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RESEARCH ARTICLE

NEURODEVELOPMENTAL IMPAIRMENTS IN CHILDHOOD AFTER MODERATE AND LATE PRETERM BIRTH IN FINLAND

A SUMMARY OF NATIONAL REGISTER STUDIES

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ABSTRACT

About 80% of premature (< 37 gestational weeks) infants have been born moderately preterm (32+0-33+6 weeks) and late preterm (34+0-36+6 weeks). Very preterm birth (<32 weeks) is a well-known risk factor for adverse neurodevelopmental outcome, but the risks concerning moderately and late preterm infants have earlier been underestimated. Lately, concern about later neurodevelopmental impairments among these children has been emerged. Our project was to undertake a national register study on the incidence and risk factors of sensory impairments, cerebral palsy (CP) and intellectual disabilities (ID). The aim of this review article is to provide a summary of our work and earlier publications on this topic.

Our study comprised all children (N= 1039263) born alive in Finland in 1991-2008. After exclusions (missing data on gestational age (N=5520), major congenital malformations (N= 13007) and death before the age of one year (N=2659) the population consisted of 1018256 children, who were followed up to the age of seven years or up to 2009. They were divided into four groups as follows: very preterm (N= 6329), moderately preterm (N=6796), late preterm (N= 39928) and term (N=965203). Incidences of sensory impairments, CP and ID (intellectual quotient ≤ 70) were explored by linking health register data. Antenatal, birth-related and neonatal predictors of disabilities were established by multivariate analysis.

The incidences of sensory impairments, CP and ID decreased with increasing gestational age. Compared with term birth, moderately and late preterm births were significantly associated with the risk of visual disturbances, blindness and CP. Late preterm birth predicted a risk of hearing loss. Preterm birth seemed not to be associated with an increased risk of intellectual disability. The most significant predictors of neurodevelopmental disabilities among moderately and late preterm born children included one-minute Apgar score < 7, intracranial hemorrhage, male sex, small for gestational age, smoking during pregnancy and early antibiotic treatment. These results are mostly in accordance with other reports on the outcome of moderately and late preterm born children.

In conclusion, moderately and late preterm born children seemed to be at an increased risk of sensory impairments and cerebral palsy, but not intellectual disability.

INTRODUCTION

Moderately preterm (MP, born at 32^{+0}-33^{+6} gestational weeks) and late preterm (LP, born at 34^{+0}-36^{+6} gestational weeks) comprise the majority (about 80%) of all prematurely born children[1, 2]. Earlier they have been generally held to have low risk in terms of neurodevelopmental outcome and appropriate guidelines for follow-up programs for this group are missing. The brain of the fetus is growing fast during the third trimester of pregnancy and at 34 weeks of gestation the brain weight is about 65% of the brain weight at term[3]. Thus, the last six weeks of pregnancy are important for central nervous system growth and maturity and birth before term might disturb markedly this vulnerable period. Lately, awareness has increased on the fact that children born MP and LP are also at higher risk of long-term neurodevelopmental morbidity compared to those born at term (born at 37^{+0} gestational weeks or more)[4,5]. Because the moderately and late preterm infants form the greatest proportion of all preterm infants, morbidity among them represents a significant burden on individuals, families, and the society. This concern applies to the entire global health care systems. Therefore, it is important to evaluate long-term consequences of moderately and late preterm births and to seek potential predictors of long-term neurological morbidity. More research was needed in order to complete the picture further.

Our research project[6] focused on the incidences and antenatal, perinatal and neonatal risk factors of visual and hearing impairments[7], cerebral palsy (CP) [8] and intellectual disabilities (ID)[9], in children born MP and LP, in comparison to those born very preterm (VP, less than 32^{+0} gestational weeks) and term (37^{+0} gestational weeks or more) children in Finland. We decided to undertake a national register study, because our registers are validated, and the data has been proven to be very reliable[10, 11]. Gaining knowledge is of use when planning guidelines for follow-up programs in MP and LP children. It also raises questions for further research. The aim of this review article is to summarize our work and discuss earlier publications on this topic.

METHODS

The population consisted of all children (n= 1039263) born in Finland between years 1991-2008[6]. Infants with missing data on gestational age (n= 5520) were excluded in all studies. In addition infants with at least one major congenital anomaly (n= 13007) and infants who died before the age of one year (n=2659) were excluded. The final numbers of included infants were 1 018 302 in CP study[8], and 1 018 256 in the ID the sensory impairments studies[7,9].

The subjects were divided into four subgroups according to the gestational age at birth, as follows: VP ($<32^{+0}$ weeks, n= 6329, MP (32^{+0}-33^{+6} weeks, n=6796), LP (34^{+0}-36^{+6} weeks, n= 39928) and term ($\geq 37^{+0}$ weeks, n=965203), including 47318 subjects born post term ($\geq 42^{+0}$ weeks). The children were followed to the age of seven years or up to the year 2009.

The data were obtained from the Finnish national health registers, including the Medical Birth Register, containing data on all live births and stillbirths, mothers, pregnancies, deliveries and data on infants up to the age of seven days, Hospital Discharge Register, recording information on patients on admission and discharge, diagnoses, procedures and interventions, Register of Congenital Malformations (data on major structural and chromosomal abnormalities), Register of Social Insurance Institution (data on granted reimbursements for prescribed medicines and disability allowances) and Causes of Death Register, kept by Statistics Finland. Data on sensory impairments, CP and ID and were established by linking the health register data.

The study period was divided into three subsections: 1991-1995, 1996-2001, and 2002-2008, because the data collection forms of the Medical Birth Register were revised on 1.10.1990 and 1.1.1996, and because of the changes in the coding of the diagnoses.

The diagnoses were coded according to the International Classification of Diseases, 9th Revision (ICD-9) in 1991-1995 and according to International Classification of Diseases, 10th Revision (ICD-10) from the year 1996 onwards.

Hearing loss, including conductive, sensorineural and other types of hearing loss, was coded as 389 and H90-H91 and visual disturbances or blindness as 368-369 and H53-H54 in ICD-9 and ICD-10, respectively. Accordingly, other ophthalmologic problems were defined with codes 367, 378 and H49-H52 and retinopathy of prematurity with codes 362.22-27 and 35.1.

A CP case was recorded according to the ICD-9 with codes 342-344 and according to the ICD-10 with codes G80-G83. Subtypes of CP were traced from the registers as follows: hemiplegia 343.1 and 343.4 (ICD-9), and G80.2 (ICD-10), diplegia 343.0 and G80.1, quadriplegia 343.2 and G80.0. Other types of CP included the remaining CP diagnoses in the ICD-9 and ICD.10, respectively.

Intellectual disability was recorded by ICD-9 and ICD-10 codes 317-319 and F70-F79, respectively. Codes 318.1-318.2 and F72-F73 in ICD-9 and ICD-10 contained mild and moderate ID (IQ 35-70) and codes 318.1-318 and F72-F73 severe and profound ID (IQ 34 and below). Unspecified ID's were coded as 319 in ICD-9 and F78-F79 in ICD-10.

Details of risk factors for disabilities were sought from mother´s background characteristics, pregnancy and delivery-related characteristics, and from infant´s characteristics, diagnoses and procedures during the neonatal period are given in the original publications[6-10]. Sepsis diagnosis contained only blood culture positive infections (P36.0-P36.8 in ICD-10). Neonatal jaundice was coded in ICD-10 with P59.0-P59.9, intracranial hemorrhages (including all grades of hemorrhages) with P52.0-P52.9 and convulsions with P90.

Infants with birth weights less than two standard deviations (SD) below the mean weight for gestational age (GA) were defined

as small for gestational age (SGA) and those with birth weights more than 2 SD above the mean for GA as large for gestational age (LGA). The Finnish fetal growth curves[12] were used.

Risk factors were analyzed by Generalized Linear Mixed Model for sensory impairments logistic regression analysis for CP and risk factors for ID by Cox regression analysis. The logistic regression analysis for CP included all three time periods. The analyses for sensory impairments and intellectual disabilities were made only for the period 1996-2008.

RESULTS

Altogether 53 053 infants were born preterm, being 5.13% of the total population of 1 033 349 infants. Late preterm infants consisted of the largest proportion (75%) of the preterm infants, whereas 13% were moderately preterm and 12% very preterm born children. Characteristics of mothers and infants are presented in the Table 1.

Table 1 Characteristics of infants and their mothers

	Very preterm (VP, <32 weeks) N= 6389	Moderately preterm (MP, (32^{+0}-33^{+6} weeks) N=6796	Late preterm (LP, 34^{+0}-36^{+6} weeks) N=39928	Term (≥37 weeks) N=965203	P[1] MP vs VP P[2] LP vs VP P[3] MP vs Term P[4] LP vs Term
Mothers					
Age years, mean (SD)	30.2 (5.8)	29.8 (5.7)	29.7 (5.5)	29.2 (5.3)	$p^{1-4} < 0.001$
Smoking during pregnancy, N (%)	1187 (18.8)	1184 (17.4)	6602 (16.5)	144094 (14.9)	$p^{1-4} < 0.001$
Primiparous, N (%)	3314 (52.4)	3792 (55.8)	20040 (50.2)	392574 (40.7)	$p^{1-4} < 0.001$
Pregnancies					
Singleton pregnancy, N (%)	4517 (71.4)	4591 (67.6)	31062 (77.8)	948695 (98.3)	$p^{1-4} < 0.001$
Mode of delivery					
Cesarean section, N (%)	3793 (59.9)	3582 (52.7)	13210 (33.1)	143491 (14.9)	$p^{1-4} < 0.001$
Infants					
Boys, N (%)	3428 (54.2)	3728 (54.9)	21658 (54.2)	490211 (50.8)	P[1] 0.426 P[2] 0.906
Birth weight g (Md, IQR)	1290 (1000-1570)	1970 (1730-2200)	2670 (2360-2985)	3590 (3276-3910)	$p^{1-4} < 0.001$
SGA, N(%)	1019 (16.1)	883 (13.0)	3245 (8.1)	16662 (1.7)	$p^{1-4} < 0.001$

Pearson's chi-square test, Fisher's exact test or the Mann-Whitney test were used in the statistical analysis, as appropriate
Md = median
IQR = interquartile range
Modified from Hirvonen, M, 2018[6].

Sensory impairments[7]

In total 3801 (0.37% of the population) subjects were diagnosed with hearing loss. Out of these 156 (2.46% were VP, 58 (0.85%) MP, 222 (0.56%) LP and 3365 (0.37%) were born at term. Visual disturbance or blindness was diagnosed in 8118 (0.79% of the total population) children, including 230 (3.63%) born VP, 133 (1.96%) MP, 745 (1.19 %) LP and 31 995 (0.1%) born at term.

Statistically significant risk factors associated with hearing loss included smoking during pregnancy (OR 1.16; 95% CI 1.05-1.29), SGA (OR 1.32; 95% CI 1.32; 95% CI 1.07-1.62), intracranial hemorrhage (OR 2.39; 95% CI 1.48-3.86) and convulsions (OR 2.38; 95% CI 1.24-4.54) in the analysis.

Risk factors associated with visual disabilities or blindness included smoking during pregnancy (OR 1.48; 95% CI 1.38-1.58), SGA (OR 1.23; 95% CI 1.06-1.43), Apgar score < 4 (OR 1.27; 95% CI 1.05-1.54) intracranial hemorrhage (OR 2.13; 95% CI 1.43-3.16) and convulsions (OR 2.87;95% CI 1.79-4.64).

Cerebral palsy[8]

Incidence of CP was in total 0.22% (N= 2 242 children). The incidence was 8.7% in the VP group, 2.4% in the MP group, 0.6% in the LP group and 0.1% in the term group. Hemiplegia was diagnosed in 599 (26.7%), diplegia in 478 (21.3%) and quadriplegia in 148 (6.6%) cases. The remaining 1017 cases had been recorded as unspecified CP.

Intellectual disability[9]

Out of altogether 3814 (0.37% of the total population) children with intellectual disability 157 (2.48%) were VP, 55 (0.81%) MP, 218 (0.55%) LP and 3814 (0.35%) born at term. The greatest percentage (66%, N= 2259) had been recorded to have mild/moderate ID, whereas 6.2% (N=237) had severe/profound ID and 27% (N=1048) were unspecified cases.

Statistically significant risk factors associated with CP and ID are presented in Table 2. Intracranial hemorrhage was the only significant predictor of CP and ID among both MP and LP born children. Also preterm rupture of membranes (PROM), low one-minute Apgar score, low umbilical artery pH, male sex, small for gestational age, smoking during pregnancy and early antibiotic treatment were among significant predictors of CP and/or ID in MP and LP born children. Antenatal glucocorticoid treatment seemed to be associated with a decreased risk of CP in MP born children. The risk of CP was significantly increased in all gestational age groups during the two earliest time periods, when the last period 2002-2008 was used as a reference. (Table 2)

Table 2 Risk factors associated significantly with cerebral palsy and intellectual disability and sensory impairments in very preterm, moderately preterm, late preterm and term born children

	Very preterm	Moderately preterm	Late preterm	Term
Cerebral Palsy				
PROM[1]		3.05; 95% CI 1.02-9.12		
1-min Apgar< 7[1]	1.26; 95%CI 1.01-1.56	1.70; 95% CI 1.15-2.52	1.8; 95% CI 1.21-2.67	1.84; 95% CI 1.47-2.29
SGA[1]			1.85;95% CI 1.25-2.75	2.35, 95% CI 1.84-3.01
Intracranial hemorrhage[1]	3.05; 95% CI 2.08-1.47	7.18; 95% CI 3.60-14.3	12.8; 95% CI 5.58-29.2	4.89; 95% CI 2.13-11.2
Antibiotic treatment[1]		1.63; 95% CI 1.08-2.45	1.67;95% CI 1.13-2.44	1.69, 95% CI 1.32-2.17
Antenatal glucocorticoid treatment[1]		0.24;95% CI 0.08-0.76		
Birth between years				
1991-1995	4.03; 95% CI 3.12-5.94	2.55; 95% CI 1.55-4.20	2.41;95% CI 1.62- 3.60	1.77;95% CI 1.53-2.05
1996-2001	2.63; 95% CI 1.94-3.57		1.97;95% CI 1.36-2.87	1.57;95% CI 1.36-1.80
2002-2008 (reference)	1	1	1	1
Intellectual disability				
Intracranial hemorrhage[2]	2.92; 95% CI 1.58-5.41	5.59 95% CI 1.57-19.9	4.58; 95% CI 1.36-15.4	2.94;95% CI 1.08-8.00
Male sex[2]	1.88; 95% CI 1.57-19.9		1.93, 95% CI 1.32-2.81	1.71;95% CI 1.55-1.87
SGA[2]	1.94; 95% CI 1.19-3.16		3.27; 95% CI 2.03-5.24	2.34; 95% CI 1.90-2.94
Smoking during pregnancy[2]			1.94; 95% CI 1.31-2.86	1.31;95% CI 1.16-1.47
Low umbilical artery pH[2]			4.62;95% CI 1.67-1.28	
1-min Apgar< 4[2]	2.17;95% CI 1.38-3.42			1.77;95%CI 1.10-1.43
Antibiotic treatment[2]			1.74; 95% CI 1.01-3.0	
Convulsions[2]	4.76;95% CI 1.36-16.6			5.23;95% CI 3.19-8.58

[1] Logistic regression multivariate model, indicated as ORs and 95% CIs

[2] Cox hazard regression multivariate model, indicated as HRs and 95% CIs

[3] Multivariate generalized mixed model, indicated as ORs and 95% Cis

PROM= preterm rupture of membranes

SGA=small for gestational age

Summary of the results from separate multivariate models studying the association of sensory impairments, CP and intellectual disabilities in VP, MP and LP children

compared to the term born children are presented in Table 3. Compared with term birth, MP and LP births were significantly associated with the risk of visual disturbances, blindness and CP. LP predicted an increased risk of hearing loss. Preterm birth seemed not to be associated with an increased risk of intellectual disability.

Table 3 Association of major disabilities with very preterm, moderately preterm, and late preterm birth using the term birth as a reference

Disability	Very preterm	Moderately preterm	Late preterm	Term (reference)
Hearing loss[1]	2.34, 95% CI 1.75-3.14	1.14, 95% CI 0.79-1.65	1.26, 95% CI 1.04-1.52	1.00
Visual disabilities[1]	1.94, 95% CI 1.55-2.44	1.42, 95% CI 1.11-1.80	1.32, 95% CI 1.16-1.49	1.00
Cerebral palsy[2]	9.37; 95% CI 7.34-11.9	5.12; 95% CI 4.13-6.34	2.35, 95% CI 1.99-2.77	1.00
Intellectual disability[3]	1.37, 95% CI 0.85-2.20	0.63, 95% CI 0.40-0.98	0.99, 95% CI 0.80-1.22	1.00

[1] Multivariate generalized mixed model, indicated as ORs and 95% Cis

[2] Logistic regression multivariate model, indicated as ORs and 95% CIs

[3] Cox hazard regression multivariate model, indicated as HRs and 95% CIs

DISCUSSION

Our findings strengthen the assumption, that in addition to very preterm born children, also moderately and late preterm born children are at an increased risk of neurodevelopmental impairments compared with term born children. The risk of either visual or hearing impairments after moderately and late preterm birth has been poorly studied and the results are somewhat conflicting. A small study from India[13] traced auditory brain responses (ABR) from 52 very preterm, 44 moderately preterm and 52 late preterm born infants at term age. No differences in the latencies and amplitude of ABRs among the different gestational age groups were found. Thus, prematurity seemed not have any marked effect on the maturity of the auditory system. Our data suggested that VP, MP and LP births were associated with an increased risk of visual disabilities or blindness and LP birth with hearing loss. At the opposite of this, a French study,[14] where1461 infants at risk of hearing loss were screened by means of otoacustic emissions, completed by ABRs, did not reveal an association with either birth weight less than 1500 g or preterm birth less than 34 weeks and sensorineural hearing loss. In addition, a Norwegian case control study, [15] where 327 children with hearing loss, detected from registers, and 391992 children with normal hearing were included, showed a significant association with decreasing birth weight and hearing loss, but not gestational age at birth.

Very preterm, moderately preterm and late preterm birth was associated with an increased risk of visual disturbances (including disorders of ocular muscles, accommodation and refraction) and blindness in our population. Accordingly, a small Swedish study[16], where 78 MP and LP born children and 35 full term born children were evaluated at preschool age, found significantly worse results in terms of impaired motility, heterophoria at distance and refraction in MP and LP born children. Gestational age was the strongest predictor of visual acuity outcome. Compared to full-term born children MP and LP preterm birth was associated with an increased risk of refractive errors (RR 2.39:95% CI 1.10-5.20).

The current knowledge on the risk of CP in MP and LP infants looks rather congruent. In our population the risk was about five fold in MP and more than two fold in LP infants compared with term born infants. Similarly, a cohort study from Northern California, including about 140000 children born at ≥30 weeks' gestation, found that LP children were more than three times to be diagnosed with CP compared to those born at term[17]. Also, a Norwegian national register study, including more than 900000 infants born between 1967 and 1983, who were followed to adult life, detected an 1.9% incidence of CP, the relative risk of CP being 14.1 (95% CI 11.6-17.2) in subjects born at 31-33^{+6} weeks' gestation and an 0.3% incidence and a relative risk of CP 2.7 (95%CI 2.2-3.3) in subjects born LP, respectively[18]. Later, a register study[19] comprising about 215217 births between 1995-2014 in a southern region of Sweden found 381 (0.2%) cases with CP. Out of these 56 (14.7%) were born moderately or late preterm and 57 (15.0%) were born very preterm.

The prevalence of ID in our population was more than twofold in MP and 1.5 fold in LP children compared with term born children. However, MP and LP births did not significantly predict an increased risk of ID compared to term births. The risk of ID appeared to be even decreased in the MP group in the analysis. The Norwegian register study, [18] where significant congenital anomalies were excluded, found that the relative risk of mental retardation was 2.1 (95%CI 1.7-2.8) in subjects born at 31-33^{+6} weeks' gestation and 1.6 (95%CI 1.4-1.8) in subjects born LP. The association with developmental delay or mental retardation in LP infants was modest in the cohort study from California, the hazard ratio being 1.25 and 95% CI 1.01-1.54. [18] An Australian study[20] sought the association between MP and LP birth and neurodevelopment at age of two years and assessed 201 MP and LP and 183 term born children. The odds of developmental delay (less than -1 SD relative to the mean in controls in any domain) in the MP and LP group was for cognitive delay 1.8 (95%CI 1.1-1.3), for language delay 3.1 (95%CI 1.8-5.2) and for motor delay 2.4 (95% CI 1.3-4.5).[20] Woythaler et al[21] assessed neurodevelopmental outcomes in a longitudinal cohort of 4900 full term and 950 late preterm infants. The predictive value of having the total school readiness score in the lowest 5% and mental developmental index < 70 turned out to be poor (10.4%). Recently, a

systematic review and meta-analyses were undertaken in order to establish long-term neurodevelopmental outcomes of adults born MP and LP.[22] Altogether 16 publications were included and ten of these assessed cognition. No significant differences were detected in cognitive functioning between MP and LP adults compared to adults at term. Small insignificant effect size of 0.38 [-0.39; 1.14] was found for poorer intellectual performance in MP and LP adults compared to those at term. Moreover, a systematic review on 16 selected studies,[23] establishing cognitive and learning outcome in LP infants at school age, revealed mild, subtle difficulties compared to full-term control groups. Some of the difficulties seemed to be transient.[23] In summary, it looks, that although MP and LP born children have a greater risk for suboptimal cognitive function from school age to adulthood compared to subjects born at term, the risk of severe mental retardation seems not to be significantly increased.

Our results showed, that small birth weight for gestational age, low one-minute Apgar score, intracranial hemorrhage, male sex, smoking during pregnancy and early antibiotic treatment were significant risk factors associated with CP, ID as well as visual and hearing disabilities. A meta-analysis,[24] including three cohort and four case control studies, established the association of SGA and CP in moderate to late premature infants. The risk estimate for SGA was statistically significant (OR 2.34; 95%CI 1.43-3.82). In the subgroups, including LP birth, SGA<2 SDs and malformation, the association was even stronger.[24] SGA was also a significant risk factor of CP among children born MP or LP children in the Swedish cohort study.[19] In addition, an Australian study[25] on 2625 children with ID and 217252 control children without ID found also an association between severe intrauterine growth restriction and mild to moderate ID among preterm and term born children. Abnormal growth might make the neonates prone to adverse perinatal events, including asphyxia and hypoglycaemia. Common causative factors might also exist behind both abnormal growth and brain injury[24].

Maternal smoking causes intrauterine hypoxia and has an adverse effect on fetal growth. Smoking is also more common among women lower socioeconomic status and fewer years of education. A recent systematic review and meta-analysis was undertaken on maternal smoking during pregnancy and intelligence quotient in childhood, adolescence and adulthood.[26] After exclusion, 25 publications were selected into the review and 14 into the meta-analysis. Individuals exposed to maternal smoking during pregnancy had lower IQ scores compared to those not exposed. An inverse association was also seen among those adjusted for maternal education. However, a great heterogeneity among studies made it difficult to draw conclusions from the results.[26] Although smoking during pregnancy has inevitably untoward effects on the pregnancy and offspring outcome, the accuracy of the data is mostly hampered by the fact that data on smoking is collected from self-reporting.

Our register study implies that intracranial hemorrhages might cause brain damage, which seems to constitute a risk for later CP, ID and sensory impairments. A recent systematic review and meta-analysis on prospective cohort studies sought the impact of peri-intraventricular hemorrhage (PIVH) and periventricular leukomalacia on the neurodevelopment of preterm infants. Altogether 24 articles were selected into the analyses, where severe PIVH was associated with an increased risk of CP (RR4.2, 95% CI 1.8-9.9), but mild PIVH was not. Furthermore, PIVH was not significantly associated with either a lower mean Mental Developmental Index or hearing and visual impairments. However, the authors stated that the evidence was poor due to small numbers of studies.

Preterm rupture of membranes and antibiotic treatment were among significant risk factors of CP and ID in our analyses. Perinatal infection can induce systemic inflammation, which predisposes the brain of the offspring to coexisting and subsequent insults (see for review: Korzeniewski et al, 2018[28]). Epigenetic dysfunction induced by noxious stimuli, including inflammation, hypoxia and hyperoxia, has also been suggested.[29] Antibiotic treatment is also obviously a marker of general sickness of the subject, and low Apgar score a marker of severe birth asphyxia.

Our study found, that birth during the two earliest time periods seemed to be associated with an increased risk of cerebral palsy, when the last period was used as a reference. This association is probably due to advances in perinatal and neonatal care. Because the same association was seen in all gestational age groups, it is unlikely that this finding might be a significant confounder in our analyses. A shorter time period was used in the analyses for sensory impairments and ID. This decreases the possibility of the impact of improvements in the treatment practices by time on the main results.

According to our national register studies, moderately and late preterm birth is associated with an increased risk of CP and sensory impairments, but not of significant intellectual disability, when term birth was the reference in the analysis. As a curiosity, moderately preterm birth seemed even be associated with less risk of ID compared to term birth, probably because small numbers of cases. The last trimester is critical for brain development and growth and the last weeks before term might be a period of especial vulnerability of the central nervous system (see for review Favrais et al, 2019[30]). Imaging studies at term equivalent age have shown brain white matter microstructural alterations and lower fractional anisotropy in moderate and late preterm infants compared to infants born at term.[31,32] Alterations in brain growth in MP and LP born children might play a role behind the mild difficulties in cognitive and learning performances of these children at preschool and school age. Relevant screening programs for moderately and late preterm born children are needed, in order to detect early the individuals at risk o later problems with academic performance.

CONCLUSION

Although neurodevelopmental disabilities are more common after very preterm birth, also moderately and late preterm births seem to be associated with an increased risk of CP and sensory impairments, but not with significant intellectual disability. Compared to children born at term, mild difficulties in cognitive and learning performances of moderately and late preterm children at preschool and school age have been observed, but some of these problems might resolve into adulthood.

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