



Long-Term Neurodevelopmental Outcomes after Moderate and Late Preterm Birth: A Systematic Review

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Objective To systematically review and perform meta-analyses on the long-term neurodevelopmental outcomes of adults born moderate and late preterm (MLPT) in relation to cognitive functioning and psychiatric disorders.

Study design A search was conducted to identify any studies that involved prematurity in adulthood. From these studies, reports that included a group of MLPT adults and included description of cognitive and/or mental health domains (including specific long-term outcomes) were selected.

Results In total, 155 publications were identified, but only 16 papers met the inclusion criteria. A small effect size ($g = 0.38$) was found in MLPT to demonstrate poorer intellectual performance compared with those born at term. Moreover, MLPT adults exhibited greater odds for any psychiatric (OR 1.14), substance use (OR 1.16), mood (OR 1.06), and psychotic disorders (OR 1.40).

Conclusions Despite inconsistency due to the methodologic differences between the selected studies, MLPT showed minor long-term effects into adulthood. However, more studies are needed, because prematurity seems to confer some vulnerability to biological and environmental factors that enhance susceptibility to adverse neurodevelopment outcomes. (*J Pediatr* 2021;237:168-76).

Preterm birth is defined as any delivery before 37 completed weeks of gestation. Considering that prematurity is described as a chronic condition,¹ adverse long-term neurodevelopmental consequences are known to occur even in infants born at 34 to 36 weeks of gestation. There are a wide variety of terms (ie, near-term and marginally preterm delivery) to label different gestational age ranges of infants born preterm considered as having a lower risk of neurodevelopmental disorders compared with infants born extremely premature.² Neonates born moderate and late preterm (MLPT), however, are born during a sensitive period for brain development,³ with a commensurate greater risk of morbidity and mortality than their peers born at full term.⁴ These subgroups account for >80% of preterm deliveries,⁵ and some may need early intervention, therapeutic services, and special educational support.^{6,7}

Little is known about whether there are any long-lasting effects of MLPT birth on cognition and mental health in adulthood, although these preterm subgroups might be shown to be at a greater risk of adverse neurodevelopmental outcomes compared with those born at term.¹ The limited evidence gathered among adults in heterogeneous preterm samples of participants whose gestational age was 28-36 weeks indicates that cognitive performance is commonly affected and there is a greater prevalence of behavioral and psychiatric disorders.⁸ However, because previous studies comprised preterm samples with different gestational ages, more studies are needed to specifically assess the neurodevelopmental effects of MLPT birth on adult outcomes.

We focused on the cognitive and mental health characteristics of adults born preterm, who are less likely to present adverse neurodevelopmental outcomes compared with those born extremely or very preterm. Further, in contrast to previous reviews,^{8,9} which focused especially on late prematurity or other gestational ages (ie, early-term birth) and medical/academic outcomes, this review aims to systematically identify empirical studies on the long-term neurodevelopmental outcomes of MLPT adults in relation to cognitive functioning and psychiatric disorders.

Methods

Search Strategy

Databases used included PubMed, Google Scholar, and Medline. The original search strategy was developed for its use in PubMed. The search specified that the terms to be found in the title, abstract and/or key words of the studies

MLPT	Moderate and late preterm
RR	Relative risk
SES	Socioeconomic status
SGA	Small for gestational age

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were: (a) premature birth/prematurity; (b) moderate preterm/late preterm/near-term/marginally preterm; (c) cognition/cognitive functioning; (d) psychiatric*/mental health; (e) adult*; and (f) specific long-term outcomes (IQ f_1 , educational status f_2 , anxiety f_3 , depression f_4 , attention deficit/hyperactivity disorder f_5 , autism spectrum disorder f_6 , and schizophrenia f_7). First, a search was made for any studies written in English that involved prematurity in adulthood. Once the search was completed, only those studies that included a group of adults born preterm who were considered to be at lower risk of presenting neurodevelopmental alterations were selected (ie, non-uniform definitions comprising the following terms: moderate preterm, late preterm, near-term, and/or marginally preterm). Finally, those studies that considered at least 1 of the domains under study (cognition, mental health, and/or specific long-term outcomes) were chosen. Therefore, searches were conducted in the databases using the following set of key words: first (a)+(e); then (a)+(b)+(e) or (a)+(c)+(e) or (a)+(d)+(e) or (a)+(e)+ [f (each f individually)]; and finally, (a)+(b)+(c)+(e) or (a)+(b)+(d)+(e) or (a)+(b)+(e)+[f (each f individually)]. The search strategy is detailed in **Table I** (available at www.jpeds.com).

Inclusion Criteria

Studies from January 2000 to February 2021 were included if they involved MLPT adults (ie, they included adults born with a gestational age between 32^{0/7} and 36^{6/7} weeks); and if their main objective or secondary outcome was to investigate at least 1 of the following domains: cognition and/or mental health.

The results on the effect of the socioeconomic status (SES) included in the studies that fulfilled the aforementioned criteria also were reported. Similarly, some parents' data such as marital status were considered to be important confounders relevant to the interpretation of the results. Additional clinical data also were considered to characterize the samples under study, including having been born small for gestational age (SGA). Hence, some supplementary information was collected when the studies were conducted (eg, SES) and data on other attributes such as neonatal information (eg, birth weight) were retrospectively obtained by consulting medical records.

Eligibility Criteria

Studies were de-duplicated and screened by title, abstract and full-text by 2 reviewers. Study eligibility for inclusion was assessed and full data extraction was conducted independently by the same reviewers. Disagreement between the 2 main reviewers was settled by a third reviewer, who determined the conclusive decision. Published data extracted from the selected publications were also approached for further information if needed.

Study Selection and Data Extraction

Reports for this review were obtained through a 3-step process. **Figure 1** provides an overview of the literature

identification process by means of an adapted flow diagram using PRISMA guidelines.¹⁰ First, 155 articles were retrieved from a systematic database search. After removal of duplicates ($n = 49$), 106 reports were obtained through title search and 44 studies were excluded after title screening. Second, the abstracts of 62 papers were screened to exclude those papers that did not fulfill the selection criteria. Finally, the full-text versions of 24 reports were assessed, and only those that matched the inclusion criteria were included. Eight articles were excluded because they studied long-term outcomes other than those selected for the present review (eg, cortisol profiles, exercise capacity, etc). Therefore, the final number of publications for review and subsequent analysis consisted of 16 research papers. Studies evaluating cognition and mental health are shown in **Table II** and **Table III**, respectively (available at www.jpeds.com) details those studies based on mental health.

Protocol and Registration

The review was conducted according to the “The PRISMA 2020 statement: an updated guideline for reporting systematic reviews” guidelines.¹⁰ This systematic review protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (CRD42020153096).

Risk of Bias in Individual Studies

Two reviewers independently assessed the quality of the selected studies using the Newcastle–Ottawa Scale (**Table IV**; available at www.jpeds.com).¹¹ This scale's standards are split into 3 sections: (1) selection, (2) comparability, and (3) outcome. Each study was scored for each section. More specifically, a maximum of 1 star could be assigned to each item within the selection and outcome categories, and a maximum of 2 stars could be given to the comparability category. According to the specific acceptability criteria considered for the present review, studies achieving 6 or more stars were considered of high quality. To address the consistency of the system, interrater reliability was performed and a Cronbach alpha of 0.94 was obtained.

Data Synthesis

Regarding quantitative cognitive results, Hedge g effect sizes were calculated to analyze the magnitude of the effects found when comparing group mean differences and in regression analyses. A score of 0.2 shows a small effect size, 0.5 indicates a medium effect size, and values >0.8 reflect a large effect size. The effect size from 2 studies was not included because adults' educational attainment was categorized in a qualitative way.^{12,13} Likewise, the effect size from another study¹⁴ was not obtained, as it provided logarithmically transformed data.

To quantitatively analyze the results from the psychiatric domain, the ORs, hazard ratios, and relative risks (RRs) provided by the studies included in this review are summarized in **Table V**. The ORs represent the odds that a psychiatric disorder will occur in MLPT adults compared with the odds that a full-term born adult would suffer a psychiatric

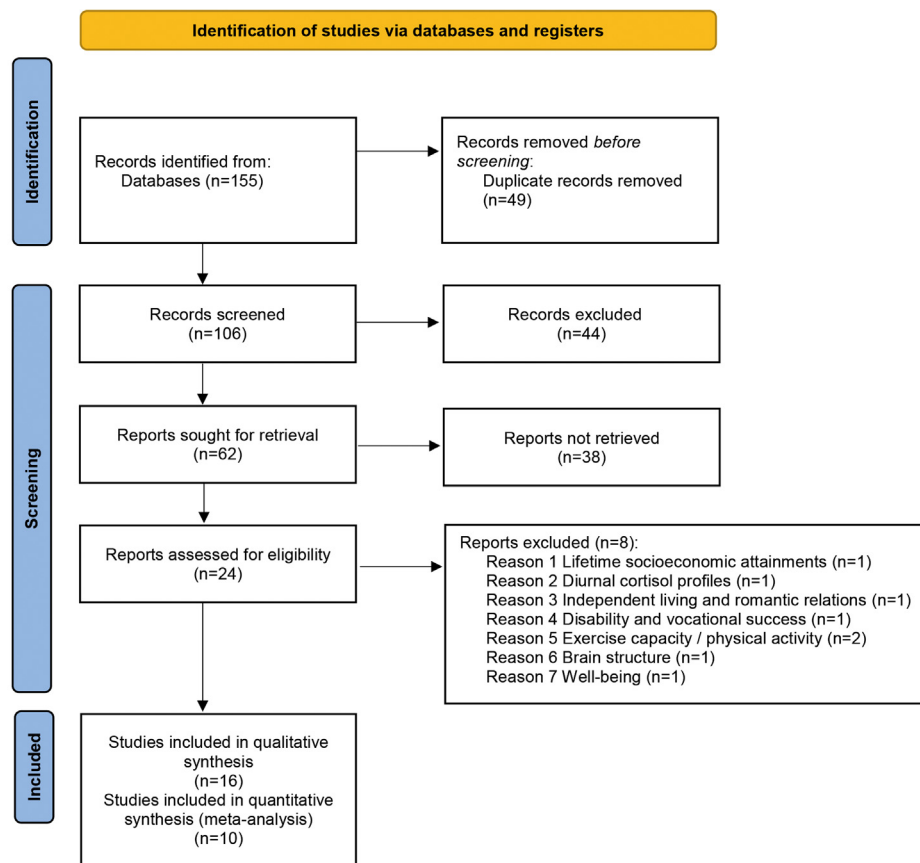


Figure 1. PRISMA 2020 flow diagram for new systematic reviews that included searches of databases and registers only. From Page et al.¹⁰ For more information, visit: <http://www.prisma-statement.org/>.

disorder; hazard ratios and RRs indicate the risk that 1 MLPT adult out of the total number of MLPT adults under study will suffer a psychiatric disorder. Because none of these ratios were described in one of the studies,¹⁵ prevalence data and percentages reported for this case are included in **Table V**.

Finally, RStudio software (version 1.2.5001)¹⁶ was used to analyze the data of those cognitive and psychiatric domains specified in at least 3 or more studies included in the present review. Specifically, the *meta* package was used to analyze generic inverse variance (ie, cognitive data) and binary outcome data (ie, psychiatric domains) through a random-effects model. Regarding heterogeneity, Tau-squared (t^2) and I^2 were calculated to assess whether heterogeneity was statistically significant, and the respective degree of heterogeneity between the studies. An I^2 value of percentages of around 25%, 50%, and 75% would result in low, medium, and high heterogeneity, respectively. Forest plots were used to visualize the overall effects (ie, standardized mean difference and OR) derived from combining the individual studies, and funnel plots were also obtained to assess publication bias. Lastly, meta-regression analyses were conducted to evaluate the impact of four moderator variables (ie, study quality, age at evaluation, gestational age, and year of publication) on the effect sizes of the selected studies.

Results

Study Characteristics

Of the 16 studies, 14 were conducted in 3 European countries—Sweden, Norway, and Finland,^{13-15,17-27} 1 in New Zealand,²⁸ and another 1 in the US (Maryland).¹² All studies were published within the past 13 years. However, they included a substantial range of birth dates (1934-1989) and age at assessment (16-77 years). Ten studies were birth/prospective cohorts,^{12-15,17-21,28} and only 6 were conducted by using national records in a retrospective way.²²⁻²⁷ Sample sizes ranged considerably in studies that included adults born moderately preterm (eg, from $n = 126$ to $n = 1088$),^{27,28} and studies that assessed adults born late preterm (eg, from $n = 47$ to $n = 664$).^{17,20} Three studies were performed on military conscription populations when only male subjects were accepted for this purpose.^{22,24,27} Two publications submitted results relating to both cognition and mental health for the samples under study.^{15,28} Therefore, 10 studies were related to cognition (**Table II**) and 8 to mental health (**Table III**). Finally, all the studies that met the inclusion criteria were rated as being of high quality. In fact, 5 of the selected studies obtained the maximum score from both reviewers (**Table IV**).^{14,17-19,25}

Table V. Effect sizes on mental health outcome data in adults who were MLPT

Mental health outcome	Dalziel et al, 2007 ^{28*}	Heinonen et al, 2016 ^{18†}	Lahti et al, 2015 ^{20‡}	Lindström et al, 2009 ^{21§}	Moster et al, 2008 ^{25¶}	Nosarti, 2012 ^{23**}	Sammallahti et al, 2017 ¹⁵	Upadhyaya et al, 2020 ^{26††}
Any psychiatric disorder	RR 0.37 (0.12-1.1) ^{‡‡}	OR 1.08 (0.66-1.80)	HR 1.06 (0.86-1.31)	OR 1.3 (1.2-1.4)			34 (35%)	
Mood disorder		OR 1.08 (0.53-2.21)	HR 0.81 (0.54- 1.23)	OR 1.3 (1.1-1.5)				
Anxiety disorder	RR 0.69 (0.41-1.2)	OR 1.00 (0.40-2.49)	HR 0.89 (0.52-1.52)	OR 1.5 (1.3-1.9)				
Psychotic disorders			HR 1.33 (0.87-2.04)	OR 1.3 (1.1-1.7)	RR 1.3 (1.0-1.7)			
Personality disorders			HR 0.85 (0.43-1.67)					
Organic/neuropsychiatric disorder				OR 2.1 (1.7-2.4)				
Nonaffective psychosis						HR 1.6 (1.1-2.3)		
Depressive disorder	RR 0.56 (0.30-1.0)					HR 1.3 (1.1-1.7)		OR 1.0 (0.81-1.24) OR 0.91 (0.76-1.08) ^{§§}
Bipolar affective disorder						HR 2.7 (1.6-4.5)		
Autism spectrum disorder					RR 0.8 (0.4-1.4)			
Suicides			HR 1.70 (0.91-3.17)	OR 1.2 (1.0-1.4)				
Suicide attempts			HR 0.69 (0.22-2.21)	OR 1.2 (1.0-1.4)				
Substance use and addictive disorders		OR 1.30 (0.73; 2.29)	HR 1.13 (0.85-1.50)	OR 1.2 (1.1-1.3)		HR 1.2 (1.0-1.4)		
Eating disorder						HR 1.4 (0.9; 2.4)		
Alcohol dependency						HR 1.3 (1.1-1.5)		
Discharged from a hospital at least once with a main psychiatric diagnosis				HR 1.16 (1.07; 1.26) (d)				

HR, hazard ratio.

Values are HR, OR, RR (95% CI) or n (%) prevalence (percentage).

*Adjusted for sex, and antenatal betamethasone.

†Adjusted for sex, age and maximum educational level of either parent(s), own educational level, maternal age, and prepregnancy body mass index, multiple pregnancy, parity, SGA, large for gestational age, 5-minute Apgar score, smoking during pregnancy, maternal diabetes, hypertension, and preeclampsia, length of hospitalization after birth, and mother's self-reported mental health.

‡Adjusted for sex and year of birth and adjusted for fetal growth, socioeconomic position in childhood and mothers' marital status at childbirth.

§Adjusted for age, sex, housing, social welfare in 1990, SES, parental psychiatric disorder, low Apgar score, and SGA.

¶Adjusted for sex, year of birth, multiple births, single motherhood, maternal age, mother's level of education, father's level of education, and whether parents were immigrants.

**Adjusted for sex, parity, maternal age at delivery, maternal education, and maternal psychiatric family history.

††Adjusted for parents (age, psychopathology) and just mothers (substance abuse, depression, number of previous births, marital status, SES, smoking during pregnancy and infant's birthplace), and just fathers (immigration status).

‡‡Participants' reported previous psychiatric diagnosis.

§§Boys vs girls.

Summary of Results on Cognition

No differences were found in cognitive functioning between MLPT adults and those born at term (Table II).^{14,28} Small effect sizes were found when assessing moderate prematurity for either Full ($g = 0.11$), Verbal ($g = 0.14$), and Performance IQ ($g = 0.06$),²⁸ as well as in late prematurity ($g = 0.20$; $g = 0.13$; $g = 0.20$, respectively).¹⁹ In addition, in Heinonen's¹⁹ regressions, the weight of gestational age groups in adulthood obtained no or small effect sizes for the following cognitive domains: (1) memory $g = -0.28$; (2) verbal fluency $g = -0.03$; (3) sustained attention $g = -0.20$; (4) divided attention $g = -0.34$; and (5) suppression of interference $g = 0.28$ when assessing late preterm birth. In line with the aforementioned results, moderate prematurity was not associated with working memory and attention performance at 31 years of age.²⁸

However, other authors described that those adults who had been born MLPT showed poorer intellectual performance than their peers born at full term.^{17,22,24} Intellectual performance showed the largest effect size ($g = -3.25$) when studying its association with preterm birth in adults born at a gestational age of 33-34 weeks.²⁷ Even though a large effect size related to intellectual performance also was observed in those born at a gestational age of 35-36 weeks, a lower effect size was obtained ($g = -1.25$).²⁷ Studies by both Lundgren et al and Eide et al, in contrast, presented small effect sizes when assessing the association between gestational age and intellectual performance in adults who had been born MLPT ($g = 0.12$; $g = 0.11$).^{22,24} Nonetheless, when the relationship between gestational age and general neurocognitive performance was assessed in late adulthood, medium effect sizes were obtained ($g = -0.46$; $g = -0.78$).¹⁷ Moreover, late preterm birth was related to worse episodic memory and executive functions as well as to a greater risk for mild cognitive impairment in late maturity.¹⁷

Postnatal Growth after MLPT Birth and Long-Term Cognitive Outcomes. SGA was a risk factor for learning and cognitive deficits in childhood, but it was not related to lower educational attainment in adulthood.¹² In connection with this, it was seen that late preterm birth might not enhance the risk of poorer neurocognitive functioning in adulthood, and the double burden of being born late preterm and SGA may increase this risk due to more intrauterine adversities. Namely, those born late preterm and SGA obtained lower scores in Full and Performance IQ compared with those born at term,¹⁹ which indicated long-term cognitive problems in adults born preterm and SGA.¹⁴ Similar conclusions were established in the report by Lundgren et al, in which adults born moderately preterm who were of short stature or had a high body mass index were associated with an even greater risk for poorer cognitive performance.²² In a similar vein, faster growth during the critical early period after late preterm birth was related to better adult neurocognitive performance. Specifically, the effect sizes with respect

to the IQ were larger when the head circumference was taken into account ($g = 0.61$).¹⁵ Likewise, the effect size of executive functioning was larger when weight was considered as a predictor ($g = 0.56$).¹⁵ Hence, faster growth from birth to 5 months in weight and head circumference was associated with a greater IQ and better executive functions during adulthood, and with lower odds of having received special education.¹⁵

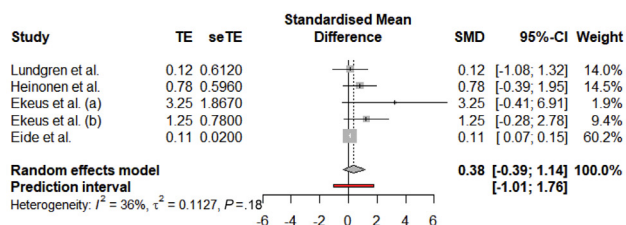
SES Background in MLPT Adults and Long-Term Cognitive Outcomes. Adults born late preterm are more likely to achieve a basic or upper secondary educational level.¹³ However, the negative impact of near-term births on adult educational attainment was approximately 3 times greater in those who lived in poverty conditions during childhood.¹² In the same way, low SES was a stronger determinant of cognitive functioning than moderate prematurity and therefore, low SES augmented the impact of moderately preterm delivery on cognition. The magnitude of the impact of prematurity on intellectual performance was shown to decrease by 26%-33% after adjustment for SES.²⁷

Meta-Analysis Results: Long-Term Cognitive Outcomes in Adults Born MLPT. As a final point, results of the meta-analysis based on the intellectual performance domain showed a small standardized mean difference when considering Hedge g effect sizes ($g = 0.38$, CI -0.39 to 1.14) (Figure 2). Moreover, a heterogeneity of 36% was found, which is regarded as small ($t^2 = 0.113$, $P = .18$). The funnel plot displayed the presence of publication bias among the selected studies (Figure 3; available at www.jpeds.com). Finally, a meta-regression analysis showed that none of the 4 variables significantly moderated the effect size obtained (ie, study quality $F = 0.12$, $P = .75$; age at evaluation $F = 0.35$, $P = .59$; gestational age $F = 0.01$, $P = .92$; and year of publication $F = 1.99$, $P = .25$).

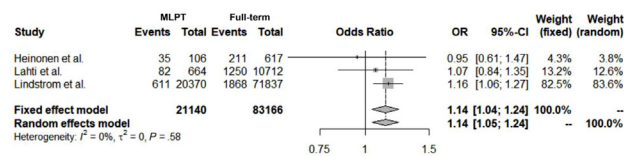
Summary of Results on Mental Health

Some authors have suggested that MLPT does not trigger pervasive impact on mental health and leads to similar^{15,20} or even better²⁸ psychological functioning in adulthood in relation to those who were born at term (Table III and Table V). More specifically, MLPT has not been found to be related to later symptoms of schizotypy or an increased risk of suffering from mood, anxiety or substance use disorders.^{18,28} Neither has late prematurity (RR 0.8; 0.4-1.4) been associated with an increased risk of autistic spectrum disorders.²⁵ Further, a depression diagnosis has been associated with post-term birth (OR 1.28; 1.07-1.54) in young male adults,²⁶ whereas differences in terms of suffering from depression were only marginally significant (RR 0.56; 0.30-1.0; $P = .06$) among adults who had been born moderately preterm.²⁸ In fact, fewer symptoms of depression have been associated with those born moderately preterm ($P = .02$), and better indexes of general health perception (7; 1-13; $P = .03$) and social functioning (8; 1-15; $P = .04$) have been reported.²⁸ Moreover, adults

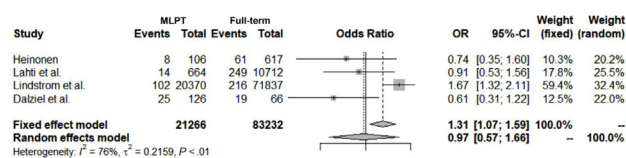
A Intellectual Performance



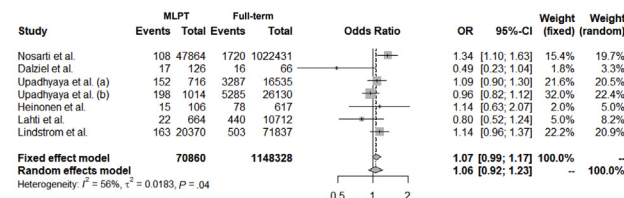
B Any Psychiatric Disorder



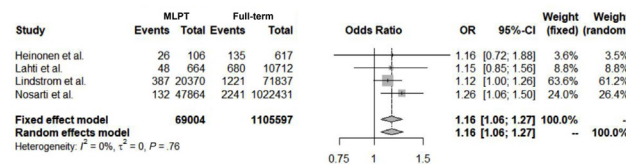
C Anxiety Disorders



D Mood Disorders



E Substance Use Disorders



F Psychotic Disorders

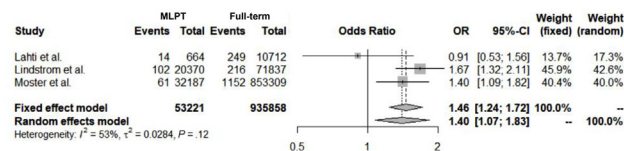


Figure 2. Forest plots of meta-analyses of intellectual performance and psychiatric disorders. *seTE*, standard error; *SMD*, standardized mean difference; *TE*, effect size (Hedges' g).

born late preterm have been found to have lower odds of having any common mental disorder (OR 0.37; 0.15-0.94; $P = .04$) and mood disorders (OR 0.27; 0.08-0.92; $P = .04$) than those born early preterm (24 to <34 weeks of gestation). Therefore, within preterm subgroups, the lower the gestational age, the greater the risk to suffer from a psychiatric disorder in adulthood.^{18,25}

Nonetheless, other authors have suggested that adults who are MLPT are at a greater risk of having poorer mental health, as will be outlined herein. Adults born moderately preterm have been found to have a 1.16 greater risk of having a psychiatric disorder.²¹ In this line, consistent with Nosarti et al, adults born moderately preterm have been found to be 60% more likely to have nonaffective psychosis, 34% to have depressive disorder, and more than twice as likely to suffer from a bipolar affective disorder in comparison with adults who were born at term (ie, with a gestational age of 37-41 weeks).²³ Moreover, moderate preterm birth has been associated with a 30% increased risk of alcohol abuse and a 20% increased risk of drug dependency.²³ Hence, the prevalence for substance use disorders decreased as gestational age increased.¹⁸ Finally, only men born late preterm presented an increased suicide risk in adulthood, which means that men born late preterm were found to have a 2.01-fold increased risk of committing suicide in comparison with those men born at term (1.03-3.90; $P = .03$).²⁰

Postnatal Growth after MLPT Birth and Mental Health. The prevalence of mood disorders and comorbidity for

mental disorders increased as the length at birth decreased,¹⁸ and possible complications in the neonatal period such as being SGA had a greater impact on mental health in adulthood. For instance, being SGA accounted for a 1.4-fold increased risk of having a mental disorder (1.07-1.87; $P = .02$), and for a 1.7-fold increased risk of having substance use disorders (1.16-2.41; $P = .01$).²⁰ However, poor fetal growth also has been related to an increased risk of depression with greater gestational ages at birth (ie, full- and post-term birth).²⁶

SES Background in Adults Born MLPT and Mental Health. Susceptibility to being hospitalized due to a psychiatric diagnosis increased as gestational age decreased, and was even greater in preterm-born adults from low SES families.^{21,23} Those born moderately preterm from low SES backgrounds had a 1.44 increased risk of being hospitalized due to a psychiatric disorder ($P = .001$).²¹

Meta-Analysis Results: Mental Health in Adults Born MLPT. In addition, by using a random-effects model, it was found that adults born MLPT are more likely to suffer from any psychiatric (OR 1.14; CI 1.05-1.24), substance use (OR 1.16; CI 1.06-1.27), mood (OR 1.06; CI 0.92-1.23), or psychotic disorders (OR 1.40; CI 1.07-1.83) (Figure 2). Nevertheless, adults born MLPT did not have greater odds of suffering from anxiety disorders (OR 0.97; CI 0.57-0.66). Moreover, the selected studies showed a low heterogeneity regarding any psychiatric ($t^2 = 0$, $P = .58$, $I^2 = 0%$) and substance use disorders ($t^2 = 0$, $P = .76$, $I^2 = 0%$). Mood

and psychotic disorders, in contrast, displayed a moderate heterogeneity ($t^2 = 0.018$, $P = .04$, $I^2 = 56\%$; $t^2 = 0.028$, $P = .12$, $I^2 = 53\%$). Anxiety disorders ($t^2 = 0.216$, $P < .01$, $I^2 = 76\%$) were found to be highly heterogeneous. Funnel plots exhibited publication bias in 2 of the 6 psychiatric domains (ie, mood and anxiety disorders) (Figure 3). In the results from the meta-regression analyses, only the resulting effect size based on studies concerning anxiety disorders was found to be moderated by gestational age (Q-statistic for model fit = 12.36, $P = .002$), and studies related to psychotic disorders were moderated by age at evaluation (Q-statistic for model fit = 4.09, $P = .04$). None of the findings based on the other psychiatric domains were moderated by any of the 4 moderating variables (study quality, age at evaluation, gestational age, and year of publication).

Discussion

Whereas children who were born MLPT have been found to be at a greater risk of more compromised educational outcomes, cognitive deficits, and psychiatric disorders at early school age,^{5,29} findings in adulthood remain controversial. Numerous studies have assessed long-term neurodevelopmental outcomes among those born MLPT during childhood and adolescence,³⁰ but there is still a paucity of scientific research on the adult stage.

Findings in this review suggested that MLPT birth does not increase predisposition to a greater risk of poorer cognitive functioning during adulthood.^{14,19,28} However, 3 studies established the opposite.^{17,22,24} Because preterm birth is considered a chronic condition,¹ there might be an impact on neurocognitive performance in the adult stage through to late adulthood, as has been found in adults born moderately preterm.²² Being born at 33-34 weeks was shown to have a greater impact on intellectual performance than being born at 35-36 weeks²⁷; studies that have regrouped these gestational age ranges together exhibited weaker outcomes with respect to the effect of preterm birth.²² This could be interpreted as a possible difference between newborns born moderately and late preterm during adulthood. Nevertheless, consistent with a meta-analysis study, MLPT had a small impact on intellectual performance during adulthood.

Worse episodic memory, executive functions, and general cognition have been related to late prematurity from 60 years old onwards.¹⁷ Nonetheless, because greater differences have been identified between preterm and full-term births at younger ages,³⁰ maximum attained lifetime education might mitigate aging-related neurocognitive decline¹⁷ as well as the increased risk for having a socioeconomic disadvantage.¹³ Thus, the identification of early preterm-related neurodevelopmental alterations will enable early interventions to mitigate possible cognitive impairment of preterm-born adults in their old age.

Concerning mental health, although MLPT birth did not trigger an extensive impact on the prevalence of psychiatric disorders in adulthood,^{15,20,26,28} the risk of suffering a psychi-

atric disorder and being hospitalized for it was found to increase with younger gestational age.^{21,23,25} However, fewer symptoms of depression and better scores on some variables of quality of life were also found in moderately preterm-born adults.²⁸ Due to the lack of consensus, further research focused on the psychiatric characteristics of preterm birth during adulthood is needed, especially on the greater risk of substance use disorders, as it is also found in adults born very preterm and those with very low birth weight,³¹ and on suicide risk in male subjects.^{18,20,23}

We found that the long-term effects of MLPT per se on cognition and mental health are usually mild, if any, compared with those born extremely or very preterm. However, MLPT together with other clinical and/or sociodemographic variables might carry the risk of long-term adverse outcomes in this population. In fact, the double burden of prematurity and other neonatal factors related to immaturity at birth such as postnatal growth (ie, being SGA) might compromise cognition and mental health in adults born preterm.^{12,14,18-20} For instance, measures such as adult stature and body mass index, as well as growth after birth in weight and head circumference, are related to cognitive performance in MLPT adults.^{15,22} Similarly, because preterm delivery exhibits greater biological vulnerability, MLPT might also lead to greater susceptibility to environmental factors. The impact of SES on preterm cognitive functioning and mental health seems to persist during adulthood, suggestive of the possible impact of MLPT if aggravated by a disadvantaged SES.^{21,23,27} Prematurity seems to confer some vulnerability to biological and environmental factors, which involves greater susceptibility to cognitive alterations and a diagnosis of a psychiatric disorder. Nevertheless, the paucity of studies, together with the variability of the results and the lack of consistency of effect sizes (ie, ranging from small to large) mean that findings are somewhat obscure.

In accordance with the studies of meta-analysis, MLPT adults showed a small likelihood of displaying poorer intellectual performance and greater odds of having any psychiatric, substance use, mood, and psychotic disorders compared with those born at term. The lack of heterogeneity and publication bias in the analyzed studies suggests that our findings could be taken into consideration for future studies. Nonetheless, the moderate heterogeneity in intellectual performance and mood and psychotic disorders, as well as the impact of a moderating variable (ie, age at evaluation) on the results obtained from studies assessing psychotic disorders, suggest that caution would be required regarding the current outcomes in these domains.

Concerning the limitations of this review, there are few studies available concerning cognition and mental health in adults born MLPT, and the different sample selection criteria and assessment tools mean that it is difficult to compare them. For instance, samples were categorized according to different gestational ages, that is, some studies focused on moderate prematurity and others concentrated on late prematurity, and some articles even made a single group containing both. One study¹² recruited its sample by focusing

on the definition of near-term. In addition, some studies used assessment tools that had only been validated in the country of study, or provided little information about their validity, which again made comparability challenging. In addition, although some studies used the same birth cohort,^{13,15,17-19} different clinical data (SGA) and environmental factors (SES) also may have been taken into account as an inclusion criterion. Another limitation of this report is that the reviewed studies assessed Nordic populations who had been treated in prenatal and neonatal care units a long time ago, mostly born before and around the 1980s, when neonatology underwent some major changes, such as the widespread use of antenatal corticosteroid protocols and less-invasive oxygenation strategies. That is, data related to their daily functioning may not be at all accurate for newborns treated with current medical techniques. The generalizability of the current findings to other ethnicities also may be limited. Finally, the impossibility of carrying out studies of meta-analysis with all cognitive and psychiatric domains due to the small number of studies involved in each of them (ie, more than 2 studies per domain) reduces the quality of our results. In fact, in domains such as mood and psychotic disorders, studies based on specific psychiatric disorders such as depression or schizophrenia have been included. Therefore, the procedure (ie, the inclusion criteria) of the present meta-analyses means that the findings related to heterogeneity and publication bias must be treated with due caution.

This review suggests that infants born MLPT have a low risk of developing long-term neurodevelopmental alterations in adulthood compared with those born extremely or very preterm. Despite the relatively lower risk of developmental complications, this review supports that disruptions to the immature nervous system at an early age could contribute to long-term neurodevelopmental alterations that impact cognitive and mental health outcomes in adulthood.^{32,33} Therefore, follow-up care should be re-evaluated to include those low-risk infants born preterm, especially because developmental care programs to date are still inconclusive for cognitive performance and long-term behavioral outcomes.³⁴ Hence, identifying dysfunctional cognitive performance and mental health in low-risk adults born preterm enables specific interventions to be applied to future newborns who are preterm during childhood. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

The Discovery of the Horizontal Transmission of Hepatitis B Virus in Children

Smithwick EM, Cheng Go S. Hepatitis-associated antigen in urban children. *J Pediatr* 1971;79:594-8.

Despite available vaccines, hepatitis B virus (HBV) continues to be a global health burden, causing chronic liver infection and 60%-80% of primary liver cancers.¹ Before discovering HBV, 50 years ago, physicians believed that serum hepatitis could be transmitted via blood/plasma transfusions or from infected mothers to infants by passing on hepatitis-associated antigen (HAA)—a term used before scientists could visualize the HBV particle. Therefore, serum hepatitis was considered the consequence of perinatal and parenteral transmission and, thereby, to have a different etiology from “infectious hepatitis.” A few months after the HBV discovery, Smithwick and Cheng published their observation from a community hospital in Brooklyn, New York City, that challenged this dogma. Their study suggested the horizontal transmission of HAA across family members. Using a novel immunodiffusion assay, the authors tested blood from a series of children with hepatitis. They found that 4 of 7 patients with hepatitis tested positive for HAA. The team also screened through available blood from more than 600 hospitalized patients, and 0.31% tested positive for HAA. Most children who were HAA positive had no perinatal or parenteral risk factors but, instead, close contact with individuals with known hepatitis or intravenous drug abuse at home. The investigators proceeded to find that many of these home contacts were HAA-positive themselves. This contact tracing confirmed that HBV was transmitted horizontally.

Today, horizontal HBV transmission from highly infective individuals is well known, albeit the exact route often remains unknown. In some parts of the world, this is the primary transmission mode, eg, in sub-Saharan Africa. We also understand that exposure early in life is associated with immunologic virus tolerance, persistent infection, and worse outcomes. Prevention remains the most cost-effective strategy for HBV. Different from hepatitis C, there is no cure, but there are effective vaccines. Current treatments aim at reducing the viral burden and preventing complications; however, viral clearance remains challenging. More effective treatment, with lower rates of drug resistance and fewer side effects, are needed.

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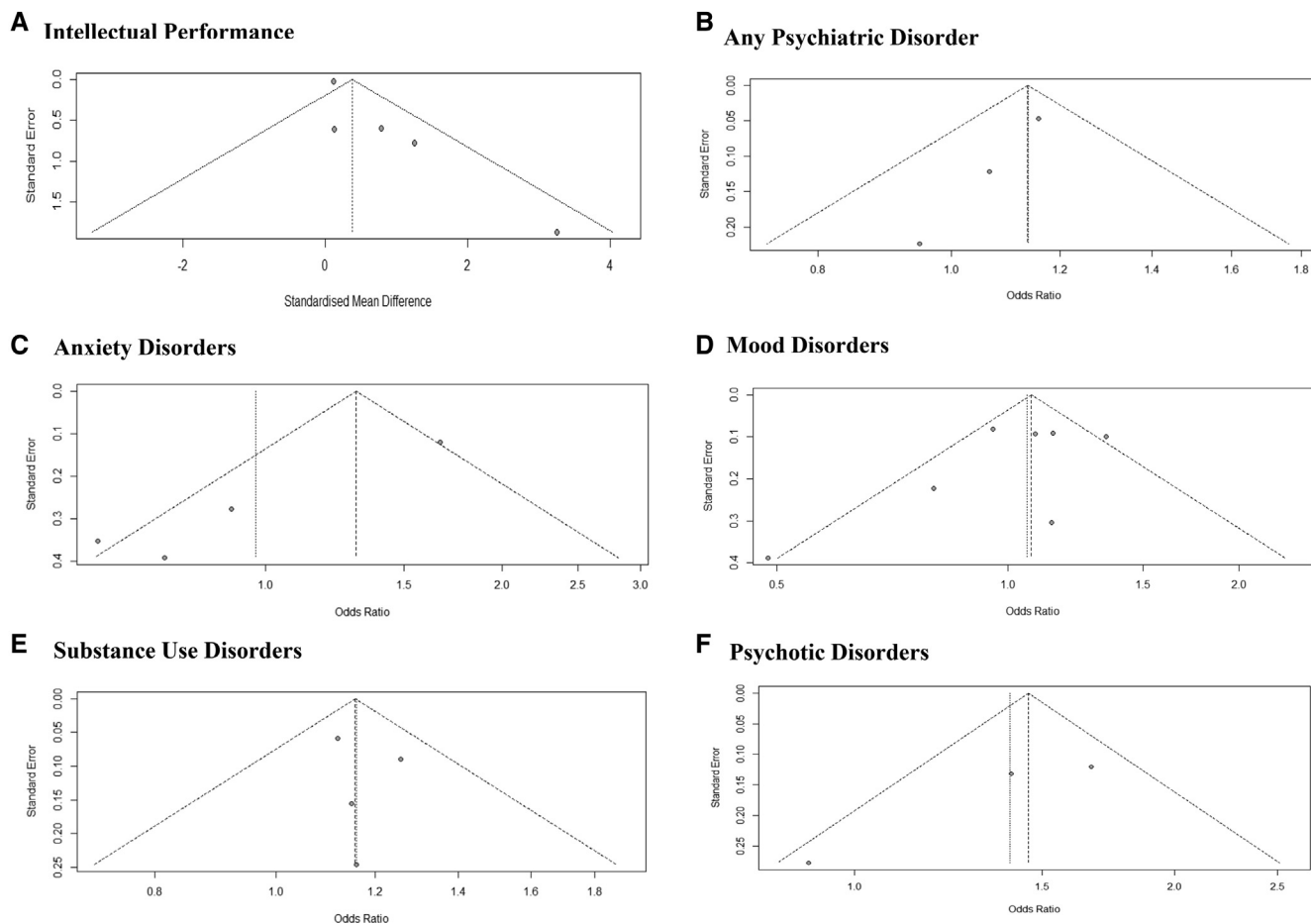


Figure 3. Funnel plots of meta-analyses of intellectual performance and psychiatric disorders.

Table I. Search strategy			
Concept 1		Concept 2	
("Premature birth" [MeSH] OR "Prematurity")	AND	(Adult* [MeSH])	
Concept 1	Concept 2	Concept 3	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Cognition" [MeSH] OR "Cognitive functioning")	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Mental health" [MeSH] OR "Psychiatric*")	
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("IQ" OR "Educational Status" [MeSH] OR "Anxiety" [MeSH] OR "Depression" [MeSH] OR "ADHD" [MeSH] OR "Autism Spectrum Disorder" [MeSH] OR "Schizophrenia" [MeSH])	
Concept 1	Concept 2	Concept 3	Concept 4
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	AND ("Cognition" [MeSH] OR "Cognitive functioning")
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	AND ("Mental health" [MeSH] OR "Psychiatric*")
("Premature birth" [MeSH] OR "Prematurity")	AND (Adult* [MeSH])	AND ("Moderate preterm" OR "Late preterm" OR "Near-term" OR "Marginally preterm")	AND ("IQ" OR "Educational Status" [MeSH] OR "Anxiety" [MeSH] OR "Depression" [MeSH] OR "ADHD" [MeSH] OR "Autism Spectrum Disorder" [MeSH] OR "Schizophrenia" [MeSH])

ADHD, attention deficit/hyperactivity disorder; MeSH, Medical Subject Headings.
 Using the asterisk at the end of adult* will pick up variations such as adults or adulthood.
 Using the asterisk at the end of psychiatric* will pick up variations such as psychiatric disorders or psychiatric diagnoses.

Table II. Summary of the studies assessing cognition in adults who were MLPT

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Dalziel et al, 2007 ²⁸	New Zealand	1969-1974	32.3-35.0 (n = 126) 37.0-40.4 (n = 66)	31.0 ± 0.12 y (mean ± SD)	PC, birth cohort	<ol style="list-style-type: none"> 1. Only included mothers who were expected to deliver between 24 and 36 weeks of gestation. 2. Subjects who lived within Auckland area at 30 years. 	WASI, BVRT, PASAT, and the Brown ADD Scales.	Full-scale IQ Verbal IQ Visual memory Performance IQ	<ol style="list-style-type: none"> 1. No differences were found in IQ scores between adults born moderately preterm and full term. 2. Moderately preterm birth was not associated with later educational attainment, SES, cognitive functioning, working memory, or attention. 	<ol style="list-style-type: none"> 1. Selection bias.
Eide et al, 2007 ²⁴	Norway	1967-1979	26-29 (n = 409) 30-33 (n = 565) 34-36 (n = 10836) 37-38 (n = 37484) 39-41 (n = 209 191) 42-44 (n = 46577)	18 y	RC, national registry	<ol style="list-style-type: none"> 1. Missing data on maternal educational. 2. Missing data on intellectual performance. 	A 53-minute standardized group intelligence test (1953) for the Norwegian draft board and revised in 1962. The test included time-limited subtests covering 3 categories: verbal analogues, number series and geometric figures.	Intellectual performance	Birth weight, birth length, and gestational age are associated with intellectual performance, even after adjustment for social factors and adult body size; however, the associations are weak.	<ol style="list-style-type: none"> 1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, intellectual performance).

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Ekeus et al, 2010 ²⁷	Sweden	1973-1976	24-28 (n = 63) 29-32 (n = 565) 33-34 (n = 1088) 35-36 (n = 3981) 37-38 (n = 19 146) 39-41 (n = 94 821)	18-19 y	RC, national registry	Implausible combinations of birth weight and gestational age	Enlistment Battery 80, with 4 subtests (logical, spatial, verbal, and technical capabilities).	Intellectual performance	<ol style="list-style-type: none"> Low SES is a more powerful determinant of cognitive competence than moderately preterm birth. Low SES enhances the effect of moderately preterm birth on cognitive competence. 	<ol style="list-style-type: none"> Selection bias. Lack of detailed information on exposed cohort (ie, familiar SES).
Heinonen et al, 2013 ¹³	Finland	1934-1944	34-36 (n = 486) 37-41 (n = 8507)	Follow-up: 26-56 y 36-66 y	PC, birth cohort*	<ol style="list-style-type: none"> Gestational age before 34 or after 41 weeks. People born to single mothers. 	SEP in adulthood were obtained based on occupational status, educational attainment, and taxable incomes.	Educational attainment	Adults born late preterm had greater odds of belonging to the manual worker category, to have attained only a basic level of education, and to belong to the lowest income category.	<ol style="list-style-type: none"> Lack of detailed information on exposed cohort (ie, impairments and their severity).

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Heinonen et al, 2015 ¹⁷	Finland	1934-1944	34-36 (n = 47) 37-41 (n = 872)	61.2-77.0 y	PC, birth cohort*	1. Subjects with a history of stroke or other brain injury. 2. Large birth weight for length of gestation. 3. Participants who were born before 34 or after 41 weeks.	CERAD-NB	Intellectual performance Verbal fluency Memory	1. Late preterm birth is a novel risk factor for neurocognitive impairment in late adulthood. 2. Late preterm birth was associated with lower episodic memory, executive functioning, visual reproduction, and general neurocognition. 3. Late prematurity had a greater risk of MCI. 4. Maximum attained lifetime education may mitigate aging-related neurocognitive impairment, especially among those born late preterm.	1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, smoking mothers). 3. Lack of generalizability.

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Heinonen et al, 2018 ¹⁹	Finland	1985-1986	34-36 (n = 119) 37-41 (n = 667)	25.4 ± 0.8 y (mean ± SD)	PC, birth cohort [†]	<ol style="list-style-type: none"> 1. Unverified gestational age. 2. Intellectual developmental disability, severe congenital malformations, or chromosomal abnormality. 	WAIS III, TMT, the Stroop Test, verbal fluency, CPT II, and WMS III.	Full-scale IQ Verbal IQ Memory Performance IQ Sustained attention Divided attention Incongruence	<ol style="list-style-type: none"> 1. Late preterm birth did not increase the risk of poorer neurocognitive functioning in adulthood. 2. The double burden of being born late preterm and being SGA did increase this risk. 	<ol style="list-style-type: none"> 1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, SGA was based only on birth weight). 3. Lack of sample representability (ie, late preterm and SGA).
Lundgren et al, 2011 ²²	Sweden	1973-1978	<32 (n = 574) 32-36.9 (n = 9579) 37-42 (n = 210935) >42 (n = 27359)	18-25 y	RC, national registry	<ol style="list-style-type: none"> 1. Birth weight, birth lengths, and head circumferences below 5 SD and above 3 SD. 2. Non-Nordic mothers and multiple births. 3. Congenital malformations. 4. Born SGA. 	Health examination, tests of psychological performance, and general intellectual performance with 4 subtests (logical/inductive, verbal, spatial and theoretical/technical).	Intellectual performance	<ol style="list-style-type: none"> 1. Being born moderately preterm is associated with a greater risk of having poor intellectual performance, as compared to being born at term. 2. Short adult stature or a high body mass index is associated with an even higher risk, indicating the occurrence of common mechanisms underlying growth and cognitive development. 	<ol style="list-style-type: none"> 1. Selection bias.

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Nomura et al, 2009 ¹²	US	1960-1964	33–37 (n = 226) >37 (n = 1393)	Period from 7-8 y to 27-33 y	PC, birth cohort	<ol style="list-style-type: none"> 1. Participants who were born before 33 weeks of gestation. 2. Lack of information on childhood cognitive and learning performance. 3. No information on gestational age. 	During childhood psychological and/or language, hearing, and speech assessment. During adulthood standard questionnaire covering personal characteristics and social and psychological functioning.	Educational attainment	<ol style="list-style-type: none"> 1. Negative consequences of near-terms for their educational success. 2. Negative consequences of near-term birth are stronger when they lived in poverty during childhood. 	<ol style="list-style-type: none"> 1. Lack of detailed information on exposed cohort (ie, raw scores).
Sammallahti et al, 2017 ¹⁵	Finland	1985-1986	34–36 (n = 108)	24-26 y	PC, birth cohort [†]	<ol style="list-style-type: none"> 1. Intellectual developmental disability, congenital malformations, or chromosomal abnormalities. 2. No available data on birth or childhood anthropometry. 3. Not precise gestational age or adult cognitive, school, or psychiatric data. 	WAIS III, WMS III, phonetic and categorical verbal fluency, TMT, and the Bohnen Stroop test.	Full-scale IQ Memory Executive functioning	<ol style="list-style-type: none"> 1. Faster growth during the critical early period after late-preterm birth is associated with better adult neurocognitive functioning. 	<ol style="list-style-type: none"> 1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, rare mental disorders, life-long prevalence of mental disorders, or educational level). 3. Lack of generalizability. 4. Lack of sample representability (ie, late prematurity).

(continued)

Table II. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Cognitive outcome	Main findings	Limitations
Suikkanen et al, 2020 ¹⁴	Finland	1985-1986	<34 wk (n = 133) 34-36 (n = 241) >37 (n = 348)	23.3 ± 1.2 y (mean ± SD)	PC, birth cohort	1. Severe mental disability, cerebral palsy, or other severe physical disability. 2. Missing data in all tasks or had outliers in several tasks that indicate poor compliance.	Cogstate Research a computer-based cognitive test battery (Continuous Paired Associate Learning Test, Detection Test, GML Test, Identification Test, One Card Learning Test, One Back Test, and Social Emotional Cognition Test for the battery).	Executive functioning Attention Memory (working, visual, and spatial)	1. Cognitive weaknesses established in childhood among late prematurity may not persist to adulthood. 2. SGA may be an additional risk factor for cognitive problems in adults born late preterm.	1. Measure used to collect the data. 2. Lack of detailed information on exposed cohort (ie, previous cognitive testing).

ADD, attention deficit disorder; BVRT, Benton Visual Retention Test; CERAD-NB, Consortium to Establish a Registry for Alzheimer's disease Neuropsychological Battery; CPT, Conner's Continuous Performance Test; GML, Groton Maze Learning; MCI, mild cognitive impairment; PASAT, Paced Auditory Serial Addition Test; PC, prospective cohort; RC, retrospective cohort; SEP, socioeconomic position; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale.

*Results derived from the same birth cohort.

†Results derived from the same birth cohort.

Table III. Summary of the studies assessing mental health in adults who were MLPT

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Psychiatric outcome	Main findings	Limitations
Dalziel et al, 2007 ²⁸	New Zealand	1969-1974	32.3-35.0 = 126 37.0-40.4 = 66	31.0 ± 0.12 y (mean ± SD)	PC, birth cohort	1. Only included mothers who were expected to deliver between 24 and 36 weeks of gestation. 2. Subjects who lived within Auckland area at 30 years.	BDI-II, STAI, and the Schizotypy Traits Questionnaire, SF-36.	Any psychiatric disorder Anxiety disorder Depressive disorder	1. Moderate preterm birth was not associated with later marital status, symptoms of anxiety, or schizotypy. 2. Moderate preterm birth associated with fewer symptoms of depression and greater levels of satisfaction.	1. Selection bias.
Heinonen et al, Finland 2016 ¹⁸	Finland	1985-1986	24-33 (n = 37) 34-36 (n = 106) 37-41 (n = 617) ≥42 (n = 40)	24.4-27.1 y	PC, birth cohort*	1. Organic mental disorder. 2. Unreliable information on gestational age. 3. Congenital malformations or chromosomal abnormalities.	M-CIDI and ICD-10.	Any psychiatric disorder Mood disorder Anxiety disorder Substance use and addictive disorders	1. Individuals born late preterm born preterm are not at risk for common mental disorders in young adulthood. 2. The prevalence of mood disorders and comorbidity for mental disorders decreased as the length of gestation increased in adults born late preterm. 3. Prevalence for substance use disorders decreased as GA increased in adults born late preterm.	1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, lifetime mental disorder risk). 3. Lack of generalizability. 4. Lack of sample representability (ie, mothers who had smoked more often during pregnancy and parents with a lower level of education).

(continued)

Table III. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Psychiatric outcome	Main findings	Limitations
Lahti et al, 2015 ²⁰	Finland	1934-1944	34-36 (n = 664) 37-41 (n = 10 712) 42-43 (n = 1221)	66-76 y	PC, birth cohort	1. Biologically implausible values for gestational age. 2. Gestational age <34 weeks. 3. Missing or imprecise data from register. 4. Diagnosis of injuries of undetermined intent or of poisonings with no history of psychopathology.	ICD-8 and DSM-3.	Any psychiatric disorder Mood disorder Anxiety disorder Psychotic disorder Personality disorder Suicide Suicide attempts Substance use and addictive disorders	1. Men born late preterm had an increased suicide risk. 2. Late preterm birth did not exert widespread effects on adult psychopathology. 3. The risks of severe mental disorders across adulthood were increased among individuals born SGA and individuals born post-term.	1. Lack of sample representability (ie, anxiety and mood disorders). 2. Lack of detailed information on exposed cohort (ie, hospitalized or died people with mental disorders before 1969).
Lindström et al, 2009 ²¹	Sweden	1973-1979	24-28 (n = 3256) 29-32 (n = 2894) 33-36 (n = 20 370) 37-38 (n = 71 837) 39-41 (n = 450 165)	23-29 y	PC, birth cohort	1. Birth weight less than 3SD and more than 6SD. 2. Improbable measures of length in relation to their recorded weight. 3. Major malformation at birth.	ICD-9.	Any psychiatric disorder Mood disorder Anxiety disorder Psychotic disorder Organic/neuropsychiatric disorder Suicide Suicide attempts Substance use and addictive disorders Discharged from a hospital at least once with a main psychiatric diagnosis Schizophrenia Autism	1. Moderate preterm birth carries some risk for psychiatric disorders requiring hospitalization in young adulthood.	1. Selection bias. 2. Procedure used to collect the data.
Moster et al, 2008 ²⁵	Norway	1967-1983	23-27 (n = 1822) 28-30 (n = 2805) 31-33 (n = 7424) 34-36 (n = 32 945) >37 (n = 858 406)	20-36 y	RC, national registry	1. Sex-specific weight for gestational age that was more than 3 SD. 2. Disability benefits for medical reasons.	ICD.		Continuous relationship between decreasing gestational age at birth and a wide range of adverse outcomes.	1. Lack of detailed information on exposed cohort (ie, severity of disabilities or on any functional capacity related to cognitive-social skills). 2. Procedure used to collect the data.

(continued)

Table III. Continued

Studies	Country	Years of birth	n (depending on gestational age, wk)	Age	Study design	Exclusion criteria	Assessment tools	Psychiatric outcome	Main findings	Limitations
Nosarti et al, 2012 ²³	Sweden	1973-1985	<32 (n = 5125) 32-36 (n = 47 864) 37-41 (n = 1 022 431) ≥42 (n = 221 022)	23.0 ± 4.1 y (mean ± SD)	RC, national registry	1. Participants that had been hospitalized with any psychiatric diagnoses before 16 years	ICD 8th, 9th, and 10th Revisions.	Nonaffective psychosis Depressive disorder Bipolar affective disorder Substance use and addictive disorders Eating disorder Alcohol dependency Any psychiatric disorder	1. Moderate preterm birth was associated with an increased risk of drug and alcohol dependency.	1. Selection bias. 2. Lack of detailed information on exposed cohort (ie estimation of GA based on the mother's last menstrual period).
Sammallahti et al, 2017 ¹⁵	Finland	1985-1986	34-36 = 108	24-26 y	PC, birth cohort*	1. Intellectual developmental disability, congenital malformations or chromosomal abnormalities. 2. No available data on birth or childhood anthropometry. 3. Not precise gestational age or adult cognitive, school, or psychiatric data.	ASEBA ASR.	Any psychiatric disorder	1. Faster growth during the critical early period after late-preterm birth is not associated with better adult mental health outcomes.	1. Selection bias. 2. Lack of detailed information on exposed cohort (ie, rare mental disorders, life-long prevalence of mental disorders, or educational level). 3. Lack of generalizability. 4. Lack of sample representability (ie, late prematurity).
Upadhyaya et al, 2020 ²⁶	Finland	1987-2007	<28 28-31 32-36 37-41 ≥42	19-25 y	RC, national registry	Severe or profound mental disabilities.	ICD-9 and -10.	Depression	Post-term birth was associated with depression diagnosed at adulthood.	1. Selection bias. 2. Procedure used to collect the data. 3. Lack of sample representability (ie, limited age range).

ASEBA, Achenbach System of Empirically Based Assessment; ASR, adult self-report; BDI-II, Beck Depression Inventory II; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; M-CIDI, Munich Composite International Diagnostic Interview; SF-36, Short Form-36 Health Survey; STAI, State-Trait Anxiety Inventory.

*Results derived from the same birth cohort.

Table IV. Newcastle–Ottawa scale for quality

Quality assessments	Acceptable★	Dalziel et al, 2007 ²⁸	Eide et al, 2007 ²⁴	Ekeus et al, 2010 ²⁷	Heinonen et al, 2013 ³	Heinonen et al, 2015 ¹⁷	Heinonen et al, 2016 ¹⁸	Heinonen et al, 2018 ⁹	Lahti et al, 2015 ²⁰	Lindström et al, 2009 ²¹	Lundgren et al, 2011 ²²	Moster et al, 2008 ²⁵	Nomura et al, 2009 ¹²	Nosarti et al, 2012 ²³	Sammallahti et al, 2017 ¹⁵	Suikkanen et al, 2020 ¹⁴	Upadhyaya et al, 2020 ²⁶
Selection																	
Representativeness of the exposed cohort?	Near-term, moderate, marginally or late preterm cohort and of both sexes.	★★			★★	★★	★★	★★	★★	★★		★★	★★	★★	★★	★★	★★
Selection of the non-exposed cohort?	Term and/or full-term cohort	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★		★★	★★
Ascertainment of exposure?	Hospital birth records, hospital discharge medical registers, etc.	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★
Demonstration that outcome of interest was not present at start of study?	The absence of intellectual disability and/or psychiatric disorders (ie, congenital malformations, chromosomal abnormality, etc)					★★	★★	★★	★★		★★	★★		★★	★★	★★	★★
Comparability																	
Adjust for sex?	Yes	★★			★★	★★	★★	★★		★★		★★	★★	★★	★★	★★	★
Adjust for any additional factors?	Age, maternal age, BMI before delivery, parity, SES, marital status, subject's maximum attained education, etc.	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★	★★	★★	★★	★★
Outcome																	
Assessment of outcome?	Neuropsychological evaluations, psychometric tests, validated psychiatric manuals, and educational attainment.	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★		★★	★★	★★	★★
Was follow-up long enough for outcome to occur?	Follow-up ≥16 years	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★	★★
Adequacy of follow-up of cohorts?	Complete follow-up, small number lost, or description provided of those lost	★★	★★	★★	★★	★★	★★	★★	★★	★	★★	★★	★★	★	★★	★★	★★
Overall quality score (maximum = 9)	reviewer 1/ reviewer 2	8/8	6/6	6/6	8/8	9/9	9/9	9/9	8/8	8/7	7/7	9/9	7/6	8/9	8/8	9/9	8/9

BMI, body mass index. Each column of stars for each included study corresponds to the score given by each reviewer according to the specific acceptability criteria.