A Systematic Review and Meta-Analysis of Long-Term Development of Early Term Infants

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Key Words

Early term infants · Developmental outcomes · Neurodevelopment

Abstract

Background: Births between 37 0/7 and 38 6/7 weeks of gestation are newly defined as early term infants (ETIs), and are increasingly considered to be at higher risk of adverse outcomes than infants born at 39–41 weeks' gestation. To date, the long-term development of ETIs has not been systematically reviewed. **Objective:** To assess the effect of being born early term on long-term developmental outcomes. **Methods:** The literature of MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials, and abstracts from the Society of Pediatric Research were searched. If two or more studies regarding the same outcome were retrieved, a meta-analysis was conducted by RevMan 5. A sensitivity analysis was performed to assess the heterogeneity. **Results:** Eleven studies involving 4 categories of long-term development were included. Compared with infants born at 39–41 weeks' gestation, ETIs had poorer outcomes in school performance, neurodevelopment, behavior and emotional status and long-term social outcomes. Meta-analyses showed that being born early term significantly increased the risk of cerebral palsy [relative risk, RR, 1.75 (95% confidence interval, CI, 1.32, 2.31)] and

mathematical difficulties [RR 1.13 (95% CI 1.04, 1.21)]. The statistical test of heterogeneity for cerebral palsy was significant. Sensitivity analysis demonstrated that variations in follow-up periods were associated with heterogeneity. **Conclusion:** Emerging evidence suggests that ETIs are at risk of adverse long-term outcomes. Due to paucity and heterogeneity of the existing data, future research is needed to clarify the long-term risk of being born early term.

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Introduction

Historically, gestation has been treated as a binary factor, with 37 gestational weeks defined as the threshold of fetal maturity [1]. Compared with term infants (37 0/7 to 41 6/7 gestational weeks), neonates delivered before 37 weeks are associated with a significantly higher risk of morbidity and mortality, and the risk increases with increasing degree of preterm birth [2]. Infants born at term, on the other hand, are considered healthy and treated as a homogeneous group with respect to neonatal outcomes. However, emerging evidence shows that term births prior to 39 gestational weeks are more likely to have adverse outcomes than those after 39 weeks, indicating gestation is a biologic continuum and the dose-effect exists even within the term spectrum [3]. In the last decade, births

occurring between 37 0/7 and 38 6/7 weeks, newly defined as early term infants (ETIs), increased by nearly 20%, while the delivery of late preterm infants (34 0/7 to 36 6/7 weeks) increased by 12% and births after 40 gestational weeks have declined [1, 4]. ETIs are the fastest growing subgroup of neonates, and account for 17.5% of the annual live births in the United States, whereas preterm births constitute approximately 12.5% in the same cohort [5, 6]. Data from other regions in the world are largely unknown due to the general unawareness of infants born early term. From a public health perspective, ETIs are the main target of health services because the majority of adverse outcomes are attributable to this special subgroup of neonates.

The negative effect of being born early term on short-term morbidity and mortality has been well documented [3, 6]. Although ETIs have a significantly higher risk of morbidity and are more likely to die in infancy when compared with term neonates born after 39 gestational weeks, an increasing number of infants born early term can survive into adolescence or adulthood on account of the progress in neonatal care [3]. In contrast to the abundance of information on short-term outcomes, there is a dearth of research relating to the long-term development of ETIs, and this problem has not been systematically evaluated as far as we are aware. Addressing this issue will help optimize management of a majority of neonates and improve general public welfare. In light of the fact, we undertook a systematic review to explore the long-term effect of being born early term on development.

Method

Search Strategy

A list of literature was identified by searching electronic databases including MEDLINE (1980–2012), EMBASE (1980–2012), Cochrane Database of Systematic Reviews (the Cochrane Library, issue 1, 2012) and Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, Issue 1, 2012) in January, 2012. The following terms were used for searching: early term, or 37 to 38 weeks, and long-term outcome, development, neurodevelopment, child development, health, cognitive, motor, behavior, attention deficit, intelligence, and school. No language restriction was applied. Additionally, the abstract books from the Society of Pediatric Research from 1998 onwards were manually searched during the same time. The reference list of identified studies and reviews were sought for additional citations.

Data Extraction

Retrieved articles were assessed for eligibility. To be included in the study, the participants had to be ETIs (37 0/7 to 38 6/7 gestational weeks). The control group (term infants born after 38

completed gestational weeks) was defined; long-term developmental outcomes of both ETIs and infants in the control group were reported; data and research methodology were adequately described. Studies reporting outcomes by week of gestation were also deemed eligible as long as term births were included. Reviews and follow-up studies on a certain preexisting disorder (e.g. small for gestational age, SGA) that would possibly increase the likelihood of a compromised developmental outcome were excluded. Two reviewers searched literature independently, and discrepancies were resolved by discussions until consensus was achieved. Data on authors, study location, study design, participants, age at assessment and outcomes were tabulated. Where data were incomplete, the corresponding author was contacted for further information.

Methodological Quality of the Studies

Included were non-randomized prognostic studies aimed at investigating long-term outcomes of infants. In light of limited information on the appraisal of such studies, we performed the quality assessment by referring to previous studies [7]. Hayden's framework and the International Society for Pharmacoeconomics and Outcomes Research retrospective database checklist were used to assess the following 7 areas of potential bias: data source, study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement and analysis [8, 9]. An ultimate appraisal of yes, partly, no or unsure was given to each area after generally assessing a list of quality items relevant to it [8]. This type of quality assessment tool is recommended against a score scale because scales are considered to reduce scientific judgment and are more likely to include criteria that do not directly relate to study validity [8, 10]. Two reviewers assessed the quality of studies independently. Kappa value was used to evaluate the inter-rater agreement.

Statistical Analysis

Outcomes of included studies were divided into the following 4 categories: neurodevelopment, schooling problems, behavior and emotional status, and long-term social outcomes. Relative risk (RR) and 95% confidence interval (CI) were calculated for dichotomous outcome variables. Continuous outcome variables were expressed as mean difference and 95% CI. If two or more studies regarding the same outcome were retrieved, a meta-analysis was conducted by using RevMan 5. If appropriate, a fixed effect model was used for combining results in the meta-analysis. Heterogeneity was defined as a significant test of $p < 0.1$, and the I^2 statistic was used to estimate the heterogeneity. In addition, a sensitivity analysis was carried out to assess the heterogeneity. On the other hand, a descriptive methodology was chosen and a narrative synthesis was performed for studies with irrelevant outcomes.

Results

Included Studies

The initial search yielded 1,671 potential related citations. After excluding reviews, irrelevant studies and studies not reporting on ETIs, a total of 12 studies were

Fig. 1. Selection process.

identified. Attempts were made to contact authors of 2 studies for further information [11, 12]. One of them (Dr. Mathiasen) gave a response and the other failed to be contacted. Finally 11 eligible studies were included and the selection process is detailed in figure 1. Characteristics of the 11 studies are summarized in table 1 and quality assessment is presented in table 2 [11, 13–22]. None of the 11 studies focused solely on ETIs, and all of them included a subgroup of infants born at 37–38 gestational weeks within the study population. Most of the included studies showed an overall low level of risk for bias. The quality assessment demonstrated high concordance between the 2 raters as measured by kappa value ($\kappa = 0.741$; $p < 0.0001$), indicating there were no major systematic disagreements. A summary of the results of included studies were shown in table 3.

Neurodevelopment

Neurodevelopmental disabilities have been defined as ‘a group of heterogeneous conditions that share a disturbance in the acquisition of basic developmental skills in a chronologically appropriate manner [23].’ Cerebral palsy (CP) and intellectual disability were included in this broad definition. Data for CP were reported in 3 studies [11, 17, 22], and a random-effects meta-analysis showed that the pooled risk of CP was 1.75 (95% CI 1.32, 2.31) times higher for ETIs than infants born at 39–41 weeks’ gestation (fig. 1). However, the χ^2 test for heterogeneity was significant ($\chi^2 = 20.38$, $p < 0.0001$). Among the 3 studies, Moster et al. [22] showed the lowest risk of CP for ETIs, which could be explained by the fact that their data are retrieved by using a disability register, and only children surviving to 4 years old are included, thus fewer patients may be included. Heterogeneity was no longer significant after excluding the data reported by Moster et al. [22] from this

meta-analysis, and the pooled risk of CP was 1.99 (95% CI 1.79, 2.22), suggesting that the follow-up period is a factor explaining the heterogeneity. There were 3 studies that focused on the impact of being born early term on intelligence scores [13, 18, 21]. However, the data were not eligible for quantitative syntheses due to the widely varying scales used for measurement. It is noteworthy that the score gap between early term group and control group narrowed down when confounding factors like maternal education and family socioeconomic status (SES) were adjusted [13, 21]. Ekeus et al. [18] showed that accounting for perinatal factors such as SGA would further dilute the association between gestation and intelligence scores.

Schooling Problems

Schooling problems have been broadly defined as the need for special education, education below age level, special support in regular school, or poor performance in comparison with pupils in the same class [24]. The 5 studies relating to schooling problems were highly variable with respect to the population size, demographic factors, outcomes and follow-up periods [11, 14–16, 19]. Two of the 5 studies reported data on difficulties in requiring mathematical skills and were subjected to meta-analysis [14, 15]. We noted that the risk of having mathematical difficulties for ETIs was not significant in Kirkegaard’s study [RR 0.82 (95% CI 0.42, 1.6)], which could be explained by the small population size and a low reporting rate [15]. However, the pooled result showed a significantly higher risk of having mathematical difficulties among early term group than their controls [RR 1.13 (95% CI 1.04, 1.21)] with no significant heterogeneity between the studies ($I^2 = 0\%$; $p = 0.35$), indicating the power of detecting an effect was increased after data combination (fig. 2). It can be seen from table 3 that after taking a series of

Table 1. Description of included studies

Study	Location	Study design	Birth of cohort year	Follow-up years	Description of infants		Exclusions	Outcome definitions
					study	control		
Mathiasen et al. [11]	Denmark	Retrospective cohort population based	1988–1989	18–19	37–38 weeks GA n = 16,586	39–41 weeks GA n = 84,560	BW above 6 SD or less than –6 SD	(1) Exam performances after the 9-year compulsory school; (2) cerebral palsy diagnosed by ICD-8 and ICD-10
Eide et al. [13]	Norway	Retrospective cohort population based	1967–1979	18	37–38 weeks GA men n = 37,487	39–41 weeks GA men n = 209,191	Permanent disability	Intellectual performance by the Norwegian draft revised in 1962 including verbal analogues, number series and geometric figures
Quigley et al. [14]	UK	Retrospective cohort population based	2000–2001	5	37–38 weeks GA n = 1,956	39–41 weeks GA n = 5,407	Implausible BW for GA	School performances measured by the foundation stage profile assessing six areas of learning
Kirkegaard et al. [15]	Denmark	Prospective cohort	1990–1992	10	37–38 weeks GA n = 633	39–40 weeks GA n = 3,081	Loss to follow-up	Skills in reading, spelling and math assessed by questionnaires completed by parents and teachers
MacKay et al. [16]	UK	Retrospective cohort population based	1986–2001	4–19	37–38 weeks GA n = 71,403	39–41 weeks GA n = 297,000	Maternal height <100 cm or >200 cm, BW <400 g or >5,000 g and multiple births	Special educational needs of school age children
Lindström et al. [17]	Sweden	Retrospective cohort population based	1987–2000	6–19	37–38 weeks GA n = 214,475	39–41 weeks GA n = 813,606	At least 1 significant malformation, BW above 3 SD or less than –6 SD	(1) ADHD medication with ATC-codes NO6BA01- NO6BA04 or NO6BA01; (2) cerebral palsy was defined as at least 1 hospital admission after 2 years old with a diagnosis of ICD-10
Ekeus et al. [18]	Sweden	Retrospective cohort population based	1973–1976	18–19	37–38 weeks GA men n = 19,146	39–41 weeks GA men n = 94,812	BW above 3 SD or less than –6 SD	Intellectual test scores measured by 'Enlistment Battery 80' representing logical, spatial, verbal and technical capabilities
Lindström et al. [19]	Sweden	Retrospective cohort population based	1973–1979	23–29	37–38 week GA n = 68,541	39–41 weeks GA n = 431,656	At least 1 reported malformation, BW above 3 SD or less than –6 SD	(1) Educational achievement; (2) long-term social outcomes
Lindström et al. [20]	Sweden	Retrospective cohort population based	1973–1979	23–29	37–38 weeks GA n = 71,837	39–41 weeks GA n = 450,165	At least 1 reported malformation, BW above 3 SD or less than –6 SD, improbable measures of length in relation to BW	Psychiatric and addictive disorders defined by using ICD-9 and ICD-10
Yang et al. [21]	Canada	Prospective cohort	1996–1997	6.5	37–38 weeks GA n = 2,569	39–41 weeks GA n = 16,074	BW <2,500 g	Cognitive ability measured by the Wechsler Abbreviated Scales of Intelligence
Moster et al. [22]	Norway	Retrospective cohort population based	1967–2001	At least 4	37–38 weeks GA n = 218,911	39–41 weeks GA n = 1,215,350	BW above 3 SD, registered congenital anomalies, multiple births	Cerebral palsy diagnosed by ICD-9 or ICD-10

GA = Gestational age; BW = birthweight; SD = standard deviation; ICD = International Classification of Disease.

Table 2. Quality assessment of included studies

Summary of quality assessment	Eide et al. [13]	Quigley et al. [14]	Kirkegaard et al. [15]	MacKay et al. [16]	Lindström et al. [17]	Ekeus et al. [18]	Lindström et al. [19]	Lindström et al. [20]	Yang et al. [21]	Mathiasen et al. [11]	Moster et al. [22]
Data source [7, 9] There are sufficient details on the data source to limit selection and measurement bias	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Study participation [8] The study sample represents the population of interest on key characteristics, sufficient to limit potential bias in the results	partly	yes	yes	yes	yes	partly	yes	yes	partly	yes	partly
Study attrition [8] Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias	partly	partly	partly	yes	unsure ^a	no	unsure ^a	unsure ^a	yes	unsure ^a	unsure ^a
Prognostic factor measurement [8] The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Outcome measurement [8] The outcome of interest is adequately measured in study participants to sufficiently limit potential bias	yes	yes	partly	yes	yes	yes	yes	yes	yes	yes	yes
Confounding measurement and account [8] Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	partly	partly	yes	yes	yes	yes	yes	yes	yes	yes	yes
Analysis [8] The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results	yes	yes	partly	yes	yes	yes	yes	yes	yes	yes	yes

^a Attempts to collect information on participants who drop out and characteristics of participants lost to follow-up are not described.

confounders into account, the risks of having several schooling problems for ETIs decreased [14–16]. However, the significance remained even after an extensive adjustment was performed.

Behavior and Emotional Status

Lindström et al. [17] carried out a population-based cohort study to analyze the effect of preterm birth on the

risk of attention-deficit/hyperactivity disorder (ADHD) among school age children. The adjusted risk of receiving ADHD medications was significantly higher among ETIs than that among infants born at 39–41 weeks of gestational age (GA). However, the actual risk for ETIs might be underestimated due to the fact that receiving ADHD medications indicates severe cases of ADHD, and it is highly probable that much milder cases may be left unac-

Table 3. A summary of results of studies

Study	Age at assessment years	Participants	Adverse outcomes	Unadjusted result	Confounding factors	Adjusted result
<i>School outcomes</i>						
Quigley et al. [14]	5	37–38 vs. 39–41 weeks	Not in good level of overall achievement Not working securely in math	RR (95% CI): 1.09 (1.03, 1.15) RR (95% CI): 1.19 (1.09, 1.3)	Sex, ethnicity, birth order, multiple birth, breast feeding duration, month of birth, mother's age, marital status, education, social class and language	aRR (95% CI): 1.05 (1.00, 1.11) aRR (95% CI): 1.13 (1.05, 1.22)
Kirkegaard et al. [15]	10	37–38 vs. 39–40 weeks	Having difficulty in reading Having difficulty in spelling Having difficulty in mathematics	OR: 1.55 OR: 1.54 OR: 0.82	Gender, breastfeeding, and parental educational level	aOR (95% CI): 1.46 (1.01, 2.10) aOR (95% CI): 1.47 (1.01, 2.14) aOR (95% CI): 0.71 (0.36, 1.41)
MacKay et al. [16]	4–19	37 vs. 40 weeks 38 vs. 40 weeks 39 vs. 40 weeks	Requiring special educational provision	OR (95% CI): 37 weeks: 1.43 (1.34, 1.52) 38 weeks: 1.24 (1.18, 1.29) 39 weeks: 1.09 (1.05, 1.14)	Sex, marital status, parity, birth weight centile, induction of labor, mode of delivery, year of delivery, previous spontaneous and therapeutic deliveries, 5-min Apgar score	aOR (95% CI): 37 weeks: 1.36 (1.27, 1.45) 38 weeks: 1.19 (1.14, 1.25) 39 weeks: 1.09 (1.04, 1.14)
Lindström et al. [19]	23–29	37–38 vs. 39–41 weeks	Missing or not completing the compulsory 9 years of school	Prevalence (%): 0.6 vs. 0.4%	Not reported	Not reported
Mathiasen et al. [11]	18–19	37–41 weeks no comparison was made	Failing to pass the exam after 9 years of compulsory school	Prevalence (%): 37 weeks: 11.9%, 38 weeks: 10.5%, 39 weeks: 9.4%, 40 weeks: 8.7%, 41 weeks: 8.5% ^a	Not reported	Not reported
<i>Neurodevelopment</i>						
Mathiasen et al. [11]	18–19	37–41 weeks no comparison was made	Cerebral palsy	Prevalence (%): 37 weeks: 0.6%, 38 weeks: 0.4%, 39 weeks: 0.3%, 40 weeks: 0.2%, 41 weeks: 0.2%	Not reported	Not reported
Moster et al. [22]	4	37 vs. 40 weeks 38 vs. 40 weeks 39 vs. 40 weeks	Cerebral palsy	RR (95% CI): 37 weeks: 1.9 (1.6, 2.4) 38 weeks: 1.3 (1.1, 1.5) 39 weeks: 1.1 (1.0, 1.3) 40 weeks: 1.0	Year of birth, infant sex, maternal age, presence or absence of a partner, educational level of the mother and father, immigrant status of the parents	aRR was identical with crude RR
Lindström et al. [17]	6–19	37–38 vs. 39–41 weeks	Cerebral palsy	Prevalence (%): 0.2 vs. 0.1%	Not reported	Not reported
Eide et al. [13]	18	37–38 vs. 39–41 weeks men	Intelligence score	Mean difference (95% CI): –0.1 (–0.11, –0.09)	Maternal age, maternal education, parity, height and body mass index	Mean difference (95% CI): –0.06 (–0.07, –0.05)
Ekeus et al. [18]	18–19	37–38 vs. 39–41 weeks	Intellectual test score	Mean difference (95% CI): –0.07 (–0.10, –0.04)	Year of birth, age at conscription, conscription office, SES, maternal education, marital status of mother, maternal age, and parity Above factors plus SGA and low Apgar score	Mean difference (95% CI): –0.03 (–0.06, 0.00) Mean difference (95% CI): –0.02 (–0.06, –0.01)

Table 3 (continued)

Study	Age at assessment years	Participants	Adverse outcomes	Unadjusted result	Confounding factors	Adjusted result
Yang et al. [21]	6.5	37 vs. 39–41 weeks 38 vs. 39–41 weeks	Intelligence score	Mean difference (95% CI): 37 weeks: –2.6 (–3.7, –1.4) 38 weeks: –0.6 (–1.1, –0.01)	BW for GA, sex, maternal height and age, smoking and drinking during pregnancy Above factors plus parental marital status, number of children in household, parental education and occupation	Mean difference (95% CI): 37 weeks: –2.4 (–3.5, –1.3) 38 weeks: –0.5 (–1.0, –0.1) Mean difference (95% CI): 37 weeks: –1.7 (–2.7, –0.7) 38 weeks: –0.4 (–1.1, –0.2)
<i>Behavior and emotional status</i>						
Lindström et al. [17]	6–19	37–38 vs. 39–41 weeks	Receiving at least 1 prescription of ADHD medication	OR (95% CI): 1.2 (1.1, 1.3)	Year of birth, gender, residence, birth order, maternal age, maternal education, single parenthood, public welfare, maternal smoking, maternal/paternal, psychiatric/addictive disorders, low Apgar score and SGA	aOR (95% CI): 1.1 (1.1, 1.2)
Lindström et al. [20]	23–29	37–38 vs. 39–41 weeks	Having been discharged from hospital at least once with a main psychiatric diagnosis	HR (95% CI): 1.11 (1.05, 1.16)	Age, gender, housing, social welfare, SES, parental psychiatric disorder, low Apgar score and SGA	aHR (95% CI): 1.06 (1.01, 1.12)
^a Data not published.						

counted for [17]. In another cohort from the same country, Lindström et al. [20] explored the hazard ratio of having a psychiatric disorder for ETIs. The risk was reduced from 1.11 (95% CI 1.05, 1.16) to 1.06 (95% CI 1.01, 1.12) after taking perinatal factors, SES and the home environment into account [20].

Long-Term Social Outcome

A large-scale cohort study analyzed the effect of GA on disability and vocational success among young adults [19]. Potential confounding factors included maternal factors, SES and single-parent household. In comparison to adults born at 39–41 gestational weeks, those born early term carried significantly increased risk for disability [adjusted RR 1.26 (95% CI 1.17, 1.35)]. However, the chance of getting employed [adjusted RR 0.99 (95% CI 0.98, 1.02)] and the mean net salary (mean difference: –6 EUR; $p = 0.907$) were identical between the two groups,

suggesting the adverse effect of being born early term on certain social outcomes might be attenuated by long-term postnatal environments [19].

Discussion

ETIs are a newly defined subgroup of neonates who are beginning to arouse attention due to their suboptimal long-term outcomes shown by emerging evidence. In this systematic review of long-term developmental outcomes of ETIs, none of the 11 retrieved articles focused solely on ETIs, highlighting a paucity of relative literature. Although wide heterogeneity existed among included studies, all authors reported a consistent trend of poorer outcomes among ETIs than that among infants born at 39–41 weeks of GA. It should be noted some cohorts were born before ultrasound became a routine procedure to

Fig. 2. Meta-analyses of the risk of adverse long-term outcomes for ETIs compared with term infants born at 39–41 gestational weeks. **a** Forest plot of the risk and 95% CI of cerebral palsy for ETIs. **b** Forest plot of the risk and 95% CI of mathematical difficulties for ETIs.

measure GA, and a considerable number of individuals born term were miscoded as preterm, which may lead to underestimation of the effect of being born early term on long-term risks [11, 13, 17–20, 22]. Compared with infants of 39–41 gestational weeks, a significant increase in the risk of CP and mathematical difficulties among ETIs was shown by our meta-analyses.

The traditional assumption of gestation to be a dichotomous developmental course has been challenged as

mounting evidence demonstrates that the dose-dependent effect of gestation on neonatal outcomes exists not only across the spectrum of preterm but also within the boundary of term [1, 2]. Over the last several years, risks posed to late preterm infants, a marginally term group, have been sufficiently realized, and much effort has been dedicated to prevent late-term deliveries [25, 26]. Recently, ETIs were defined to raise concerns for infants born at the more optimistic stage of term, stressing the fact that

gestation is a biological continuum, and any classification tends to be arbitrary [3]. A reverse J-shaped relationship between the risk of suboptimal outcomes and GA across the whole gestational spectrum indicates that the optimal time of gestation occurs somewhere between 39 and 41 completed weeks, a much narrower interval than the historically held 5-week term period [16, 22]. A delivery occurring earlier or later may increase the risk of adverse outcomes.

Our results demonstrated that each additional week of gestation prior to 39 gestational weeks was accompanied by increased intelligence scores and a reduced risk of CP. The gradient suggests that the relation between GA and brain development is present across the whole gestation and not confined solely to preterm infants. Active myelination and significant growth in various kinds of brain cells are observed between 34 and 40 weeks of GA, which contributes to the 50% increase in cortical volume and the 25% increase in cerebellar development [27]. Inge et al. [28] assessed the brain volumes of normally developing children when they were 9 years old, finding that ETIs had a smaller cerebellar volume than their counterparts who were born at 39–41 weeks' gestation even after adjusting for birthweight, age, sex and head size. Davis et al. [29] found that among healthy term infants without any perinatal risk factors such as intraventricular hemorrhage and periventricular leukomalacia, a longer gestation was associated with an increase in gray matter density of certain brain regions. These data suggest that shortened gestations even within the spectrum of term can interrupt the process of brain maturity. Additionally, perinatal risk factors such as neonatal morbidities and medical treatments can compound existing biological vulnerabilities and impede postnatal brain development [29]. Apart from obvious disabilities like CP, early term births are at risk of subtle developmental impairments such as schooling problems, behavioral and emotional problems, and social disadvantages, the underlying mechanisms being largely unknown [11, 13–16, 19]. It is noted that associations between GA and adverse long-term outcomes are attenuated with adjustment for potential confounders, most of which are associated with parental characteristics and housing conditions, suggesting that postnatal environments may compensate for neonatal disadvantages. Therefore, a long-term follow-up combined with appropriate interventions may help identify and alleviate potential problems encountered by ETIs during their process of development.

The risk of bias is considered to be higher in a systematic review of non-randomized studies due to the lack of

randomization and loss to follow-up. The strength of this review is that most included studies are high-quality population-based cohort studies, which is considered helpful in reducing selection bias. Even though current evidence generally supports that ETIs have an increased risk of suboptimal long-term development, a conclusive statement cannot be reached given the limitations of included studies and the wide heterogeneity among them. Although extensive adjustments are conducted in included studies, most of the participants retrospectively enrolled were born prior the last decade or even as much as 4 decade ago, during which time the medical technology evolved rapidly, and the care provided to ETIs may not be uniform; therefore, the chance of confounding bias remains high. Additionally, the prevalence rate of an adverse outcome among ETIs is considerably low when compared with that among infants born more preterm; a large sample of population might be needed to detect an effect. Therefore, reporting biases will arise as small-size studies with negative results are not likely to be reported or published. As demonstrated in our review, wide variations exist in population size, demographic characteristics, follow-up period and outcomes of interest. The results of our meta-analysis should be interpreted with caution due to the limited number of included studies. Standardization of future study protocols is needed, so that more studies can be quantitatively assessed and the risk of suboptimal outcomes under different categories can be adequately evaluated for ETIs.

Conclusion

ETIs are a subgroup of neonates assuming great importance in public health. However, the long-term risks associated with early term births have not been well understood due to the heterogeneity and paucity of current data. A complex series of factors can impact the trajectory of development in ETIs, which needs to be clarified by further studies with an adequate population size and a standardized study design. As evidence accumulates, the management of ETIs can be guided and optimized.

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References

- 1 Fleischman AR, Oinuma M, Clark SL: Re-thinking the definition of 'term pregnancy'. *Obstet Gynecol* 2010;116:136–139.
- 2 Saigal S, Doyle LW: An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;371:261–269.
- 3 Engle WA: Morbidity and mortality in late preterm and early term newborns: a continuum. *Clin Perinatol* 2011;38:493–516.
- 4 Davidoff MJ, Dias T, Damus K, Russell R, Bettegowda VR, Dolan S, Schwarz R, Green NS, Petrini J: Changes in the gestational age distribution among US singleton births; impact on rates of late preterm birth, 1992 to 2002. *Semin Perinatol* 2006;30:8–15.
- 5 Hankins GDV, Clark S, Munn MB: Cesarean section on request at 39 weeks: impact on shoulder dystocia, fetal trauma, neonatal encephalopathy, and intrauterine fetal demise. *Semin Perinatol* 2006;30:276–287.
- 6 Engle WA, Kominiarek MA: Late preterm infants, early term infants, and timing of elective deliveries. *Clin Perinatol* 2008;35:325–341.
- 7 McGowan JE, Alderdice FA, Holmes VA, Johnston L: Early childhood development of late-preterm infants: a systematic review. *Pediatrics* 2011;127:1111–1124.
- 8 Hayden JA, Cote P, Bombardier C: Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–437.
- 9 Moher B, Brooks J, Clark MA, Crown WH, Davey P, Hutchins D, Martin BC, Stang P: A checklist for retrospective database studies – report of the ISPOR Task Force on Retrospective Databases. *Value Health* 2003;6:90–97.
- 10 Higgins J, Green S: *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, John Wiley & Sons, 2008, pp 190–191.
- 11 Mathiasen R, Hansen BM, Andersen AM, Forman JL, Greisen G: Gestational age and basic school achievements: a national follow-up study in Denmark. *Pediatrics* 2010;126:e1553–e1561.
- 12 Wolke D, Schulz J, Meyer R: Entwicklungs-slangzeitfolgen bei ehemaligen, sehr unreifen Frühgeborenen Bayerische Entwicklungsstudie. *Monatsschr Kinderheilkd* 2001;(suppl 1):S53–S61.
- 13 Eide MG, Oyen N, Skjaerven R, Bjerkedal T: Associations of birth size, gestational age, and adult size with intellectual performance: evidence from a cohort of Norwegian men. *Pediatr Res* 2007;62:636–642.
- 14 Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, Kurinczuk JJ: Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Arch Dis Child Fetal Neonatal* 2012;97:F167–F173.
- 15 Kirkegaard I, Obel C, Hedegaard M, Henriksen TB: Gestational age and birth weight in relation to school performance of 10-year-old children: a follow-up study of children born after 32 completed weeks. *Pediatrics* 2006;118:1600–1606.
- 16 MacKay DF, Smith GC, Dobbie R, Pell JP: Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med* 2010;7:e1000289.
- 17 Lindström K, Lindblad F, Hjern A: Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. *Pediatrics* 2011;127:858–865.
- 18 Ekeus C, Lindström K, Lindblad F, Rasmussen F, Hjern A: Preterm birth, social disadvantage, and cognitive competence in Swedish 18- to 19-year-old men. *Pediatrics* 2010;125:e67–e73.
- 19 Lindström K, Winblad B, Haglund B, Hjern A: Preterm infants as young adults: a Swedish national cohort study. *Pediatrics* 2007;120:70–77.
- 20 Lindström K, Lindblad F, Hjern A: Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. *Pediatrics* 2009;123:e47–e53.
- 21 Yang S, Platt RW, Kramer MS: Variation in child cognitive ability by week of gestation among healthy term births. *Am J Epidemiol* 2010;171:399–406.
- 22 Moster D, Wilcox AJ, Vollset SE, Markestad T, Lie RT: Cerebral palsy among term and postterm births. *JAMA* 2010;304:976–982.
- 23 Shevell MI: Present conceptualization of early childhood neurodevelopmental disabilities. *J Child Neurol* 2010;25:120–126.
- 24 Wolke D: Psychological development of prematurely born children. *Arch Dis Child* 1998;78:567–570.
- 25 Barros MC, Mitsuhiro S, Chalem E, Laranjeira RR, Guinsburg R: Neurobehavior of late preterm infants of adolescent mothers. *Neonatology* 2011;99:133–139.
- 26 Raju TN, Higgins RD, Stark AR, Leveno KJ: Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. *Pediatrics* 2006;118:1207–1214.
- 27 Arpino C, Compagnone E, Montanaro ML, Cacciatore D, De Luca A, Cerulli A, Di Girolamo S, Curatolo P: Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139–1149.
- 28 Inge LC, van Soelen IL, Brouwer RM, Peper JS, van Beijsterveldt TC, van Leeuwen M, de Vries LS, Kahn RS, Hulshoff Pol HE, Boomsma DI: Effects of gestational age and birth weight on brain volumes in healthy 9 year-old children. *J Pediatr* 2010;156:896–901.
- 29 Davis EP, Buss C, Muftuler LT, Head K, Hasso A, Wing DA, Hobel C, Sandman CA: Children's brain development benefits from longer gestation. *Front Psychol* 2011;2:1.