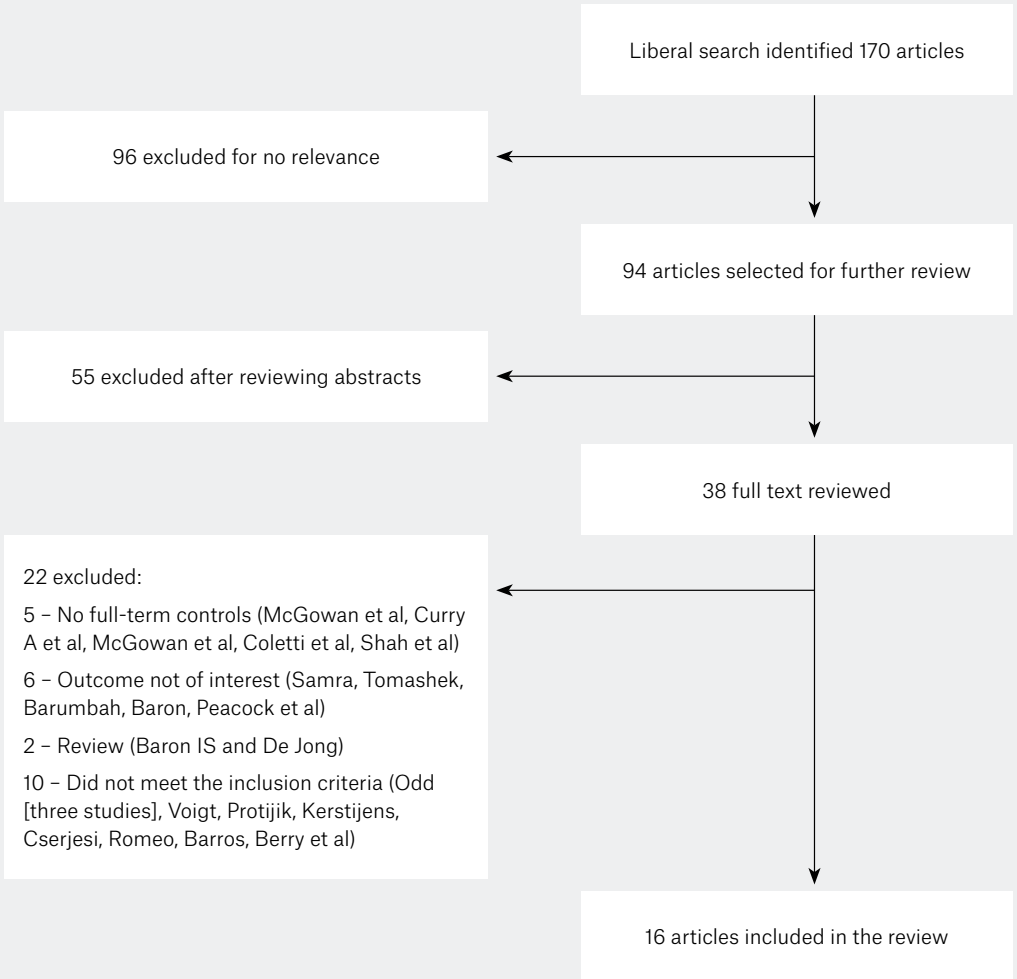

Figure 1. Study selection log