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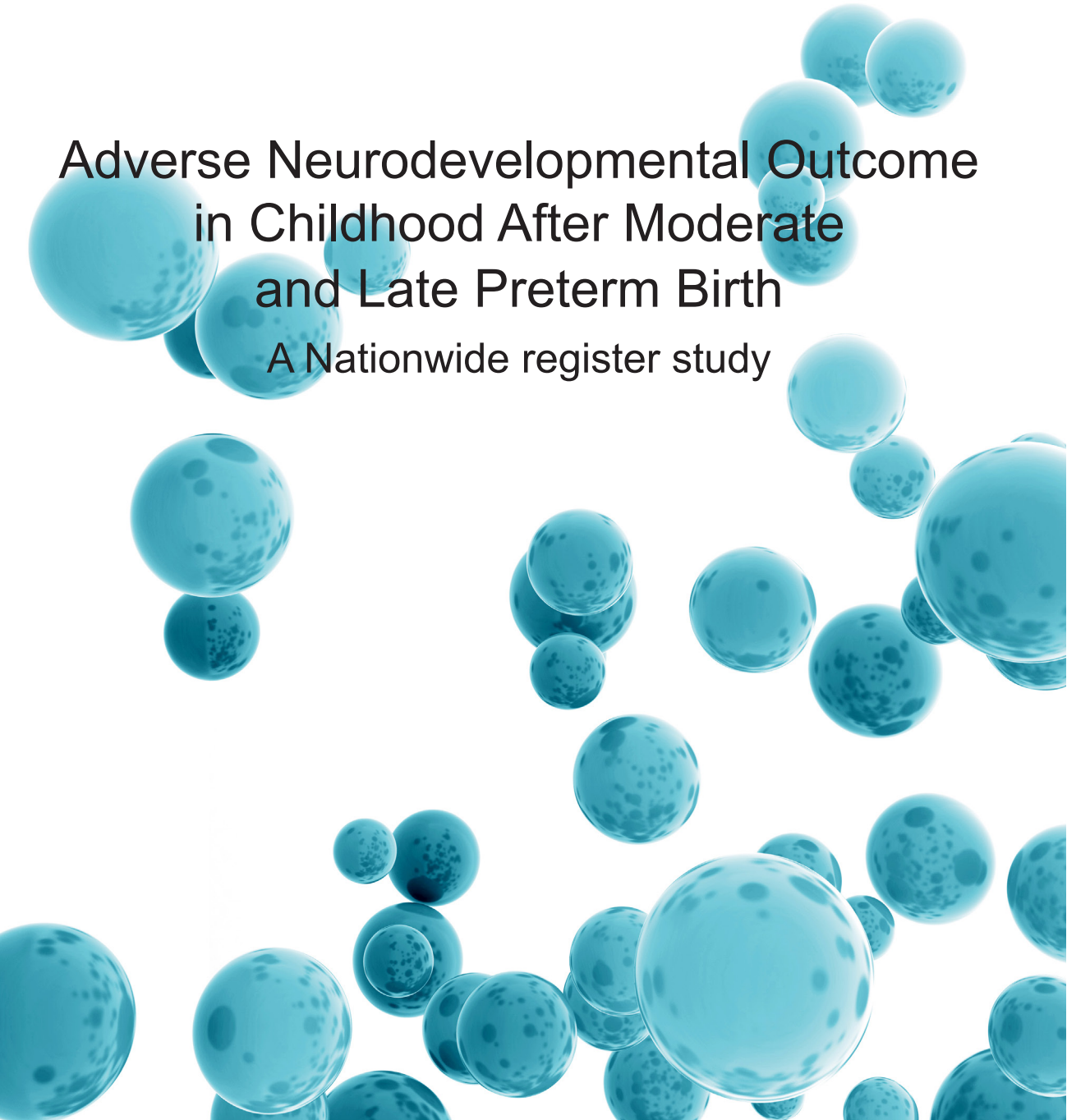
MIKKO HIRVONEN

Adverse Neurodevelopmental Outcome in Childhood After Moderate and Late Preterm Birth

A Nationwide register study



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ACADEMIC DISSERTATION
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of the University of Tampere, for public discussion
in the auditorium F114 of the Arvo building,
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on 25 May 2018, at 12 o'clock.

UNIVERSITY OF TAMPERE

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To my family

ABSTRACT

Background: Moderately preterm (MP; gestational weeks 32^{+0}–33^{+6}) and late preterm (LP; 34^{+0}–36^{+6} weeks) infants together comprise more than 80% of all prematurely (<37 weeks) born children. Very preterm birth (VP; <32 weeks) has been associated with an increased risk of neurodevelopmental disabilities, such as cerebral palsy (CP) and developmental delay. Since last decade, there has been growing concern about neurodevelopmental disabilities among MP and LP born children.

Objectives: The aim was to establish and compare incidences and risk factors of CP, intellectual disability (ID), epilepsy, and sensory impairments in MP and LP children to those in VP and term (>37 weeks) born children.

Methods: The national register study included all children born in Finland in 1991–2008 as per data on the Medical Birth Register (n=1,039,263). Infants with missing data on gestational age (GA; n=5,520), with any major congenital malformations (n=13,007), and who died before the age of one year (n=2,659) were excluded. The remaining 1,018,256 (98.0% of all) infants constituted the cohort for analysis and were analysed in four groups according to gestational age (GA), as follows: VP (n=6,329), MP (n=6,796), LP (n=39,928), and term (n=965,203). Incidences of CP, ID, epilepsy, and sensory impairments in childhood were assessed by linking the health register data. Antenatal, delivery-related, and neonatal factors predictive of neurodevelopmental disabilities were sought by multivariate analysis.

Results: The occurrences of CP, ID, epilepsy, and sensory impairments decreased with increasing GA. The incidence of cerebral palsy was 24-fold in MP and sixfold in LP infants compared with term infants. MP and LP births were associated with an increased risk of CP, epilepsy, and visual disturbances and blindness compared with term birth. Further, LP birth predicted an increased risk of hearing loss. Preterm birth seemed not to be associated with an increased risk of ID compared with term birth. The most significant predictors of neurodevelopmental disabilities were intracranial hemorrhages and convulsions during the neonatal period. Smoking during pregnancy also seemed to be associated with later neurodevelopmental problems in the offspring.

Conclusions: Although neurodevelopmental disabilities are more common after VP birth than in infants born at term, it seems that MP and LP births also are associated with an increased risk of CP, epilepsy, and sensory impairments, but not with ID.

TIIVISTELMÄ

Taustaa: Kohtalaisen ennenaikaisesti (raskausviikot 32^{+0}-33^{+6}) ja hieman ennenaikaisesti (raskausviikot 34^{+0}-36^{+6}) syntyneet lapset muodostavat yhteensä yli 80% kaikista ennenaikaisesti (alle 37 raskausviikkoa) syntyneistä lapsista. Hyvin ennenaikaiseen syntymään (alle 32 raskausviikkoa) on osoitettu liittyvän lisääntynyt neurologisten ongelmien, kuten CP-vamman ja lisääntyneen kehityksen viiveen vaara. Huoli myös isompien keskosten mahdollisista ennenaikaisuuteen liittyvistä neurologisen kehityksen ongelmista on lisääntynyt.

Tutkimuksen tarkoitus: Selvittää ja verrata kohtalaisen ja hieman ennenaikaisesti syntyneiden keskosten CP-vamman, kehitysvamman, epilepsian ja aistivammojen ilmaantuvuutta ja mahdollisia ennustavia tekijöitä ja verrata näitä hyvin ennenaikaisesti syntyneiden keskosten ja täysiaikaisena (>37 raskausviikkoa) syntyneiden lasten neurologisen vamman ilmaantuvuuteen ja riskitekijöihin.

Menetelmät: Tutkimus on kansallinen rekisteritutkimus, johon otettiin mukaan kaikki Suomessa syntymärekisterin tietojen mukaan vuosina 1991–2008 syntyneet lapset (n=1,039,263). Tutkimuksesta suljettiin pois ne lapset, joilta puuttui tieto raskaudenkestosta (n=5,520), jotka kuolivat ennen yhden vuoden ikää (n=2,659) ja ne, joilla oli jokin merkittävä synnynnäinen epämuodostuma (n=13,007). Lopulliseen analyysiin otettiin mukaan 1,018,256 lasta (98.0% kaikista) ja heidät jaettiin neljään ryhmään raskausviikkojen perusteella: hyvin ennenaikaiset (n=6,329), kohtalaisen ennenaikaiset (n=6,796), hieman ennenaikaiset (n=39,928) ja täysiaikaiset (n=965,203). Rekisteritietoja yhdistämällä selvitettiin CP-vamman, epilepsian, kehitysvamman ja aistivammojen ilmaantuvuutta eri raskausviikkoryhmissä lapsuusiässä. Lisäksi monimuuttuja-analyysillä selvitettiin sairautta selittäviä raskaudenaikaisia sekä synnytykseen ja vastasyntyneisyyskauteen liittyviä riskitekijöitä.

Tulokset: CP-vamman, kehitysvamman, epilepsian ja aistivammojen ilmaantuvuus vähenee raskausviikkojen lisääntyessä. CP-vamman ilmaantuvuus oli 24-kertainen kohtalaisen ja kuusinkertainen hieman ennenaikaisesti syntyneillä verrattuna täysiaikaisena syntyneisiin lapsiin. Kohtalaisen ja hieman ennenaikaiseen syntymään liittyy suurentunut riski CP-vammaan, epilepsiaan ja näön poikkeavuuksiin sekä sokeuteen verrattuna täysiaikaisena syntyneisiin lapsiin. Lisäksi

hieman ennenaikaisesti syntyneillä on enemmän kuulovammoja. Ennenaikaisesti syntyneillä lapsilla ei näyttäisi olevan merkitsevästi lisääntynyttä älyllisen kehitysvamman vaaraa täysiaikaisina syntyneisiin lapsiin verrattuna. Merkittävimpiä neurologista vammaa ennustavia tekijöitä ovat kallonsisäiset verenvuodot ja vastasyntyneisyyskauden kouristelu. Myös äidin raskaudenaikaisella tupakoinnilla näyttäisi olevan yhteys lapsen myöhäisempiin neurologisen kehityksen ongelmiin.

Johtopäätökset: Vaikka neurologisen kehityksen ongelmat ovat yleisempiä hyvin ennenaikaisesti syntyneillä lapsilla, näyttäisi myös kohtalaisen ja hieman ennenaikainen syntymä lisäävän neurologisia ongelmia verrattuna täysiaikaisena syntyneisiin lapsiin, erityisesti CP-vamman, epilepsian ja aistivammojen, mutta ei älyllisen kehitysvamman osalta.

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, which are referred in the text by their Roman numerals I–IV.

I Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, Luukkaala T & Tammela O. (2014) Cerebral palsy among children born moderately and late preterm. Pediatrics 134(6): e1584-93.

II Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Rantanen K, Gissler M, Luukkaala T & Tammela O. (2017) Intellectual disability in children aged less than seven years born moderately and late preterm compared with very preterm and term-born children – a nationwide birth cohort study. J Intellect Disabil Res 61(11): 1034-1054.

III Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, Luukkaala T & Tammela O. (2017) The incidence and risk factors of epilepsy in children born preterm: A nationwide register study. Epilepsy Res 138: 32-38.

IV Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, Luukkaala T & Tammela O. Visual and hearing impairments arising from preterm birth – a nationwide register study. Submitted.

ABBREVIATIONS

AGA Appropriate for gestational age
CI Confidence interval
CP Cerebral palsy
EEG Electroencephalography
GA Gestational age
HDR Hospitals Discharge Register
HIE Hypoxic ischemic encephalopathy
HR Hazard ratio
ICD-9 International Classification of Diseases, 9th Revision
ICD-10 International Classification of Diseases, 10th Revision
ICF International Classification of Functioning, Disability and Health
ID Intellectual disability
IVH Intraventricular hemorrhage
IQ Intelligence quotient
LGA Large for gestational age
LP Late preterm
MBR Medical Birth Register
GMs General movements
MP Moderately Preterm
OR Odds ratio
PAIS Perinatal arterial ischemic stroke
PVHI Periventricular hemorrhagic infarction
PVL Periventricular leucomalacia
RDS Respiratory distress syndrome
ROP Retinopathy of prematurity
RR Relative risk
SD Standard deviation
SGA Small for gestational age
SII Social Insurance Institution
THL National Institute for Health and Welfare

US Ultrasound
VP Very preterm
WHO World Health Organization

1 INTRODUCTION

Moderately preterm (MP; born at 32^{+0}–33^{+6} gestational weeks) and late preterm (LP; born at 34^{+0}–36^{+6} gestational weeks) infants together comprise more than 80% of all prematurely born children (Kochanek *et al.* 2012, Vohr 2013). This group of prematurely born infants has been generally considered low-risk, and there are currently no guidelines for follow-up programs for this group. However, MP and LP infants seem to have more short-term neonatal morbidity, such as respiratory morbidities (Colin *et al.* 2010), temperature (Wang *et al.* 2004) and glucose regulation instability, and jaundice, as well as feeding difficulties, compared with term infants (Teune *et al.* 2011). MP and LP infants are at higher risk of hospital readmission during the first month after discharge from the birth hospital (Kuzniewicz *et al.* 2013).

Neurodevelopmental impairment is a marked long-term complication in children born preterm, and the risk is highest among the most prematurely born infants (Larroque *et al.* 2008, Johnson *et al.* 2009, Kuban *et al.* 2016, Serenius *et al.* 2016). There is increasing evidence that MP and LP infants also are at higher risk of long-term neurological morbidity compared with term (born ≥37 gestational weeks) infants (de Jong *et al.* 2012, Natarajan & Shankaran 2016). The risk of cerebral palsy (CP) has been estimated to be threefold in LP children compared with term infants (Petrini *et al.* 2009). Further, LP children have higher rates of hospital admissions due to central nervous system diseases and mental or psychiatric disorders throughout childhood compared with term born children (Isayama *et al.* 2017).

MP and LP infants form the majority of all prematurely born infants, and morbidity in this group represents a burden on individuals, families, and the healthcare system. Thus, it is essential to evaluate the long-term consequences of MP and LP births and to establish potential factors predictive of long-term neurological morbidity.

The purpose of this study was to compare incidences of long-term neurodevelopmental disabilities in MP and LP children to those in very preterm (VP; born at <32 gestational weeks) and term children in a national birth cohort of all children born in Finland between 1991 and 2008, by linking the data from several national health registers of mothers and infants. Further, we aimed to establish

antenatal, perinatal, and neonatal risk factors associated with increased neurological morbidity.

2 REVIEW OF THE LITERATURE

2.1 Preterm birth

2.1.1 Gestational age (GA)

The World Health Organization defines preterm birth as a birth before 37 completed weeks of gestation (World Health Organization 1977). Preterm infants are divided into sub-categories according to GA. Extremely preterm infants are born at less than 28^{+0} weeks of gestation. Infants born between weeks 28^{+0} and 32^{+0} are defined as very preterm (VP) and those born between weeks 32^{+0} and 33^{+6} as moderately preterm (MP) infants. Late preterm (LP; 34^{+0}–36^{+6}) infants were earlier called "near term" infants, but it is recommended that this term be dispensed with, because it underestimates the risks to which these preterm infants are prone (Raju *et al.* 2006) (Figure 1).

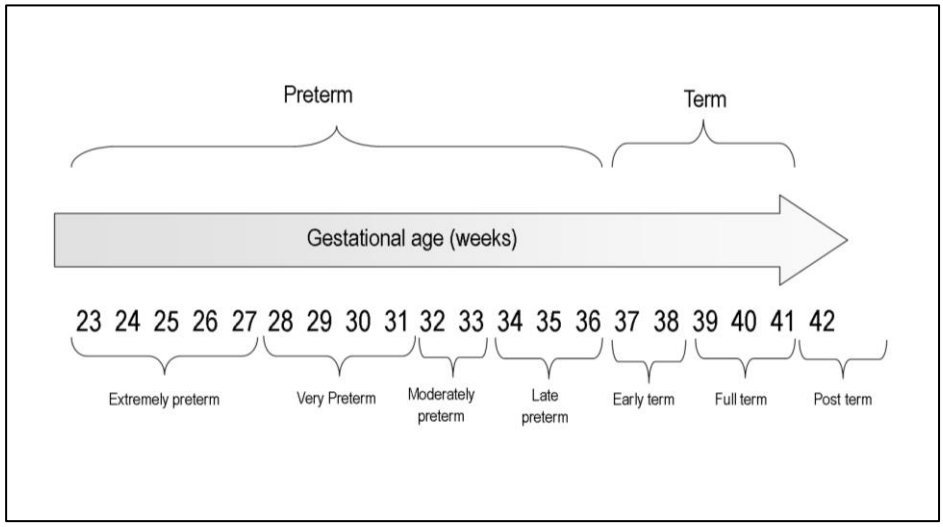

Figure 1. Definitions of infants according to gestational age (modified from Gill & Boyle 2017).

2.1.2 Birth weight

Preterm infants can also be classified according to birth weight. Low birth weight means weight of less than 2,500g. Very low birth weight is defined as less than 1,500g and extremely low birth weight less than 1,000g (World Health Organization 2004).

Additionally, term newborns can be low birth weight infants. Small for gestational age (SGA) infants have a birth weight more than two standard deviations (SDs) below the mean weight for GA and large for gestational age (LGA) infants have a birth weight more than two SDs over the mean weight for GA according to the sex-specific fetal growth curves (Pihkala *et al.* 1989).

2.1.3 Epidemiology of preterm birth

In total, there are estimated to be 14.9 million preterm births per year in the world (11.1% of all live births worldwide). The preterm birth rate varies greatly according to geographic area, being 5% in northern European countries and 18% in sub-Saharan African countries (Blencowe *et al.* 2012). The complications of preterm birth have been reported to be the second main cause of death after pneumonia in children less than five years of age (Liu *et al.* 2012).

The preterm birth rate has increased during the last decades, mostly owing to the increase of LP births in several countries, especially in the USA (Davidoff *et al.* 2006, Shapiro-Mendoza & Lackritz 2012). LP births account for 70% of all prematurely born infants in the USA (Davidoff *et al.* 2006, Raju *et al.* 2006), and LP and MP births together constitute over 80% of all preterm births (Kochanek *et al.* 2012, Vohr 2013). Compared to several other countries, the preterm birth rate has not increased markedly in Finland (Jakobsson *et al.* 2008). The mortality rates of infants born between gestational weeks 34–36 have been shown to be greater than those of term born children (Young *et al.* 2007).

2.2 Brain development and injury

The development of the brain occurs during gestation but also after birth. The brain development of MP and LP infants is at a particularly critical and vulnerable stage. The cortical surface area increases 50% between 34 and 40 gestational weeks, and the weight of the brain of an LP infant at 34 gestational weeks is only 65% of that of a term infant (Huppi *et al.* 1998, Kapellou *et al.* 2006) (Figure 2). The total gray

matter volume increases 1.4% (15 mL) per week between 29 and 41 gestational weeks, and gyral development is incomplete in late preterm infants. The brain undergoes structural maturation during late prematurity, including dramatic changes in molecular, neurochemical, and structural parameters (Huppi *et al.* 1998, Kinney 2006).

Despite the immaturity and vulnerability of MP and LP infants' brain, they are commonly considered to have similar risks for neurological problems to term born infants in clinical settings. Brain ultrasound (US) is not routinely performed in the neonatal period, and MP and LP infants do not commonly go through neurodevelopmental follow-up programs. LP and MP infants are more mature than VP infants, but their brain is still developing and can be damaged under unfavorable conditions. This hierarchy of vulnerability is recommended to be taken into account when evaluating MP and LP infants (Kinney 2006, Kugelman & Colin 2013).

The most important mechanisms of white matter brain injury in premature infants are periventricular leucomalacia (PVL) and intraventricular hemorrhage (IVH), particularly with periventricular hemorrhagic infarction (PVHI). These cause serious neurodevelopmental disabilities for survivors. Perinatal or postnatal hypoxic–ischemic insult leading to hypoxic ischemic encephalopathy (HIE) is an important cause of neurodevelopmental disabilities in term infants (Volpe 2009).

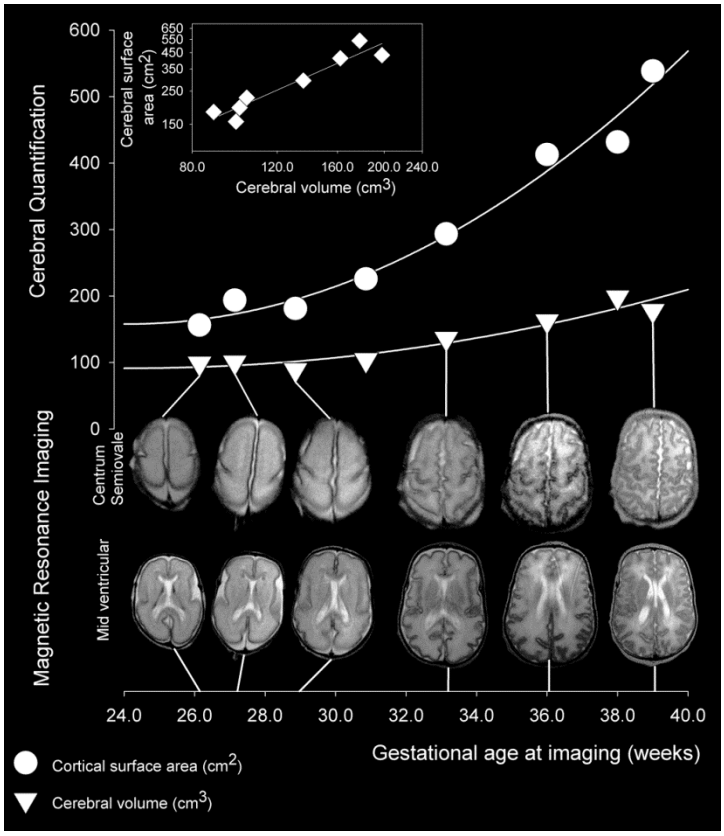

Figure 2. Brain growth in a normal female preterm infant (Kapellou *et al.* 2006).

2.2.1 Periventricular leucomalacia (PVL)

Suggested etiologies of PVL are hypoxia–ischemia, inflammation, and infection. The injury leads to disturbances of oligodendrocytes, which are myelin-producing cells of the central nervous system. The pathophysiology of PVL is a complex process leading to secondary maturation and trophic disturbances of the brain. It has been classified to subtypes of local and diffuse forms of PVL (Figure 3) (Volpe 2009, Elitt & Rosenberg 2014).

PVL is classified by cranial ultrasound (US) using the four-grade classification by de Vries *et al.* (1992). Grade I PVL is a non-cystic form of PVL, diagnosed by US as periventricular echogenicity present for more than seven days. In grade II PVL, there are focal cystic lesions, and in grade III PVL, these lesions are evolving into extensive cysts. Grade IV PVL includes periventricular and subcortical cystic lesions.

VP infants are at the highest risk of PVL, but it has been reported to occur also among LP and term infants, although the overall incidence and long-term outcome in LP infants are not known (Kinney 2006). According to a systematic review (Hielkema & Hadders-Algra 2016), the median rate of cerebral palsy (CP) was 78% (474/670) in infants with cystic PVL. The prevalence of CP was higher in infants with grade III and IV PVL compared with infants with grade II PVL. The CP was bilateral in 92% of infants with cystic PVL.

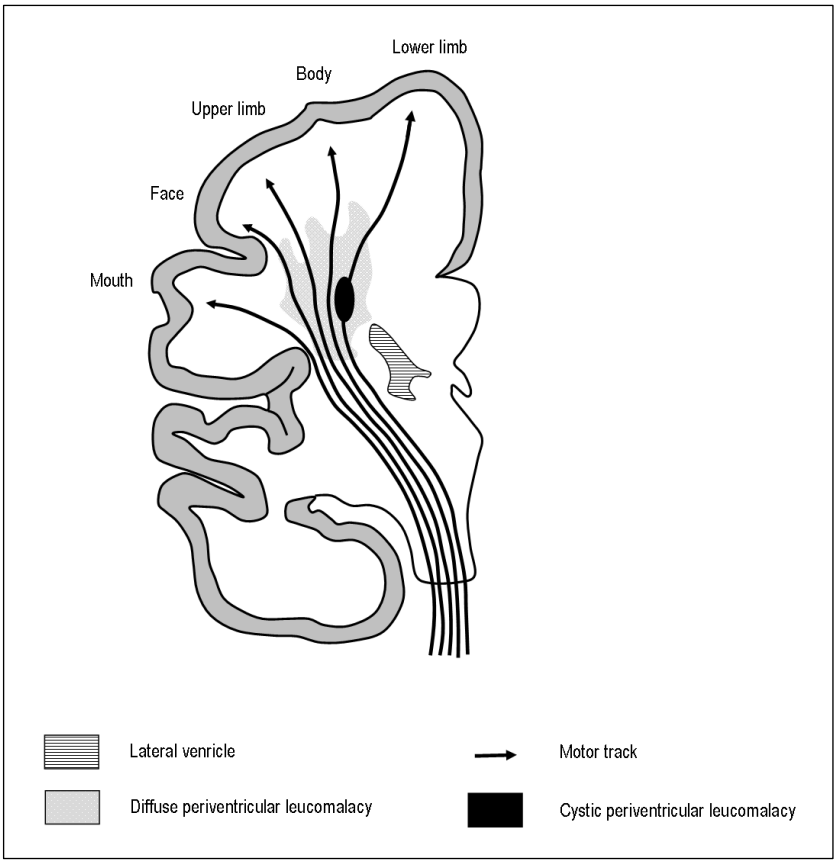

Figure 3. Periventricular leucomalacia usually bilaterally affecting lower limb motor tracts, leading to diplegia (modified from Olsen & Vainionpää 2000).

2.2.2 Intraventricular hemorrhage (IVH)

IVH usually originates from the germinal matrix area. The germinal matrix, situated on the head of the caudate nucleus and underneath the ventricular ependyma, is highly vascular and fragile. Disturbances in the cerebral blood flow may cause germinal matrix hemorrhage, which may progress to IVH (Figure 4). The pathogenesis of IVH is multifactorial, including the fragility of the germinal matrix vasculature, disturbances in cerebral blood flow, coagulation disorders, and platelet dysfunction. Neonatal risk factors of IVH include those associated with disturbed cerebral blood flow, such as low Apgar score, respiratory distress syndrome, pneumothorax, hypoxia, hypercapnia, seizures, and patent ductus arteriosus (Ballabh 2010).

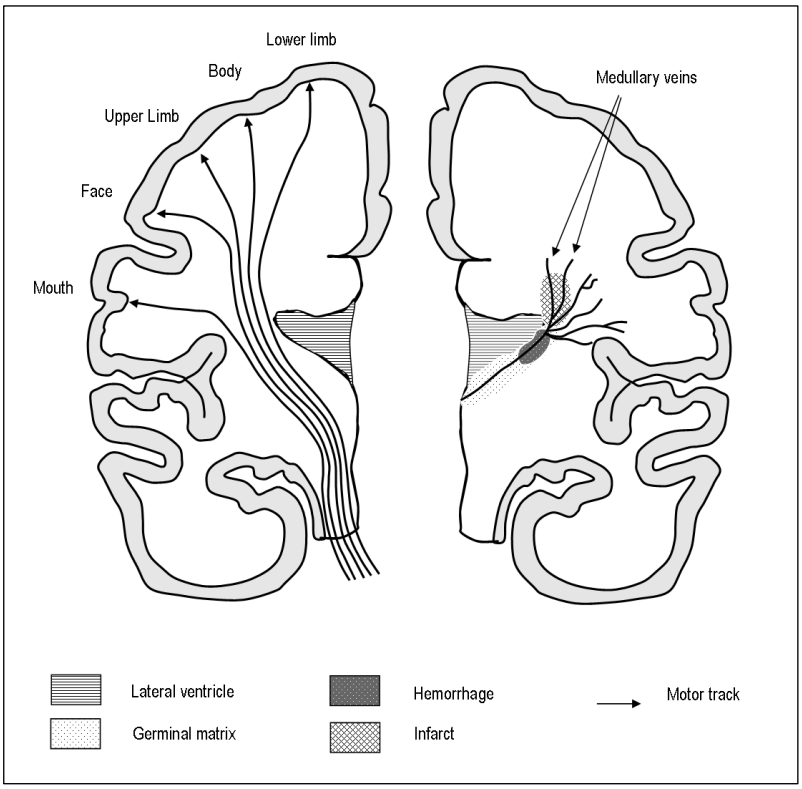

Figure 4. Intraventricular hemorrhage with periventricular hemorrhagic infarction. Motor tracts of the lower limb are usually affected unilaterally, causing hemiplegia (modified from Olsen & Vainionpää 2000).

IVHs are graded according to the Papile classification in grades I–IV (Papile *et al.* 1978). This classification was originally developed for computed tomography, but it has since been applied also to US. A grade I hemorrhage is limited to the germinal matrix area. A grade II IVH extends into the ventricles without ventricular dilatation (Figure 5), whereas grade III shows ventricular dilatation. A grade IV IVH is called PVHI and is defined as IVH with parenchymal involvement. PVHI is caused by obstruction of the periventricular terminal vein that drains the cerebral hemisphere. This causes congestion in the periventricular white matter and leads to ischemia and hemorrhage. PVHI is considered as venous infarction and a complication of germinal matrix hemorrhage (Figure 4) (Volpe 1998, Roze *et al.* 2008).

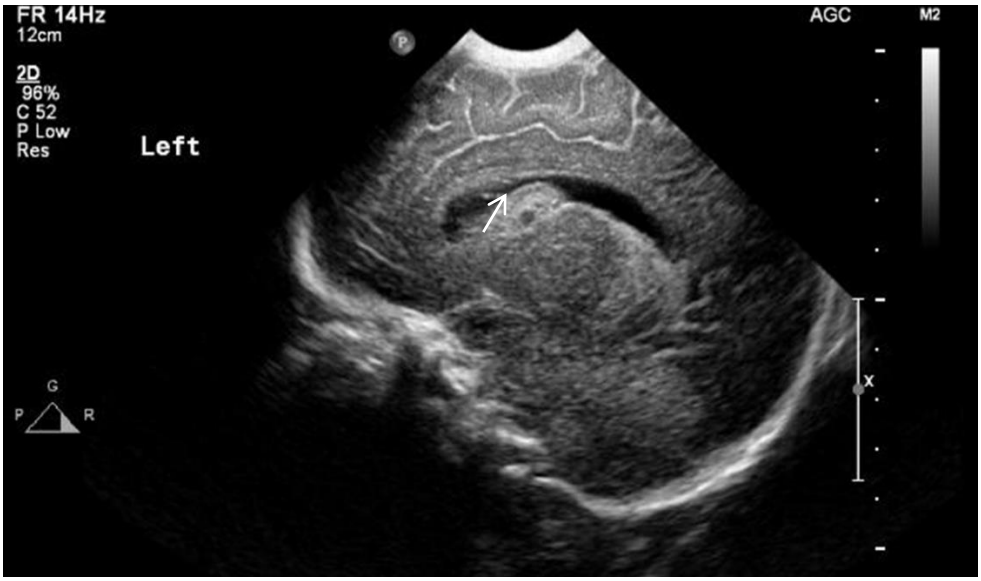

Figure 5. Brain US showing grade II intraventricular hemorrhage (arrow) in the left lateral ventricle in a full-term born newborn (Tampere University Hospital 2008).

The risk of IVH is highest among VP infants, and the incidence decreases with increasing GA. In a study from the USA of 9,575 infants of extremely low GA (22–28 weeks) and very low birth weight (401–1,500g), 16% had severe IVH (grades III and IV), and the overall rate of all grades of IVHs was 36%, increasing with decreasing GA (Stoll *et al.* 2010). In a study of 505 healthy term born infants (born at GA ≥37 weeks) on whom cerebral US was performed, the incidence of subependymal germinal matrix hemorrhage was 4% (Hayden *et al.* 1985). According to a systematic review (Teune *et al.* 2011) of 22 studies, including 2,368,471 late-

preterm infants and 27,007,204 term infants, IVH (grades I–IV) occurred in 0.41% in the LP group compared to 0.09% in the term group.

The long-term outcome after IVH is dependent on the grade of IVH and GA. The rate of CP has been reported to be 7.8% among infants with grade III IVH and nearly 50% in those with grade IV IVH (Brouwer *et al.* 2008). According to recent reports, low-grade IVHs (grades I–II) also are associated with poorer neurodevelopmental outcome. In a meta-analysis including infants born at less than 34 completed weeks of gestation, there was an association also with mild IVH (grades 1–2) and moderate to severe neurodevelopmental impairment (CP, cognitive delay, visual or hearing impairment) (adjusted OR 1.39; 95% CI 1.09–1.77) compared with preterm children without IVH at the age of 18–24 months. Severe IVH (grades III–IV) increased the risk of moderate to severe neurodevelopmental impairment (adjusted OR 2.44; 95% CI 1.73–3.42) (Mukerji *et al.* 2015). According to a multicenter trial of 44 preterm infants (birth weight 600–1250g) with isolated grade II IVH, these children had an increased risk of cognitive and executive function impairment compared with preterm children without IVH and term controls (Vohr *et al.* 2014). On the other hand, several reports indicate that low-grade IVHs do not affect long-term neurodevelopmental outcomes (Payne *et al.* 2013, Ann Wy *et al.* 2015).

2.2.3 Hypoxic ischemic encephalopathy (HIE)

The estimated incidence of HIE is 1.5 per 1,000 live births. Perinatal asphyxia is the most significant risk factor of HIE, causing inadequate blood flow and oxygen supply to the brain, resulting in focal or diffuse brain injury (Kurinczuk *et al.* 2010, Bano *et al.* 2017). The main pathophysiology of brain damage in HIE resulting from hypoxemia is deprivation of glucose and oxygen supply, causing a primary energy failure. This initiates a cascade of biochemical events contributing to cell dysfunction and cell death. The following reperfusion injury disturbs the brain metabolism by increasing oxidative stress damage, mediated particularly by glutamate, calcium, and free radicals (Lai & Yang 2011). The further outcome of HIE is dependent on the severity of the damage and on the GA of the infant (Ferriero 2004).

The majority of follow-up studies of neurodevelopmental outcome after birth asphyxia were published before the use of therapeutic hypothermia, which has been shown to improve survival and neurodevelopmental outcome in infants with moderate and severe HIE (Tagin *et al.* 2012).

2.2.4 Perinatal arterial ischemic stroke (PAIS)

Perinatal arterial ischemic strokes constitute a group of arterial ischemic injuries that may happen in the prenatal, perinatal, and postnatal period in both preterm and term infants. The majority of all PAISs are unilateral, affecting the left hemisphere in the middle cerebral artery territory (Lehman & Rivkin 2014). The incidence of PAIS has been estimated to be between one in 2,300 and one in 5,000 births, and it accounts for 30% of those late preterm and term born children who have suffered hemiplegic CP (Raju *et al.* 2007).

2.3 Clinical assessment and prognostication after brain injury in neonates

Neurologic prognostication after neonatal brain injury is a challenging and complicated process for the clinician. The prognostication should aid the detection of neonates who may need and benefit from neurodevelopmental interventions. It plays a major role when making decisions on life-sustaining and end-of-life care and interventions (Natarajan & Pardo 2017).

2.3.1 Clinical examination

2.3.1.1 Dubowitz neurological examination

Clinical neonatal neurological examination plays an important role in the assessment of newborns to detect neurologic abnormalities, despite advances in brain imagining. A widely used systematic test for neurological examination of preterm and term newborns was developed by Dubowitz and colleagues in 1981 and subsequently updated (Dubowitz *et al.* 1998). It includes 34 items subdivided into six categories (tone, tone patterns, reflexes, movements, abnormal signs, and behavior), and full examination is supposed to take 10 to 15 minutes (Dubowitz *et al.* 2005).

According to a study of 66 very low birth weight infants born in New Zealand in 1998–2000, Dubowitz examination had a sensitivity of 88% and a specificity of 46% for identifying children with significant MRI abnormalities. Brain abnormalities were especially associated with lower mean tone and tone pattern scores (Woodward et al. 2004).

2.3.1.2 General movements (GMs)

General movements (GMs) assessment is based on the observation of spontaneous movement patterns of the infant. Spontaneous fetal movements referred to as GMs can be detected in fetuses from the age of ten weeks of postmenstrual age. After birth, GMs are called writhing movements, which change to fidgety pattern-type movements at the age of six to nine weeks of post-term age. Fidgety movements are small, circular movements of the trunk, neck, and limbs, and they should disappear by the age of 14 to 20 weeks of post-term age in low-risk infants (Ferrari *et al.* 1990, Prechtl *et al.* 1997).

A systematic review of 19 studies found that the sensitivity of the GMs test was 98% (95% CI 74–100%) and the specificity 91% (95% CI 83–93%) in predicting CP (Bosanquet *et al.* 2013).

2.3.1.3 Apgar scores

Apgar scores were developed for the evaluation of the newborn condition. Points are given for respiratory effort, reflex irritability, muscle tone, heart rate, and color, and 10 points mean the best possible condition (Apgar 1953).

In a systematic review (Harrington *et al.* 2007) of 94 infants with an Apgar score of zero at 10 minutes, 88 infants (94%) either died or were severely handicapped; two infants (2%) were moderately handicapped, and one infant (1%) was mildly handicapped. In a study of 174 children with HIE (90 hypothermic and 84 controls) from the era in which therapeutic cooling was practiced, 64/85 (75%) of those with Apgar scores less than 3 at 10 minutes died or had a disability, and respectively 40/89 (45%) of those with scores more than 3 evaluated at the age of 6-7 years. Five (20.8%) of a total 24 children with an Apgar score of zero at 10 minutes survived without disability to school age (Natarajan *et al.* 2013).

2.3.1.4 Scores of encephalopathy

The Sarnat grading is used to grade the severity of encephalopathy in infants with HIE. It is based on clinical evaluation and electroencephalography (EEG) findings, according to which HIE is classified into three stages: mild, moderate, and severe. Clinical signs evaluated in the grading include level of consciousness, muscle tone, autonomic function, reflexes, and presence or absence of seizures (Sarnat & Sarnat

1976). Subsequently, the Sarnat grading has been modified for clinical settings, and in the modified scoring system the severity of HIE is assessed according to clinical observations (Levene *et al.* 1985).

Thompson scores use features of Sarnat scores and include evaluation of nine clinical signs. These are tone, level of consciousness, seizures, posture, primitive reflexes, respiration, and fontanel tension. Each sign is scored from zero to three points, and the maximum possible score is 22, meaning severe HIE (Thompson *et al.* 1997). In a recent study of 142 term newborns with HIE and threatened with therapeutic hypothermia, a Thompson score of more than 12 was associated with death (OR 3.9; 95% CI 1.3–11.2) and with epilepsy (OR 8.4; 95% CI 2.5–27.8), but no association with multi-organ failure was found (Thorsen *et al.* 2016).

The Clinical Risk Index for Babies (CRIB) and its revision (CRIB-II) have been used for risk-adjustment for VP infants at the age of one hour to predict mortality in the neonatal intensive care units. Scores consist of data on sex, birth weight, gestational age, temperature at admission, and base excess (Parry *et al.* 2003.) The CRIB-II score has been shown to predict also major neurodevelopmental impairment at a corrected age of three years in very low birth weight infants (Lodha *et al.* 2009).

2.3.2 Magnetic resonance imaging (MRI)

Imaging of the brain with MRI after brain injury is nowadays of prime importance, and MRI abnormalities detected in the neonatal period have been shown to correlate with later neurodevelopmental outcomes (Massaro 2015). Structural brain MRI with volumetric measurements at term equivalent age predicts neuromotor outcome in very preterm born children, even at school age (Setänen *et al.* 2016). However, normal MRI findings do not guarantee normal neurodevelopment.

Abnormal findings in MRI in term born infants with HIE predicted a neurodevelopmental delay (IQ<70) at the age of six to seven years, in hypothermia study including 208 infants (Shankaran *et al.* 2015). The location and magnitude of brain injury seen in MRI imaging correlates with the neurologic outcome after HIE. Lesions of the basal ganglia and thalamus are associated with an increased risk of CP (Ferrari *et al.* 2011), watershed injury is a predictor of cognitive and language disabilities (Steinman *et al.* 2009), and abnormalities in the posterior limb of the internal capsule are associated with poorer motor outcome (Rutherford *et al.* 1998, Hunt *et al.* 2004).

An Australian study of 197 children born MP or LP investigated the association between MRI scans at term-equivalent age and neurodevelopmental outcomes at the age of two years. They found that larger total brain volumes were associated with better neurodevelopment. After adjustment for perinatal factors, cerebellar volume was associated with cognitive and language development (Cheong *et al.* 2016). White matter abnormalities in VP infants at term-equivalent age are associated with an increased risk of cognitive and motor delay, CP, and neurosensory impairment (Woodward *et al.* 2006).

2.3.3 Electroencephalography (EEG)

Electroencephalography (EEG) provides functional information on brain electrical activity. It has long been used for the evaluation of neonates with HIE and the prediction of neurologic outcomes, as well as for monitoring for seizures in neonates with clinical events. Amplitude-integrated EEG (aEEG) is a bedside monitoring tool for the continuous evaluation of background activity and for the detection of seizures (Natarajan & Pardo 2017).

In term infants with HIE, normal or mildly abnormal EEG results within hours after birth have been shown to correlate with normal neurodevelopment at two years of age. Low background amplitude (<30 μV), interburst interval more than 30 seconds, electrographic seizures, and absence of sleep–wake cycling at 48 hours have shown to be associated with abnormal outcomes in HIE (Murray *et al.* 2009). In preterm infants born at less than 33 weeks of gestation, serial EEG evaluations have shown that a disorganized pattern of EEG predicts CP and dysmature pattern of later mental retardation (Watanabe *et al.* 1999). Finally, abnormalities in aEEG in asphyxiated LP infants seem to be associated with later mental retardation (Jiang *et al.* 2015).

2.4 Long-term neurodevelopmental outcome of moderate and late preterm infants

Adverse neurodevelopmental outcome is a marked long-term consequence associated with preterm birth. The risk of disabilities increases with decreasing GA (Moster *et al.* 2008). Numerous studies on the neurodevelopmental outcomes of infants born preterm have focused on very preterm and extremely preterm infants,

but the outcomes for moderately and late preterm infants have rarely been reported. MP and LP infants have been considered to be low-risk neonates and there are no routine follow-up programs for these groups of preterm infants after discharge. There is growing evidence that MP and LP births are associated with an increased risk of neurodevelopmental problems compared with term births (Samra *et al.* 2011, Kugelman & Colin 2013, Vohr 2013, Natarajan & Shankaran 2016).

Neurodevelopmental disabilities are a group of heterogeneous disorders that disturb development (Shevell 2010). According to The World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF), disability is a hypernym of impairments and activity limitations. Impairment is described as a problem in body function or structure (World Health Organization 2001). In outcome studies of preterm born children, neurodevelopmental disability has commonly been defined as one or more of the following: CP, cognitive delay, or sensory impairments (Allen 2008). Recently, behavioral and functional outcomes have also been reported in an increasing number of studies. The following reviews the current evidence of neurodevelopmental outcomes in MP and LP infants.

2.4.1 Limitations in comparing outcome studies

Some important factors are to be considered when evaluating and comparing the results of neurodevelopmental outcome studies. First, the definitions may vary from one study to another. This includes instances in which the study population has been classified according to GA or by birth weight and SGA infants are either included or excluded from analysis when using the birth weight classification. Second, exclusion criteria and the definition of GA categories may differ from one study to another. Third, clinical assessment and methods of diagnosing the outcome may vary between studies, and there may also be confounding background factors affecting the results. Fourth, treatment practices in obstetric and neonatal care have changed over time, and this may have an influence on neurodevelopmental outcomes, including, for example, the use of antenatal corticosteroids, non-invasive ventilation strategies, and nursing methods. Fifth, most studies do not take into account the admission status of infants to the neonatal ward and comorbidities in the neonatal period, especially in the LP group. Consequently, it is difficult to find a group of healthy, non-admitted infants to compare with a complicated, admitted group of LP infants (McGowan *et al.* 2011). Finally, it is important to take the correction of prematurity into account,

and variations in this method may explain differences between results (de Jong *et al.* 2012).

2.4.2 Cerebral palsy (CP)

2.4.2.1 Definition and general aspects

CP is a group of disorders causing impairments in motor behavior due to injuries occurring in the fetal or infant brain. There are commonly additional symptoms in CP, including disturbances of sensation, cognition, communication, perception, and behavior, as well as seizure disorders (Bax *et al.* 2005). The diagnosis is based on medical history, imaging, and clinical multidisciplinary evaluations. CP affects two out of every 1,000 live born infants, and, despite advances in the survival of preterm infants, the rate has remained constant since 1980 (Nelson & Blair 2015). Low gestational age is strongly associated with an increased risk of CP, and the risk decreases with increasing GA (Moster *et al.* 2008). According to a systematic review (McIntyre *et al.* 2013b) of 21 studies including 6,297 term born children with CP and 3,804,791 without CP, 10 risk factors predictive of an increased risk of CP were identified, as follows: placental abnormalities, birth defects, low birth weight, meconium aspiration, operative delivery, asphyxia, seizures, respiratory distress syndrome, hypoglycemia, and neonatal infections. Intrauterine growth restriction with major birth defects has been shown to be strongly associated with the risk of CP in children born at term (McIntyre *et al.* 2013a).

2.4.2.2 The occurrence and risk estimates of CP in moderate and late preterm children

The risk of CP has been reported, in a few studies, to be higher among MP and LP infants than in term infants (Table 1). A Californian study included 142,735 infants born at ≥30 gestational weeks and found that the rate of CP was 17.7 per 1,000 children in those who were born between 30 and 33 weeks and 7.3 per 1,000 in LP infants, compared to 2.0 per 1,000 in term (37–41 weeks) born children by the age of 5.5 years. The adjusted HR for CP was 7.87 (95% CI 5.38–11.51) in the group of 30–33 weeks gestation and 3.39 (95% CI 2.54–4.52) in the LP group, using the term group as reference (Petrini *et al.* 2009). In a large, Norwegian register-based study of

1.7 million children born in 1967–2001, the overall prevalence of CP was 1.8 per 1,000 births and the absolute risk of CP was 2.0% among children born at 31 to 33 weeks, 0.4% in LP children, and 0.1% in term children. LP birth (OR 2.9; 95% CI 2.5–3.3) and birth at 31–33 gestational weeks (OR 13.0; 95% CI 11.3–14.9) predicted an increased risk of CP compared with term (37–41) birth (Tronnes *et al.* 2014). Finally, in a Norwegian register study of 903,402 infants without congenital anomalies, the rate of CP was 1.9% (RR 14.1; 95% CI 11.6–17.2) in infants born at $31–33^{+6}$ weeks and 0.3% (RR 2.7; 95% CI 2.2–3.3) in LP infants compared to 0.1% in term (≥37 weeks) born children (Moster *et al.* 2008).

2.4.2.3 Contributing factors for CP in MP and LP infants

There are fewer reports of risk factors for CP in MP and LP infants (Table 1). In very low birth weight infants, perinatal factors such as hypoxic events and infections have been shown to have cumulative effects on the risk of CP (Wang *et al.* 2014). Most obviously, several factors including intrauterine, perinatal, and neonatal factors interact in the etiological pathway of CP.

In a systematic review including seven studies, an association was found between SGA and CP in MP and LP infants (OR 2.34; 95% CI 1.43–2.82) (Zhao *et al.* 2016). This association is well established in term infants (Jarvis *et al.* 2003) but among LP and MP infants there are contrasting results. In a Swedish population-based, case-control study including 27 LP infants (born in 1983–1990) with CP, no association was found with restricted growth status and the risk of developing CP at the age of 4–8 years (Jacobsson *et al.* 2008). Other established risk factors for CP in infants born in gestational weeks 32–36 include placental abruption, chorioamnionitis, premature rupture of fetal membranes, congenital malformations, and sepsis (Greenwood *et al.* 2005, Tronnes *et al.* 2014).

Table 1. Studies of cerebral palsy in moderate and late preterm children

Study	Study design, subjects	Gestational age definitions and sample size (MP and LP)	Cerebral palsy (N (%), estimated risk with 95% CI, term as reference)	Significant perinatal risk factors of CP for LP and MP children
Thygesen S. *et al.* 2016 (Denmark)	Population-based cohort, birth years 1997-2007 N=39,420 (birth at 32-36 full gestational weeks)	32-33 weeks, N=6,518 34-36 weeks, N=32,902	107 (1.64%) 113 (0.34%)	The risk of CP in children with respiratory distress syndrome compared to those without was HR 2.0; 1.4-2.9[1]
Petrini J. *et al.* 2009 (California, USA)	Cohort, birth years 2000-2004 N=141,321	30-33 weeks, N=1,921 34-36 weeks, N=8,341	34 (1.8%), HR 7.87 (5.38-11.51)[2] 61 (0.7%), HR 3.39 (2.54-4.52)	NA
Tronnes H. *et al.* 2014 (Norway)	Population-based cohort, birth years 1967-2001 N=1,764,509 (Birth weight >3SD from the mean, GA<23 weeks or >43 weeks and died under the age of one year excluded)	31-33 weeks, N=15,464 34-46 weeks, N=70,437	309 (2.0%), OR 13.0 (11.3-14.9)[3] 285 (0.4%), OR 2.9 (2.5-3.3)	Risk factors for infants born between 32-36 weeks (N=82,702): placental abruption (OR 2.5; 95% CI 1.7-3.6), chorioamnionitis (3.8; 2.2-6.6), prolonged rupture of membranes (1.5; 1.0-2.3), intrauterine growth restriction (3.9; 3.0-5.1), congenital malformation (2.6; 1.8-3.6)
Andersen L. *et al.* 2011 (Europe)	Register-based cohort, birth years 1980-1998 N=2,744 infants with CP born at 32-36 weeks or birthweight 1,500-2,499g (postneonatal cause of CP excluded)	32-36 weeks: 1,664 cases	Annual prevalence 12.2 (95% CI 8.5-17.1) per 1,000 births in 1983 and 4.5 (3.2-6.3) in 1997	NA
Greenwood C. *et al.* 2005 (United Kingdom)	Case-control, birth years 1984-1993 235 cases and 646 controls (CP due to genetic or fetal malformation syndrome and hypoxic event after 28 days excluded)	33-36 weeks: 36 cases and 70 controls	5.9 per 1,000 live births (based on population data held by the register; Oxford Register of Early Childhood Impairment)	Neonatal sepsis (OR 3.3; 1.1-10.1)
Moster D. *et al.* 2008 (Norway)	Population-based cohort, birth years 1967-1983 N=903,402 (Congenital anomalies excluded)	31^{+0}-33^{+6} weeks, N=6,591 34^{+0}-36^{+6} weeks, N=32,187	125 (1.9%), RR 14.1 (11.6-17.2)[4] 112 (0.3%), RR 2.7 (2.2-3.3)	NA

[1]Adjusted for sex, gestational age, birth year, multiplicity, major malformations, and maternal age. [2]Adjusted for maternal race/ethnicity, infant sex, multiple gestation, SGA, and LGA. [3]Adjusted for placental abruption, chorioamnionitis, prolonged rupture of membranes, intrauterine growth restriction, pre-eclampsia, multiple births, placenta previa, unspecified bleeding, cervical conization, congenital malformation, sociodemographic factors, and year of birth. [4]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. NA= not available.

2.4.3 Cognitive outcomes

During recent years there has been increasing evidence that MP and LP born children have poorer cognitive outcomes compared to term born children (McGowan *et al.* 2011, de Jong *et al.* 2012, Kugelman & Colin 2013, Natarajan & Shankaran 2016). A systematic review included 10 studies (published between 1980 and 2010) concerning the early childhood development of LP infants at the ages of one to seven years. LP children were reported to have more neurodevelopmental disabilities, educational disabilities, and early-intervention requirements compared with term born children. They concluded that LP children are at an increased risk of poorer developmental outcomes and have more academic difficulties up to the age of seven years compared to term children (McGowan *et al.* 2011.) A meta-analysis of 15 studies showed that the mean cognitive scores of preterm born cases and term born controls were directly proportional to GA throughout the continuum of gestational weeks (Bhutta *et al.* 2002). In contrast, a prospective study of 53 LP children and 1,245 term controls found no differences in cognition, achievement, behavior, and socio-emotional development (Gurka *et al.* 2010). Further, another prospective study of 741 infants born at 32–36 weeks of gestation and 13,102 term controls, found no difference in reduction of intelligence quotient (IQ), memory, or attention at school age. However, preterm infants had an increased risk for special educational needs. (Odd *et al.* 2012).

2.4.3.1 Cognitive functioning

Cognitive delay is typically assessed by standardized cognitive tests and is defined by scores more than two SDs below the mean. The Bayley Scales of Infant Development are widely used, and Mental Developmental Index scores less than 70 indicate cognitive delay (Bayley 1993). The current edition, the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), includes scores for cognitive, language, motor, socio-emotional, and adaptive behavior domains (Bayley 2006).

A review of 28 articles found that MP and LP children had lower IQ scores than their full term peers. However, when the correction for GA was done, differences in developmental test scores, done in infancy (0–2 years of age), were no longer observable. The mean scores in a standardized intelligence test did not differ between MP/LP and term infants (de Jong *et al.* 2012). In a study using large compulsory national register data from Norway, infants born at 31–33 weeks (RR

2.1; 95% CI 1.7–2.8) and LP infants (RR1.6; 95% CI 1.4–1.8) were at higher risk for developmental delay compared with term infants (Moster *et al.* 2008). A population-based cohort study from the United Kingdom of 1,130 LP/ MP infants and 1,255 term controls found that MP and LP infants were more likely to have moderate or severe cognitive impairment (adjusted RR 2.09; 95% CI 1.19–3.64) at the age of two years corrected age when compared with children in the control group (Johnson *et al.* 2015). In a recent Australian longitudinal cohort study of 198 infants born at weeks 32 to 36 and 183 term born controls, the adjusted odds for cognitive delay in MP and LP infants was 1.8 (95% CI 1.8–5.2) compared with controls at the age of 24 months. The cognitive delay was assessed by the Bayley Scales of Infant Development and defined by -1SD relative to the mean of the control group. Further, there were no differences between groups in moderate to severe (less than -2SD) cognitive delay (Cheong *et al.* 2017). According to a Finnish prospective study of 119 LP infants and 667 term controls, there was no difference in the full-scale IQ in early adulthood after adjusting for parental education. However, LP children born SGA had significantly lower IQ scores compared with term children born appropriate for gestational age (AGA) (Heinonen *et al.* 2017). Faster growth in weight and head circumference from birth to five months corrected age in LP infants seems to predict higher IQ in adulthood (Sammallahti *et al.* 2017).

2.4.3.2 Language skills

The previously mentioned cohort study of 198 MP and LP infants and 183 term controls found that MP and LP children had developmental delay that was most marked in the language abilities (OR 3.1; 95% CI 1.8–5.2) assessed by Bayley-III at the age of two years corrected age compared with term controls (Cheong *et al.* 2017). Similarly, in a German longitudinal study of 276 MP and LP children, they had lower language performance than term born children at the age of three and five years (Putnick *et al.* 2017).

2.4.3.3 School outcomes

MP and LP children have been found to have an increased risk for school problems compared with term children. They more frequently have special educational needs and are at increased risk of having to repeat grades (MacKay *et al.* 2010, de Jong *et al.* 2012). In a population-based cohort (UK Millennium Cohort Study) including 7,650

children, LP children had a slightly elevated risk (adjusted OR 1.12; 95% CI 1.04–1.22) of poorer educational achievement at the age of five years (Quigley *et al.* 2012). According to a longitudinal prospective cohort of 203 MP children, 767 LP children, and 13,761 term controls, LP children had an increased risk of poor reading ability from kindergarten to fifth grade and lower math scores in kindergarten and first grade at school. MP children showed poorer scores in reading and math at all grades from kindergarten to fifth grade at school (Chyi *et al.* 2008). A Danish national register study of 118,281 children born between 1988 and 1989 found that birth at 33 (adjusted OR 1.62; 95% CI 1.23–2.13) and 34 (aOR 1.35; 1.07–1.71) gestational weeks increased the risk of not completing basic school. The risk increased 0.5% per week between gestational weeks 31 and 36. (Mathiasen *et al.* 2010). Finally, in the Helsinki Birth Cohort Study of 8,993 Finnish men and women born in 1934–1944, LP children were more likely to lower level of education compared with term children (Heinonen *et al.* 2013). In contrast, a population-based cohort study found no differences in learning disabilities between LP and term born individuals by 19 years of age (Harris *et al.* 2013).

2.4.3.4 Behavioral and mental health outcomes

The previously mentioned meta-analysis found that preterm born children have more externalizing or internalizing behaviors and higher rates of attention problems compared with term controls (Bhutta *et al.* 2002). A prospective cohort of 995 MP and 577 term born children found that MP children scored higher on behavioral and emotional problems at preschool age compared with term children (Potijk *et al.* 2012). On the other hand, up to 39% of MP and LP children with developmental delay also had emotional and behavioral problems (Potijk *et al.* 2016). LP birth has been shown to increase the risk of attention-deficit/hyperactivity disorder, and being SGA seems to further increase the risk (Sucksdorff *et al.* 2015). There are also controversial results. A prospective cohort study of 53 LP infants who had no health problems before or immediately following birth and 1,245 term controls found no differences in behavior or socio-emotional development by the age of 15 years (Gurka *et al.* 2010). A higher risk for psychiatric disorders (Lindstrom *et al.* 2009) and schizophrenia (Moster *et al.* 2008) has been found in some studies comparing MP and LP born adolescents and adults with term in some studies, although not in all (Dalziel *et al.* 2007).

2.4.4 Sensory impairments

A few studies report sensory outcomes, including impairments in vision and hearing, in MP and LP infants. Rates of hearing impairment have been estimated to be 0.5% higher and rates of vision impairment 0.5% higher in MP and LP children compared with term born children (Johnson *et al.* 2015). The rate of hearing deficiency in children born at 34 gestational weeks has been reported to be 1.5% and visual deficiency 0.8% at the age of five years, and there were no differences in these rates compared with children born between 30 and 33 weeks (Marret *et al.* 2007). Refractive errors seem to be more common in MP and LP children compared with term children (Raffa *et al.* 2015).

2.5 Summary

MP and LP infants are at an increased risk of poorer neurodevelopmental outcomes compared with children born at term. The risk of adverse neurodevelopment in MP and LP children seems to be lower compared with VP children and slightly, but significantly, higher compared with term born children (McGowan *et al.* 2011, de Jong *et al.* 2012, Vohr 2013, Chan *et al.* 2016, Natarajan & Shankaran 2016). However, outcome studies of MP and LP infants vary substantially in their study methods and populations.

The mechanism leading to poor outcomes in LP and MP born children is likely to be multifactorial (Blencowe *et al.* 2013, Kugelman & Colin 2013) (Figure 6). The last trimester of pregnancy is the time for rapid brain growth, and preterm delivery may disturb the brain maturation process (Kapellou *et al.* 2006). LP infants are at an increased risk for respiratory complications, infections, intraventricular hemorrhage, feeding problems, hypothermia, and hypoglycemia (Teune *et al.* 2011). Short-term neonatal morbidity may influence the long-term neurodevelopmental outcome. On the other hand, maternal conditions and complications in pregnancy increase newborn morbidity in LP infants (Shapiro-Mendoza *et al.* 2008).

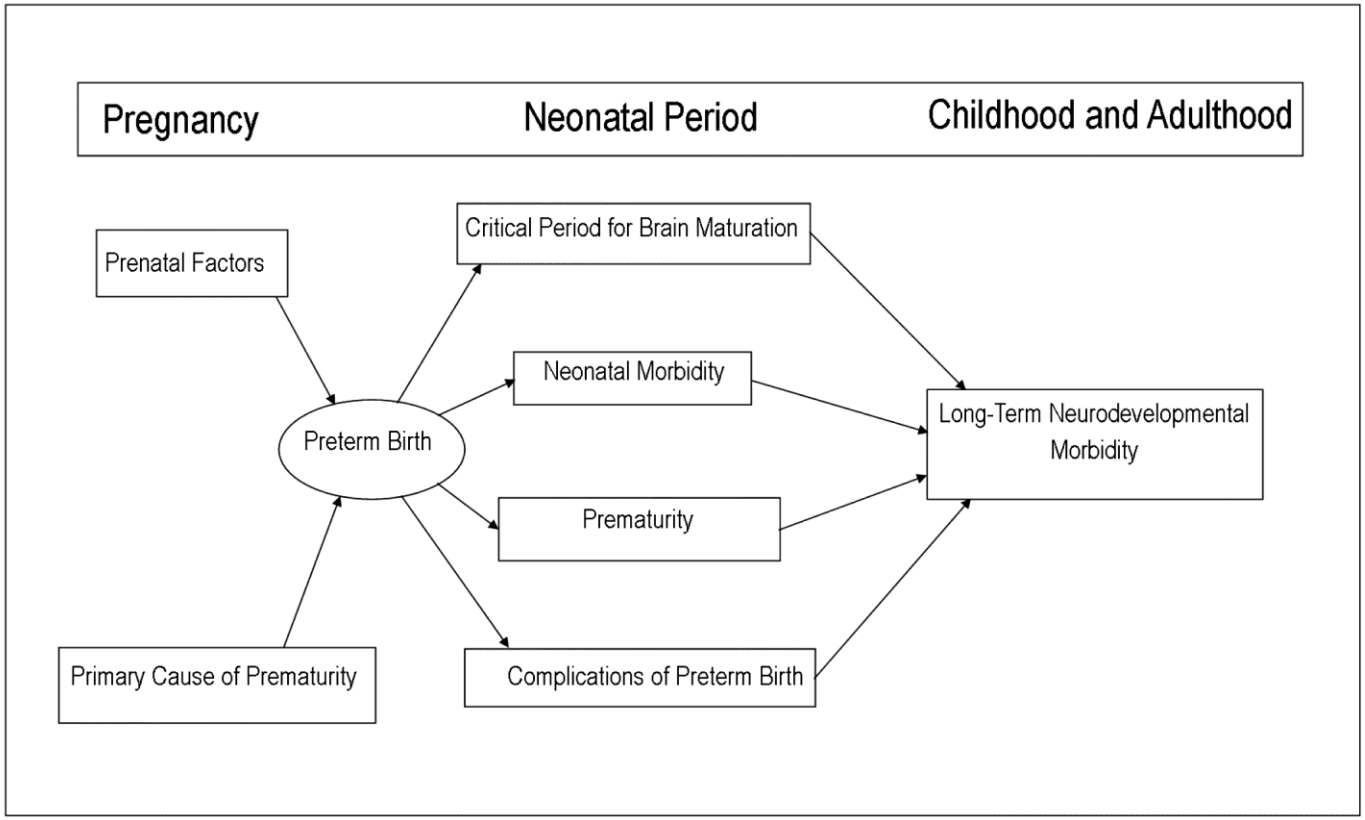

Figure 6. Schema for suggested pathways of neurodevelopmental morbidity after preterm birth (modified from Blencowe *et al.* 2013 and Kugelman & Colin 2013).

3 AIMS OF THE STUDY

The principal aim of this study was to assess the neurodevelopmental outcome of MP and LP infants in relation to VP and term infants. A further aim was to identify perinatal and neonatal risk factors associated with a risk of neurodevelopmental disabilities.

We hypothesized that MP and LP infants are at higher risk of neurodevelopmental disorders compared with term born infants.

The specific aims were:

1. To determine the incidence of CP in MP and LP born children and to establish risk factors predicting an increased risk of CP (I).

2. To assess the incidence and risk factors of ID in preterm born children (II).

3. To establish the incidence and risk factors of epilepsy in MP and LP children (III).

4. To evaluate the incidence and factors predictive of sensory impairments in MP and LP children (IV).

4 MATERIALS AND METHODS

4.1 Register study

This is a retrospective, population-based cohort study using national administrative health registers. We used linked data from several national registers, and the cohort consisted of all children born in Finland between 1991 and 2008 according to the Medical Birth Register (MBR). A flow chart of the study is presented in Figure 7.

4.1.1 National health registers

4.1.1.1 Medical Birth Register (MBR)

The MBR is maintained by the National Institute for Health and Welfare (THL) and contains data from maternity hospitals and home births, the Population Information System of the Population Register Center, and Statistics Finland. Data collection and reporting to the register-holding authority is obligated by Finnish legislation (Act on National Personal Data Registers Kept under the Healthcare System). The MBR collects data on all live births and stillbirths with a birth weight 500g or more or gestational age of 22 weeks or more. The data include information about background factors of the mother and her previous and present pregnancies and deliveries. It also includes data on the infant up to the age of seven days. Data collection forms were revised on 1.10.1990 and 1.1.1996. The MBR is well-established and validated, and the data have been shown to be reliable in register studies (Teperi 1993, Gissler *et al.* 1995, Gissler & Shelley 2002).

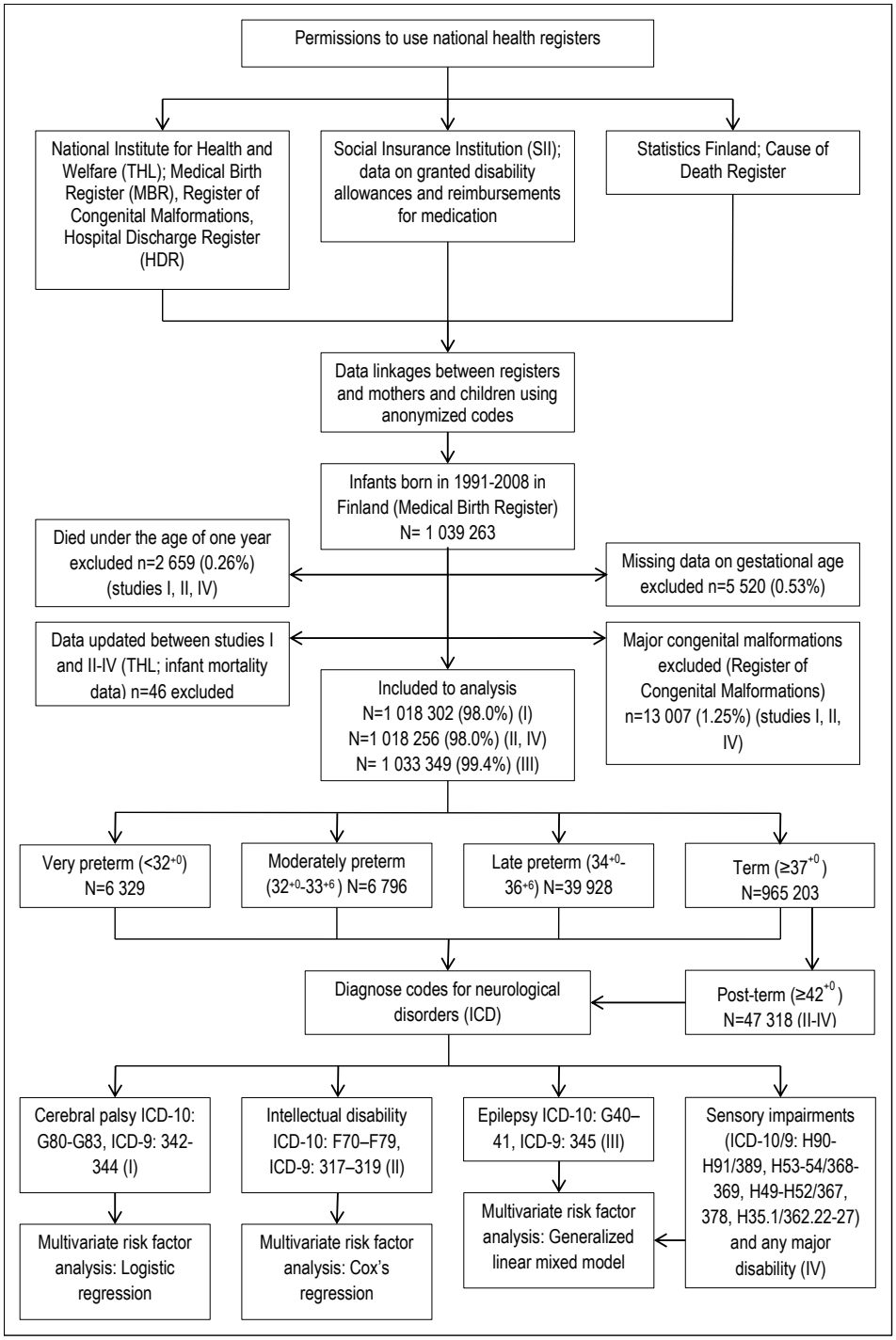

Figure 7. Flow chart of the study.

4.1.1.2 Hospital Discharge Register (HDR)

The HDR includes data on patients discharged from hospitals from the year 1969. It is maintained by THL and contains information on admission and discharge, diagnoses, procedures, and interventions. Diagnoses are coded according to the International Classification of Diseases, 9th Revision (ICD-9) between 1987 and 1995 and according to the 10th Revision (ICD-10) from 1996. The HDR data are considered to be reliable (Sund 2012).

4.1.1.3 Register of Congenital Malformations

The Register of Congenital Malformations contains data on major structural anomalies and chromosomal abnormalities. It is maintained by THL and was established in 1963. It collects information about the mother, pregnancy-related factors, and the infant. The data are obtained from birth hospitals and cytogenetic laboratories, as well as from other registers including the MBR and the HDR. Diagnoses are coded according to ICD codes, and minor abnormalities are excluded in line with international consensus (EUROCAT Guide 1.3 and reference documents, 2005).

4.1.1.4 Register of Social Insurance Institution (SII)

The SII keeps a register of granted reimbursements for medicine and disability allowances. Children below 16 years can receive a disability allowance if they need care or rehabilitation for at least six months in Finland. Special reimbursements for medicines are granted for chronic diseases by the Social Insurance Institution, based on a medical statement issued by a specialist.

4.1.1.5 Causes of Death Register, Statistics Finland

Statistics Finland keeps a Causes of Death Register based on death certificates, supplemented with the data from the Population Information System. The register contains data on the circumstances of death and demographic features, as well as on perinatal, neonatal, and infant mortality, and is validated (Lahti & Penttilä 2001).

4.2 Cohort

Records of all infants born between 1991 and 2008 were collected from MBR (n=1,039,263). Infants with missing data on gestational age were excluded (n=5,520). Infants with at least one major congenital anomaly were excluded (n=13,007) (studies I, II, and IV). Infants who died before the age of one year were excluded (n=2,659) in studies I, II, and IV. The infant mortality data were updated between study I and II leading to the exclusion in studies II and IV of 46 more infants who died before the age of one year.

4.2.1 Gestational age groups

The general practice was that the GA was based on early pregnancy ultrasound, and correction of GA was made if the estimation exhibited a discrepancy of 5–7 days or more in relation to the last menstrual period. Infants were divided according to GA into four subgroups, as follows: VP ($<32^{+0}$ weeks, n=6,329), MP (32^{+0}–33^{+6} weeks, n=6,796), LP (34^{+0}–36^{+6} weeks, n=39,928), and term ($\geq 37^{+0}$ weeks, n=965,203). The term group included also post-term born children ($\geq 42^{+0}$ weeks, n=47,318).

4.3 Main outcomes

Diagnoses of neurodevelopmental impairments were traced from the HDR and register of SII using ICD codes. These diagnoses were coded according to the ICD-9 in 1991–1995 and according to ICD-10 from 1996 to 2008. Data of the children were followed up to the age of seven years or up to 2009. The age at diagnosis was the age of children when the first detection was recorded in the registers.

Three time periods were compared: years 1991–1995, 1996–2001, and 2002–2008. These periods were chosen because Finland changed the classification system of diseases from the ICD-9 to the ICD-10 in 1996 and the MBR changed the data collection forms on 1.10.1990 and again on 1.1.1996.

In Finland, all children under school age undergo routine regular physical and developmental assessments in a child care center. In the case of suspicion of neurodevelopmental disability, children are referred to special healthcare in the pediatric neurology unit. Diagnoses are made in public healthcare, which is easily accessible to all, of whatever socioeconomic status.

4.3.1 Cerebral palsy (CP) (I)

CP is defined as a disorder of motor behavior attributable to disturbances in the developing fetal or infant brain (Bax *et al.* 2005). The diagnosis is based on medical history, imaging data, and clinical multidisciplinary evaluations in the pediatric neurology units. CP has been commonly classified according to motor type and topographic distribution. More recently, classification systems to describe functional performance have been created. The Gross Motor Function Classification System (GMFCS) is a five-level grading system to evaluate motor function, the Manual Ability Classification System (MACS) evaluates the function of the upper extremities, the Communication Function Classification System (CFCS) assesses everyday communication, and the Eating and Drinking Ability Classification System (EDACS) evaluates eating and drinking abilities in children with CP (Paulson & Vargus-Adams 2017).

A CP case was recorded if the child was detected with ICD-10 codes G80–G83 in 1996–2008 and ICD-9 codes 342–344 in 1991–1995, as has also been done elsewhere (Korvenranta *et al.* 2010). These codes included CP and other paralytic syndromes. Subtypes of CP were defined by topographic involvement (hemiplegia, diplegia, quadriplegia, and other types) and traced from registers with corresponding ICD codes (hemiplegia ICD-10 G80.2/ ICD-9 343.1 and 343.4; diplegia G80.1/ 343.0; quadriplegia G80.0/ 343.2 and other types including the remaining CP diagnosis according to ICD code definitions).

4.3.2 Intellectual disability (ID) (II)

ID has been defined as marked limitations in intellectual and adaptive functioning, which refers to the age-appropriate behaviors necessary for a person to function safely and to adapt to the daily demands of living. Intellectual quotient (IQ) at or below 70 was required for a diagnosis of ID. The diagnosis is based on assessments of cognitive development and adaptive behavior, conducted by a multidisciplinary team in a pediatric neurology unit. Standardized tests, e.g., the Bayley Scales of Infant Development (Bayley 1993) or Finnish versions of the Wechsler Intelligence Scales for Children (Wechsler 1989, Wechsler 1991) have been used. Adaptive functioning has typically been examined by means of parental interviews, observations, and rating scales (e.g., Vineland Scales) (Sparrow *et al.* 1984).

ID was detected by ICD-10 codes F70–F79 in 1996–2008 and ICD-9 codes 317–319 in 1991–1995 from the registers. These codes included mild, moderate, severe,

profound, other, and unspecified intellectual disabilities. ID was divided into three subtypes according to IQ level. The mild and moderate ID (IQ 35–70) was traced by ICD-10 codes F70–F71 and by ICD-9 codes 317–318.0. Severe and profound ID (IQ below 34) included ICD-10 codes F72–F73 and ICD-9 codes 318.1–318.2. The "unspecified" ID group covered the remaining ID diagnoses according to the ID definitions including ICD-10 codes F78–F79 and ICD-9 code 319.

4.3.3 Epilepsy (III)

Epilepsy is diagnosed by a pediatric neurologist by reference to the national Current Care Guidelines. According to these practice guidelines, any type of seizure disorder or suspicion of epilepsy is an indication for referral to a pediatric neurology unit. The diagnosis is based on medical history and clinical examination, supplemented with EEG, brain imaging, and laboratory tests (Epilepsy and Febrile Seizures (Children), Current Care Guidelines 2013).

A case with epilepsy was traced from the register by ICD codes ICD-9: 345 and ICD-10: G40–41, as recommended by literature (Jette *et al.* 2010, St Germaine-Smith *et al.* 2012). These codes included epilepsy and epileptic status.

4.3.4 Sensory impairments (IV)

Hearing loss (ICD-10: H90–H91and ICD-9: 389), visual disturbances or blindness (ICD-10: H53–H54 and ICD-9: 368–369), other ophthalmologic problems (ICD-10: H49–H52 and ICD-9: 367, 378) (including disorders of ocular muscles, binocular movement, refraction, and accommodation), and retinopathy of prematurity (ROP) (ICD-10: H35.1 and ICD-9: 362.22–27) were recorded according to the corresponding ICD codes, as elsewhere (Korvenranta et al. 2010). Hearing loss included conductive, sensorineural, and other types of hearing loss.

4.4 Variables

Risk factors for neurodevelopmental disabilities were extracted from mothers' background characteristics, pregnancy and delivery-related factors, and from infants' characteristics, diagnoses, and procedures undergone during the neonatal period.

Ventilator treatment included invasive ventilation and resuscitation included chest compression and intubation in the delivery unit. Antibiotic treatment was recorded if it was established during the first week of life. Sepsis included only blood culture positive infections (ICD-10: P36.0–8; bacterial sepsis of newborn), and hyperbilirubinemia was traced by ICD-10 codes P59.0–9 (neonatal jaundice from other and unspecified causes). Intracranial hemorrhages included all grades of hemorrhages (ICD-10: P52.0–9; intracranial nontraumatic hemorrhage of newborn) and convulsions during the neonatal period were obtained by using ICD-10 code P90 (convulsions of newborn).

SGA infants were defined as those with a birth weight more than two SDs below the mean weight for GA and LGA infants as those with a birth weight more than 2 SDs over the mean weight for GA, according to the Finnish sex-specific fetal growth curves (Pihkala *et al.* 1989).

4.5 Data linkages

Data linkages between registers were performed by Statistics Finland and carried out using unique personal identity codes anonymized by the register-holding authorities. The study group accessed unidentifiable data by using a very secure Micro Data Remote Access System run by the Finnish Information Center for Register Research and the IT Center for Science Ltd (a non-profit-making, state-owned company administered by the Ministry of Education and Culture).

4.6 Statistical methods

Characteristics of infants and their mothers were described by means of SDs in the case of normal distributed continuous variables, by medians with an interquartile range in skew distributed variables, and by number of values with percentages if the variables were categorical. The Mann-Whitney test, Chi-square test or Fisher's exact test was used in group comparisons, as appropriate. P-values <0.05 (I) or < 0.001 (II–IV) were considered statistically significant in group comparisons.

Risk factors for CP were analyzed by logistic regression analysis using a multivariate model for each GA group. All variables were entered simultaneously into the model for each GA group. The multivariate model was adjusted by gestation week classes to study the association of GA with the risk of CP, term class being the

reference. Results were shown by ORs with 95% Cis, and p-values less than 0.05 were considered statistically significant. Logistic regression models were carried out by IBM SPSS Statistics version 20.0.0.(I)

Risk factors of ID in GA groups were sought by Cox regression using IBM SPSS Statistics version 23 software. Results were presented as HRs with 95% CIs. Proportional-hazards assumptions were tested by Schoenfeld residuals with Stata/SE 14.0 for Windows. The association between GA and ID was studied by adjusting the multivariate model by GA categories, using the term group as a reference. P-values less than 0.05 were considered statistically significant in the multivariate model. Risk factors for ID were analyzed separately for preterm GA groups (VP, MP, and LP), term and post-term groups ($\geq 42^{+0}$ gestational weeks), and further separately for term boys and girls by Cox regression analysis. The methodological aim of these separate analyses was to assess the proportional-hazards assumption and they were tested using Schoenfeld residuals (assumption holds with $p>0.05$).(II)

The Generalized Linear Mixed Model (III and IV) was used to search for risk factors for epilepsy and sensory impairments. Results were presented as ORs with 95% CIs. The Generalized Linear Mixed Model with an *lmer* function was used to take into account the number of deliveries by one mother. Explanatory variables were modeled as a fixed variable, and the number of deliveries per mother was added as a random effect. The analyses were performed with the Statistical Package R version 3.3.0 package lme4 (www.r-project.org). All p-values are two-tailed and values less than 0.05 were considered statistically significant in the multivariate model.

4.7 Ethics

Unidentifiable register data were used and patients or families were not contacted. Children and their mothers were coded with unidentifiable codes anonymized by the register-holding institutions. Permissions to use registries in this study were obtained from THL (Dnro THL/1636/5.05.00/2009), SII (Kela 76/522/2009), and Statistics Finland (TK-53-1541-09). An approval statement by the national data protection ombudsman was requested and obtained. The study was approved by Pirkanmaa Hospital District and local ethics committee (ETL R09209). This study has been carried out in accordance with the Declaration of Helsinki.

5 RESULTS

5.1 Characteristics of infants and their mothers

Baseline characteristics are presented in Table 2. The preterm birth rate was 5.13% and remained constant during the study. MP and LP births accounted for 88% of all preterm births (Figure 8). The multivariate model covered the years 1996–2008 (studies II–IV) and included 592,260 (83%) vaginal deliveries, 53,057 (7.5%) planned cesarean sections (C-sections), and 63,817 (9.0%) non-elective C-sections. Vaginal deliveries included 4,715 breech infants, and the C-section rate was 16%. Data on the mode of delivery were missing in 372 infants.

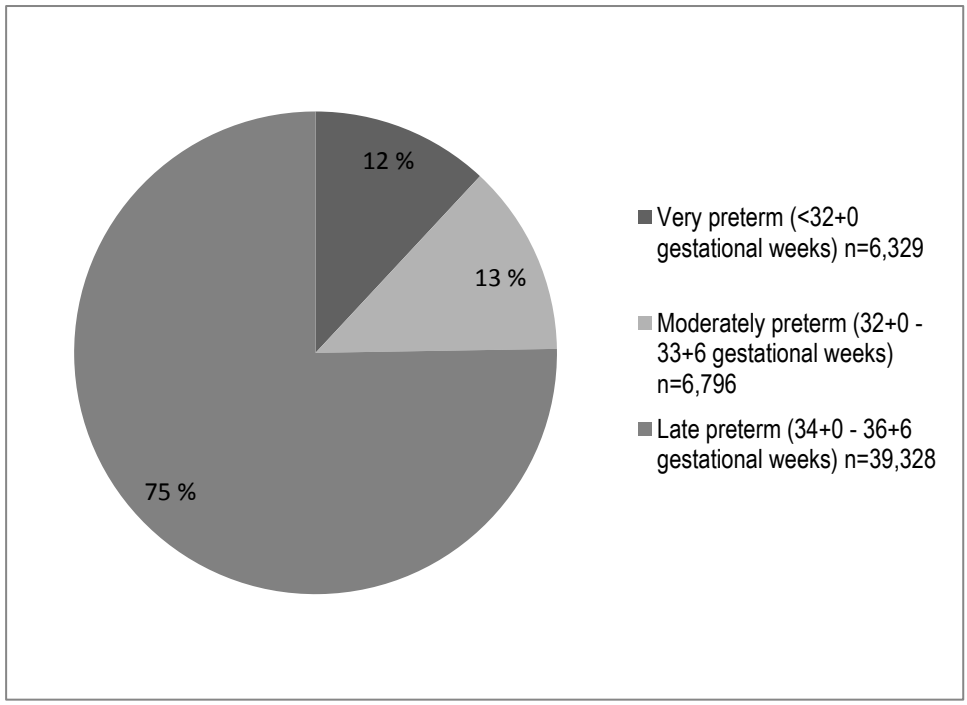

Figure 8. Distribution of preterm births in 1991–2008 in Finland (n=53,053 of 1,033,349).

Table 2. Baseline characteristics of infants and their mothers, years 1991-2008 (n=1,033,349).

	Very preterm <32 wk (n=6,329)		Moderately preterm 32+0–33+6 wk (n=6,796)		Late preterm 34+0–36+6 wk (n=39,928)		Term ≥37 wk (n=965,203)		p[1] MP vs. VP	p[2] LP vs. VP	p[3] MP vs. T	p[4] LP vs. T
Study periods, years									0.677	0.084	0.003	<0.001
1991–1995, n (%)	1,780	(0.58)	1,937	(0.63)	11,777	(3.82)	293,228	(95.0)				
1996–2001	2,159	(0.66)	2,269	(0.69)	13,361	(4.08)	309,889	(94.6)				
2002–2008	2,390	(0.63)	2,590	(0.68)	14,790	(3.87)	362,086	(94.8)				
Mothers												
Age, mean (SD)	30.2	(5.8)	29.8	(5.7)	29.7	(5.5)	29.2	(5.3)	<0.001	<0.001	<0.001	<0.001
Smoking, n (%)	1,187	(18.8)	1,184	(17.4)	6,602	(16.5)	144,094	(14.9)	<0.001	<0.001	<0.001	<0.001
Primipara, n (%)	3,314	(52.4)	3,792	(55.8)	20,040	(50.2)	392,574	(40.7)	<0.001	0.001	<0.001	<0.001
Pregnancies												
Number of fetuses at birth, n (%)									<0.001	<0.001	<0.001	<0.001
1	4,517	(71.4)	4,591	(67.6)	31,062	(77.8)	948,695	(98.3)				
2	1,614	(25.5)	1,954	(28.8)	8,548	(21.4)	16,489	(1.7)				
≥3	198	(3.1)	251	(3.7)	318	(0.8)	19	(<0.1)				
Deliveries												
Place of birth, n (%)									<0.001	<0.001	<0.001	<0.001
University hospital (level III)	4,943	(78.1)	3,993	(58.8)	17,154	(43.0)	299,470	(31.0)				
Central hospital (level II)	1,340	(21.2)	2,726	(40.1)	17,551	(44.0)	444,952	(46.1)				
Other*	41	(0.6)	77	(1.1)	5,220	(13.1)	220,654	(22.9)				
Mode of delivery, n (%)									<0.001	<0.001	<0.001	<0.001
Vaginal	2,524	(39.9)	3,211	(47.2)	26,685	(66.8)	820,942	(85.1)				
Cesarean section	3,793	(59.9)	3,582	(52.7)	13,210	(33.1)	143,491	(14.9)				
Newborns												
Boys, n (%)	3,428	(54.2)	3,728	(54.9)	21,658	(54.2)	490,211	(50.8)	0.426	0.906	<0.001	<0.001
Birth weight, g, Md (IQR)	1,290	(1,000-1,570)	1,970	(1,730-2,200)	2,670	(2,360-2,985)	3,590	(3,276-3,910)	<0.001	<0.001	<0.001	<0.001
Weight by gestational age, n (%)									<0.001	<0.001	<0.001	<0.001
SGA	1,019	(16.1)	883	(13.0)	3,245	(8.1)	16,662	(1.7)				
AGA	4,972	(78.6)	5,637	(82.9)	34,681	(86.9)	919,970	(95.3)				
LGA	284	(4.5)	276	(4.1)	2,002	(5.0)	28,571	(3.0)				
Death by 7 years of age, n (%)	13	(0.2)	4	(0.1)	36	(0.1)	627	(0.1)	0.020	0.009	1.000	0.055
Age at death, years, Md (IQR)	2.08	(1.42-4.52	2.07	(1.04-3.25)	3.27	(2.04-4.92)	3.17	(1.92-4.94)	0.477	0.135	0.099	0.797

Statistical differences were assessed using Pearson's chi-square test, Fisher's exact test or the Mann–Whitney test.
p[1]=*Moderately preterm vs. very preterm*, p[2]=*Late preterm vs. very preterm*, p[3]=*Moderately preterm vs. term*, p[4]=*Late preterm vs. term*
P-values <0.001 were considered statistically significant.
* Regional hospital, private hospital, health center, home birth
AGA=appropriate for gestational age; IQR=interquartile range; LGA=large for gestational age; LP=late preterm; Md=median; MP=moderately preterm; SD=standard deviation; SGA=small for gestational age; T=term; VP=very preterm

5.2 Cerebral palsy (I)

5.2.1 Incidence of CP

Up to the age of seven years, 2,242 children in total with CP were detected, equaling the overall incidence of 0.22%. The incidence decreased non-linearly by GA and was in the VP group 8.7%, in the MP group 2.4%, in the LP group 0.6%, and in the term group 0.1%. The steepest decline in incidence occurred after 28 gestational weeks, and the incidence also seemed to diminish over time (Table 3, Figure 9). The median age at the time of diagnosis was 1.4–1.6 years according to the GA group.

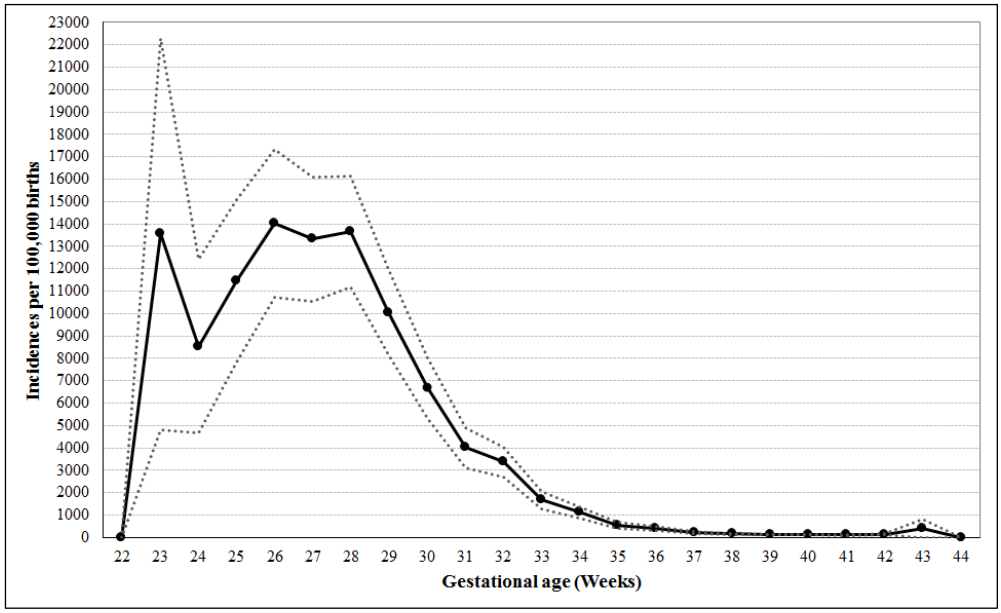

Figure 9. Incidences of cerebral palsy (n=2,242) per 100,000 births with 95% CIs by age of seven years by gestational age, birth years 1991–2008 (n=1,018,302).

5.2.2 Distribution of subtypes among GA groups

Subtypes of CP were sought according to topographic involvement. Hemiplegia was overrepresented in the term group, and diplegia was more common in the VP group (Table 3).

Table 3. Diagnoses of cerebral palsy (CP) (n=2,242) and distribution of CP subtypes in gestational week categories (N=1,018,302)

	Very preterm <32 wk (n=6,347)		Moderately preterm 32+0-33+6 wk (n=6,799)		Late preterm 34+0-36+6 wk (n=39,932)		Term ≥37 wk (n=965,224)		**Total** (n=1,018,302)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	%
Cerebral palsy, n (%)	550	(8.7)	160	(2.4)	225	(0.6)	1,307	(0.1)	2,242	(0.2)
Age at diagnosis (years), Md (IQR)	1.5	(1.0-2.3)	1.4	(0.9-2.4)	1.6	(0.8-3.0)	1.5	(0.8-3.3)		
CP subtype, n (%)										
Hemiplegia	80	(14.5)	37	(23.1)	57	(25.3)	425	(32.5)	599	(26.7)
Diplegia	213	(38.7)	48	(30.0)	52	(23.1)	165	(12.6)	478	(21.3)
Quadriplegia	37	(6.7)	11	(6.9)	16	(7.1)	84	(6.4)	148	(6.6)
Other types	220	(40.0)	64	(40.0)	100	(44.4)	633	(48.4)	1,017	(45.4)

Statistical differences were tested by Pearson chi-square test or Fisher's exact or by Mann-Whitney test: all p<0.001.
CP=cerebral palsy; IQR=interquartile range; Md=median

5.2.3 Risk factors for CP

5.2.3.1 Association of preterm birth with CP

Preterm birth was associated with an increased risk of CP compared to term birth, as follows: VP group OR 9.37; 95% CI 7.34–11.96, MP OR 5.12; 95% CI 4.13–6.34, and LP OR 2.35; 95% CI 1.99–2.77.

5.2.3.2 Common risk factors for CP in all GA groups

Birth between years 1991–2008 (VP: OR 4.03; 95% CI 3.12–5.94, MP: OR 2.55; 95% CI 1.55–4.20, LP: OR 2.41; 95% CI 1.62–3.60, term: OR 1.77; 95% CI 1.53–2.05), one minute Apgar score less than seven (VP: OR 1.26; 95% CI 1.01–1.56, MP: OR 1.70; 95% CI 1.15–2.52, LP OR 1.80; 95% CI 1.21–2.67, term: OR 1.84; 95% CI 1.47–2.29), and intracranial hemorrhage (VP: OR 3.05; 95% CI 2.08–4.47, MP: OR

7.18; 95% CI 3.60–14.3, LP: OR 12.8; 95% CI 5.58–29.2, term: OR 4.89; 95% CI 2.13–11.2) were associated with an increased risk of CP in all GA groups.

5.2.3.3 GA group specific risk factors for CP

Resuscitation at birth predicted an elevated risk in MP, LP, and term groups. SGA and antibiotic treatment was associated with an increased risk of CP in the LP and the term groups. In the MP group, preterm rupture of membranes was associated with an increased risk of CP, and antenatal steroid with a decreased risk of CP. Data on antenatal steroids were registered from 2004 onward, and in sub-analysis (years 2004–2008), the MP group with antenatal steroid was associated with a decreased risk: OR 0.24; 95% CI 0.08–0.76. Respiratory distress syndrome (RDS) seemed to predict a decreased risk of CP in the LP group.

5.3 Intellectual disability (ID)

5.3.1 Incidence of ID

In total, 3,814 children with ID in childhood were detected. The overall incidence was 0.37%. The incidence was highest in the VP group, and it decreased with advancing GA. The median age at the point of diagnosis was 5.7–6.3 years (Table 4, Figure 10.)

Table 4. Incidence and subtype of intellectual disability in four gestational age groups

	Very preterm <32 wk (n=6,329)		Moderately preterm 32+0–33+6 wk (n=6,796)		Late preterm 34+0–36+6 wk (n=39,928)		Term/Post-term ≥37 wk (n=965,203)		**Total** (n=1,018,256)		p
ID, n (%)	**157**	**(2.48)**	**55**	**(0.81)**	**218**	**(0.55)**	**3,384**	**(0.35)**	**3,814**	**(0.37)**	p<0.001
ID subtype, n (%)											
Mild /moderate ID	103	(66)	35	(64)	140	(64)	2,251	(67)	2,529	(66)	
Severe /profound ID	15	(10)	2	(3.6)	13	(6.0)	207	(6.1)	237	(6.2)	
Unspecified ID	39	(25)	18	(33)	65	(30)	926	(27)	1,048	(27)	
Age at diagnosis (years), Md (IQR)	5.7	(4.1-8.0)	6.3	(5.2-10.9)	6.0	(4.4-8.8)	6.0	(4.4-9.0)			

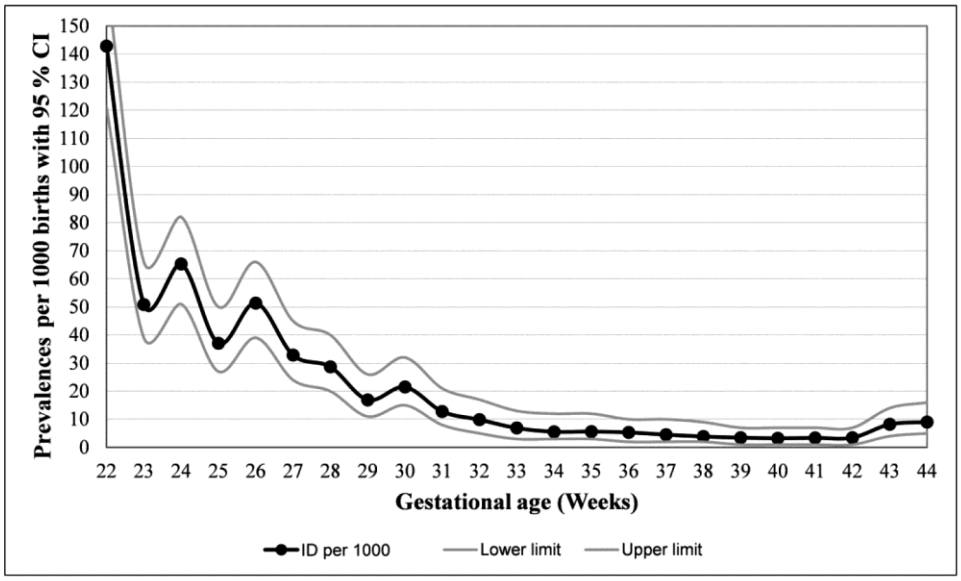

Figure 10. Incidences of intellectual disability (n=3,814) per 1,000 births according to gestational weeks. Years 1991–2008 (n=1,018,256).

5.3.2 Risk factors for ID

VP (HR 1.37; 95% CI 0.85–2.20) and LP (HR 0.99; 95% CI 0.80–1.22) births were not associated with an increased risk of ID compared to the term group. MP birth was associated with a decreased risk of ID (HR 0.63; 95% CI 0.40–0.98) compared with term born infants after adjusting for background factors.

5.3.2.1 Risk factors of ID among preterm born infants

Intracranial hemorrhage was associated with an increased risk of ID among all prematurely born groups (VP: HR 2.92; 95% CI 1.58–5.41, MP: HR 5.59; 95% CI 1.57–19.9, and LP: HR 4.58; 95% CI 1.36–15.4). Male sex (VP: HR 1.88; 95% CI 1.23–2.89, LP: HR 1.93; 95% CI 1.32–2.81) and SGA (VP: HR 1.94; 95% CI 1.19–3.16, LP: HR 3.27; 95% CI 2.03–5.24) predicted an increased risk in VP and LP groups. Apgar scores less than four (HR 2.17; 95% CI 1.38–3.42), as well as convulsions (HR 4.76; 95% CI 1.36–16.6) in the VP group and smoking during pregnancy (HR 1.94; 95% CI 1.31–2.86), low umbilical artery pH (HR 4.62; 95% CI

1.67–12.8), and antibiotic treatment (HR 1.74; 95% CI 1.01–3.00) in the LP group seemed to increase the risk of ID. Being the first child of the mother was associated with a decreased risk in the LP group (HR 0.53; 95% CI 0.36–0.77).

5.3.2.2 Risk factors for ID in term born children

The most prominent factors predictive of an increased risk of ID in the term group (37^{+0}–41^{6} weeks) were convulsions (HR 5.23; 95% CI 3.19–8.58), intracranial hemorrhage (HR 2.94; 95% CI 1.08–8.00) and SGA (HR 2.34; 95% CI 1.90–2.94). Smoking during pregnancy (HR 1.31; 95% CI 1.16–1.47), birth in other than a level II or III hospital (HR 1.16; 95% CI 1.01–1.33), cesarean section (HR 1.26; 95% CI 1.10–1.43), male sex (HR 1.71; 95% CI 1.55–1.87), low Apgar scores (HR 1.77; 95% CI 1.27–2.47), and admission to a neonatal unit (HR 1.88; 95% CI 1.58–2.23) were associated with an increased risk of ID in the term group. Being the first child was associated with a decreased risk (HR 0.81; 95% CI 0.73–-0.89), in the term group as well as in the LP group.

In the post-term group ($\geq 42^{+0}$ gestational weeks) mothers' age 40 years or more (HR 3.80; 95% CI 1.38–10.5), SGA (HR 12.5; 95% CI 5.66–27.5), and resuscitation at birth (HR 4.78; 95% CI 1.42–16.1) seemed to increase the risk of ID.

Term boys and girls were also analyzed separately. There was no association between maternal smoking during pregnancy and ID in girls and there was not any more association with intracranial hemorrhages with ID in boys; otherwise, the results were similar for term girls and boys.

5.4 Epilepsy (III)

5.4.1 Incidence of epilepsy

The overall incidence of epilepsy was 0.54%, and it decreased with increasing GA up to 41 weeks of gestation. The deepest drop in incidence occurred between 27 and 28 gestational weeks. The median age at diagnosis was 2.4–2.8 years (Table 5, Figures 11 and 12).

Table 5. Diagnoses of epilepsy in children between 1991 and 2008 (N=1,033,349)

	Very preterm <32 wk (n=7,657)		Moderately preterm 32^{+0}-33^{+6} wk (n=6,971)		Late preterm 34^{+0}-36^{+6} wk (n=40,621)		Term ≥37 wk (n=978,100)		Total (n=1,033,349)		P
Epilepsy, n (%)	**194**	**(2.53)**	**75**	**(1.08)**	**306**	**(0.75)**	**5036**	**(0.51)**	**5,611**	**(0.54)**	<0.001
Years, n (%)											
1991-1995	69	(3.0)	25	(1.2)	100	(0.8)	1653	(0.6)	1,847	(0.60)	
1996-2001	82	(3.2)	28	(1.2)	127	(0.9)	1923	(0.6)	2,160	(0.65)	
2002-2008	43	(1.5)	22	(0.8)	79	(0.5)	1460	(0.4)	1,604	(0.41)	
Age at diagnosis (years), Md (IQR)	2.4	(0.5-4.1)	2.7	(0.6-4.6)	2.7	(0.7-4.7)	2.8	(1.0-4.8)			

Statistical differences were tested by Pearson chi-square test or Fisher's exact or by Mann-Whitney test: p1=Very preterm vs. term, p2=Moderately preterm vs. term, p3=Late preterm vs. term. P-values <0.001 were considered statistically significant.

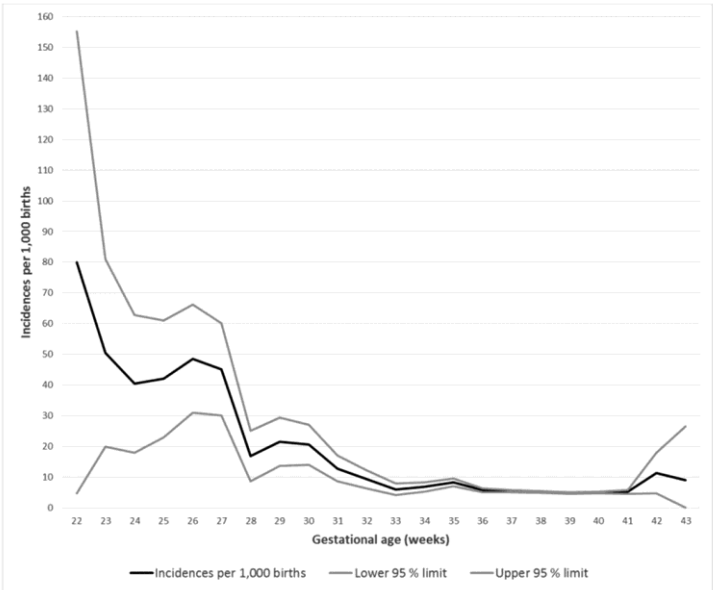

Figure 11. Incidences of epilepsy (n=5,492) per 1,000 births after excluding infants who died before the age of one year and/or with at least one major congenital anomaly by the age of seven years by gestational age, birth years 1991–2008 (N=1,018,256).

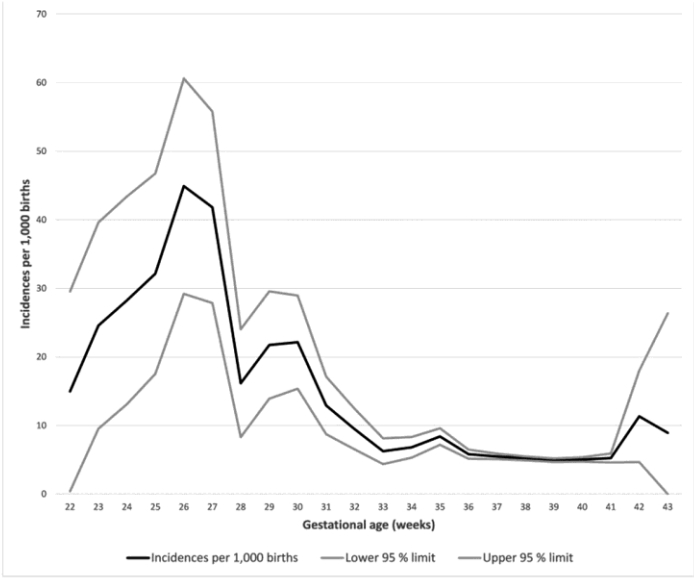

Figure 12. Incidences of epilepsy (n=5,611) per 1,000 births by gestational age, birth years 1991–2008 (N=1,033,349) (infants who died before the age of one year and with major congenital malformations included). (Hirvonen *et al.* 2017)

5.4.2 Risk factors for epilepsy

Risk factors for epilepsy were analyzed with two separate models. The first model is a risk factor analysis for epilepsy as a function of gestational age, considering maternal, pregnancy, delivery, and sex variables as potential confounders. The second is a risk factor analysis for epilepsy, considering newborn items as contributing factors proffered by gestational age. Also, cumulative hazard for GA groups was studied using Cox's model (Figure 13).

5.4.2.1 Maternal, pregnancy, delivery, and gender variables

VP (OR 4.59; 95% CI 3.79–5.57), MP (OR 1.97; 95% CI 1.48–2.63), and LP (OR 1.44; 95% CI 1.25–1.68) births were associated with an increased risk of epilepsy compared to term infants after adjusting for maternal, pregnancy, delivery, and sex variables. Post-term birth did not have a significant impact on the risk. Smoking during pregnancy (OR 1.11; 95% CI 1.01–1.12), birth at level II hospital (central

hospital) (OR 1.20; 95% CI 1.12–1.30) and cesarean section (OR 1.30; 95% CI 1.19–1.42) predicted an increased risk of epilepsy. There was an association between female sex and decreased risk of epilepsy (OR 0.90; 95% CI 0.84–0.96).

5.4.2.2 Newborn variables

Convulsions during the neonatal period (OR 13.4; 95% CI 10.2–17.6) and intracranial hemorrhage (OR 3.48; 95% CI 2.47–4.89) were the strongest predictors of epilepsy after adjusting for newborn variables. SGA (OR 1.30; 95% CI 1.09–1.54), low Apgar scores at one minute of age (OR 1.82; 95% CI 1.52–2.19), admission to neonatal unit (OR 1.58; 95% CI 1.41–1.78), mechanical ventilation (OR 1.87; 95% CI 1.48–2.36), use of antibiotics during the first week of life (OR 1.25; 95% CI 1.06–1.47), and congenital anomalies were associated with an increased risk of epilepsy. After adjusting for newborn variables, VP birth (OR 1.32; 95% CI 1.02–1.70) predicted an increased risk. Blood culture positive proven sepsis (OR 0.70; 95% CI 0.53–0.91) and hyperbilirubinemia (OR 0.83; 95% CI 0.71–0.96) seemed to decrease the risk of epilepsy.

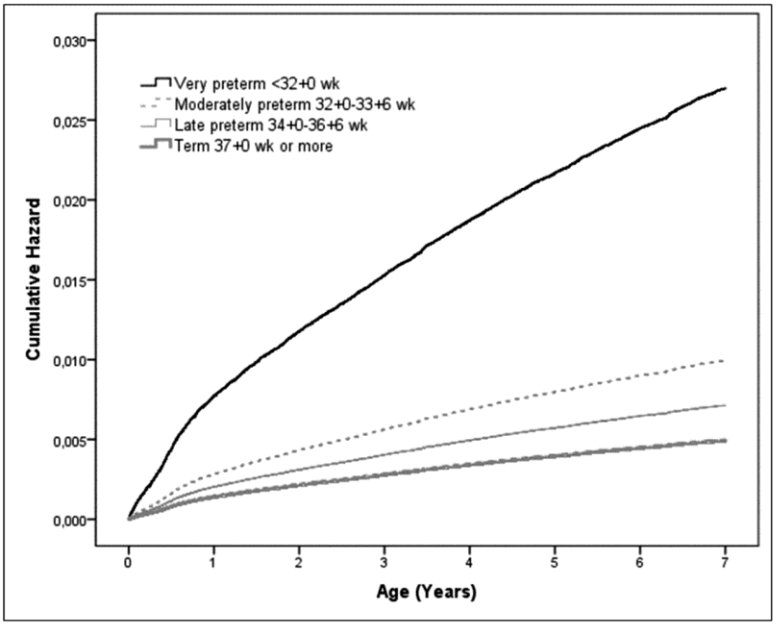

Figure 13. Cumulative hazard of epilepsy (n=5,492) according to gestational age group by the age of seven years (unadjusted Cox's model). Birth years 1991–2008 (N=1,018,256).

5.5 Hearing and visual impairments (IV)

5.5.1 Incidences of sensory impairments

Incidences of hearing loss, visual disabilities or blindness, and other ophthalmologic problems decreased with advancing GA (p<0.001). ROP was mainly the problem in VP born infants (Table 6, Figure 14).

Table 6. Sensory impairments in gestational age groups. Years 1991–2008 (N=1,018,256)

	Very preterm <32 wk (n=6,329)		Moderately preterm 32+0-33+6 wk (n=6,796)		Late preterm 34+0-36+6 wk (n=39,928)		Term ≥37 wk (n=965,203)		**Total** (n=1,018,256)		p
	n	(%)	n	(%)	n	(%)	n	(%)	n	%	
Hearing loss[1]	156	(2.46)	58	(0.85)	222	(0.56)	3,365	(0.35)	3,801	(0.37)	<0.001
Visual disturbances or blindness[2]	230	(3.63)	133	(1.96)	475	(1.19)	7,280	(0.75)	8,118	(0.79)	<0.001
Other ophthalmologic problems[3]	943	(14.9)	541	(8.0)	1,970	(4.9)	31,995	(3.3)	35,449	(3.5)	<0.001
Retinopathy of prematurity[4]	608	(9.6)	20	(0.3)	5	(0.0)	35	(0.0)	668	(0.1)	<0.001

Statistical differences were tested by Pearson chi-square test. P-values <0.001 were considered statistically significant. 1-4= Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9): 1= H90-91/389; 2= H53-54/368- 369; 3= H49-52/367, 378; 4= H35.1/362.22-27.

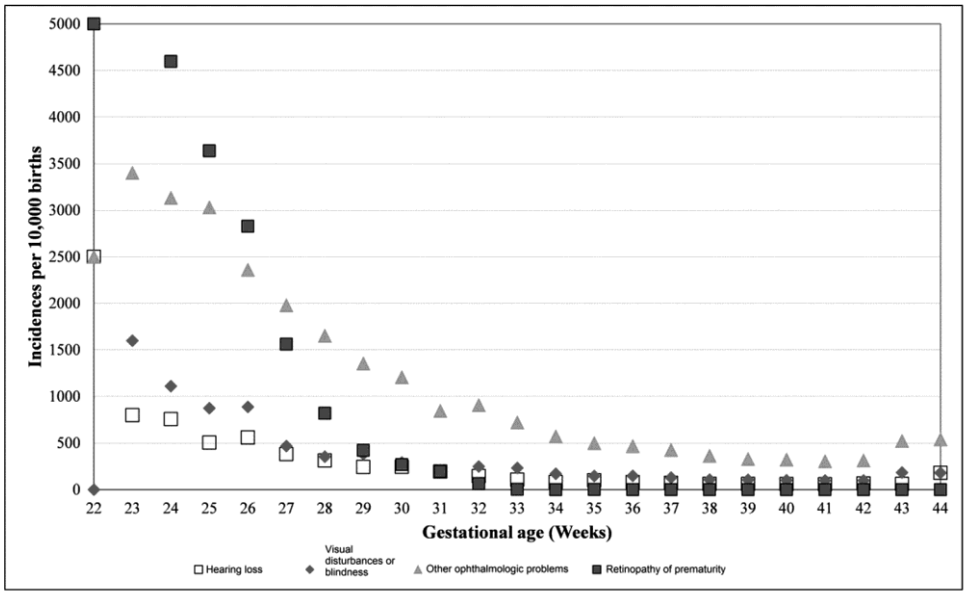

Figure 14. Incidences of hearing loss, visual disturbances or blindness, other ophthalmologic problems, and retinopathy of prematurity in 1991–2008 (N=1,018,256).

5.5.2 Risk factors for sensory impairments

Hearing loss and visual disabilities or blindness were considered as major disabilities, and risk factors for these were analyzed.

5.5.2.1 Risk factors for hearing loss

VP (OR 2.34; 95% CI 1.75–3.14) and LP (OR 1.26; 95% CI 1.04–1.52) births were associated with an increased risk of hearing loss after adjusting for background variables. Other factors associated with an increased risk included smoking during pregnancy (OR 1.16; 95% CI 1.05–1.29), birth at a level II hospital (OR 1.09; 95% CI 1.00–1.20), SGA (OR 1.32; 95% CI 1.07–1.62), Apgar score less than four at one minute (OR 1.55; 95% CI 1.22–1.98), admission to a neonatal unit (OR 1.32; 95% CI 1.13–1.53), mechanical ventilation (OR 2.11; 95% CI 1.59–2.80), antibiotic treatment (OR 1.29; 95% CI 1.04–1.58), intracranial hemorrhage (OR 2.39; 95% CI 1.48–3.86) and convulsions (OR 2.38; 95% CI 1.24–4.54). Being the first child seemed to be associated with a decreased risk (OR 0.80; 95% CI 0.69–0.92).

5.5.2.2 Risk factors for visual disabilities or blindness

Preterm birth predicted an increased risk of visual disability (VP: OR 1.94; 95% CI 1.55–2.44, MP: OR 1.42; 95% CI 1.11–1.80, LP: OR 1.32; 95% CI 1.16–1.49). Factors predictive of an increased risk of visual disabilities or blindness were mother's age ≥40 years (OR 1.29; 95% CI 1.10–1.52), smoking during pregnancy (OR 1.48; 95% CI 1.38–1.58), SGA (OR 1.23; 95% CI 1.06–1.43), low Apgar scores (OR 1.27; 95% CI 1.05–1.54), admission to a neonatal unit (OR 1.21; 95% CI 1.09–1.35), mechanical ventilation (OR 1.75; 95% CI 1.41–2.18), intracranial hemorrhage (OR 2.13; 95% CI 1.43–3.16), and convulsions (OR 2.87; 95% CI 1.79–4.64).

5.6 Summary of the results (I–IV)

Incidences of the impairments are shown in Table 7 and in Figure 15. The associations of preterm born groups with disabilities compared to the term group in separate multivariate analyses are summarized in Table 8.

Table 7. Summary of impairments in gestational age groups. Years 1991–2008 (N=1,018,256). Infants who died before the age of one year (n=2,659) or with congenital malformations (n=13,007) or with missing data on gestational age (=5,520) were excluded (studies I, II, IV).

	Very preterm <32 wk		Moderately preterm 32^{+0}-33^{+6} wk		Late preterm 34^{+0}-36^{+6} wk		Term ≥37 wk		**Total**		p
	n	(%)	n	(%)	n	(%)	n	(%)	n	%	
Major disabilities											
Cerebral palsy (I)	550	(8.69)	160	(2.35)	225	(0.56)	1,307	(0.14)	2,242	(0.22)	<0.001
Intellectual disability (II)	157	(2.48)	55	(0.81)	218	(0.55)	3,384	(0.35)	3,814	(0.37)	<0.001
Epilepsy (III)	187	(2.95)	73	(1.07)	300	(0.75)	4,932	(0.51)	5,492	(0.54)	<0.001
Hearing loss (IV)	156	(2.46)	58	(0.85)	222	(0.56)	3,365	(0.35)	3,801	(0.37)	<0.001
Visual disabilities or blindness (IV)	230	(3.63)	133	(1.96)	475	(1.19)	7,280	(0.75)	8,118	(0.79)	<0.001
Number of any major disability*	**953**	**(15.06)**	**393**	**(5.78)**	**1,246**	**(3.12)**	**18,474**	**(1.91)**	**21,066**	**(2.07)**	**<0.001**
Number of major disabilities											<0.001
One disability	719	(11.36)	328	(4.83)	1,105	(2.76)	16,977	(1.76)	19,129	(1.88)	
Two disabilities	161	(2.54)	46	(0.68)	99	(0.25)	1,230	(0.13)	1,536	(0.15)	
Three disabilities	55	(0.87)	17	(0.25)	32	(0.08)	237	(0.02)	341	(0.03)	
Four disabilities	16	(0.25)	2	(0.03)	9	(0.02)	30	(<0.01)	57	(<0.01)	
Five disabilities	2	(0.03)	0	(0)	1	(<0.01)	0	(0)	3	(<0.01)	
Minor sensory problems											
Other visual disturbances (IV)	943	(14.9)	541	(8.0)	1,970	(4.9)	31,995	(3.3)	35,449	(3.5)	<0.001
Retinopathy of prematurity (IV)	608	(9.6)	20	(0.3)	5	(0.0)	35	(0.0)	668	(0.1)	<0.001

Statistical differences were tested by Pearson chi-square test. P-values <0.001 were considered statistically significant.

*=Cerebral palsy and/or intellectual disability and/or epilepsy and/or hearing loss and/or visual disturbances or blindness.

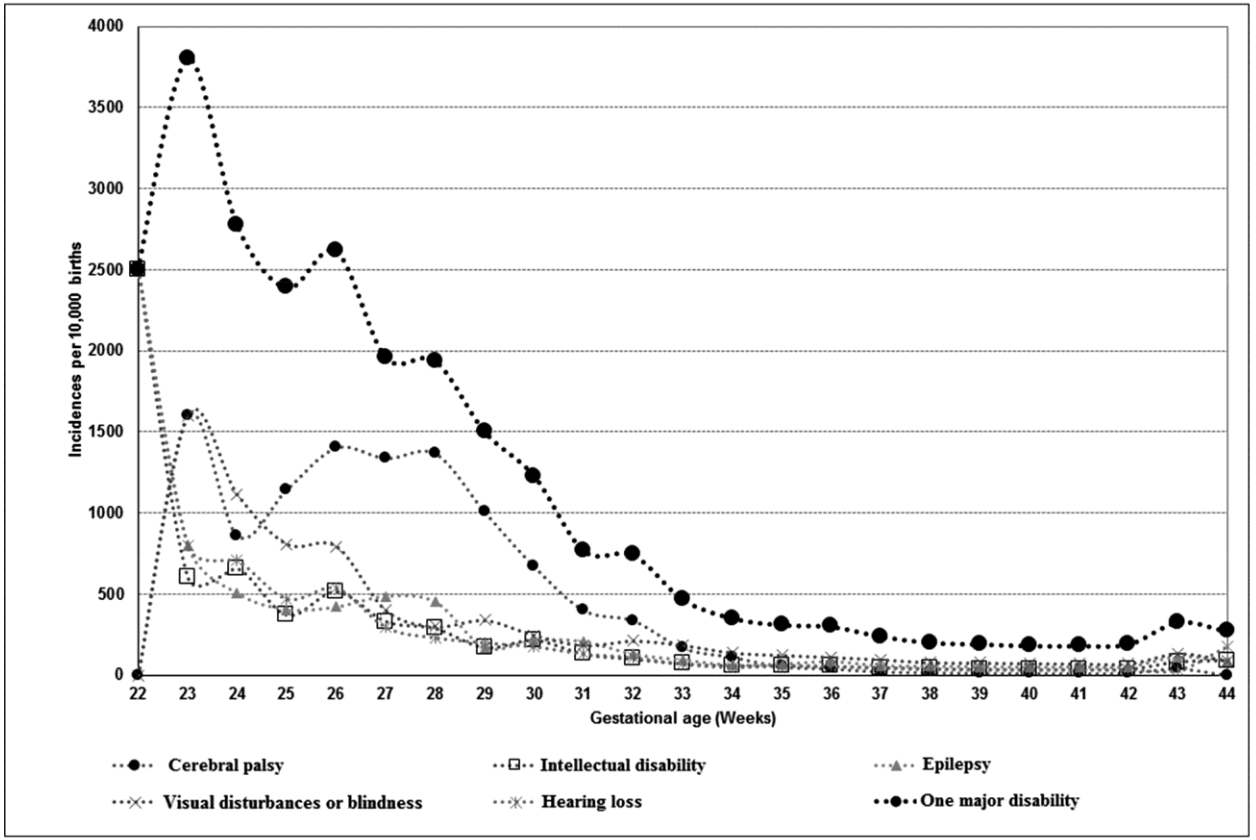

Figure 15. Incidences of childhood impairments in children born in Finland in 1991–2008.

Table 8. Summary of the results from separate multivariate models studying the association of major neurodevelopmental disabilities with birth in preterm GA group using the term group as reference.

	Very preterm <32 wk			Moderately preterm 32^{+0}-33^{+6} wk			Late preterm 34^{+0}-36^{+6} wk			Term ≥37 wk	
	n	OR/HR	(95% CI)	n	OR/HR	(95% CI)	n	OR/HR	(95% CI)	n	OR/HR
Cerebral palsy[1]	538	**9.37**	**(7.34-11.9)**	157	**5.12**	**(4.13-6.34)**	216	**2.35**	**(1.99-2.77)**	1,244	1.00
Intellectual disability[2]	157	1.37	(0.85-2.20)	55	**0.63**	**(0.40-0.98)**	218	0.99	(0.80-1.22)	3,384	1.00
Epilepsy[3]	194			75			306			5,036	
Model a[4]		**4.59**	**(3.79-5.57)**		**1.97**	**(1.48-2.63)**		**1.44**	**(1.25-1.68)**		1.00
Model b[5]		**1.32**	**(1.02-1.70)**		0.98	(0.73-1.33)		1.07	(0.92-1.25)		1.00
Hearing loss[3]	156	**2.34**	**(1.75-3.14)**	58	1.14	(0.79-1.65)	222	**1.26**	**(1.04-1.52)**	3,365	1.00
Visual disabilities or blindness[3]	**230**	**1.94**	**(1.55-2.44)**	**133**	**1.42**	**(1.11-1.80)**	**475**	**1.32**	**(1.16-1.49)**	7,280	1.00

[1] Logistic regression multivariate model, results given as the ORs and 95% CIs (Study I).

[2] Cox hazard regression multivariate model, results given as the HRs and 95% CIs (Study II).

[3] Multivariate generalized mixed model, results given as ORs and 95% CIs (Studies III and IV).

[4] Adjusted for maternal, pregnancy, delivery, and sex variables.

[5] Adjusted for newborn variables.

6 DISCUSSION

In this large national register study we found that, considering neurological morbidity in preterm born children, GA is a continuum, and rates of CP, ID, epilepsy, and sensory impairments decrease with advancing GA. MP and LP children are at an increased risk of CP, epilepsy, and visual disturbances or blindness in childhood compared with term born children. Further, LP birth predicts an increased risk of hearing loss, and MP birth is associated with a decreased risk of ID. Intracranial hemorrhages predict an increased risk of all studied neurodevelopmental disabilities in all GA groups.

To the best of my knowledge, there are no previous large register-based studies on the long-term neurodevelopmental outcomes of MP and LP children in Finland, even though these children comprise the majority of all prematurely born children. Further, there are only a few earlier similar national studies worldwide that have focused on the same issues as in the present study. Owing to the large numbers of MP and LP children, even small differences in outcomes compared with term children may have significant and broader consequences (Moster *et al.* 2008, Chan *et al.* 2016).

6.1 Cerebral palsy (I)

The significant and important finding in this study was that MP and LP birth predicted an increased risk of CP compared with term. In comparison, in a retrospective study from the USA, the risk of CP was more than threefold (HR 3.39; 95% CI 2.54–4.52) in LP infants compared with term, and they also had a higher risk for mental retardation and developmental delays (Petrini *et al.* 2009). Similarly, In a Norwegian register study of 903,402 infants born in 1976–1983 and followed up to 2003, an increased risk of CP and developmental delay was found among MP and LP children compared with term born children (Moster *et al.* 2008).

Gestational age has been strongly associated with the risk of CP (Moster *et al.* 2008, Tronnes *et al.* 2014). On the other hand, it has been suggested that prenatal factors account for 70–80% and birth asphyxia for only less than 10% of the etiology

of CP (Jacobsson & Hagberg 2004). In the present study, several pregnancy-related and neonatal factors were shown to predict the risk of CP. However, significant risk factors varied within GA groups, and intracranial hemorrhages and low Apgar scores were the only risk factors associated with CP in all GA groups.

We found that SGA seemed to increase the risk of CP in the LP and term groups, but not in the MP and VP groups. According to a meta-analysis of MP and LP born children, being born SGA was associated with an increased risk of CP (OR 2.34; 95% CI 1.43–3.82) (Zhao *et al.* 2016), but conflicting results have also been reported (Jacobsson *et al.* 2008). An important finding in our study was that antenatal steroid was associated with a decreased risk of CP in the MP group, which is a well-known association in extremely preterm infants (Chawla *et al.* 2016). This finding seems to be in line with the current guidelines, according to which antenatal steroid is administered to mothers excepted to deliver before 35^{+0} gestational weeks (Antenatal Corticosteroid Treatment for Women at Risk of Preterm Labor, Current Care Guidelines, 2011).

6.2 Intellectual disability (II)

We found that the prevalence of ID in childhood was over twofold in MP and 1.5-fold in LP children compared with term born children. The diagnosis was typically established at preschool age. Compared with an earlier Finnish register-based study with the overall prevalence of ID 0.53% in children aged 0–15 years (Westerinen *et al.* 2007), we found a slightly lower overall prevalence of 0.37%. This might be due to methodological differences between studies, and Westerinen *et al.* included children with anomalies and chromosomal abnormalities in their analysis. In the present study, the prevalence of ID seemed not to increase with time. It may be impossible to draw clear conclusions about secular trends in the prevalence of ID, because children who were born in the latest years of the study period may have been too young for neuropsychological testing, and they had a shorter follow-up owing to the study design.

We found no association between an increased risk of ID and preterm birth. However, here too contrasting data exist. A Norwegian register study found an increased risk of ID with preterm birth at 31–33 weeks (RR 2.1; 95% CI 1.7–2.8) and at 34–46 weeks (1.6; 1.4−1.8) compared with term birth (Moster *et al.* 2008). They excluded infants with congenital anomalies, as did we, but they used an older cohort (birth years 1967 to 1983) and followed them up to adult life (to year 2003).

Similarly, a retrospective cohort study found a modest association (HR 1.25; 95% CI 1.01–1.54) between birth at 34–36 weeks and developmental delay or mental retardation (Petrini *et al.* 2009). Interestingly, we found a decreased risk with MP birth and ID. This result is difficult to explain. It may be due to a smaller number of ID cases in the MP group.

6.3 Epilepsy (III)

The prominent result of this study was that preterm birth (including VP, MP, and LP birth) was associated with an increased risk of epilepsy when the model was adjusted for maternal, pregnancy, delivery, and sex variables. On the other hand, when the model was adjusted for newborn variables as contributing factors of epilepsy, only VP birth was predictive of childhood epilepsy compared with term birth. The association between LP birth and epilepsy (OR 1.76; 95% CI 1.30–2.38) has been shown in a Swedish national cohort of infants born between years 1973 and 1979 and followed up until adulthood (Crump *et al.* 2011). Contrary to these findings, a Danish register study of 1.4 million children born between 1976 and 2002 and followed up to 2002 found no association between LP birth and epilepsy, even though the incidence of epilepsy increased with decreasing GA and birth weight (Sun *et al.* 2008).

Convulsions during the neonatal period were the strongest predictor of childhood epilepsy. Most seizures in neonates are symptomatic and are a sign of neurologic dysfunction. The etiology of seizures is the most important predictor for outcome. The rates of CP, ID, and childhood epilepsy have been reported to be higher among infants with convulsions during the neonatal period (Scher *et al.* 1993, Ronen *et al.* 2007). The association with intracranial hemorrhage, with worse neurodevelopmental outcomes, has been established and was also confirmed in our study (Mukerji *et al.* 2015). Obviously, convulsions and intracranial hemorrhages indicate brain injury leading to neurodevelopmental impairments.

SGA was associated with an increased risk of having childhood epilepsy. The link between neurodevelopmental problems and SGA has been shown earlier (O'Keeffe *et al.* 2003). The etiology of SGA is heterogeneous, but it has been suggested that neurodevelopmental problems in SGA infants are due to structural and functional changes in brain development (de Kieviet *et al.* 2012, Li *et al.* 2016). Maternal smoking is a risk factor for intrauterine growth restriction and may have an influence on fetal brain development (Rivkin *et al.* 2008). SGA and maternal smoking during pregnancy

may together constitute a continuity leading to poorer neurodevelopment during childhood, which should be taken into account when counseling parents against tobacco smoking during pregnancy.

Male gender was associated with the risk of epilepsy. In an Italian study of 188 low-risk infants, male sex was an independent risk factor for neurodevelopmental delay among prematurely born children at the age of two years (Romeo *et al.* 2016). Differences in neurodevelopmental outcomes have been suggested to be due to variation of hormonal, neuronal, neurobiological, structural, and genetic factors between males and females (Johnston & Hagberg 2007). It may be also partly due to X-linked disorders among males (Stevenson & Schwartz 2009).

6.4 Hearing and visual disabilities (IV)

Few reports have focused on sensory impairments in MP and LP children. To fill this gap, we estimated incidences of sensory impairments and analyzed further factors associated with hearing loss and visual disturbances or blindness, which we considered to be major sensory impairments arising from preterm birth.

The major findings were that not only VP but also MP and LP births were associated with an increased risk of visual disabilities or blindness, and LP birth with hearing loss. By contrast, a French study did not find an increased risk of hearing loss in infants at risk of hearing impairment and born before 34 weeks gestation (Ohl *et al.* 2009). Similarly, a Norwegian study found an association with decreasing birth weight and hearing loss, but not with GA (Engdahl & Eskild 2007). Differences between the studies are probably due to different outcome definitions and study methods.

The incidence of other ophthalmologic problems (including disorders of the ocular muscles, binocular movement, accommodation, and refraction) was 2.4-fold in the MP group compared with the term group of children, which is in accordance with a Swedish study of children born in 2002–2004 between gestational weeks 32 and 36 and assessed at preschool age (Raffa *et al.* 2015).

6.5 Any impairment and comorbidity (I-IV)

The number of instances of any major impairment decreased with increasing GA, and there was comorbidity with recorded impairments. In agreement with our

results, a Californian study of 142,735 children found that the combined category of CP, developmental delay, and seizures decreased between 31 and 38 gestational weeks (Petrini *et al.* 2009). The impairments investigated in our study were detected according to ICD codes, which do not describe the functional status of the children. Obviously, multiple comorbid impairments lead to worse functional status.

6.6 Strengths and limitations

The main strength of this study is that it drew on a large national cohort including 98% of all infants born between 1991 and 2008 in Finland. National health registers are validated, and the data has been shown to be reliable in register studies (Teperi 1993, Gissler *et al.* 1995, Gissler *et al.* 1998, Penttilä 2001, Gissler & Shelley 2002, Lahti & Sund 2012). Second, public healthcare is easily accessible to all, of whatever socioeconomic status, and all children undergo regular physical and developmental assessments in child health centers. If any neurodevelopmental problems are detected, children are referred to special healthcare units, where diagnoses are made. Finally, all healthcare providers are obligated to report diagnoses to register-holding authorities, as required by legislation.

There are some important limitations in this study. The recording practices for administrative register data may vary between regions and time periods, and some unknown confounding factors may exist in the large data. The follow-up time in the last time period was probably too short to draw further conclusions about trends in neurodevelopmental disabilities over time. Because of the nature of this study, we did not have detailed information on the functional status of the children. Further, the register data may underestimate the true neurological morbidity of children, and there may be children with milder disabilities who do not have diagnoses of conditions studied here. On the other hand, the diagnoses here studied obviously constitute a major burden on society. Our data did not include reliable information on parents' socioeconomic status, which has been shown to correlate with worse neurodevelopmental outcomes in extremely low birth weight infants (Gargus et al. 2009). However, we had data on maternal smoking during pregnancy, which is more common in Finland among women with fewer years of education and/or with a lower socioeconomic status. We did not have data on five-minute Apgar scores, which have been shown to be associated with poor neurodevelopmental outcomes, especially when combined with one-minute scores (Leinonen *et al.* 2018). The umbilical artery pH was not systematically taken during the study period. Finally, it

would have been valuable to analyze the significance of different grades of IVH leading to neurological morbidity. We did not have detailed data on the severity of IVH and therefore we included all intracranial hemorrhages into this variable.

Access to the national health data takes time and involves a complex process of gaining permissions, followed by time-consuming data collection and creation of linkages. This leads to a time gap between the follow-up time of the registers and the time of writing, which can also be considered a general limitation of register study.

6.7 Future considerations

This study revealed that MP and LP born children are at risk of long-term neurological morbidity. A number of prenatal and perinatal as well as neonatal factors showed an association with long-term neurodevelopmental disabilities. On the other hand, these factors may also be associated with preterm birth and may be considered complications of pregnancy. Most obviously, the mechanism leading to neurodevelopmental disabilities is a multifactorial combination of these factors, including also the vulnerability of the preterm brain and the harmful effects on the central nervous system of transition to the extrauterine environment too early.

It is important to recognize in clinical practice the long term risks to which LP and MP infants are subject. The optimal timing of elective cesarean section should be strictly assessed. During the neonatal period, potential morbidities should be detected and timely managed, including metabolic and respiratory problems, as well as feeding difficulties and jaundice. There should be guidelines for discharge routines from the birth hospital for MP and LP infants. The challenge is to recognize, out of a large number of MP and LP infants, those at risk of further long-term neurodevelopmental disabilities and offer this group of children adequate follow-up and potential early interventions.

Earlier research has substantial heterogeneity, which makes comparing the results of studies challenging. It would be beneficial for future research if GA categories were similar. Also, using similar standard outcome measures and reference groups would be an advantage in future research on MP and LP children. From the clinical research aspect, specific treatments should be studied in MP and LP children. The safety and efficacy of cooling therapy in MP and LP infants should be studied in randomized controlled trials. In addition, long-term consequences in adulthood of MP and LP births need further research. Finally, high-quality national health registers should be made more easily accessible for scientific use.

7 CONCLUSIONS

The following conclusions can be drawn:

1. Preterm birth, including MP and LP birth, was associated with an increased risk of CP. The incidence of CP was 24-fold among MP children and sixfold in LP children compared with term born children. The most prominent factor predictive of later CP was intracranial hemorrhage in all GA groups.
2. The incidence of ID decreased with increasing gestational age. Preterm birth had no clear association with an increased risk of ID. Intracranial hemorrhage predicted an increased risk of ID.
3. The incidence of epilepsy decreased with advancing gestational age at birth. Preterm birth, including MP and LP birth, predicted an increased risk of epilepsy in childhood after adjusting for maternal, pregnancy, delivery, and sex variables. Intracranial hemorrhage and neonatal convulsions were strongly associated with an increased risk of epilepsy.
4. Incidences of visual and hearing impairments decreased with increasing GA at birth. VP and LP births were associated with an increased risk of hearing loss, and VP, MP, and LP births with an increased risk of visual impairment. The most important risk factors predictive of visual and hearing disabilities were intracranial hemorrhage and convulsions.
5. Incidence of any major impairment decreased with advancing GA, and there is neurological comorbidity with impairments.

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Cerebral Palsy Among Children Born Moderately and Late Preterm

WHAT'S KNOWN ON THIS SUBJECT: The incidence of cerebral palsy is dependent on the gestational age in very preterm infants and risk factors have been identified for term infants. The risk has also proved to be greater among late preterm births compared with term.

WHAT THIS STUDY ADDS: The incidence of cerebral palsy was 24-fold in moderately preterm and 6-fold in late preterm infants compared with full-term infants. The most prominent risk factors included asphyxia and intracranial hemorrhage. The incidence diminished over time and with increasing gestational age.

abstract

OBJECTIVE: To compare the incidence of and risk factors for cerebral palsy (CP) in moderately preterm (MP) (32^{+0}–33^{+6} weeks) and late preterm (LP) (34^{+0}–36^{+6} weeks) infants with those in very preterm (VP) ($<32^{+0}$ weeks) and term infants ($\geq$37 weeks).

METHODS: The national register study included all live-born infants in Finland from 1991 to 2008. Infants who died before the age of 1 year, had any major congenital anomaly, or had missing data were excluded. A total of 1 018 302 infants were included in the analysis and they were analyzed in 4 subgroups (VP, MP, LP, and term) and 3 time periods (1991–1995, 1996–2001, and 2002–2008).

RESULTS: By the age of 7 years, 2242 children with CP were diagnosed (0.2%). CP incidence was 8.7% in the VP, 2.4% in the MP, 0.6% in the LP, and 0.1% in the term group. The risk of CP was highest in the study period 1991–1995 in all groups. Factors predictive of an increased CP risk in the MP and LP groups included resuscitation at birth (odds ratio 1.60; 95% CI 1.01–2.53 and 1.78; 1.09–2.90), antibiotic treatment during the first hospitalization (1.63; 1.08–2.45 and 1.67; 1.13–2.44), 1-minute Apgar score <7 (1.70; 1.15–2.52 and 1.80; 1.21–2.67) and intracranial hemorrhage (7.18; 3.60–14.3 and 12.8; 5.58–29.2).

CONCLUSIONS: The incidence of CP is higher in LP and MP infants compared with term infants. There is a nonlinear decrease in incidence over time and with increasing gestational age. *Pediatrics* 2014;134:e1584–e1593

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KEY WORDS

cerebral palsy, preterm, moderately preterm, late preterm, infant

ABBREVIATIONS

CI—confidence interval
CP—cerebral palsy
GA—gestational age
HDR—Hospital Discharge Register
ICD—*International Classification of Diseases*
LP—late preterm
MBR—Medical Birth Register
MP—moderately preterm
MRI—magnetic resonance imaging
NIHW—National Institutes of Health and Welfare
OR—odds ratio
PROM—premature rupture of membranes
RDS—respiratory distress syndrome
SGA—small for gestational age
VP—very preterm

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The preterm birth rate has increased markedly during the past decades, mainly due to the increase in late preterm (LP) births in a number of countries, especially in the United States.[1,2] LP infants are defined as infants born between gestation weeks 34^{+0} and 36^{+6}; they account for more than 70% of all prematurely born infants in the United States.[2,3] This group has commonly been referred to as "near term" infants, but the description has been felt inappropriate in that it underestimates the risks of these preterm infants.[3] Moderately preterm (MP) (32^{+0}–33^{+6} gestation weeks) and LP infants comprise >80% of all preterm births together.[4,5] The rate of preterm delivery in Finland has not increased significantly, in contrast to trends in other countries.[6]

The brain of the MP and LP infant is more vulnerable to injury than the brain of full-term infants. The weight of the brain at 34 weeks of gestation is only 65% of the term brain and the total brain volume increases linearly with increasing gestational age (GA).[7] Morbidity and mortality levels among MP and LP infants are higher compared with term.[8–10] In the United States and the United Kingdom, LP infants have been found to have poorer neurodevelopmental outcomes than term infants,[4,11–18] but some studies did not find more neurodevelopmental problems among healthy LP children.[19] Outcome data may vary due to diverse conditions in different countries and populations. Thus, more data and large prospective studies are needed. No statistics on the long-term outcome of MP and LP infants have been reported from the Nordic countries.

Cerebral palsy (CP) is defined as a disorder of motor behavior attributable to disturbances in the developing fetal or infant brain.[20] According to the standard guideline, the diagnosis of CP is based on medical history, imaging (ultrasound, high-resolution magnetic resonance imaging [MRI]) data, and clinical multidisciplinary evaluations in the pediatric neurology units. The CP incidence has been shown to be dependent on GA in very preterm (VP) infants.[21] Also in LP infants, the risk has been almost threefold compared with the term group.[22] Risk factors of CP have been identified for term infants,[23] but less for MP and LP infants.

Our aim was to compare the CP incidence among LP and MP infants to that among VP and term infants and to identify risk factors for CP in the Finnish population. The hospitalizations, reimbursements for medicine expenses, and disability allowances due to CP were established to study the burden of CP. Also the effect of time period on the incidence of CP was studied.

METHODS

This national register study population consisted of all, a total of 1 039 263 infants born in Finland from 1991 to 2008. The baseline characteristic data were collected from the Medical Birth Register (MBR), maintained by the National Institutes of Health and Welfare (NIHW). This register contains information on the mother's health and interventions during pregnancy and delivery and on the infant's health and procedures undergone during the first 7 days of life. It collects data on all live births and stillbirths from the GA of 22^{+0} weeks onward and/or birth weight of at least 500 g.

Data on deaths were obtained from the Cause-of-Death Register maintained by Statistics Finland and data on major structural anomalies and chromosomal defects[24] from the Register of Congenital Malformation, maintained by the NIHW. Infants who died before the age of 1 year (n = 2613), children with at least 1 major congenital anomaly (n =13 007), and cases lacking data on GA were excluded (n = 5520).

The remaining 1 018 302 infants (98.0% of all) comprised the cohort for analysis. Infants were followed up to 7 years of age or to 2009. The study population was divided into subgroups, the gestation-week categories being VP ($\leq 32^{+0}$ weeks, n = 6347), MP (32^{+0}–33^{+6} weeks, n = 6799), LP (34^{+0}–36^{+6} weeks, n = 39 932), and term ($\geq$37 weeks, n = 965 224). The GA was based on early pregnancy ultrasound and correction of GA was made if the ultrasound-based estimation had a discrepancy of 5 to 7 days or more compared with menstrual anamnesis.

Pregnancy- and delivery-related diagnoses of mothers were collected from the Hospital Discharge Register (HDR). This is also maintained by the NIHW and contains information on admission and discharge dates, diagnoses, and surgical procedures. Since 1998, the data also cover hospital outpatient visits. Diagnoses were coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) in 1987 to 1995 and according to the *10th Revision* (ICD-10) from 1996. Three different time periods were compared: 1991 to 1995, 1996 to 2001, and 2002 to 2008. These periods were chosen because the classification system of disease was changed in 1996 from ICD-9 to ICD-10 and the MBR changed the data collection forms 1.10.1990 and 1.1.1996.

Preeclampsia was defined as high blood pressure, edemas, and proteinuria by ICD-10 codes O10 to O16 (ICD-9 codes 6420–6429). Premature rupture of membranes (PROM) was sought via ICD-10 codes O42.0 to O42.9 (ICD-9 codes 6581–6583) in the mothers' diagnoses. Pregnancy-related risk factors were the number of fetuses and their order, timing of birth, in vitro fertilization, and cervical cerclage. Resuscitation at birth included intubation, mechanical ventilation, and/or chest compressions. Phototherapy has been given according to guidelines depending on gestation weeks and some minor variance may exist in guidelines between hospitals. Respiratory distress syndrome (RDS) was diagnosed on the basis of typical changes in chest radiograph, excessive

need of oxygen supply, and surfactant therapy. It was traced in the register with ICD-10 code P22.0 (ICD-9 code 769). Small for GA (SGA) infants were defined as those with a birth weight <2 SDs below the mean weight for GA and large for GA infants as those with a birth weight >2 SDs over the mean weight for GA according to the Finnish gender-specific fetal growth curves.[25] Umbilical artery pH cutoff <7.05 was used to define fetal acidemia.[26,27]

Only variables with good validity in the registers were chosen for the analysis.[28,29] Intracranial hemorrhage diagnosis was based on the head ultrasound or MRI findings and classified according to the Papile classification system.[30] MP and LP infants do not undergo routine head ultrasounds but infants with asphyxia and/or neurologic symptoms, and/or with need of intensive care are routinely examined with head ultrasound. One-minute Apgar scores were included in the multivariate analysis, but 5-minute scores were excluded because it was found from the register only from 2004 onward. Information on maternal hypertension was available only in combination with preeclampsia. Mother's diabetes included gestational diabetes, and type 1 and 2 diabetes. Neither data on chorioamnionitis nor antenatal viral infection was possible to define reliably according to registers. Infants were defined to be asphyxiated when they had a 1-minute Apgar score <7 and needed intubation during delivery room resuscitation.

All inpatient and outpatient visits due to a CP diagnosis in public hospitals were registered according to the HDR. The diagnosis of CP in Finland is based on medical history, ultrasound and MRI data, and multidisciplinary evaluations in the pediatric neurology units of 20 secondary-level central hospitals and 5 tertiary-level university hospitals. CP is usually evident within first 2 years of life and almost always by the age of 3 to 4 years, and the diagnosis is included in the HDR as soon as it has been established. Information on special reimbursements and benefits for disability were collected from the register of the Social Insurance Institution of Finland. All data linkages were done by using unique personal identity codes anonymized by the authorities.

A case with CP was recorded if the individual was detected in the HDR and/or in the Reimbursement Register of the Social Insurance Institution with ICD-10 codes G80 to G83 in 1996 to 2008 and ICD-9 codes 342 to 344 in 1991 to 1995. Subtypes of CP were defined by topographic involvement (hemiplegia, diplegia, quadriplegia, and other types) and sought from registers with corresponding ICD codes (hemiplegia ICD-10 G80.2/ICD-9 343.1 and 343.4; diplegia G80.1/343.0; quadriplegia G80.0/343.2 and other types including the rest of CP diagnoses according to the baseline ICD code definitions).

Statistical Analysis

Characteristics of infants alive at age of 1 year and those of their mothers were described by means with SDs in the case of normal distributed continuous variables, by medians with interquartile range in skew distributed variables, and otherwise if variables were categorical by number of values with percentages. GA groups were compared for each other by Mann-Whitney test, χ^2 test, or Fisher's exact test (Tables 1, 2, and 3). Risk factors for CP were sought by logistic regression analysis by using multivariate enter models for each GA group separately (Table 4). In enter model, all variables were entered simultaneously into the model separately for each gestational week class. Association of gestation weeks for CP was studied by adjusting a multivariate model by gestation week classes, term class as reference. Results were shown by odds ratios (ORs) with 95% confidence intervals (95% CIs) in modeling risk factors for CP. A large number of variables were included in the analysis, because in a large population, also less well-known predictors for CP can be detected. Statistical analyses were performed on IBM SPSS Statistics version 20.0.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). $P < .05$ was considered statistically significant.

RESULTS

LP infants accounted for 75% and MP infants for 13% of all prematurely born infants in Finland during this study period. Characteristics of newborns and mothers are shown in Table 1. Proportion of all preterm births was 5.02% from 1991 to 1995, 5.43% from 1996 to 2001, and 5.18% from 2002 to 2008. The proportion of MP and LP infants remained constant; MP infants accounted for 0.63% to 0.69% and LP infants from 3.82% to 4.08% of all births.

After combining the register data, 2242 CP cases were identified. The incidence of CP was 0.22%, and it decreased nonlinearly with increasing GA, and with time. The decrease by time was greatest in the VP group, and during the latest time period (ie, after 2001) (Table 2, Fig 1). The analysis of CP subtypes showed that the proportion of diplegia cases was greatest in the VP group and of hemiplegia cases in the term group (Table 3).

Birth during the earliest period, 1991 to 1995, 1-minute Apgar score <7, and intracranial hemorrhage predicted CP in all GA categories in the logistic regression model (Table 4). Resuscitation at birth was associated with an increased risk in MP and LP groups and in the term group. SGA and antibiotic treatment during the first hospitalization seemed to predict an increased risk of CP in the LP and the term groups. PROM was associated with an increased and antenatal steroid treatment with a decreased risk of CP in the MP group. Antenatal steroid administration was registered from 2004 onward. In the analysis for 2004 to 2008, the OR for CP

TABLE 1 Characteristics of Infants Alive at Age of 1 Year and Their Mothers, Followed to Age of 7 Years, 1991–2008 (n = 1 018 302; Infants Who Died When Younger Than 1 Year and Infants With Major Congenital Malformations Excluded)

	VP <32 wk, n = 6347		MP 32^{+0}–33^{+6} wk, n = 6799		LP 34^{+0}–36^{+6} wk, n = 39 932		Term ≥37 wk, n = 965 224		p^1 MP versus VP	p^2 LP versus VP	p^3 MP versus T	p^4 LP versus T
Study period, y, n (%)									P = .725	P = .080	P = .002	P < .001
1991–1995	1780	(0.58)	1937	(0.63)	11 779	(3.82)	293 233	(95.0)				
1996–2001	2159	(0.66)	2270	(0.69)	13 362	(4.08)	309 893	(94.6)				
2002–2008	2408	(0.63)	2592	(0.68)	14 791	(3.87)	362 098	(94.8)				
Mother												
Age, mean (SD)	30.2	(5.8)	29.8	(5.7)	29.7	(5.5)	29.2	(5.3)	P < .001	P < .001	P < .001	P < .001
Smoking, n (%)	1192	(18.8)	1186	(17.4)	6605	(16.5)	144 097	(14.9)	P < .001	P < .001	P < .001	P < .001
Primipara, n (%)	3329	(52.4)	3792	(55.8)	20 041	(50.2)	392 588	(40.7)	P < .001	P = .001	P < .001	P < .001
Earlier deliveries, Md (IQR)	0	(0–1)	0	(0–1)	0	(0–1)	1	(0–2)	P < .001	P = .092	P < .001	P < .001
Diabetes, n (%)	92	(1.4)	148	(2.2)	969	(2.4)	8468	(0.9)	P = .002	P < .001	P < .001	P < .001
Pregnancy												
No. of fetuses, n (%)									P < .001	P < .001	P < .001	P < .001
1	4525	(71.3)	4593	(67.6)	31 065	(77.8)	948 715	(98.3)				
2	1621	(25.5)	1955	(28.8)	8549	(21.4)	16 490	(1.7)				
≥3	201	(3.2)	251	(3.7)	318	(0.8)	19	(0.0)				
Assisted reproductive technology, n (%)	609	(9.6)	768	(11.3)	2764	(6.9)	16 264	(1.7)	P = .001	P < .001	P < .001	P < .001
Cervical cerclage, n (%)	69	(1.1)	40	(0.6)	102	(0.3)	515	(0.1)	P = .002	P < .001	P < .001	P < .001
Delivery												
Place of birth, n (%)									P < .001	P < .001	P < .001	P < .001
University hospital (level III)	4957	(78.1)	3995	(58.8)	17 156	(43.0)	299 477	(31.0)				
Central hospital (level II)	1343	(21.2)	2727	(40.1)	17 553	(44.0)	444 961	(46.1)				
Other[a]	42	(0.7)	77	(1.1)	5220	(13.1)	220 659	(22.9)				
Mode of delivery, n (%)									P < .001	P < .001	P < .001	P < .001
Vaginal	2537	(40.0)	3212	(47.2)	26 687	(66.8)	820 961	(85.1)				
Cesarean	3798	(59.8)	3584	(52.7)	13 212	(33.1)	143 493	(14.9)				
Newborn												
Boys, n (%)	3441	(54.2)	3730	(54.9)	21 660	(54.2)	490 223	(50.8)	P = .457	P = .967	P < .001	P < .001
Birth weight, g, Md (IQR)	1290	(995–1570)	1970	(1730–2200)	2670	(2360–2985)	3590	(3276–3910)	P < .001	P < .001	P < .001	P < .001
≤1500 g	4406	(69.4)	735	(10.8)	253	(0.6)	23	(<0.1)				
>1500 g	1925	(30.3)	6056	(89.1)	39 658	(99.3)	964 956	(100)				
Gestational weight, n (%)									P < .001	P < .001	P < .001	P < .001
SGA	1021	(16.1)	883	(13.0)	3245	(8.1)	16 664	(1.7)				
AGA	4974	(78.4)	5639	(82.9)	34 685	(86.9)	919 989	(95.3)				
LGA	284	(4.5)	277	(4.1)	2002	(5.0)	28 571	(3.0)				
Apgar 1 min, Md (IQR)	7	(5–8)	8	(7–9)	9	(8–9)	9	(9–9)	P < .001	P < .001	P < .001	P < .001
Apgar 1 min 0–3, n (%)	1014	(16.0)	326	(4.8)	891	(2.2)	7495	(0.8)	P < .001	P < .001	P < .001	P < .001
Apgar 1 min 0–6, n (%)	2958	(46.6)	1350	(19.9)	3560	(8.9)	35 072	(3.6)	P < .001	P < .001	P < .001	P < .001
Admission to neonatal unit, n (%)	5703	(89.9)	5975	(87.9)	19 158	(48.0)	58 370	(6.0)	P < .001	P < .001	P < .001	P < .001
Ventilator, n (%)	3665	(57.7)	1416	(20.8)	1667	(4.2)	2797	(0.3)	P < .001	P < .001	P < .001	P < .001
Resuscitation at birth, n (%)	1909	(30.1)	626	(9.2)	795	(2.0)	3076	(0.3)	P < .001	P < .001	P < .001	P < .001
Phototherapy, n (%)	4203	(66.2)	3822	(56.2)	14 153	(35.4)	36 673	(3.8)	P < .001	P < .001	P < .001	P < .001
Antibiotic therapy, n (%)	4511	(71.1)	2961	(43.6)	5038	(12.6)	23 852	(2.5)	P < .001	P < .001	P < .001	P < .001
Died by 7 y of age, n (%)	31	(0.5)	7	(0.1)	40	(0.1)	648	(0.1)	P < .001	P < .001	P = .235	P = .013
Age of death, y, Md (IQR)	0.03	(0.00–1.96)	1.01	(0.24–3.01)	3.17	(1.81–4.70)	3.07	(1.81–4.87)	P = .192	P < .001	P = .003	P = .634

Statistical differences were tested by Pearson χ^2 test or Fisher's exact or by Mann-Whitney test: p^1 = MP versus VP; p^2 = LP versus VP; p^3 =MP versus term; p^4 =LP versus term. AGA, appropriate for gestational age; IQR, interquartile range; LGA, large for gestational age; Md, median; T, term.

[a] Regional hospital, private hospital, health center, home birth.

TABLE 2 Diagnoses of CP and Data on Reimbursements Due to CP

	VP <32 wk, *n* = 6347		MP 32^{+0}–33^{+6} wk, *n* = 6799		LP 34^{+0}–36^{+6} wk, *n* = 39 932		Term ≥37 wk, *n* = 965 224	
CP (HDR), *n* (%), total	538	(8.5)	157	(2.3)	216	(0.5)	1244	(0.1)
Years, *n* (% of study period)								
1991–1995	244	(13.7)	75	(3.9)	85	(0.7)	446	(0.2)
1996–2001	205	(9.5)	45	(2.0)	82	(0.6)	442	(0.1)
2002–2008	89	(3.7)	37	(1.4)	49	(0.3)	356	(0.1)
Hospital, *n* (% of level)								
University hospital	399	(8.0)	104	(2.6)	105	(0.6)	358	(0.1)
Central hospital	139	(10.3)	50	(1.8)	91	(0.5)	617	(0.1)
Other	0	(0)	3	(3.9)	18	(0.3)	269	(0.1)
No. of admissions, Md (IQR), total	12	(6–22)	11	(4–19)	7.5	(2–17)	6	(2–14)
Days in hospital, Md (IQR), total	62	(16-cont)	37	(9-cont)	23	(8-cont)	14	(4–116)
The age at diagnosis, y, Md (IQR), total	1.5	(1.0–2.3)	1.4	(0.9–2.4)	1.6	(0.8–3.0)	1.5	(0.8–3.3)
Reimbursements for medicine expenses due to CP, *n* (%)	16	(0.3)	2	(<0.1)	5	(<0.1)	27	(<0.1)
The age (years) of child at first reimbursement, Md (IQR)	3.5	(1.6–5.5)	1.0	(0.1–1.9)	1.6	(1.1–3.2)	1.9	(1.1–3.5)
Disability allowance due to CP by the age of 7 y, *n* (%)	266	(4.2)	96	(1.4)	121	(0.3)	602	(0.1)
The age (years) of child at start of the allowance, Md (IQR)	1.9	(0.8–3.6)	1.4	(0.6–3.3)	1.5	(0.7–3.2)	1.5	(0.7–3.3)
The duration of the allowance (years), Md (IQR)	2.0	(1.0–3.3)	2.0	(1.2–3.9)	1.7	(1.0–3.3)	1.7	(1.0–3.0)
The number of granted allowance periods, Md (IQR)	1	(1–2)	1	(1–2)	1	(1–2)	1	(1–2)

Diagnosis of CP from the HDR; reimbursements due to CP from the social insurance institution. Data include newborns alive at age of 1 year, followed to age of 7 years without major congenital anomalies, 1991–2008 (*n* = 1 018 302).

Statistical differences were tested by Pearson χ^2 test or Fisher's exact or by Mann-Whitney test: MP versus VP: all $P < .001$; LP versus VP: all $P < .001$; MP versus term: all $P < .001$; LP versus term: all $P < .001$; cont, continuing; IQR, interquartile range; Md, median.

in the MP group with antenatal steroid was 0.24 (95% CI 0.08–0.76). RDS predicted a decreased risk of CP in the LP group. Independent ORs for CP in premature gestational week groups compared with the full-term group were in the VP group 9.37 (95% CI 7.34–11.96), in the MP group OR 5.12 (95% CI 4.13–6.34), and in the LP group OR 2.35 (95% CI 1.99–2.77).

DISCUSSION

In this population the incidence and risk for CP were higher among MP and LP infants compared with those born at term. The burden of CP to the families of the MP and LP children, in terms of medicine expenses, is comparable with term-born babies. Also the need of disability allowance seems to be significantly less common in the MP and LP groups than in the VP cases. Birth at an earlier period, being SGA, and having asphyxia and intracranial hemorrhage emerged as significant predictors for CP, whereas antenatal corticosteroid therapy seemed to reduce the risk. Our results can be used in the counseling of parents and in planning guidelines for follow-up practices of MP and LP newborns.

The most prominent weakness of register studies is that recording practices may differ significantly among individuals, sites, and regions. The classification system of diseases was changed in 1996. Although diagnoses were converted to be identical, this change might have affected the diagnostic categories. Children born during the last years of the latest study period 2002 to 2008 had shorter follow-up time, which also may have influenced the decrease in CP risk compared with the earlier periods. However, the CP diagnosis was usually made by the age of 1.5 years. Data of 5-minute Apgar score were not available from the register during this study period and we used the 1-minute score, which is a relatively vague marker

TABLE 3 Diagnoses of CP (*n* = 2242) and Distribution of CP Subtypes in Gestational Week Categories

	VP <32 wk, *n* = 6347		MP 32^{+0}–33^{+6} wk, *n* = 6799		LP 34^{+0}–36^{+6} wk, *n* = 39 932		Term ≥37 wk, *n* = 965 224	
CP total, *n* (% of children in GA group)	550	(8.7)	160	(2.4)	225	(0.6)	1307	(0.1)
CP subtype, *n* (% of CP cases in GA group)								
Hemiplegia	80	(14.5)	37	(23.1)	57	(25.3)	425	(32.5)
Diplegia	213	(38.7)	48	(30.0)	52	(23.1)	165	(12.6)
Quadriplegia	37	(6.7)	11	(6.9)	16	(7.1)	84	(6.4)
Other types	220	(40.0)	64	(40.0)	100	(44.4)	633	(48.4)

Diagnoses of CP from combined data of HDR and social insurance institution. Newborns alive at age of 1 year, followed to age of 7 years without major congenital anomalies, 1991–2008 (*n* = 1 018 302).

Statistical differences were tested by Fisher's exact test: MP versus VP: all $P < .001$; LP versus VP: all $P < .001$; MP versus term: all $P < .001$; LP versus term: all $P < .001$.

TABLE 4 Risk Factor Analysis for CP (n = 2242) in 1991–2008 by the Age of 7 Years Using Time From Birth to First Hospital Visit as Following Time Separately for 4 Gestation Week Categories (n = 1 018 302)

	VP <32 wk, n =550/N = 6347			MP 32^{+0}–33^{+6} wk, n =160/N = 6799			LP 34^{+0}–36^{+6} wk, n =225/N = 39 932			Term ≥37 wk, n =1307/N = 965 224)		
	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)
Study period												
1991–1995	1780	4.03[a]	(3.12–5.94)[a]	1937	2.55[a]	(1.55–4.20)[a]	11 779	2.41[a]	(1.62–3.60)[a]	293 233	1.77[a]	(1.53–2.05)[a]
1996–2001	2159	2.63[a]	(1.94–3.57)[a]	2270	1.28	(0.78–2.09)	13 362	1.97[a]	(1.36–2.87)[a]	309 893	1.57[a]	(1.36–1.80)[a]
2002–2008	2408	1.00		2592	1.00		14 790	1.00		362 095	1.00	
Mother												
Age												
<40	6124	1.00		6579	1.00		38 897	1.00		947 588	1.00	
≥40	223	1.14	(0.69–1.89)	220	0.85	(0.33–2.17)	1034	1.40	(0.70–2.78)	17 633	1.10	(0.75–1.61)
Smoking												
No	4814	1.00		5393	1.00		32 293	1.00		799 160	1.00	
Yes	1192	1.06	(0.84–1.33)	1186	1.20	(0.81–1.79)	6605	1.28	(0.92–1.80)	144 097	1.25[a]	(1.08–1.44)[a]
Primipara												
No	3018	1.00		3007	1.00		19 890	1.00		572 633	1.00	
Yes	3329	1.00	(0.82–1.22)	3792	0.60[a]	(0.42–0.85)[a]	20 041	1.01	(0.76–1.36)	392 588	0.94	(0.84–1.06)
Earlier cesarean delivery												
No	5779	1.00		6228	1.00		36 445	1.00		890 139	1.00	
Yes	568	1.26	(0.92–1.74)	571	0.94	(0.52–1.69)	3486	0.97	(0.58–1.60)	75 082	0.99	(0.81–1.22)
Diabetes												
No	6255	1.00		6651	1.00		38 962	1.00		956 753	1.00	
Yes	92	0.71	(0.30–1.68)	148	1.46	(0.55–3.89)	969	0.70	(0.27–1.80)	8468	1.11	(0.70–1.77)
Pregnancy												
No. fetuses												
1	4525	1.00		4593	1.00		31 064	1.00		948 712	1.00	
2	1621	0.94	(0.70–1.26)	1955	0.83	(0.48–1.44)	8549	0.77	(0.47–1.27)	16 490	0.98	(0.58–1.66)
3 or more	201	1.24	(0.63–2.45)	251	0.88	(0.28–2.81)	318	0.51	(0.07–3.92)	19	[b]	
Order of fetuses												
A	5418	1.00		5670	1.00		35 468	1.00		956 983	1.00	
B	857	0.98	(0.68–1.41)	1046	1.11	(0.57–2.13)	4359	0.99	(0.54–1.80)	8233	1.25	(0.66–2.39)
C	70	0.59	(0.19–1.82)	82	2.02	(0.45–8.97)	104	1.79	(0.11–29.7)	5	[b]	
D	2	[b]		1	[b]		0	[b]		0	[b]	
Assisted reproductive technology												
No	5738	1.00		6031	1.00		37 167	1.00		948 957	1.00	
Yes	609	1.08	(0.76–1.53)	768	0.93	(0.48–1.78)	2764	1.50	(0.89–2.51)	16 264	0.98	(0.65–1.48)
Cervical cerclage												
No	6278	1.00		6759	1.00		39 829	1.00		964 706	1.00	
Yes	69	0.93	(0.43–2.00)	40	2.70	(0.76–9.63)	102	[b]		515	2.22	(0.54–9.11)
Chorion villus biopsy												
No	6266	1.00		6727	1.00		39 540	1.00		956 213	1.00	
Yes	81	0.98	(0.46–2.10)	72	0.59	(0.08–4.41)	391	1.43	(0.51–4.04)	9008	1.15	(0.68–1.94)
PROM (042.0–9/658.1–3)[c]												
No	6213	1.00		6661	1.00		39 469	1.00		962 977	1.00	
Yes	134	1.39	(0.58–3.34)	138	3.05[a]	(1.02–9.12)[a]	462	1.11	(0.26–4.75)	2244	0.84	(0.21–3.41)
Preeclampsia (010.0–0.16/642.0–9)[c]												
No	6069	1.00		6516	1.00		38 617	1.00		953 440	1.00	
Yes	278	0.30[a]	(0.09–0.97)[a]	283	1.33	(0.48–3.66)	1314	0.30	(0.07–1.26)	11 781	0.68	(0.37–1.24)
Delivery												
Time of birth												
Mon–Fri 08.00–15.59	2516	1.00		2643	1.00		14 051	1.00		300 069	1.00	
Mon–Fri 16.00–07.59	2335	0.94	(0.76–1.17)	2600	0.79	(0.54–1.17)	16 771	1.08	(0.80–1.47)	434 806	1.00	(0.88–1.14)
Weekend	1496	0.98	(0.77–1.24)	1556	1.10	(0.73–1.67)	9109	0.85	(0.58–1.25)	230 346	0.95	(0.81–1.12)
Antenatal steroid[d]												
No	5509	1.00		6163	1.00		39 017	1.00		963 782	1.00	
Yes	838	0.80	(0.49–1.30)	636	0.27[a]	(0.09–0.80)[a]	914	1.01	(0.35–2.91)	1439	2.31	(0.85–6.26)

TABLE 4 Continued

	VP <32 wk, *n* =550/*N* = 6347			MP 32^{+0}–33^{+6} wk, *n* =160/*N* = 6799			LP 34^{+0}–36^{+6} wk, *n* =225/*N* = 39 932			Term ≥37 wk, *n* =1307/*N* = 965 224)		
	n	OR	(95% CI)	*n*	OR	(95% CI)	*n*	OR	(95% CI)	*n*	OR	(95% CI)
Place of birth												
University hospital	4957	1.00		3995	1.00		17 156	1.00		299 477	1.00	
Central hospital	1343	1.15	(0.91–1.45)	2727	0.80	(0.55–1.16)	17 552	0.94	(0.70–1.28)	444 958	1.22[a]	(1.06–1.39)[a]
Other[e]	42	[b]		77	1.71	(0.50–5.85)	5220	0.88	(0.51–1.52)	220 659	1.15	(0.98–1.37)
Mode of delivery												
Vaginal	2537	1.00		3212	1.00		26 687	1.00		820 961	1.00	
Cesarean	3798	0.87	(0.71–1.16)	3584	0.87	(0.59–1.27)	13 212	1.23	(0.90–1.67)	143 493	1.55[a]	(1.34–1.78)[a]
Newborn												
Gender												
Boy	3441	1.34[a]	(1.11–1.61)[a]	3730	1.11	(0.80–1.55)	21 659	0.98	(0.75–1.28)	490 221	1.23[a]	(1.10–1.37)[a]
Girl	2906	1.00		3069	1.00		18 272	1.00		475 000	1.00	
Gestational weight												
SGA	1021	0.75	(0.57–0.99)	883	1.10	(0.57–2.13)	3244	1.85[a]	(1.25–2.75)[a]	16 661	2.35[a]	(1.84–3.01)[a]
LGA	284	1.35	(0.89–2.06)	277	1.02	(0.45–2.31)	2002	1.11	(0.58–2.11)	28 571	0.93	(0.68–1.27)
AGA	4974	1.00		5639	1.00		34 685	1.00		919 989	1.00	
Birth weight <1500g												
No	1925	1.00		6056	1.00		39 658	1.00		964 956	1.00	
Yes	4406	1.84[a]	(1.44–2.36)[a]	735	2.12	(1.08–4.15)	253	1.47	(0.62–3.46)	21	5.14	(0.63–41.8)
Apgar 1 min												
4–10	5222	1.00		6397	1.00		38 907	1.00		956 467	1.00	
0–3	1014	1.35[a]	(1.05–1.73)[a]	326	0.87	(0.44–1.70)	891	1.79[a]	(1.07–3.01)[a]	7495	1.71[a]	(1.27–2.30)[a]
Apgar 1 min												
7–10	3278	1.00		5373	1.00		36 238	1.00		928 890	1.00	
0–6	2958	1.26	(1.01–1.56)[a]	1350	1.70[a]	(1.15–2.52)[a]	3560	1.80[a]	(1.21–2.67)[a]	35 072	1.84[a]	(1.47–2.29)[a]
Umbilical artery pH												
≥7.05	4097	1.00		4258	1.00		22 583	1.00		465 861	1.00	
<7.05	90	1.13	(0.58–2.24)	85	1.00	(0.33–3.07)	313	1.84	(0.94–3.63)	6343	1.87[a]	(1.37–2.56)[a]
Unknown	2160	1.17	(0.96–1.44)	2456	0.80	(0.55–1.18)	17 035	0.90	(0.66–1.22)	493 017	1.10	(0.97–1.25)
Admission to neonatal unit												
No	644	1.00		824	1.00		20 773	1.00		906 851	1.00	
Yes	5703	0.68	(0.50–0.94)	5975	0.87	(0.50–1.50)	19 158	1.58[a]	(1.10–2.25)[a]	58 370	1.89	(1.55–2.30)[a]
Ventilator												
No	2682	1.00		5383	1.00		38 265	1.00		962 424	1.00	
Yes	3665	1.53[a]	(1.17–2.01)[a]	1416	1.22	(0.77–1.93)	1666	3.25[a]	(2.06–5.12)[a]	2797	3.27[a]	(2.39–4.48)[a]
Resuscitation at birth												
No	4438	1.00		6173	1.00		39 136	1.00		962 145	1.00	
Yes	1909	1.20	(0.98–1.46)	626	1.60[a]	(1.01–2.53)[a]	795	1.78[a]	(1.09–2.90)[a]	3076	2.08[a]	(1.53–2.85)[a]
Phototherapy												
No	2144	1.00		2977	1.00		25 778	1.00		928 548	1.00	
Yes	4203	0.76[a]	(0.60–0.96)[a]	3822	0.99	(0.68–1.43)	14 153	0.89	(0.65–1.22)	36 673	1.34[a]	(1.03–1.74)[a]
Antibiotic therapy												
No	1836	1.00		3838	1.00		34 893	1.00		941 369	1.00	
Yes	4511	1.14	(0.87–1.50)	2961	1.63[a]	(1.08–2.45)[a]	5038	1.67[a]	(1.13–2.44)[a]	23 852	1.69[a]	(1.32–2.17)[a]
Respiratory distress syndrome (P22.0/769)[c]												
No	3811	1.00		5794	1.00		38 883	1.00		964 874	1.00	
Yes	2536	1.01	(0.82–1.24)	1005	1.05	(0.66–1.66)	1098	0.34[a]	(0.17–0.68)[a]	347	0.85	(0.30–2.38)
Sepsis (P36.0–8/77181)[c]												
No	5924	1.00		6561	1.00		39 231	1.00		959 163	1.00	
Yes	423	0.94	(0.62–1.43)	238	1.35	(0.60–3.05)	700	1.50	(0.73–3.10)	6058	0.76	(0.48–1.20)
Intracranial hemorrhage (P52.0–9/7721)[c]												
No	6111	1.00		6693	1.00		39 852	1.00		965 082	1.00	
Yes	236	3.05[a]	(2.08–4.47)[a]	106	7.18[a]	(3.60–14.3)[a]	79	12.8[a]	(5.58–29.2)[a]	139	4.89[a]	(2.13–11.2)[a]
Convulsions (P90/7790)[c]												
No	6325	1.00		6795	1.00		39 897	1.00		964 757	1.00	

TABLE 4 Continued

	VP <32 wk, *n* =550/*N* = 6347			MP 32^{+0}–33^{+6} wk, *n* =160/*N* = 6799			LP 34^{+0}–36^{+6} wk, *n* =225/*N* = 39 932			Term ≥37 wk, *n* =1307/*N* = 965 224)		
	n	OR	(95% CI)	*n*	OR	(95% CI)	*n*	OR	(95% CI)	*n*	OR	(95% CI)
Yes	22	4.28[a]	(1.52–12.0)[a]	4	9.86	(0.92–106)	34	2.18	(0.28–17.0)	464	7.42[a]	(4.75–11.6)[a]
Hyperbilirubinemia (P59.0–9/774)[c]												
No	4904	1.00		5005	1.00		31 851	1.00		942 250	1.00	
Yes	1443	0.87	(0.65–1.15)	1794	0.58	(0.34–0.98)	8080	0.82	(0.52–1.28)	22 971	1.07	(0.74–1.53)

Logistic regression multivariate models were used, with results given as the ORs and 95% CIs. AGA, appropriate for gestational age; LGA, large for gestational age.

[a] Statistically significant ($P < .050$) ORs with 95% CIs. Categories of missing values are not shown.

[b] Cannot be computed due to the small sample size.

[c] Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9).

[d] Register data available from year 2004.

[e] Regional hospital, private hospital, health center, home birth.

for outcome. Recording practices for hypoxic-ischemic encephalopathy and multiorgan failure had substantial variance and, thus, could not be included in analysis.

Strengths of this study are reliable and comprehensive population-based register data and the substantial number of infants. The national health registers in Finland are well-established and validated. The MBR is a high-quality register covering more than 99.9% of all births.[29,31] The data quality, completeness, and accuracy of the HDR have been varied from satisfactory to very good in a systematic review.[28] Infants were followed to the age of 7 years, by which time the diagnosis of CP is generally made. CP diagnoses can be regarded as reliable, because they are made in public hospitals in specialized units of child neurology. The prevalence of congenital anomalies has been 2.2 times greater in infants born at 32 to 36 weeks of gestation compared with term infants,[32] which is a significant confounder when seeking perinatal risk factors. Here, as elsewhere,[33] all infants with major congenital anomalies were excluded.

The CP incidence was in accordance with the literature.[34] It was higher in the preterm groups compared with the term group and began to decrease clearly after 28 weeks of gestation. Small rates of CP at 24 and 25 weeks of gestation are probably due to small numbers of cases. In our study, the risk of CP was 5.12 (OR) in the MP compared with the term group. In the United States, the risk of CP has been threefold in LP subjects compared with children born at term,[22] whereas the risk in our population was 2.35 (OR) compared with term-born children. In the current study, the risk of CP decreased over time in all subgroups. The drop was greatest in the VP group,

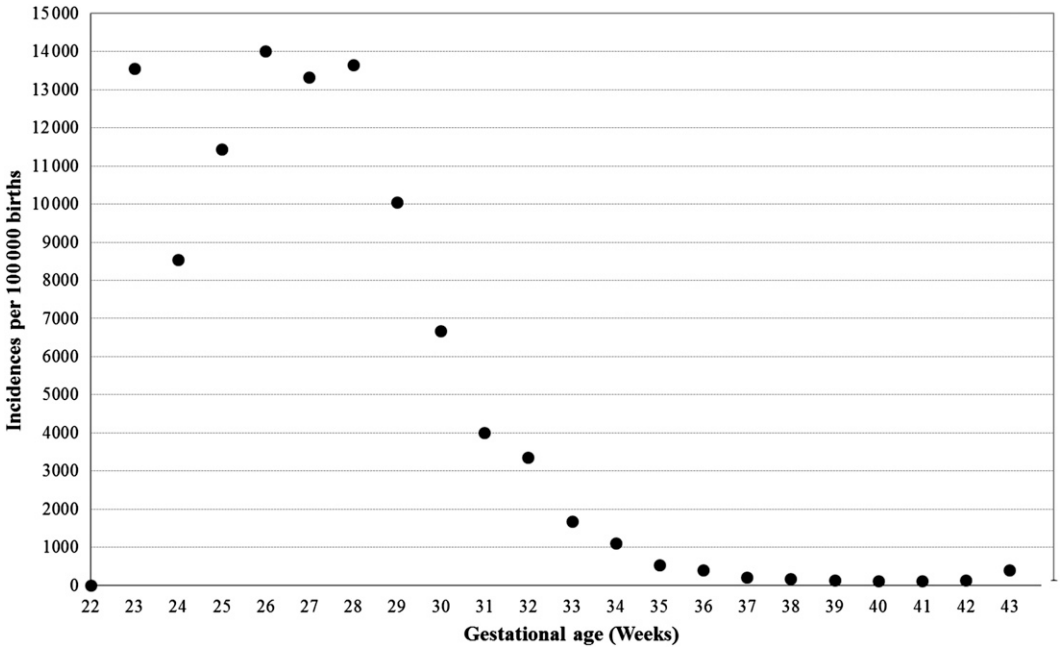

FIGURE 1
Incidences of cerebral palsy (*n* = 2242) per 100 000 births by age of 7 years by gestational age, birth years 1991–2008 (*n* = 1 018 302).

probably due to advances in perinatal and neonatal care. The prevalence of CP among MP infants also decreased in the European register study between 1980 and 1998.[35] In contrast, according to a recent systematic review and meta-analysis, the overall CP prevalence has remained constant in recent years.[36]

SGA predicted the CP risk in the Finnish LP and term infants. In contrast, in a Swedish cohort of 334 cases with CP and 668 controls matched for gestation, gender, and delivery unit, SGA associated with CP in term, but not LP infants.[37] In their study, growth status was determined by using customized birth weight percentiles, based on the growth potential calculated for each infant, whereas we used population-based birth weight standards. The different study designs probably explain the conflicting results.

Resuscitation at birth and low Apgar score were significant risk factors for CP in this study, showing asphyxia at birth to be a major cause of hypoxic ischemic brain injury, and of later motor disability. Efforts to prevent and treat asphyxia seem to be an effective means of preventing CP also in the MP and LP infants. Intracranial hemorrhage increased the risk of CP significantly in all subgroups. It is obvious, and also previously demonstrated, that brain injury visible in brain imaging correlates with the development of CP.[38]

An antibiotic treatment appeared to predict a CP risk in groups from moderately preterm to term infants. Premature labor might be predisposed by infection and it is thus common practice to start antibiotic therapy for a premature newborn. Also, most infants who need intensive care are treated with antibiotics in cases of suspected sepsis. Thus, antibiotic treatment is rather a marker of the sickness of the infant than a causative factor for CP. Conversely, true sepsis was not a significant risk factor, possibly because of the small number of cases with a proven sepsis diagnosis. PROM was a predictor for CP in the MP group. PROM can be regarded as a relevant marker of chorioamnionitis in register studies.[39,40] Instead, true incidence of chorioamnionitis, a well-known risk factor for CP,[41,42] cannot be established in a register study by using the ICD-9 or ICD-10 diagnoses, because histologic or clinical confirmation is rarely available.

LP infants evince a higher neonatal morbidity compared with term-born infants, this including higher rates of RDS.[43] In the current study, RDS was associated with a decreased risk of CP in the LP group and ventilator treatment with an increased risk in the VP, LP, and term groups. Infants who needed mechanical ventilation for reasons other than RDS may have had other morbidities, such as asphyxia or infection, which might be more harmful to the developing brain than RDS only. Antenatal steroid treatment predicted a decreased risk of CP in MP infants. According to earlier national guidelines, mothers expected to deliver before 34^{+0} weeks of gestation were treated with glucocorticoids. The updated guideline recommends antenatal glucocorticoid treatment to be administered later (ie, before 35^{+0} weeks' gestation).[44] This change seems to be beneficial also in reducing the risk of CP in this group.

CONCLUSIONS

The incidence of CP increases nonlinearly with decreasing GA. LP and MP infants are at a significantly greater risk compared with term infants. The risk has decreased in all GA groups over time. Asphyxia and intracranial hemorrhage emerge as the most prominent risk factors in all gestation week categories. Efforts to prevent and treat asphyxia are of prime importance in reducing the risk of CP. Antenatal steroid treatment appears to reduce the risk among MP infants. Guidelines for management and risk assessment need to be established for LP and MP infants.

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The incidence and risk factors of epilepsy in children born preterm: A nationwide register study

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ABSTRACT

Objectives: The aim was to compare the incidence of epilepsy between very preterm (VP) (< 32^{+0} weeks), moderately preterm (MP) (32^{+0}–33^{+6} weeks), late preterm (LP) (34^{+0}–36^{+6} weeks) and term infants (≥37 weeks) and to establish and compare risk factors of epilepsy in these groups.

Methods: The national register study included all live born infants in Finland in 1991–2008. Excluding infants with missing gestational age, a total of 1,033,349 infants were included in the analysis and they were analyzed in four subgroups (VP, MP, LP and term) and three time periods (1991–1995, 1996–2001 and 2002–2008).

Results: 5611 (0.54%) children with epilepsy were diagnosed. The incidence of epilepsy was 2.53% in the VP, 1.08% in the MP, 0.75% in the LP and 0.51% in the term group. Intracranial hemorrhage (OR 3.48; 95% CI 2.47–4.89) and convulsions in the neonatal period (OR 13.4; 95% CI 10.2–17.6) were associated with an increased risk of epilepsy. Compared to the term group, preterm birth (VP OR 4.59; 95% CI 3.79–5.57, MP 1.97; 1.48–2.63, LP 1.44; 1.25–1.68) was associated with an increased risk of epilepsy after adjusting for maternal, pregnancy, delivery and sex variables.

Conclusions: The incidence of epilepsy decreased by advancing gestational age at birth and preterm birth predicted an increased risk of epilepsy in childhood. Intracranial hemorrhage and neonatal convulsions were strongly associated with an increased risk of epilepsy.

1. Introduction

Intrauterine and perinatal complications as well as prematurity itself may have harmful effects to the developing brain during the critical period. Preterm birth has been shown to be associated with an increased risk of cerebral palsy (Hirvonen et al., 2014), intellectual disability (Moster et al., 2008) and epilepsy in adulthood (Sun et al., 2008; Crump et al., 2011). There are several reports on poorer neurodevelopmental outcomes of preterm infants at school age but fewer on the incidence and risk factors for epilepsy among different gestational age (GA) groups despite the fact that epilepsy is one of the major neurological impairments arising from preterm birth (Whitehead et al., 2006).

Our aim was to study the incidence of childhood epilepsy in different GA groups and to identify prenatal, perinatal and neonatal risk factors for epilepsy in a nationwide cohort. It is important, both in clinical and public health aspects, to find risk factors in large register cohorts in order to raise the question whether these factors could be influenced by changing treatment practices in obstetric and neonatal care. This study provides new insights for further research on the roles

Abbreviations: CI, confidence interval; CRHC, Care Register for Health Care; GA, gestational age; HDR, Hospital Discharge Register; HR, hazard ratio; ICD-9, International Classification of Diseases, 9th Revision; ICD-10, International Classification of Diseases, 10th Revision; IVH, intraventricular hemorrhage; LGA, large for gestational age; LP, late preterm; MBR, Medical Birth Register; MP, moderately preterm; OR, odds ratio; RDS, respiratory distress syndrome; SD, Standard deviation; SGA, small for gestational age; SII, Social Insurance Institution; THL, National Institute for Health and Welfare; VP, very preterm

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Intellectual disability in children aged less than seven years born moderately and late preterm compared with very preterm and term-born children – a nationwide birth cohort study

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Abstract

Background Prematurity has been shown to be associated with an increased risk of intellectual disability (ID).

Method The aim was to establish whether the prevalence of ID, defined as significant limitations in both intellectual (intelligence quotient below 70) and adaptive functioning among moderately preterm (MP; 32^{+0}–33^{+6} weeks) and late preterm (LP; 34^{+0}–36^{+6} weeks) infants, is increased compared with that in term infants ($\geq 37^{+0}$ weeks). Antenatal and neonatal risk factors for ID among gestational age groups were sought. The national register study included all live-born infants in Finland in 1991–2008, excluding those who died before one year age, or had any major congenital anomaly or missing data. A total of 1 018 256 infants (98.0%) were analysed: very preterm (VP; $<32^{+0}$ weeks, $n = 6329$), MP ($n = 6796$), LP ($n = 39\,928$) and term ($n = 965\,203$).

Results By the age of seven years, the prevalence of ID was 2.48% in the VP group, 0.81% in the MP group, 0.55% in the LP group and 0.35% in the term group. Intracranial haemorrhage increased the ID risk in all groups. Male sex and born small for gestational age predicted an increased risk in all but the MP group.

Conclusions The prevalence of ID decreased with increasing gestational age. Prevention of intracranial haemorrhages may have a beneficial effect on the neurodevelopmental outcomes of neonates.

Keywords intellectual disability, neurodevelopment, outcomes, preterm

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Background

Late preterm (LP) infants, defined as infants born between gestational weeks 34^{+0} and 36^{+6}, and moderately preterm (MP) infants (32^{+0} to 33^{+6} weeks) account for more than 80% of all preterm births (Raju *et al.* 2006). The outcome of very preterm (VP) infants ($<32^{+0}$) has significantly improved in recent decades due to advances in peri- and neonatal care, and survival rates have risen. In spite of the improved outcome of VP infants, there is evidence that VP, MP and LP infants experience greater morbidity compared with those born at term ($\geq 37^{+0}$ weeks) (Cheng *et al.* 2011). Long-term neurodevelopmental outcomes have been shown to be poorer among MP and LP infants than term infants (Morse *et al.* 2009).

Intellectual disability (ID) is characterised by significant limitations in both intellectual functioning and adaptive behaviour, starting from infancy or early childhood years (Schalock *et al.* 2007). According to a systematic review of population-based studies, the prevalence across the world is around 1% (Maulik *et al.* 2011). The prevalence of ID has ranged between 0.5 and 1.2% in the United States, (Yeargin-Allsopp *et al.* 1992; Croen *et al.* 2001), and estimated prevalences of ID have been 0.7% in Finland (Westerinen *et al.* 2007), 0.63% in the Republic of Ireland (McConkey *et al.* 2006) and 0.56% in Scotland (Cooper *et al.* 2015). Some studies have excluded chromosomal abnormalities (Croen *et al.* 2001), while others have not (Yeargin-Allsopp *et al.* 1992; Westerinen *et al.* 2007). In children with birth defects, the prevalence of ID was 7.9% and without birth defects 1.0% in an Australian population-based study (Petterson *et al.* 2007). There is variation between prevalence estimates as a result of different methods, designs, definitions, geographical regions and sampling strategies.

Prematurity has been associated with an increased risk of ID (Stromme 2000; Bilder *et al.* 2013; Langridge *et al.* 2013). Other established prenatal and perinatal risk factors include inappropriate intrauterine growth (Leonard *et al.* 2008), low birth weight (Croen *et al.* 2001; Chapman *et al.* 2008), maternal smoking (Drews *et al.* 1996; Braun *et al.* 2009), low Apgar scores (Jonas *et al.* 1990; Camp *et al.* 1998), intrauterine infections (Bilder *et al.* 2013) and genetic disorders (Stromme 2000; Bilder *et al.* 2013). It is important to identify prenatal and perinatal risk factors, given that improvement could lead to better obstetric and neonatal treatment practices and ultimately a reduction in prevalence of ID.

Our aim was to compare the prevalence of ID of unknown cause among LP and MP infants vs. VP and term infants. Another aim was to identify antenatal and neonatal risk factors of ID among gestational age (GA) groups and to establish morbidity patterns and need for allowances and reimbursements for medication associated with ID.

Methods

Cohort for analysis

Our Finnish national register population included all infants (1 039 263) born in 1991–2008, including all live-births and stillbirths from GA 22^{+0} weeks onwards and/or birth weight at least 500 g. The baseline data were retrieved from the Medical Birth Register (MBR), maintained by the National Institute for Health and Welfare (THL). The register personnel collect and maintain information on maternal health, interventions during pregnancy and delivery, the infant's health and procedures undergone during the first week of life. Data on major structural and chromosomal anomalies were obtained from the Register of Congenital Malformations, maintained by THL. Infants who died before the age of one year (n = 2659), or who had at least one major congenital anomaly (n = 13 007) or had missing data on GA (n = 5520) were excluded. Thus, the cohort for analysis consisted of 1 018 256 infants (98.0% of all). Gestational age was based on early pregnancy ultrasonography (US), and correction of GA was made if the US-based estimation showed a discrepancy of 5–7 days or more compared with the last menstrual period. The GA categories were as follows: VP ($<32^{+0}$ weeks, n = 6329), MP (32^{+0} to 33^{+6} weeks, n = 6796), LP (34^{+0} to 36^{+6} weeks, n = 39 928) and term (37^{+0} weeks or more, n = 965 203). The term group also included post-term infants (42^{+0} gestational weeks or more, n = 32 951 between 1996 and 2008).

Data collection and covariates

Pregnancy- and delivery-related diagnoses of mothers and diagnoses and procedures concerning

children during the neonatal period were collected from the MBR and from the Hospital Discharge Register (HDR). The HDR is also maintained by THL and contains information on admission and discharge dates, diagnoses and procedures. Hospital outpatient visits have been covered since 1998. International Classification of Diseases, 9th Revision (ICD-9) was used in 1987–1995 and the 10th Revision (ICD-10) from 1996 onwards. The prevalence of ID was also reported in three time-periods: 1991–1995, 1996–2001 and 2002–2008. These periods were chosen because the change from ICD-9 to ICD-10 took place in 1996 and the MBR data collection form was changed on 1 October 1990 and 1 January 1996.

Information on special reimbursements and benefits for disability due to ID were collected from the register of the Social Insurance Institution of Finland. Children below 16 years of age can receive disability allowance if they need care or rehabilitation for at least six months in Finland. Special reimbursements for medicines for chronic diseases are granted by the Social Insurance Institution based on a medical statement issued by a specialist. Data on reimbursements for medicinal expenses included the information that the reimbursements were granted as a result of a diagnosis of ID.

Prenatal, perinatal and neonatal risk factors of ID were sought by way of a Cox multivariate regression model. Variables concerning maternal and infant characteristics, pregnancy, delivery and neonatal care were retrieved from the MBR and the HDR. Small-for-GA (SGA) infants were defined as those with a birth weight more than two standard deviations (SDs) below the mean weight for GA and large-for-GA (LGA) infants as those with a birth weight more than 2 SDs over the mean weight for GA according to Finnish sex-specific foetal growth curves (Pihkala *et al.* 1989). Very-low-birth-weight infants were defined according to the World Health Organisation's definition as infants with birth weight less than or equal to 1500 g. Intracranial haemorrhages included intraventricular and parenchymal haemorrhages and were defined by ICD10/ICD9 codes P52.0-9/772.1. Only parameters with good validity in the registers were chosen, and therefore the risk factor analysis concerned the period 1996–2008.

Outcome definitions; intellectual disability

ID was defined as significant limitations in both intellectual and adaptive functioning, which refers to the age-appropriate forms of behaviour necessary for a person to function safely and to adapt to daily demands. For ID, an intelligence quotient (IQ) at or below 70 was required. In Finland, all children below school age are followed up regularly in public child health clinics free of charge. In cases of problems concerning neurological development, children are referred to paediatric neurology units of public special healthcare, i.e. central or university hospitals. Diagnosis of ID in Finland is based on assessments of cognitive development and adaptive behaviour conducted by a multidisciplinary team in these paediatric neurology units. As a standard procedure, standardised tests, e.g. the Bayley Scales of Infant Development (Bayley 1993) or Finnish versions of Wechsler Intelligence Scales for Children (Wechsler 1989; Wechsler 1991), are used. Adaptive functioning is typically assessed by way of parental interviews, observations and/or rating scales (e.g. Vineland Scales) (Sparrow *et al.* 1984).

A case of ID was recorded if the individual was detected in the HDR and/or in the Reimbursement Register of the Social Insurance Institution with ICD-10 codes F70–F79 in 1996–2008 and ICD-9 codes 317–319 in 1991–1995 by the age of seven years. ID was divided into three subtypes according to IQ level. Mild and moderate ID, i.e. IQ 35–70, was defined by ICD-10 codes F70–F71 and by ICD-9 codes 317–318.0. Severe and profound ID, i.e. IQ below 34, included ICD-10 codes F72–F73 and ICD-9 codes 318.1–318.2. The 'unspecified ID' group covered the rest of the ID diagnoses according to the baseline definition of ID including ICD-10 codes F78–F79 and ICD-9 code 319. The main outcome, ID, was recorded if the child was detected in at least one of the above-mentioned registers by the age of seven years. Age at diagnosis of ID was defined according to the first detection in the register, and the time to event was age at diagnosis of ID.

Unidentifiable register data were used, and the investigators did not contact the participants. Data linkages were performed by Statistics Finland, and all were carried out using unique personal identity codes anonymised by the register-keeping authorities. The investigators accessed unidentifiable data by using a

very secure Micro Data Remote Access System run by the Finnish Information Centre for Register Research and IT Center for Science Ltd. (a non-profit-making, state-owned company administered by the Ministry of Education and Culture).

Statistical analysis

Statistical analyses were performed by using IBM SPSS Statistics version 23 software (IBM SPSS Statistics, IBM Corporation, Chicago, IL). The Mann–Whitney test, the Chi-square test or Fisher's exact test were used in group comparisons, as appropriate, and *P*-values less than 0.001 were considered statistically significant in group comparisons (Tables 1, 2). Risk factors of ID among each GA group were sought by Cox regression analysis using multivariate models (Table 3a–c). All tested variables were entered simultaneously into the model for each gestational week category. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Proportional hazards were tested against each risk factor to show that the proportional hazard assumption holds. Observations should be independent, and the HR should be constant across time. The proportionality of hazards from one case to another should not vary over time. Proportional-hazards assumptions were tested based on Schoenfeld residuals with Stata/SE 14.0 for Windows. To hold the proportional hazard assumption, the term group was divided to term (37^{+0}–41^{+6} weeks) and post-term ($\geq 42^{+0}$ weeks) groups, and further in the term group boys and girls were analysed separately (Table 3b,3c). The association between GA and ID was studied by adjusting the multivariate model by gestational week categories – term category as reference. The Cochran–Armitage trend test were used to test trend for number of ID cases related to no ID cases according to GA. The trend test was carried out by using StatXact-4 version 4.0.1 software (Cytel Software Corporation). Values of *P* less than 0.05 were considered statistically significant in the multivariate model (Table 3).

Results

The characteristics of the infants and their mothers are presented in Table 1. The proportions of all preterm births and those of MP and LP infants remained constant in all three time periods. The multivariate model covered the period 1996–2008. During that time, there were 592 260 (83%) vaginal deliveries, 53 057 (7.5%) planned Caesarean sections (C-sections) and 63 817 (9.0%) non-elective C-sections. Vaginal deliveries included 4715 breech infants, and the C-section rate was 16%. Data on the mode of delivery were missing as regards 372 children.

In all, 3814 ID cases were detected – an overall prevalence of 0.37%. Term-born children accounted for 88.8%, LP infants 5.7%, MP infants 1.4% and VP infants 4.1% of the cases. The prevalence of ID was highest in the VP group and lowest in the term group (Table 2). Among post-term-born children (42^{+0} weeks or more), there were 94 cases of ID in 1996–2008, the prevalence being 0.29%. The prevalence diminished with increasing GA up to term ($P < 0.001$) (Fig. 1). Approximately two thirds of the ID cases were mild or moderate subtypes in all GA groups. The prevalence of ID seemed to decrease with time in all groups, most markedly in the MP group. The median age at diagnosis was 5.7–6.3 years. Among children with ID, reimbursements for medication due to ID were reported in 12.7% in the VP group, 14.5% in the MP group, 11.9% in the LP group and 12.4% in the term group, and disability allowances were 40.1% in the VP group, 27.3% in the MP group, 22.9% in the LP group and 26.1% in the term group (Table 2).

Intracranial haemorrhage was strongly associated with an increased risk of ID in all groups in the multivariate regression model, except the post-term group. Male sex and SGA infants were associated with an increased risk of ID in all groups except the MP group. Low umbilical artery pH predicted an increased risk in the LP group, as did 1-min Apgar scores of less than four in the VP and term groups. In the VP and term groups, convulsions during the neonatal period predicted an increased risk of ID. Smoking during pregnancy was associated with an increased risk of ID in the LP and term groups (Table 3a–c). Being SGA was more common in infants whose mothers smoked during pregnancy ($n = 3060$, 3.9%) compared with children of non-smoking mothers ($n = 11\,122$, 1.9%) ($P < 0.001$).

Very preterm (HR 1.37; 95% CI 0.85–2.20, $P = 0.194$) and LP (HR 0.99; 95%CI 0.80–1.22,

Table 1 Characteristics of the mothers and the infants alive at one year of age without major congenital malformations (n = 1 018 256). Years 1991–2008

	Very preterm <32 weeks (n = 6329)	Moderately preterm 32^{+0}–33^{+6} weeks (n = 6796)	Late preterm 34^{+0}–36^{+6} weeks (n = 39 928)	Term/Post-term ≥37 weeks (n = 965 203)	p^1 MP versus VP	p^2 LP versus VP	p^3 MP versus T	p^4 LP versus T
Study periods, years					0.677	0.084	0.003	<0.001
1991–1995, *n* (%)	1780 (0.58)	1937 (0.63)	11 777 (3.82)	293 228 (95.0)				
1996–2001	2159 (0.66)	2269 (0.69)	13 361 (4.08)	309 889 (94.6)				
2002–2008	2390 (0.63)	2590 (0.68)	14 790 (3.87)	362 086 (94.8)				
Mothers								
Age, mean (SD)	30.2 (5.8)	29.8 (5.7)	29.7 (5.5)	29.2 (5.3)	<0.001	<0.001	<0.001	<0.001
Smoking, *n* (%)	1187 (18.8)	1184 (17.4)	6602 (16.5)	144 094 (14.9)	<0.001	<0.001	<0.001	<0.001
Primipara, *n* (%)	3314 (52.4)	3792 (55.8)	20 040 (50.2)	392 574 (40.7)	<0.001	0.001	<0.001	<0.001
Earlier deliveries, Md (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–2)	<0.001	0.118	<0.001	<0.001
Pregnancies								
Number of foetuses at birth, *n* (%)								
1	4517 (71.4)	4591 (67.6)	31 062 (77.8)	948 695 (98.3)	<0.001	<0.001	<0.001	<0.001
2	1614 (25.5)	1954 (28.8)	8548 (21.4)	16 489 (1.7)				
≥3	198 (3.1)	251 (3.7)	318 (0.8)	19 (<0.1)				
Deliveries								
Place of birth, *n* (%)					<0.001	<0.001	<0.001	<0.001
University hospital (level III)	4943 (78.1)	3993 (58.8)	17 154 (43.0)	299 470 (31.0)				
Central hospital (level II)	1340 (21.2)	2726 (40.1)	17 551 (44.0)	444 952 (46.1)				
Other*	41 (0.6)	77 (1.1)	5220 (13.1)	220 654 (22.9)				
Mode of delivery, *n* (%)					<0.001	<0.001	<0.001	<0.001
Vaginal	2524 (39.9)	3211 (47.2)	26 685 (66.8)	820 942 (85.1)				
Caesarean section	3793 (59.9)	3582 (52.7)	13 210 (33.1)	143 491 (14.9)				
Newborns								
Boys, *n* (%)	3428 (54.2)	3728 (54.9)	21 658 (54.2)	490 211 (50.8)	0.426	0.906	<0.001	<0.001
Birth weight, g, Md (IQR)	1290 (1000–1570)	1970 (1730–2200)	2670 (2360–2985)	3590 (3276–3910)	<0.001	<0.001	<0.001	<0.001
≤1500 g	4388 (69.3)	735 (10.8)	253 (0.6)	23 (<0.1)				
>1500 g	1925 (30.4)	6053 (89.1)	39 654 (99.3)	964 935 (100)				
Weight by gestational age, *n* (%)					<0.001	<0.001	<0.001	<0.001
SGA	1019 (16.1)	883 (13.0)	3245 (8.1)	16 662 (1.7)				
AGA	4972 (78.6)	5637 (82.9)	34 681 (86.9)	919 970 (95.3)				
LGA	284 (4.5)	276 (4.1)	2002 (5.0)	28 571 (3.0)				
Apgar 1 min, Md (IQR)	7 (5–8)	8 (7–9)	9 (8–9)	9 (9–9)	<0.001	<0.001	<0.001	<0.001
Apgar 1 min <4, *n* (%)	1001 (15.8)	325 (4.8)	890 (2.2)	7491 (0.8)	<0.001	<0.001	<0.001	<0.001
Admission to neonatal unit, *n* (%)	5692 (89.9)	5972 (87.9)	19 155 (48.0)	58 365 (6.0)	<0.001	<0.001	<0.001	<0.001

Table 1. *(Continued)*

	Very preterm <32 weeks (*n* = 6329)	Moderately preterm 32^{+0}–33^{+6} weeks (*n* = 6796)	Late preterm 34^{+0}–36^{+6} weeks (*n* = 39 928)	Term/Post-term ≥37 weeks (*n* = 965 203)	p^1 MP versus VP	p^2 LP versus VP	p^3 MP versus T	p^4 LP versus T
Ventilator, *n* (%)	3656 (57.8)	1413 (20.8)	1667 (4.2)	2793 (0.3)	<0.001	<0.001	<0.001	<0.001
Resuscitation at birth, *n* (%)	1901 (30.1)	625 (9.2)	795 (2.0)	3074 (0.3)	<0.001	<0.001	<0.001	<0.001
Phototherapy, *n* (%)	4202 (66.4)	3821 (56.2)	14v153 (35.4)	36 671 (3.8)	<0.001	<0.001	<0.001	<0.001
Antibiotic therapy, *n* (%)	4505 (71.2)	2958 (43.5)	5038 (12.6)	23 849 (2.5)	<0.001	<0.001	<0.001	<0.001
Death by 7 years of age, *n* (%)	13 (0.2)	4 (0.1)	36 (0.1)	627 (0.1)	0.020	0.009	1.000	0.055
Age at death, years, Md (IQR)	2.08 (1.42–4.52)	2.07 (1.04–3.25)	3.27 (2.04–4.92)	3.17 (1.92–4.94)	0.477	0.135	0.099	0.797

Statistical differences were assessed by using Pearson's chi-square test, Fisher's exact test or the Mann–Whitney test:
p^1 = *Moderately preterm versus very preterm*, p^2 = *Late preterm versus very preterm*, p^3 = *Moderately preterm versus term*, p^4 = *Late preterm versus term.*
P-values <0.001 were considered statistically significant.
*Regional hospital, private hospital, health centre, home birth.
AGA, appropriate for gestational age; IQR, interquartile range; LGA, large for gestational age; LP, late preterm; Md, median; MP, moderately preterm; SD, standard deviation; SGA, small for gestational age; T, term; VP, very preterm.

P = 0.942) births were not independent risk factors of ID compared with the term group when the multivariate model was adjusted by GA categories in the period 1996–2008. There was an association with a decreased risk of ID and MP birth (HR 0.63; 95% CI 0.40–0.98, *P* = 0.040).

Discussion

In this large national cohort, we found that the prevalence of ID diminished with increasing GA up to term. The most prominent pre- and perinatal risk factors of ID were intracranial haemorrhage, male sex, being SGA and a low 1-min Apgar score. Smoking during pregnancy and convulsions in the neonatal period also seemed to predict an increased risk in more than one GA group.

In an earlier Finnish register study, the prevalence rate of ID in children aged 0–15 years was 0.53% (95% CI 0.52–0.55) (Westerinen *et al.* 2007). Higher rates compared with those in our study are probably due to the fact that chromosomal defects and birth defects were also included. In a Norwegian register study of 903 402 infants born alive in 1976–1983 without congenital anomalies, the prevalence of ID was 1.8% in infants born between weeks 28^{+0} and 30^{+6}, 1.0% in those born at 31^{+0}–33^{+6} weeks, 0.7% in infants born at 34^{+0}–36^{+6} weeks and 0.4% in the term group (≥37 weeks) (Moster *et al.* 2008). The relative risk of ID was statistically significantly increased in the GA group of 31^{+0}–33^{+6} weeks and in the LP group compared with term-born infants. In comparison with our study, the slightly higher ID rates among MP and LP infants are possibly connected to the somewhat different GA ranges, the earlier cohort of infants and a longer follow-up time.

The overall prevalence of ID also seemed to diminish with time. This decrease was greatest in the two latest time periods. This might partly be due to the fact that some of those born between 2002 and 2008 were too young for neuropsychological testing as a result of the study design. Therefore, it might be impossible to draw further conclusions concerning the temporal trends of ID prevalence. The overall incidence of ID by the age of 11.5 years has been similar among children born in Northern Finland in the 1960s and 1980s (Heikura *et al.* 2003). On the other hand, in a Taiwanese national register study, the prevalence of ID showed an increasing trend over

Table 2 Diagnoses of intellectual disability (ID) and data of reimbursements due to ID by 7 years of age in children alive at one year of age without major congenital anomalies (n = 1 018 256). Years 1991–2008

	Very preterm <32 weeks (n = 6329)	Moderately preterm 32^{+0}–33^{+6} weeks (n = 6796)	Late preterm 34^{+0}–36^{+6} weeks (n = 39 928)	Term/Post-term ≥37 weeks (n = 965 203)	Total (n = 1 018 256)	p^1 MP versus VP	p^2 LP versus VP	p^3 MP versus T	p^4 LP versus T
Intellectual disability, n (% of children in GA group)[¶]	*157 (2.48)*	*55 (0.81)*	*218 (0.55)*	*3384 (0.35)*	*3814 (0.37)*	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
ID subtype n (% of ID cases in GA group)									
Mild or moderate ID[†]	103 (66)	35 (64)	140 (64)	2251 (67)	2529 (66)				
Severe or profound ID[‡]	15 (10)	2 (3.6)	13 (6.0)	207 (6.1)	237 (6.2)				
Unspecified ID[§]	39 (25)	18 (33)	65 (30)	926 (27)	1048 (27)				
Years, *n* (% of children in GA group in years)									
1991–1995	60 (3.4)	30 (1.5)	89 (0.8)	1455 (0.5)	1634 (0.53)				
1996–2001	72 (3.3)	20 (0.9)	87 (0.7)	1367 (0.4)	1546 (0.47)				
2002–2008	25 (1.0)	5 (0.2)	42 (0.3)	562 (0.2)	634 (0.17)				
Age at diagnosis (years), Md (IQR)	5.7 (4.1–8.0)	6.3 (5.2–10.9)	6.0 (4.4–8.8)	6.0 (4.4–9.0)					
Reimbursements for medication due to ID, n (% of ID cases in GA group)	*20 (12.7)*	*8 (14.5)*	*26 (11.9)*	*421 (12.4)*	*475 (12.5)*	$P = 0.014$	$P < 0.001$	$P = 0.012$	$P = 0.046$
Mild or moderate ID[†]	10 (6.4)	3 (5.5)	13 (6.0)	219 (6.5)	245 (6.4)				
Severe or profound ID[‡]	6 (3.8)	1 (1.8)	3 (1.4)	66 (2.0)	76 (2.0)				
Unspecified ID[§]	4 (2.5)	4 (7.3)	10 (4.6)	136 (4.0)	154 (4.0)				
Age (years) of child at first reimbursement, Md (IQR) (total)	10 (8–13.75)	9.5 (7.5–13.25)	9.5 (4.5–13)	10 (6.5–13)					
Disability allowance due to ID, n (% of ID cases in GA group)	*63 (40.1)*	*15 (27.3)*	*50 (22.9)*	*882 (26.1)*	*1010 (26.5)*	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P = 0.029$
Mild or moderate ID[†]	45 (29)	10 (18)	29 (13)	561 (17)	645 (17)				
Severe or profound ID[‡]	6 (3.8)	0 (0)	6 (2.8)	88 (2.6)	100 (2.6)				

Table 2. *(Continued)*

	Very preterm <32 weeks (n = 6329)	Moderately preterm 32^{+0}–33^{+6} weeks (n = 6796)	Late preterm 34^{+0}–36^{+6} weeks (n = 39 928)	Term/Post-term ≥37 weeks (n = 965 203)	Total (n = 1 018 256)	p[1] MP versus VP	p[2] LP versus VP	p[3] MP versus T	p[4] LP versus T
Unspecified ID[§]	12 (7.6)	5 (9.1)	15 (12)	233 (6.9)	265 (6.9)				
Age (years) of child at start of the allowance, Md (IQR)	7.8(5.7–10.3)	12.9 (6.2–14.9)	7.3 (4.7–11.4)	8.1 (5.4–11.9)					

Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9):
[†]F70–F71/317–318.0.
[‡]F72–F73/318.1–318.2.
[§]F78–F79/319.
[¶]Hospital Discharge Register and/or Social Insurance Institution.
GA, gestational age; ICD, International Classification of Disease; ID, Intellectual disability; IQR, Interquartile range; Md, median.
Statistical differences were assessed by using Pearson's chi-square test, Fisher's exact test or the Mann–Whitney test:
p[1] = *Moderately preterm versus very preterm.*
p[2] = *Late preterm versus very preterm.*
p[3] = *Moderately preterm versus term.*
p[4] = *Late preterm versus term.*
P-values <0.001 were considered statistically significant.

Table 3a Risk factor analysis for intellectual disability (ID; $n = 251$) in preterm born children ($N = 37\,559$). Years 1996–2008

	Very preterm <32 weeks ($n = 97/N = 4549$)				Moderately preterm 32^{+0}–33^{+6} weeks ($n = 25/N = 4859$)†				Late preterm 34^{+0}–36^{+6} weeks ($n = 129/N = 28\,151$)			
	n	HR	(95% CI)	*P*	*n*	HR	(95% CI)	*P*	*n*	HR	(95% CI)	*P*
Mother												
Age (years)												
≤40	4364	1.00			4693	1.00			27 408	1.00		
40 or more	185	1.17	(0.47–2.93)	0.739	166	a			743	0.62	(0.19–1.98)	0.416
Smoking												
No	3478	1.00			3898	1.00			22 870	1.00		
Yes	797	1.40	(0.84–2.31)	0.196	786	0.22	(0.03–1.64)	0.139	4470	**1.94**	**(1.31–2.86)**	0.001
Primipara												
No	2080	1.00			2124	1.00			13 839	1.00		
Yes	2469	0.67	(0.43–1.05)	0.079	2735	0.73	(0.32–1.64)	0.440	14 312	**0.53**	**(0.36–0.77)**	0.001
Previous caesarean section												
No	4136	1.00			4422	1.00			25 579	1.00		
Yes	413	1.14	(0.59–2.20)	0.695	437	a			2572	0.98	(0.55–1.74)	0.938
Pregnancy												
Number of foetuses				0.634				0.431				0.800
1	3216	1.00			3250	1.00			21 755	1.00		
2	1198	0.70	(0.33–1.50)	0.361	1492	0.45	(0.10–2.11)	0.311	6241	1.06	(0.62–1.83)	0.825
≥3	135	0.98	(0.21–4.54)	0.983	117	1.46	(0.14–14.9)	0.751	155	1.97	(0.26–15.0)	0.512
Order of foetuses				0.954				0.567				0.209
A	3871	1.00			4043	1.00			24 941	1.00		
B	633	1.16	(0.45–2.95)	0.760	779	2.46	(0.47–12.9)	0.287	3160	0.49	(0.22–1.11)	0.087
C	45	a			37	a			50	1.47	(0.09–24.0)	0.789
Delivery												
Time of birth				0.812				0.476				0.904
Mon–Fri 08.00–15.59	1829	1.00			1900	1.00			9754	1.00		
Mon–Fri 16.00–07.59	1634	0.85	(0.53–1.38)	0.519	1830	0.61	(0.22–1.69)	0.342	11 951	0.93	(0.62–1.40)	0.713
Weekend	1086	0.93	(0.55–1.55)	0.771	1129	1.14	(0.42–3.09)	0.790	6446	1.01	(0.63–1.63)	0.958
Place of birth				0.983				0.309				0.707
University hospital	3664	1.00			2900	1.00			12 358	1.00		
Central hospital	857	1.11	(0.67–1.85)	0.684	1913	1.18	(0.50–2.80)	0.704	12 345	0.89	(0.60–1.30)	0.535
Other§	25	a			46	5.49	(0.62–49.0)	0.127	3445	0.68	(0.35–1.30)	0.245
Mode of delivery												
Vaginal	1725	1.00			2278	1.00			18 748	1.00		

Table 3a. *(Continued)*

	Very preterm <32 weeks (*n* = 97/*N* = 4549)				Moderately preterm 32^{+0}–33^{+6} weeks (*n* = 25/*N* = 4859)†				Late preterm 34^{+0}–36^{+6} weeks (*n* = 129/*N* = 28 151)			
	n	HR	(95% CI)	*P*	*n*	HR	(95% CI)	*P*	*n*	HR	(95% CI)	*P*
Caesarean section	2819	1.44	(0.87–2.38)	0.161	2580	0.64	(0.26–1.61)	0.348	9390	1.04	(0.69–1.58)	0.847
Newborn												
Sex												
Boy	2496	**1.88**	**(1.23–2.89)**	0.004	2672	1.18	(0.52–2.67)	0.688	15 273	**1.93**	**(1.32–2.81)**	0.001
Girl	2053	1.00			2187	1.00			12 878	1.00		
Gestational weight				0.022				0.714				<0.001
SGA	750	**1.94**	**(1.19–3.16)**	0.008	634	1.94	(0.40–9.52)	0.413	2292	**3.27**	**(2.03–5.24)**	<0.001
LGA	188	0.31	(0.04–2.32)	0.256	187	0.99	(0.12–8.04)	0.988	1408	0.65	(0.24–1.79)	0.406
AGA	3568	1.00			4038	1.00			24 451	1.00		
Birth weight ≤ 1500 g												
No	1350	1.00			4325	1.00			27 961	1.00		
Yes	3197	1.65	(0.89–3.07)	0.110	531	1.30	(0.23–7.20)	0.766	175	1.14	(0.33–3.96)	0.839
Apgar 1 min												
≥4	3748	1.00			4555	1.00			27 398	1.00		
< 4	724	**2.17**	**(1.38–3.42)**	0.001	239	0.91	(0.12–6.96)	0.929	647	1.07	(0.42–2.72)	0.889
Umbilical artery pH				0.741				0.766				0.002
7.05 or more	2968	1.00			3171	1.00			17 115	1.00		
<7.05	66	1.37	(0.41–4.59)	0.607	67	a			240	**4.62**	**(1.67–12.8)**	0.003
Not known	1515	1.16	(0.75–1.79)	0.519	1621	1.37	(0.59–3.20)	0.465	10 796	**1.57**	**(1.07–2.29)**	0.020
Admission to neonatal unit												
No	461	1.00			529	1.00			13 827	1.00		
Yes	4088	1.27	(0.59–2.72)	0.544	4330	1.46	(0.39–5.41)	0.575	14 323	1.06	(0.70–1.63)	0.775
Ventilator												
No	1927	1.00			3921	1.00			27 038	1.00		
Yes	2622	1.27	(0.71–2.27)	0.420	938	1.15	(0.33–4.06)	0.830	1113	1.64	(0.74–3.62)	0.220
Resuscitation at birth												
No	3338	1.00			4453	1.00			27 601	1.00		
Yes	1211	0.95	(0.60–1.51)	0.834	406	1.82	(0.56–5.89)	0.316	550	1.30	(0.51–3.36)	0.584
Phototherapy												
No	1491	1.00			2097	1.00			17 906	1.00		
Yes	3058	0.63	(0.38–1.03)	0.066	2762	0.93	(0.37–2.30)	0.873	10 245	0.90	(0.58–1.40)	0.643
Antibiotic therapy												

Table 3a. *(Continued)*

	Very preterm <32 weeks (n = 97/N = 4549)				Moderately preterm 32^{+0}–33^{+6} weeks (n = 25/N = 4859)†				Late preterm 34^{+0}–36^{+6} weeks (n = 129/N = 28 151)			
	n	HR	(95% CI)	P	n	HR	(95% CI)	P	n	HR	(95% CI)	P
No	1010	1.00			2543	1.00			24 133	1.00		
Yes	3539	0.94	(0.48–1.82)	0.848	2316	0.79	(0.28–2.27)	0.659	4018	**1.74**	**(1.01–3.00)**	0.047
Respiratory distress syndrome (P22.0/769)‡												
No	2671	1.00			4123	1.00			27 359	1.00		
Yes	1878	1.47	(0.93–2.33)	0.095	736	2.73	(0.92–8.04)	0.069	792	0.50	(0.17–1.49)	0.214
Sepsis (P36.0–8/771.81)‡												
No	4128	1.00			4623	1.00			27 451	1.00		
Yes	421	1.20	(0.63–2.30)	0.573	236	a			700	2.05	(0.94–4.51)	0.073
Intracranial haemorrhage (P52.0–9/772.1)‡												
No	4316	1.00			4753	1.00			28 072	1.00		
Yes	233	**2.92**	**1.58–5.41**	0.001	106	**5.59**	**(1.57–19.9)**	0.008	79	**4.58**	**(1.36–15.4)**	0.014
Convulsions (P90/779.0)‡												
No	4527	1.00			4855	1.00			28 117	1.00		
Yes	22	**4.76**	**(1.36–16.6)**	0.014	4	a			34			
Hyperbilirubinemia (P59.0–9/774)‡												
No	3106	1.00			3066	1.00			20 071	1.00		
Yes	1443	0.86	(0.52–1.41)	0.537	1793	0.55	(0.20–1.47)	0.233	8080	1.20	(0.76–1.89)	0.445

Cox hazard regression multivariate models were used, with results given as the hazard ratios (HR) and 95% confidence intervals (CI) using reference category no ID for ID group (mild, moderate, severe or unspecified ID).

Statistically significant ($P < 0.050$) hazard ratios with 95% confidence intervals were **bolded**. Categories of missing values were not shown.

Proportional-hazards assumptions were tested based on Schoenfeld residuals (assumption holds when $P > 0.05$):

$P = 0.263$ Very preterm.

$P = 0.521$ Moderately preterm.

$P = 0.185$ Late preterm.

a = Cannot be computed due to the small number of cases.

†239 cases were followed for less time than the shortest time to event in their stratum. These cases are excluded from the analysis (n = 4620 included).

‡Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9).

§Regional hospital, private hospital, health centre, home birth.

AGA = appropriate for gestational age; ID = intellectual disability; ICD = International Classification of Disease; LGA = large for gestational age; SGA = small for gestational age.

Table 3b Risk factor analysis for intellectual disability (ID; $n = 1929$) in term born children ($N = 671\,975$). Years 1996–2008

	Term 37^{+0}–41^{+6} weeks ($n = 1835/N = 639\,024$)				Post-term $\geq 42^{+0}$ weeks ($n = 94/N = 32\,951$)			
	n	HR	(95% CI)	*P*	*n*	HR	(95% CI)	*P*
Mother								
Age (years)								
≤40	626 375	1.00			32 390	1.00		
40 or more	12 649	1.26	(0.94–1.68)	0.125	561	**3.80**	**(1.38–10.5)**	0.010
Smoking								
No	530 447	1.00			27 032	1.00		
Yes	92 850	**1.31**	**(1.16–1.47)**	<0.001	5263	1.03	(0.60–1.78)	0.907
Primipara								
No	380 561	1.00			15 323	1.00		
Yes	258 463	**0.81**	**(0.73–0.89)**	<0.001	17 628	1.26	(0.81–1.96)	0.311
Previous caesarean section								
No	586 325	1.00			30 671	1.00		
Yes	52 699	0.94	(0.79–1.12)	0.502	2280	0.54	(0.16–1.76)	0.305
Pregnancy								
Number of foetuses				0.466				0.993
1	627 172	1.00			32 949	1.00		
2	11 849	0.74	(0.46–1.20)	0.217	2	a		
≥3	3	a			0	a		
Order of foetuses				0.614				1.000
A	633 107	1.00			32 950	1.00		
B	5916	1.36	(0.74–2.51)	0.324	1	a		
C	1	a			0	a		
Delivery								
Time of birth				0.287				0.776
Mon–Fri 08.00–15.59	196 855	1.00			7571	1.00		
Mon–Fri 16.00–07.59	289 093	1.06	(0.95–1.18)	0.323	17 773	1.03	(0.61–1.72)	0.924
Weekend	153 076	0.97	(0.85–1.10)	0.595	7647	1.20	(0.67–2.17)	0.538
Place of birth				0.180				
University hospital	204 851	1.00			11 273	1.00		0.565
Central hospital	295 886	1.09	(0.98–1.22)	0.115	14 934	1.44	(0.87–2.37)	0.157
Other‡	138 220	**1.16**	**(1.01–1.33)**	0.030	6739	1.24	(0.66–2.33)	0.503
Mode of delivery								
Vaginal	542 579	1.00			26 930	1.00		

Table 3b. *(Continued)*

	Term 37^{+0}–41^{+6} weeks (n = 1835/N = 639 024)				Post-term ≥42^{+0} weeks (n = 94/N = 32 951)			
	n	HR	(95% CI)	P	n	HR	(95% CI)	P
Caesarean section	96 077	**1.26**	**(1.10–1.43)**	0.001	6008	0.62	(0.34–1.14)	0.122
Newborn								
Sex								
Boy	324 684	**1.71**	**(1.55–1.87)**	<0.001	16 948	1.32	(0.87–2.00)	0.186
Girl	314 340	1.00			16 003	1.00		
Gestational weight				<0.001				<0.001
SGA	11 700	**2.34**	**(1.90–2.94)**	<0.001	214	**12.5**	**(5.66–27.5)**	<0.001
LGA	17 760	0.76	(0.56–1.02)	0.068	1003	1.09	(0.34–3.49)	0.884
AGA	609 564	1.00			31 734	1.00		
Birth weight ≤ 1500 g								
No	638 819	1.00			32 937	1.00		
Yes	13	a			0	a		
Apgar 1 min								
≥4	632 707	1.00			32 422	1.00		
< 4	5394	**1.77**	**(1.27–2.47)**	0.001	497	0.50	(0.10–2.40)	0.384
Umbilical artery pH				0.948				0.740
7.05 or more	345 477	1.00			18 775	1.00		
<7.05	4731	1.00	(0.64–1.56)	0.997	422	1.37	(0.32–5.97)	0.672
Not known	288 816	1.02	(0.92–1.12)	0.745	13 754	1.17	(0.75–1.83)	0.482
Admission to neonatal unit								
No	596 475	1.00			30 485	1.00		
Yes	42 546	**1.88**	**(1.58–2.23)**	<0.001	2466	1.85	(0.81–4.26)	0.147
Ventilator								
No	637 201	1.00			32 788	1.00		
Yes	1823	1.60	(0.98–2.60)	0.059	163	0.69	(0.14–3.57)	0.663
Resuscitation at birth								
No	639 946	1.00			32 711	1.00		
Yes	2078	1.48	(0.90–2.43)	0.120	240	**4.78**	**(1.42–16.1)**	0.011
Phototherapy								
No	612 420	1.00			32 360	1.00		
Yes	26 604	1.10	(0.84–1.44)	0.481	591	1.44	(0.34–6.23)	0.622
Antibiotic therapy								
No	621 399	1.00			31 397	1.00		

Table 3b. *(Continued)*

	Term 37^{+0}–41^{+6} weeks (n = 1835/N = 639 024)				Post-term ≥42^{+0} weeks (n = 94/N = 32 951)			
	n	HR	(95% CI)	P	n	HR	(95% CI)	P
Yes	17 625	1.18	(0.90–1.55)	0.222	1554	2.02	(0.77–5.29)	0.154
Respiratory distress syndrome (P22.0/769)†								
No	638 783	1.00			32 946	1.00		
Yes	241	0.88	(0.21–3.61)	0.856	5	a		
Sepsis (P36.0–8/771.81)†								
No	633 440	1.00			32 477	1.00		
Yes	5584	0.70	(0.43–1.12)	0.135	474	1.26	(0.40–3.95)	0.697
Intracranial haemorrhage (P52.0–9/772.1)†								
No	638 892	1.00			32 944	1.00		
Yes	132	**2.94**	**(1.08–8.00)**	0.035	7	a		
Convulsions (P90/779.0)†								
No	638 584	1.00			32 927	1.00		
Yes	440	**5.23**	**(3.19–8.58)**	<0.001	24	4.39	(0.58–33.5)	0.154
Hyperbilirubinemia (P59.0–9/774)†								
No	616 539	1.00			32 465	1.00		
Yes	22 485	1.23	(0.93–1.63)	0.155	486	1.08	(0.18–6.31)	0.935

Cox hazard regression multivariate models were used, with results given as the hazard ratios (HR) and 95% confidence intervals (CI) using reference category no ID for ID group (mild, moderate, severe or unspecified ID).

Statistically significant ($P < 0.050$) hazard ratios with 95% confidence intervals were **bolded**. Categories of missing values were not shown.

Proportional-hazards assumptions were tested based on Schoenfeld residuals (assumption holds when $P > 0.05$):

$P = 0.008$ Term.

$P = 0.798$ Post-term.

a = Cannot be computed due to the small number of cases.

†Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9).

‡Regional hospital, private hospital, health centre, home birth.

AGA, appropriate for gestational age; ID, intellectual disability; ICD, International Classification of Disease; LGA, large for gestational age; SGA, small for gestational age.

Table 3c Risk factor analysis for intellectual disability (ID; $n = 1835$) in term born children separately for boys ($n = 324\,684$) and girls ($n = 314\,340$). Years 1996–2008

	Term boys 37^{+0}–41^{+6} weeks ($n = 1182/N = 324\,684$)				Term girls 37^{+0}–41^{+6} weeks ($n = 653/N = 314\,340$)			
	n	HR	(95% CI)	*P*	*n*	HR	(95% CI)	*P*
Mother								
Age (years)								
≤40	318 233	1.00			308 142	1.00		
40 or more	6451	1.24	(0.86–1.80)	0.257	6198	1.30	(0.81–2.08)	0.278
Smoking								
No	269 433	1.00			261 014	1.00		
Yes	47 283	**1.39**	**(1.20–1.61)**	<0.001	45 567	1.16	(0.94–1.42)	0.166
Primipara								
No	193 365	1.00			187 196	1.00		
Yes	131 319	**0.81**	**(0.72–0.92)**	0.001	127 144	**0.79**	**(0.67–0.94)**	0.007
Previous caesarean section								
No	297 906	1.00			288 419	1.00		
Yes	26 778	0.83	(0.66–1.04)	0.100	25 921	1.14	(0.87–1.49)	0.347
Pregnancy								
Number of foetuses				0.728				0.631
1	318 794	1.00			308 378	1.00		
2	5888	0.78	(0.43–1.43)	0.426	5961	0.672	(0.30–1.51)	0.337
≥3	2	a			1	a		
Order of foetuses				1.000				0.172
A	321 796	1.00			311 311	1.00		
B	2887	1.00	(0.44–2.27)	0.997	3029	a		
C	1	a			0	a		
Delivery								
Time of birth				0.486				0.415
Mon–Fri 08.00–15.59	99 639	1.00			97 216	1.00		
Mon–Fri 16.00–07.59	147 092	1.07	(0.94–1.23)	0.314	142 001	1.04	(0.86–1.25)	0.701
Weekend	77 953	1.00	(0.85–1.17)	0.998	75 123	0.90	(0.72–1.13)	0.369
Place of birth				0.235				0.512
University hospital	104 497	1.00			100 354	1.00		
Central hospital	150 331	1.15	(1.00–1.32)	0.057	145 555	1.01	(0.83–1.21)	0.957
Other‡	69 825	1.16	(0.98–1.38)	0.082	68 395	1.16	(0.93–1.45)	0.197
Mode of delivery								
Vaginal	273 990	1.00			268 589	1.00		

Table 3c. *(Continued)*

	Term boys 37^{+0}–41^{+6} weeks (n = 1182/N = 324 684)				Term girls 37^{+0}–41^{+6} weeks (n = 653/N = 314 340)			
	n	HR	(95% CI)	P	n	HR	(95% CI)	P
Caesarean section	50 518	**1.20**	**(1.02–1.42)**	0.028	45 559	**1.36**	**(1.09–1.68)**	0.006
Newborn								
Gestational weight				<0.001				<0.001
SGA	5926	**1.95**	**(1.45–2.61)**	<0.001	5774	**3.17**	**(2.28–4.40)**	<0.001
LGA	8854	0.69	(0.47–1.02)	0.065	8906	0.88	(0.55–1.39)	0.580
AGA	309 904	1.00			299 660	1.00		
Birth weight ≤ 1500 g								
No	324 585	1.00			314 234	1.00		
Yes	7	a			6	a		
Apgar 1 min								
≥4	321 080	1.00			311 627	1.00		
< 4	3180	**1.73**	**(1.16–2.59)**	0.008	2214	**1.91**	**(1.08–3.39)**	0.027
Umbilical artery pH				0.648				0.639
7.05 or more	176 821	1.00			168 656	1.00		
<7.05	2556	1.21	(0.73–2.02)	0.461	2175	0.651	(0.26–1.62)	0.356
Not known	145 307	1.04	(0.92–1.18)	0.523	143 509	0.98	(0.83–1.15)	0.778
Admission to neonatal unit								
No	300 487	1.00			295 988	1.00		
Yes	24 195	**1.83**	**(1.48–2.26)**	<0.001	18 351	**1.96**	**(1.47–2.62)**	<0.001
Ventilator								
No	323 675	1.00			313 526	1.00		
Yes	1009	1.66	(0.91–3.04)	0.100	814	1.55	(0.68–3.56)	0.300
Resuscitation at birth								
No	323 543	1.00			313 403	1.00		
Yes	1141	1.50	(0.81–2.78)	0.198	937	1.38	(0.60–3.21)	0.450
Phototherapy								
No	309 504	1.00			302 916	1.00		
Yes	15 180	1.26	(0.92–1.72)	0.157	11 424	0.80	(0.48–1.32)	0.377
Antibiotic therapy								
No	314 273	1.00			307 126	1.00		
Yes	10 411	1.20	(0.87–1.66)	0.276	7214	1.13	(0.70–1.83)	0.611
Respiratory distress syndrome (P22.0/769)†								
No	324 526	1.00			314 257	1.00		

Table 3c. *(Continued)*

	Term boys 37^{+0}–41^{+6} weeks (n = 1182/N = 324 684)				Term girls 37^{+0}–41^{+6} weeks (n = 653/N = 314 340)			
	n	HR	(95% CI)	P	n	HR	(95% CI)	P
Yes	158	0.60	(0.08–4.36)	0.609	83	1.76	(0.24–13.1)	0.581
Sepsis (P36.0–8/771.81)[†]								
No	321 422	1.00			312 018	1.00		
Yes	3262	0.60	(0.33–1.11)	0.103	2322	0.92	(0.43–1.97)	0.819
Intracranial haemorrhage (P52.0–9/772.1)[†]								
No	324 591	1.00			314 301	1.00		
Yes	93	0.96	(0.13–6.94)	0.970	39	**13.6**	**(4.19–44.3)**	<0.001
Convulsions (P90/779.0)[†]								
No	324 404	1.00			314 180	1.00		
Yes	280	**3.99**	**(2.07–7.70)**	<0.001	160	**9.72**	**(4.60–20.5)**	<0.001
Hyperbilirubinemia (P59.0–9/774)[†]								
No	311 743	1.00			304 796	1.00		
Yes	12 941	1.12	(0.80–1.57)	0.525	9544	1.52	(0.92–2.51)	0.101

Cox hazard regression multivariate models were used, with results given as the hazard ratios (HR) and 95% confidence intervals (CI) using reference category no ID for ID group (mild, moderate, severe or unspecified ID).

Statistically significant ($P < 0.050$) hazard ratios with 95% confidence intervals were **bolded**. Categories of missing values were not shown.

Proportional-hazards assumptions were tested based on Schoenfeld residuals:

$P = 0.152$ boys.

$P = 0.114$ girls.

a = Cannot be computed due to the small number of cases.

[†]Associated ICD-10 and ICD-9 codes (ICD-10/ICD-9).

[‡]Regional hospital, private hospital, health centre, home birth.

AGA, appropriate for gestational age; ID, intellectual disability; ICD, International Classification of Disease; LGA, large for gestational age; SGA, small for gestational age.

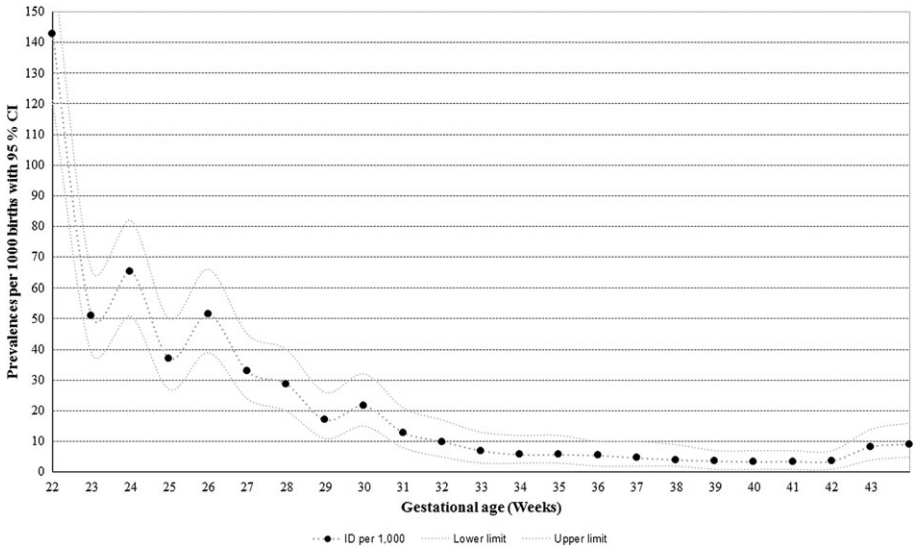

Figure 1 Prevalences of intellectual disability (n = 3814) per 1000 births by gestational age; birth years 1991–2008 (n = 1 018 256). Cochran–Armitage trend test, $P < 0.001$.

time between 2004 and 2010 in children aged 3–17 years (Lai *et al.* 2012).

Disability allowances indicate that a child needs long-term care or rehabilitation as a result of ID. In our cohort, nearly half of the ID cases in the VP group received disability allowance because of ID, but the proportion was only a quarter of ID cases in other GA groups. This trend was not seen in reimbursements for medication. The overall low percentages of disability allowances may be due the fact they were granted for comorbid reasons. The prevalence of ID was higher in the VP group. It is possible that prematurely born infants are followed up more closely and a diagnosis of ID is more readily considered. Comorbidity related to ID (e.g. cerebral palsy) might also have been taken into account in the granting process. In this light, it reminds us that disabilities arising from prematurity and in the perinatal period may have life-long consequences at public health level, shown as an increased need of resources in healthcare and rehabilitation.

Intracranial haemorrhage was strongly associated with an increased risk of ID, and a five-fold risk was detected in the MP and LP groups. In Finland, intracranial haemorrhages are diagnosed by brain US and confirmed by magnetic resonance imaging in neonates. Information on the severity of intracranial haemorrhages was not available in our population. Severe brain injury and impaired brain growth due to apoptosis, visible in brain imaging, have earlier been associated with adverse cognitive development in very preterm infants (Kidokoro *et al.* 2014). A recent meta-analysis suggested an association also between relatively mild intraventricular haemorrhages and neurodevelopmental impairment in infants born at less than 34 weeks' GA (Mukerji *et al.* 2015). Our finding of an association between low Apgar scores and ID is in accord with the results of previous studies (Camp *et al.* 1998; Stromme 2000; Bilder *et al.* 2013). A low umbilical artery pH was associated with an increased risk of ID only in the LP group. These findings may suggest that brain injury originating in the perinatal period, foetal distress and asphyxia at birth together constitute a prominent aetiological pathway to ID in cases without significant congenital anomalies. Preventive strategies concerning intraventricular haemorrhages are of prime importance to improve neurodevelopmental outcomes. New neuroprotective agents are under investigation and treatment protocols, for example delayed clamping of the umbilical cord, may have beneficial effects in reducing the incidence of intraventricular haemorrhages (Rabe *et al.* 2012).

In the VP, LP and term groups, SGA infants had an increased risk of ID. We excluded infants with known biomedical causes of ID such as major anomalies or

chromosomal defects, although some genetic conditions may not be identifiable as such at birth. Exposure to suboptimal intrauterine nutrition affects brain growth and might lead to long-term adverse consequences in cognition. On the other hand, SGA infants are prone to severe and prolonged hypoglycaemia, which has been suggested to be a risk factor as regards compromised neurodevelopmental outcome (Lucas *et al.* 1988). In an Australian study involving 2625 children with ID of unknown cause born between 1983 and 1992 and 217 252 children without ID, severe growth restriction (<75% of optimal birth weight) was associated with mild to moderate ID among preterm (<37^{+0} weeks) and term births (Leonard *et al.* 2008).

Maternal smoking predicted ID in the LP- and term-born children. An association between maternal smoking during pregnancy and ID has been suggested earlier (Drews *et al.* 1996; Braun *et al.* 2009), but there are also studies with contrasting results. In Finland, smoking is more common among women with fewer years of education and/or with a lower socio-economic status. This can partly explain the poorer cognitive outcome of the offspring. Smoking might also be associated with other forms of health behaviour that could have an adverse effect on the foetus. Maternal smoking causes intrauterine hypoxia and intrauterine growth retardation, both having adverse effects on neurodevelopmental outcome. There was a significant difference in the frequency of infants born SGA in our cohort among smoking vs. non-smoking mothers, possibly suggesting a common aetiological pathway between smoking, intrauterine growth retardation and neurodevelopmental disabilities. These issues should be included in counselling against smoking in pregnant women.

The strengths of this study are reliable and large population-based register data and the substantial number of infants, including all live births in the country. The national health registers in Finland are well established and validated. By combining the data of several national registers, the prevalence estimates of ID are more reliable than in cohort studies and simple register-based surveys (Westerinen *et al.* 2007). Data collection and reporting to register-keeping authorities are mandatory for healthcare providers. All ID diagnoses among children in Finland are made in public hospitals in special healthcare facilities, and they are based on validated neuropsychological tests. ID is not based on a single evaluation. Developmental follow-up with psychological reassessments is needed to determine a child's developmental course, and to differentiate between global developmental delay and ID. There is a possibility of maturational catch-up in those preterm children with developmental delay as opposed to more permanent ID. We also excluded children with major congenital anomalies and chromosomal defects, which are significant confounders when seeking risk factors of ID related to the perinatal period and prematurity.

A limitation of our study includes absence of data on socioeconomic status and educational level. In register studies, recording practices may vary between regions and time periods. The ICD version changed during the study period. However, IQ levels in ID subcategories remained constant. Data on several potential factors associated with ID were reliably available from registers only from 1996 onwards, and therefore we had to conduct the risk factor analysis to cover 1996–2008. Data on chorioamnionitis and antenatal viral infections could not be reliably detected in the registers. Data on antenatal corticosteroids were registered from 2004 onwards, and we had to exclude it from the multivariate model, because the follow-up period of four years would have been too short, taking into account the fact that the median age at diagnosis of ID was 5.7–6.3 years. It must be kept in mind that in this large amount of register-based data, some significant unknown confounders may have affected our results.

A broad range of variables was included in the analysis, because in a large population, less well-known risk factors of ID can also be detected. Only variables that have been reliably recorded with very low amount of missing or false data with good validity in the registers were chosen for analysis. However, in a huge sample size, very small differences might be statistically significant without being clinically relevant.

Conclusions

The findings in this study indicate that the prevalence of ID decreased with increasing GA up to term. The prevalence of ID did not seem to increase with time. Instead, a slightly decreasing trend in prevalence with time was seen. Nearly half of the VP infants received

disability allowance compared with a quarter of the children in other GA groups. In infants without congenital anomalies or chromosomal defects, MP and LP births were not independent risk factors of ID. Several peri- and neonatal factors were associated with an increased risk of ID, the most prominent factors indicating brain injury. Intrauterine growth retardation and maternal smoking also play important roles as risk factors of ID. Improving peri- and prenatal care in order to detect foetal problems early and to prevent asphyxia seems to be important means to prevent ID in offspring.

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of prematurity as well as prenatal and neonatal factors which may be associated with the underlying epileptogenic mechanisms of childhood epilepsy.

2. Patients and methods

2.1. Cohort

Data on all infants born in Finland between years 1991–2008 were collected from Medical Birth Register (MBR) (n = 1 039 263). This register is maintained by the National Institute for Health and Welfare (THL) and contains data from maternity hospitals and home births, Population Information System of the Population Register Centre and Statistics Finland. The data collection and reporting to the recordkeeping authority is mandated by the Finnish legislation (Act on National Personal Data Registers Kept under the Health Care System). The MBR collects data on all live births and stillbirths with a birth weight 500 g or more or gestational age of 22 weeks or more. The data includes information about the mother, her previous and present pregnancies and deliveries as well as about the infant until the age of seven days. MBR is well-established and validated and the data has been shown to be reliable in register studies (Gissler et al., 1995; Gissler and Shelley, 2002).

Infants with missing data on GA (n = 5520, 0.53%) were excluded and the remaining 1,033,349 children (99.4% of all) constituted the cohort for analysis. Children were analyzed in four groups according to GA as follows: very preterm (VP) ($< 32^{+0}$ weeks, n = 7657), moderately preterm (MP) (32^{+0}–33^{+6} weeks, n = 6971), late preterm (LP) (34^{+0}–36^{+6} weeks, n = 40,621) and term (37^{+0} weeks or more, n = 978,100). The term group also included post-term infants (42^{+0} weeks or more, n = 47,875). The GA was based on early pregnancy ultrasound and correction of GA was made if the estimation had a discrepancy of 5–7 days or more compared to last menstrual period. Three different time periods (birth years 1991–1995, 1996–2001 and 2002–2008) were compared. These periods were chosen because Finland changed the classification system of diseases from the International Classification of Diseases, 9th Revision (ICD-9) to the 10th Revision (ICD-10) in 1996 and the MBR changed the data collection forms on 1.10.1990 and 1.1.1996. The cohort also included children with congenital malformations (12,928 children, 1.25% had at least one major malformation).

2.2. Outcome definition and data collection

In Finland, epilepsy is diagnosed by a pediatric neurologist in pediatric neurology units within public health care according to national Current Care Guidelines. According to these national evidence-based clinical practice guidelines, any type of seizure disorder or suspicion of epilepsy is an indication for referral to a pediatric neurology unit. The diagnosis is based on medical history and clinical examination, supplemented with EEG, brain imaging and laboratory tests (A working group appointed by the Finnish Medical Society Duodecim and the Finnish Association of Paediatric Neurology).

Diagnoses of epilepsy were obtained from the Hospital Discharge Register (HDR), the Care Register for Health Care (CRHC) and the registers of Social Insurance Institution (SII). HDR has data on patients discharged from hospitals between years 1969 and 1993 and it was replaced with CRHC from the year 1994 onwards. These registers are maintained by THL and they contain information on admission and discharge, diagnoses, procedures and interventions and they are considered to be reliable (Sund, 2012). Diagnoses are coded according to the ICD-9 in 1987–1995 and according to ICD-10 from 1996. A case with epilepsy was detected from the HDR and CRHC with corresponding ICD-codes: ICD-9: 345 and ICD-10: G40–41 as shown to be a reliable means in register studies (Jette et al., 2010; St Germaine-Smith et al., 2012). SII keeps nationwide drug reimbursement registry of refundable drugs, including antiepileptic drugs. Reimbursements for medicine expenses can be granted for children who require long-term antiepileptic therapy after epilepsy diagnosis based on medical investigations and evaluations by pediatric neurologists. Children under 16 years of age with chronic diseases can also be granted disability allowance and this can be traced from the registers of SII. The main outcome, epilepsy, was recorded if the child was detected in at least one of these above mentioned registers by the age of seven years or by the year 2009. The age at diagnosis of epilepsy was defined when the first detection in either of these registers occurred.

2.3. Data linkages and covariates

Data from MBR, HDR, CRHC, Register of Congenital Malformations and from the register of SII were linked with anonymized unique personal identity codes by recordkeeping authorities. Children were followed to the age of seven years or up to the year 2009.

Small for GA (SGA) infants were defined as those with a birth weight of less than two standard deviations (SDs) below the mean weight for GA and large for GA (LGA) infants as those with a birth weight of more than two SDs over the mean weight for GA according to the Finnish gender-specific fetal growth curves (Pihkala et al., 1989). Data on Apgar scores at five minutes of age were not available from the database throughout the study period. Resuscitation included intubation and/or chest compressions in the delivery-unit and mechanical ventilation included invasive ventilation during the first week of life. Antibiotic therapy was recorded if it was established during the first week of life. Data on blood culture proven sepsis (ICD-10: P36.0-8), intracranial hemorrhages (ICD-10: P52.0-9), convulsions in the neonatal period (ICD-10: P90) and hyperbilirubinemia (ICD-10: P59.0-9) were tracked according the corresponding ICD-10 codes. These codes were available from the year 1996 onwards and therefore the multivariate model for risk factor analysis for epilepsy included the children born in 1996–2008. Historically neonatal seizures were often diagnosed according to clinical symptoms and this might have led to high rates of false positive and false negative diagnoses. Contemporary diagnosis of neonatal convulsions is based on confirmatory electroencephalographic findings. Respiratory distress syndrome (RDS) (ICD-10: P22.0) was diagnosed with respiratory distress, need of supplemental oxygen and surfactant treatment and typical changes in the chest radiograph. Data on antenatal steroids and preeclampsia were excluded from the analysis, since these items were not registered before the year 2004. Umbilical artery pH was not systemically recorded in the birth hospitals during the whole study period.

2.4. Statistical analysis

Statistical analyses were performed on IBM SPSS Statistics version 23 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Mann-Whitney test, Chi-square test or Fisher's exact test were used in group comparisons, as appropriate, and P-values less than 0.001 were considered statistically significant (Tables 1 and 2). Risk factors for epilepsy were sought by Generalized Linear Mixed Model (Tables 3a and 3b). Results were presented as odds ratios (OR) with 95% confidence intervals (CI). The adjusted analysis for all infants born in 1996–2008 was accompanied with random effects of the number of deliveries per mother and the number of newborns per birth to correct the non-independence of twins or higher-order multiples. To take into account number of deliveries or fetuses by one mother, Generalized Linear Mixed Model with an *lmer* function was used. A binary response (epilepsy yes vs no) was used as a dependent variable showing results by ORs with 95% CIs. All included explanatory variables are shown in Tables 3a and 3b. They were modeled as a fixed variable, and the number of deliveries per mother and the numbers of fetuses per delivery were added as random effect. The association between GA and epilepsy was studied by adjusting the multivariate model by gestational week categories, using term category as reference. The

Table 1
Characteristics of live born infants and their mothers. Years 1991–2008 (N = 1,033,349).

	Very preterm < 32 wk (n = 7657)		Moderately preterm 32^{+0}–33^{+6} wk (n = 6971)		Late preterm 34^{+0}–36^{+6} wk (n = 40,621)		Term ≥37 wk (n = 978,100)		p^1 VP vs. T	p^2 MP vs. T	p^3 LP vs. T
Study period, years									0.031	0.005	< 0.001
1991–1995, n (% of infants in period)	2300	(0.73)	2003	(0.64)	11,959	(3.81)	297,235	(94.8)			
1996–2001	2568	(0.77)	2338	(0.70)	13,631	(4.09)	314,526	(94.4)			
2002–2008	2789	(0.72)	2630	(0.68)	15,031	(3.89)	366,339	(94.7)			
Mother											
Age, Mean (Sd)	30.2	(5.8)	29.8	(5.7)	29.7	(5.6)	29.2	(5.3)	< 0.001	< 0.001	< 0.001
Smoking, n (%)	1433	(18.7)	1211	(17,4)	6707	(16.5)	145,712	(14.9)	< 0.001	< 0.001	< 0.001
Primipara, n (%)	3973	(51.9)	3855	(55.3)	20,268	(49.9)	396,376	(40.5)	< 0.001	< 0.001	< 0.001
Earlier deliveries, Md (IQR)	0	(0–1)	0	(0–1)	1	(0–1)	1	(0–2)	< 0.001	< 0.001	< 0.001
Pregnancy											
Number of fetuses at birth, n (%)									< 0.001	< 0.001	< 0.001
1	5410	(70.7)	4696	(67.4)	31,589	(77.8)	961,325	(98.3)			
2	2081	(26.4)	2010	(28.8)	8711	(21.4)	16,765	(1.7)			
3 or 4	229	(3.0)	265	(3.8)	321	(0.8)	19	(< 0.1)			
Delivery											
Place of birth, n (%)									< 0.001	< 0.001	< 0.001
University hospital (level III)	5933	(77.5)	4097	(58.8)	17,497	(43.1)	304,225	(31.1)			
Central hospital (level II)	1632	(21.3)	2793	(40.1)	17,824	(43.9)	450,378	(46.0)			
Other[a]	85	(1.1)	81	(1.2)	5297	(13.0)	223,366	(22.8)			
Mode of delivery, n (%)									< 0.001	< 0.001	< 0.001
Vaginal	3272	(42.7)	3277	(47.0)	27,122	(66.8)	831,799	(85.0)			
Cesarean section	4360	(56.9)	3689	(52.9)	13,466	(33.2)	145,519	(14.9)			
Newborn											
Boys, n (%)	4227	(52.4)	3838	(47.6)	22,025	(54.2)	496,796	(50.8)	< 0.001	< 0.001	< 0.001
Birth weight, g, Md (IQR)	1200	(865–1520)	1970	(1730–2200)	2670	(2358–2990)	3590	(3280–3910)	< 0.001	< 0.001	< 0.001
< 1500 g	5642	(73.7)	748	(10.7)	264	(0.6)	26	(< 0.1)	< 0.001	< 0.001	< 0.001
1500 g or more	1996	(26.1)	6215	(89.2)	40,336	(99.3)	977,816	(100)			
Weight by gestational age, n (%)									< 0.001	< 0.001	< 0.001
SGA	1256	(16.4)	898	(12.9)	3311	(8.2)	16,900	(1.7)			
AGA	5629	(73.5)	5783	(83.0)	35,262	(86.8)	932,147	(95.3)			
LGA	316	(4.1)	290	(4.2)	2048	(5.0)	29,053	(3.0)			
Apgar 1 min, Md (IQR)	6	(4–8)	8	(7–9)	9	(8–9)	9	(9–9)	< 0.001	< 0.001	< 0.001
Apgar 1 min < 4, n (%)	1787	(23.3)	360	(5.2)	936	(2.3)	7723	(0.8)	< 0.001	< 0.001	< 0.001
Admission to neonatal unit, n (%)	6594	(86.1)	6121	(87.8)	19,521	(48.1)	59,389	(6.1)	< 0.001	< 0.001	< 0.001
Ventilator, n (%)	4351	(56.8)	1481	(21.2)	1733	(4.3)	2970	(0.3)	< 0.001	< 0.001	< 0.001
Resuscitation at birth, n (%)	2505	(32.7)	679	(9.7)	848	(2.1)	3259	(0.3)	< 0.001	< 0.001	< 0.001
Antibiotic therapy, n (%)	5117	(66.8)	3036	(43.6)	5157	(12.7)	24,264	(2.5)	< 0.001	< 0.001	< 0.001
Sepsis, n (%)	476	(6.2)	246	(3.5)	714	(1.8)	6140	(0.6)	< 0.001	< 0.001	< 0.001
Intracranial hemorrhage, n (%)	380	(5.0)	108	(1.5)	83	(0.2)	143	(< 0.1)	< 0.001	< 0.001	< 0.001
Convulsions, n (%)	24	(0.3)	4	(0.1)	34	(0.1)	482	(< 0.1)	< 0.001	0.592	0.003
Hyperbilirubinemia, n (%)	1512	(19.7)	1824	(26.2)	8208	(20.2)	23,307	(2.4)	< 0.001	< 0.001	< 0.001
Major congenital anomaly, n (%)	131	(1.7)	107	(1.5)	572	(1.4)	12,118	(1.2)	< 0.001	0.026	0.003
Death by 7 years of age, n (%)	1246	(16.3)	75	(1.1)	158	(0.4)	1425	(0.1)	< 0.001	< 0.001	< 0.001
Age of death, years, Md (IQR)	0.00	(0.00–0.01)	0.01	(0.00–0.11)	0.15	(0.01–0.76)	0.71	(0.13–2.86)	< 0.001	< 0.001	< 0.001

Statistical differences were tested by Pearson chi-square test or Fisher's exact or by Mann-Whitney test:
p^1 = *Very preterm vs. Term,* p^2 = *Moderately preterm vs. Term,* p^3 = *Late preterm vs. term.*
P-values < 0.001 were considered statistically significant.
AGA = appropriate for gestational age; IQR = interquartile range; LGA = large for gestational age; LP = late preterm; Md = median; MP = moderately preterm; Sd = standard deviation; SGA = small for gestational age; T = term; VP = very preterm.
[a] Regional hospital, private hospital, health center, home birth.

generalized linear mixed model analyses were performed with the Statistical Package R version 3.3.0 package lme4 (www.r-projcet.org). All P values are two-tailed. Cochran-Armitage trend test were used to test trend for number of epilepsy related to no epilepsy cases according to GA. Trend test was carried out with StatXact-4 version 4.0.1 (Cytel Software Corporation). P-values less than 0.05 were considered statistically significant

Table 2
Diagnoses of epilepsy in live born children between years 1991–2008 (N = 1,033,349).

	Very preterm < 32 wk (n = 7657)		Moderately preterm 32^{+0}–33^{+6} wk (n = 6971)		Late preterm 34^{+0}–36^{+6} wk (n = 40,621)		Term ≥37 wk (n = 978,100)		Total (n = 1,033,349)		P^1 VP vs. T	P^2 MP vs. T	P^3 LP vs. T
Epilepsy total, n (% of children in GA group)[a]	194	(2.53)	75	(1.08)	306	(0.75)	5036	(0.51)	5611	(0.54)	< 0.001	< 0.001	< 0.001
Years, n (% of study period in GA group)													
1991–1995	69	(3.0)	25	(1.2)	100	(0.8)	1653	(0.6)	1847	(0.60)			
1996–2001	82	(3.2)	28	(1.2)	127	(0.9)	1923	(0.6)	2160	(0.65)			
2002–2008	43	(1.5)	22	(0.8)	79	(0.5)	1460	(0.4)	1604	(0.41)			
The age at diagnosis (years), Md (IQR)	2.4	(0.5–4.1)	2.7	(0.6–4.6)	2.7	(0.7–4.7)	2.8	(1.0–4.8)					

GA = gestational age; IQR = Interquartile range; Md = median.
Statistical differences were tested by Pearson chi-square test or Fisher's exact or by Mann-Whitney test:.
p^1 = *Very preterm vs. term.*
p^2 = *Moderately preterm vs. term.*
p^3 = *Late preterm vs. term.*
P-values < 0.001 were considered statistically significant.
[a] Hospital Discharge register and/or Social Insurance Institution.

in multivariate model.

3. Results

Characteristics of infants and their mothers are shown in Table 1. The MP and LP infants accounted together for 86% of all prematurely born infants.

The overall cumulative incidence of epilepsy in the cohort was 0.54%. The incidence was lowest (0.41%) in the last study period, between years 2002–2008. The incidence in the VP group was about five times higher and in the MP group two times higher than in the term group and it decreased nonlinearly with increasing GA and appeared to increase after 41 gestational weeks. (Table 2, Fig. 1) The steepest decline in the incidence occurred between 27 and 28 gestational weeks. The incidence was lowest between weeks 38^{+0} and 40^{+6} (0.51%) and there were 257 children among post-term (42^{+0} weeks or more) children with diagnosed epilepsy (0.54%). The median age at the epilepsy diagnosis was between 2.4 and 2.8 years according to GA group.

In addition to intracranial hemorrhages and convulsions, mother's smoking during pregnancy, birth in other than university hospital, cesarean section, being born SGA, one-minute Apgar score less than four, admission to neonatal unit, ventilator treatment, antibiotic treatment during the neonatal period and a major congenital anomaly were also statistically significant predictors of epilepsy in the risk factor analysis of the whole cohort born in the years 1996–2008. Instead, female sex, hyperbilirubinemia and sepsis appeared to decrease the risk of epilepsy (Tables 3a and 3b).

In GA-group adjusted multivariate model VP, MP and LP births were associated with an increased risk of epilepsy compared to the term group while post-term birth did not predict the risk of epilepsy (Table 3a).

4. Discussion

In this large national cohort the overall incidence of epilepsy was 0.54% and it decreased with increasing GA up until 41 gestational weeks. Intracranial hemorrhages and neonatal convulsions were strongly associated with an increased risk of epilepsy. Preterm birth was associated with an increased risk of epilepsy.

4.1. Strengths and limitations

The main strength of this study is the large national cohort with a substantial number of infants. National health registers in Finland are validated high-quality registers (Gissler et al., 1995; Gissler and Shelley, 2002). Epilepsy is diagnosed according to national guidelines in public health care system in pediatric neurology units by medical specialists. In Finland public health care is available for all regardless of socioeconomic status. It is mandated by law that all health care providers report the collected health data to national recordkeeping authorities. Use of linked data of national medical registers has shown to be a reliable method to study health status in childhood (Gissler et al., 1998). We tracked epilepsy-diagnoses from the database by using ICD-9 (345) and ICD-10 (G40-41) codes which have shown to have good to excellent coding accuracy to study neurologic conditions in health register studies (St Germaine-Smith et al., 2012).

Limitations of this study include the lack of seizure/epilepsy type/syndrome sub-classifications because we included all epilepsy subclasses as recommended by the systematic review for optimal ICD-codes for studying neurologic conditions (St Germaine-Smith et al., 2012). Recording practices of administrative databases may also have variations between time periods and regions and unknown confounding factors may exist affecting our results. Register data may also underestimate the true incidence of epilepsy. Several potential risk factors for epilepsy, used as covariates in the multivariate analysis, were reliably recorded only from the year 1996 onwards and thus, we had to exclude the first time period (years 1991–1995) from the multivariate model. The follow-up time in the last time-period (years 1996–2008) was probably too short for some of the children to allow making further conclusions of the trends of the incidence of epilepsy between three different time periods, taking into account that the median age at the diagnoses was 2.4–2.8 years according to GA group. Our data did not include information on parents' socioeconomic status or on mother's epilepsy.

4.2. Incidence of epilepsy

The incidence of epilepsy has been shown to be high in young children and decline by the age in both childhood and adulthood increasing again in the elderly (Sillanpaa et al., 2006, 2011). The prevalence of childhood epilepsy in population based studies in Finland and Japan has been reported to be 0.39% and 0.53% respectively (Eriksson and Koivikko, 1997; Oka et al., 2006). In a large US-based

Table 3a
Risk factor analysis for epilepsy (n = 3764) as a function of gestational age considering maternal, pregnancy, delivery and sex variables as potential confounders. Years 1996–2008 by random effect of the number of deliveries per mother and the number of fetuses per delivery (N = 719,852).

	All children (n = 3764/N = 719,852)			P
	n	OR	(95% CI)	
Mother				
Age (years)				
< 40	704,927	1.00		
40 or more	14,925	1.21	(0.99–1.48)	0.056
Smoking				
No	596,374	1.00		
Yes	105,496	**1.11**	**(1.01–1.21)**	0.025
Primipara				
No	421,234	1.00		
Yes	298,618	0.95	(0.88–1.02)	0.126
Previous caesarean section				
No	660,050	1.00		
Yes	59,802	1.12	(0.99–1.26)	0.063
Pregnancy				
Number of fetuses				
1	698,011	1.00		
2 or more	21,841	0.82	(0.64–1.06)	0.128
Order of fetuses				
A	708,904	1.00		
B or C	10,948	0.94	(0.67–1.31)	0.714
Delivery				
Time of birth				
Mon–Fri 08.00–15.59	221,231	1.00		
Mon–Fri 16.00–07.59	326,853	1.07	(0.99–1.16)	0.080
Weekend	171,768	1.04	(0.95–1.14)	0.351
Place of birth				
University hospital	239,393	1.00		
Central hospital	330,063	**1.20**	**(1.12–1.30)**	< 0.001
Other[a]	150,316	1.09	(0.99–1.19)	0.085
Mode of delivery				
Vaginal	600,553	1.00		
Cesarean section	118,887	**1.30**	**(1.19–1.42)**	< 0.001
Newborn				
Sex				
Boy	367,412	1.00		
Girl	352,440	**0.90**	**(0.84–0.96)**	0.001
Gestational age group				
Term (37^{+0}–41^{+6} weeks)	647,551	1.00		
Very Preterm	5357	**4.59**	**(3.79–5.57)**	< 0.001
Moderately Preterm	4968	**1.97**	**(1.48–2.63)**	< 0.001
Late Preterm	28,662	**1.44**	**(1.25–1.68)**	< 0.001
Post-term (≥42^{+0} weeks)	33,314	0.99	(0.85–1.16)	0.944

Multivariate Generalized Linear Mixed Model was used, with results given as the risk ratios (OR) and 95% confidence intervals (CI).
Statistically significant (p < 0.050) odds ratios with 95% confidence intervals were **bolded**. Categories of missing values were not shown.
[a] Regional hospital, private hospital, health center, home birth.

Table 3b
Risk factor analysis for epilepsy (n = 3764) as a function of gestational age considering newborn variables as contributing factors. Years 1996–2008 by random effect of the number of deliveries per mother and the number of fetuses per delivery (N = 719,852).

	All children (n = 3764/N = 719,852)			P
	n	OR	(95% CI)	
Newborn				
Gestational weight				
SGA	15,950	**1.30**	**(1.09–1.54)**	0.003
LGA	20,944	1.02	(0.85–1.23)	0.825
AGA	682,633	1.00		
Apgar 1 min				
4–10	710,393	1.00		
0–3	8197	**1.82**	**(1.52–2.19)**	< 0.001
Admission to neonatal unit				
No	650,449	1.00		
Yes	69,399	**1.58**	**(1.41–1.78)**	< 0.001
Ventilator				
No	712,560	1.00		
Yes	7292	**1.87**	**(1.48–2.36)**	< 0.001
Resuscitation at birth				
No	714,842	1.00		
Yes	5010	1.05	(0.82–1.34)	0.705
Antibiotic therapy				
No	689,925	1.00		
Yes	29,927	**1.25**	**(1.06–1.47)**	0.008
Sepsis (P36.0 − 8)[a]				
No	712,276	1.00		
Yes	7576	**0.70**	**(0.53–0.91)**	0.009
Intracranial hemorrhage (P52.0 − 9)[a]				
No	719,138	1.00		
Yes	714	**3.48**	**(2.47–4.89)**	< 0.001
Convulsions (P90)[a]				
No	719,308	1.00		
Yes	544	**13.4**	**(10.2–17.6)**	< 0.001
Hyperbilirubinemia (P59.0 − 9)[a]				
No	685,001	1.00		
Yes	34,851	**0.83**	**(0.71–0.96)**	0.014
Congenital anomaly				
No	710,855	1.00		
Yes	8998	**1.55**	**(1.23–1.96)**	< 0.001
Gestational age group				
Term (≥37^{+0} weeks)	680,865	1.00		
Very Preterm	5357	**1.32**	**(1.02–1.70)**	0.030
Moderately Preterm	4968	0.98	(0.73–1.33)	0.906
Late Preterm	28,662	1.07	(0.92–1.25)	0.388

Multivariate Generalized Linear Mixed Model was used, with results given as the risk ratios (OR) and 95% confidence intervals (CI).
Statistically significant (p < 0.050) odds ratios with 95% confidence intervals were **bolded**. Categories of missing values were not shown.
AGA = appropriate for gestational age; ICD = International Classification of Disease; LGA = large for gestational age; SGA = small for gestational age.
[a] Associated ICD-10 codes.

study the age-adjusted incidence of epilepsy was 44 per 100,000 person years being highest in the first year of life in 1935–1984 (Hauser et al., 1993). In the UK, a cohort-study of 15,496 children born in 1958 had 0.4% incidence of epilepsy by the age of 11 years (Ross et al., 1980). The overall incidence of 0.54% in our study is in accordance with earlier reports. It diminished with increasing GA up to 41 weeks. The incidence did not increase by time and the decrease was most evident between the last two time periods, probably due to a shorter follow-up time in the last time period.

4.3. Risk factors of epilepsy

VP, MP and LP births were independently associated with an increased risk of epilepsy compared to the birth in the term group. In a Swedish national cohort study of 630,090 infants born in 1973–1979 and followed by registers to the age of 25–37 years, LP birth predicted an increased risk of epilepsy as well (OR 1.76; 95%CI 1.30–2.38) and 0.70% of the whole cohort had been hospitalized due to epilepsy in lifetime (Crump et al., 2011). On the other hand, in a register study of 1.4 million children born in Denmark in 1979–2002 and followed up to 24 years of age, the incidence of epilepsy increased with decreasing gestational age and birth weight but no association was found between LP birth and epilepsy (Sun et al., 2008). Post-term birth (≥42 weeks of gestation) has been associated with an increased risk of epilepsy during the first year of life (Ehrenstein et al., 2007) but in our study no association was found.

Convulsions during the neonatal period strongly predicted a risk of

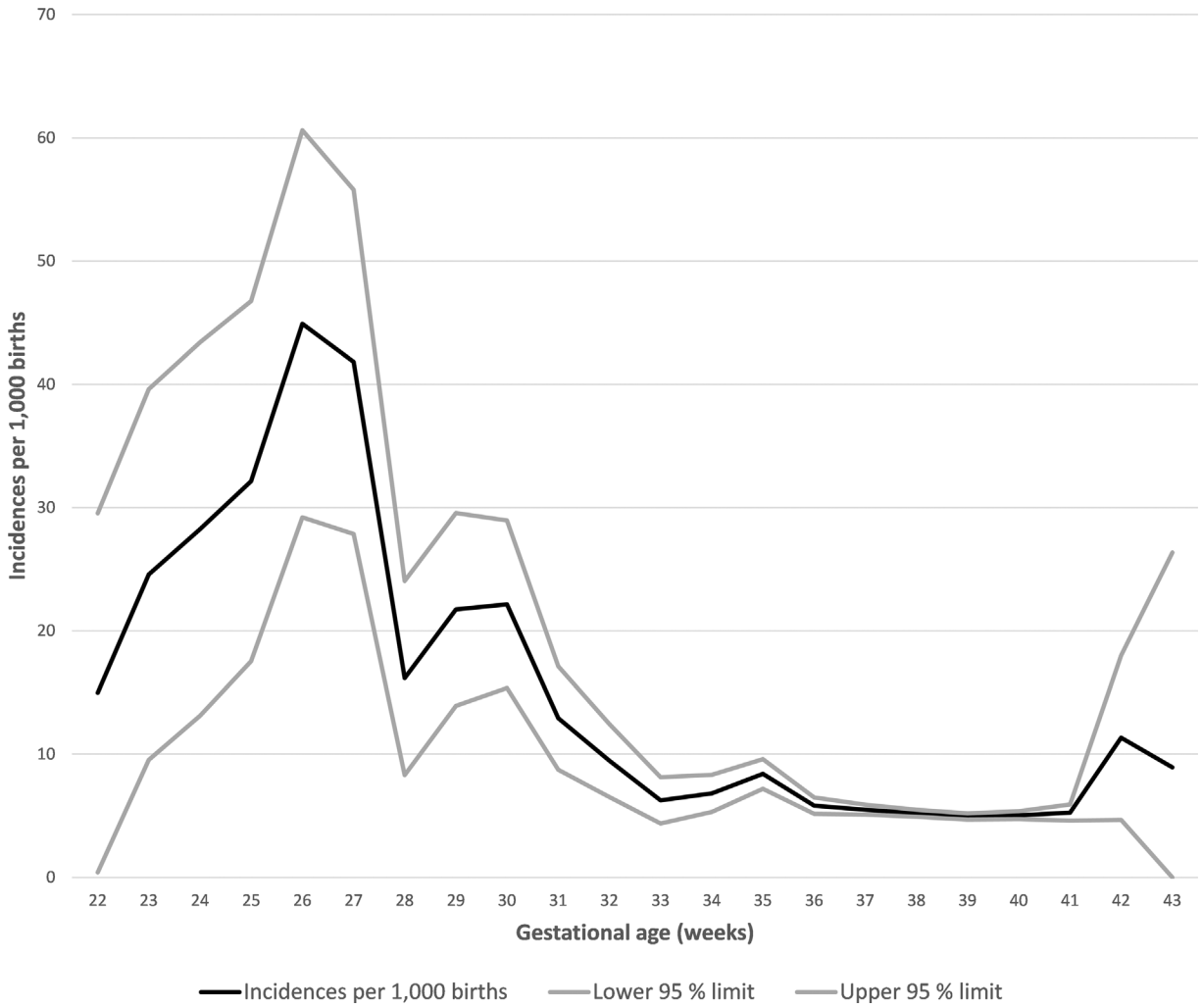

Fig. 1. Incidences of epilepsy (Hospital Discharge register and/or Social Insurance Institution; n = 5611) per 1000 births by gestational age, birth years 1991–2008 (N = 1,033,349).

childhood epilepsy. Most seizures in neonates are symptomatic and they indicate neurologic dysfunction. The etiology of seizures is the sole predictor for later outcome. In a Canadian population based study 88 children were followed after neonatal seizures and 24 (27%) of the survivors developed epilepsy later. Factors predictive of poor prognosis included severe encephalopathy, cerebral dysgenesis, intraventricular hemorrhage (IVH), infections, abnormal neonatal EEG and need for multiple drugs to treat the neonatal convulsions (Ronen et al., 2007). Hypoxic ischemic encephalopathy has been shown to be the most frequent cause of seizures in term born neonates accounting for 40% of the etiology of all neonatal seizures (Tekgul et al., 2006; Uria-Avellanal et al., 2013). In another Canadian report of 62 asphyxiated term born infants with neonatal seizures, 15 (24%) had later epilepsy with significant comorbidity to other neurodevelopmental disabilities (Garfinkle and Shevell, 2011).

Intracranial hemorrhages were associated with an increased risk of epilepsy. Subclasses of IVH were not available from our data, but on the other hand, according to a recent meta-analysis, poorer neurodevelopmental outcome was also associated with both severe and mild IVH (Mukerji et al., 2015). In accordance with our results, in a Canadian population-based cohort study of 124,207 live births between years 1986–2000 with 648 cases of epilepsy, neonatal IVH was associated with an increased risk of later epilepsy (RR 11.2; 95% CI 7.6–16.5) (Whitehead et al., 2006).

The adjusted analysis for all infants born in 1996–2008, presented inevitably mostly predictors of epilepsy in the children born at 37^{+0} weeks' gestation or more. By taking into account random effects of the number of deliveries per mother and the number of newborns per birth to correct the non-independence of twins or higher-order multiples, and by including major congenital anomalies as a covariate into the analysis, some additional risk factors of epilepsy and some protective factors were detected. Severe congenital anomalies seem to predispose to epilepsy regardless of the obvious diversity of the malformations. Intracranial hemorrhage and convulsions remained the strongest predictors of epilepsy in risk factor analyses. Surprisingly, sepsis was associated with a decreased risk of epilepsy in our analysis. We suspect that this is not a true association. The ICD 10 diagnosis requires that the pathogenic bacteria has been detected in blood cultures of the patient but the clinical criteria for sepsis have not been defined in this classification. Many of blood culture positive cases have only mild symptoms of infection and ruling out contamination in blood sampling relies on the discretion of the clinician. On the other hand in many cases of true sepsis the blood culture might remain negative because of problems in drawing reliable blood culture samples from a sick patient.

5. Conclusions

The overall cumulative incidence of epilepsy was 0.54% in this large national cohort and the incidence decreased with increasing gestational age. Preterm birth was associated with an increased risk of epilepsy compared to term infants. The most prominent factors predictive of an

increased risk of epilepsy were convulsions during neonatal period and intracranial hemorrhage. Factors indicating brain injury are of major importance when estimating the risk of epilepsy in later childhood after the neonatal period.

Conflicts of interest

None.

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