Early identification and intervention for infants at high risk of neurodevelopmental disorders

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LIST OF ABBREVIATIONS

AI	Asymmetry index
AIMS	Alberta Infant Motor Scale
AIS	Arterial ischemic stroke
Bayley-III	Bayley Scales of Infant and Toddler Development, third edition
BoHM	Both hands measure
BPD	Bronchopulmonary dysplasia
BSID-II	Bayley Scales of Infant Development, second edition
BW	Birthweight
CA	Corrected age
CI	Confidence interval
CIMT	Constraint induced movement therapy
CP	Cerebral palsy
CST	Corticospinal tract
CSVT	Cerebral Sinus Venous Thrombosis
cUS	Cranial ultrasound
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EaHS	Each hand sum score
ELBW	Extremely low birthweight
EPT	Extremely preterm
FM	Fidgety movements
GA	Gestational age
GM	General movements
GMA	General Movement Assessment
GMH	Germinal matrix hemorrhage
GMFCS	Gross motor function classification system

GMH-IVH	Germinal matrix hemorrhage - Intraventricular hemorrhage
HABIT	Hand-arm bimanual intensive training;
HAI	Hand Assessment for Infants
HINE	Hammersmith Infant Neurologic Examination
HS	Hemorrhagic stroke
IVH	Intraventricular hemorrhage
LBW	Low birthweight
M-ABC	Movement Assessment Battery for Children
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
OLs	Oligodendrocytes
PAIS	Perinatal Arterial Ischemic Stroke
PSOC	Parenting Sense of Competence scale
PTA	Post-term age
PVHI	Periventricular venous hemorrhagic infarction
PVL	Periventricular leukomalacia
RCT	Randomized controlled trial
SCPE	Surveillance of cerebral palsy in Europe
SD	Standard deviation
SGA	Small for gestational age
USCP	Unilateral spastic cerebral palsy
VLBW	Very-low-birthweight
VPT	Very preterm
WMI	White matter injury

INTRODUCTION

General introduction

Did you know that about 1 in 6 (17%) children has a developmental disability?[1]

Developmental disability is a broad term encompassing many different diagnoses. These conditions, predominantly associated with the functioning of the neurological system and brain, manifest during infancy or childhood and usually last through a person's lifetime. These are marked by delayed development or functional limitations in cognition, language, communication, behavior socialization or motor function. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[2] has defined this more specific as 'neurodevelopmental disorder' and classified it into several categories. This includes: intellectual disability, communication disorders, autism spectrum disorder, attention deficit hyperactivity disorder, specific learning disorder, and motor disorders, such as cerebral palsy (CP) and developmental coordination disorder. Vision and hearing impairments are also often considered as neurodevelopmental disorder.

Most neurodevelopmental disorders are caused by a complex mixture of factors, that may affect neurological function. This might be due to genetics, due to conditions occurring during pregnancy, such as malnutrition, infection or parental behavior (i.e. smoking, drugs and/or drinking alcohol during pregnancy,…) or due to perinatal and neonatal complications.

Neurodevelopmental problems due to injury that has occurred during the perinatal period can mainly be subdivided in 3 groups:

- Infants with congenital malformations, including syndromes, chromosomal and genetic defects and inborn errors of metabolism
- Infants that are born preterm and/or with low birth weight
- Infants with a hypoxic-ischemic insult and/or perinatal stroke

This doctoral thesis will focus on preterm birth and perinatal stroke, two main important perinatal causes of neurodevelopmental disorders. The first part of this general introduction provides an overall overview of preterm birth and its consequences. Definitions, incidence, pathophysiology and perinatal and long term consequences are described. The second part concentrates on perinatal stroke and its repercussion. An overview of definitions and classification, as well as the perinatal and long term morbidities are presented. Furthermore, the most common long term neurological impairment, i.e. unilateral CP, will be discussed in more detail. Clinical presentation of the upper limb deficits and reorganization will be outlined, as well as early diagnosis and early intervention. At the end of the general introduction, an overall background and gaps in the literature are provided, which will lead to the aims of this doctoral thesis.

PART I: Very preterm and very low birth weight infants

1. Definition

The world health organization[3] defines preterm birth as a birth before 37 weeks completed weeks of gestation or fewer than 259 days since the first day of the woman's last menstrual period. Preterm birth, can be further subdivided into:

- Moderate or late preterm : 32-36 weeks gestation
- Very preterm (VPT): 28-31 weeks gestation*
- Extremely preterm (EPT): before 28 weeks gestation

Another, classification can be made based on birth weight (BW). This is also defined by the WHO and includes following categories:

- Low BW (LBW): BW less than 2500g
- Very low BW (VLBW): BW less than 1500g*
- Extremely low BW (ELBW): BW less than 1000g

In addition, another useful term is "small for gestational age (SGA)", defined as a BW less than 10th percentile according to a given gestational age (GA) and gender.

*It is important to note that from now on in this dissertation, VPT/VLBW refers to all infants born before 32 weeks GA and BW less than 1500g, unless explicit distinction is made between VPT and EPT infants or between VLBW and ELBW infants.

2. Incidence

Preterm birth is a world-wide health challenge, affecting millions of children. Every year, an estimated 15 million babies are born preterm, affecting 11% of all livebirths worldwide.[4] The rate of preterm birth ranges from 13.4% in North Africa to 8.7% in Europe. The incidence of preterm birth is the highest in southeastern Asia, south Asia, and sub-Saharan Africa. Asian and the Sub-Saharan African countries together represent 78.9% of livebirths and 81.1% of preterm births worldwide.[5] Preterm birth in Europe represents proportionally 4.7% of all preterm births in the world.[5]

LBW is estimated to occur in more than 20 million infants each year, affecting approximately 15% to 20% of all births worldwide.[6]

Worldwide, the majority (84%) of the preterm deliveries occur in the moderate or late preterm period. Very preterm infants account for approximately 10% of all preterm birth and extremely preterm for 5%.[7]

In some northern European countries estimated rates are the lowest and vary around 5% preterm birth.[8] Belgian rates are slightly higher. In the Flemish region of Belgium 7.6% of the deliveries are preterm, of which 1.2% is very preterm (<32 weeks gestation) (Table 1).[9]

Table 1. The annual report of 2018 by the SPE (VZW Studiecentrum voor perinatale epidemiologie) gives some insight in perinatal epidemiology of the Flemish region of Belgium.[9]

Total mothers (n=62812)	**N**	**%**
Multiple birth	1024	1.6%
Conception		
Spontaneous	56711	90.3%
Assisted reproductive medicine	4539	7.2%
unknown	1562	2.5
Gestational age		
<28 weeks	310	0.5%
28-31 weeks	440	0.7%
32-36 weeks	4039	6.4%
≥ 37 weeks	58023	92.4%
Delivery		
Spontaneous	43800	68.6%
Vacuum extraction	5830	9.1%
Forceps	164	0.3%
Cesarean section	13922	21.8%
Breech vaginal	120	0.2%
Total babies (n=63836)	**N**	**%**
Birth weight		
500-1499g	767	1.2%
1500-2499g	3645	5.7%
≥2500g	59424	93.1%
Sexe		
Boys	32484	50.9%
Girls	31352	49.1%

Adapted from the annual report from 2018 from SPE[9]

The incidence of preterm births increased over the past decades.[10] For instance, in the United States, preterm birth rose with 20% between 1990 and 2006. Most of the rise resulted in late preterm infants, or between 34 and 36 weeks gestation.[11]

This overall increase can be explained by improved registration of preterm birth in lower to middle income countries, but also due to a real augmentation of preterm births in almost all countries. This is caused by numerous reasons, including increases in maternal age at first

delivery[12], use of reproductive assistance leading to more multiple pregnancy[13], and changes in obstetric practices, leading to more provider-initiated preterm births in moderate and late preterm infants.[14]

However, after this increasing trend, the incidences remained stable for a few years and then even decreased somewhat after 2006. For over 30 years, these was the first time that rates had fallen for 2 years in a row in the US [15]. Other developed countries have observed similar trends for comparable reasons.[8]

This drop in preterm birth may be explained by a more cautious use of assisted reproductive technologies, in combination with advances in prenatal diagnosis, obstetrics of high-risk pregnancies and neonatal care.[16]

3. Pathophysiology

3.1. Preterm birth

The etiology of preterm birth is complex and multifactorial. It is associated with the overall health care level, the quality of obstetrics and various gestational and maternal factors.[10]

The clinical presentation of preterm birth is commonly categorized as "spontaneous" or "indicated".[17] Most preterm births take place spontaneously, but in some cases preterm birth is due to early induction of labour or caesarean section, and this could be due to medical reasons, such as maternal or fetal indications, or non-medical reasons. The proportions of preterm birth by etiology are represented below, in Table 2.

Table 2. Proportions by etiology of preterm birth

Etiology	Frequency (%)
Spontaneous preterm labor	31-50%
Preterm premature rupture of membranes	6-40%
Multiple gestation and associated complications	12-28%
Hypertensive disorders of pregnancy (preeclampsia/eclampsia)	12%
Antepartum hemorrhage	6-9%
Intrapartum growth restriction	2-4%
Other – cervical incompetence, uterine malformation	8-9%

Adapted from: Slattery MM and Morrison JJ.[18]

Spontaneous preterm birth is a multifactorial phenomenon which arises from an interplay of factors that cause the uterus to switch from quiescence to active contractions and birth before 37 weeks of gestation. [6] The causes of spontaneous preterm labor remain mostly unknown, however there are some known risk factors (Table 3). The provider-initiated preterm birth, or birth that takes place by early induction or caesarean birth, has more variable causes.[19]

Table 3. An overview of the most important risk factors for preterm birth.

Type of preterm birth	Risk factors	Examples
Spontaneous preterm birth	Maternal Age and pregnancy interval	Adolescent pregnancy, advanced age, short inter-pregnancy interval
	Multiple pregnancy	Increased chances by assisted reproduction
	Infection	Urinary tract, malaria, HIV, syphilis, chorioamnionitis, …
	Underlying maternal chronic medical conditions	Diabetes, hypertension, anemia, asthma, thyroid disease, ..
	Nutritional	Undernutrition, micronutrient deficiencies
	Lifestyle/work related	Smoking, excess alcohol consumption, drug use, excess physical activity
	Psychological health	Depression, violence
	Genetic and other	Family history, cervical incompetence, intra-uterine growth restriction, congenital abnormality
Provider-initiated preterm birth	Medical induction or cesarean birth for obstetric or fetal indication	Prior classical cesarean section, placenta accreta
	Other – not medically indicated	

Adapted from Blencowe et al. 2013.[4]

3.2. Low birth weight

LBW is attributed to premature birth, restriction of intrauterine growth, or a combination of both. In developing countries LBW (<2500g) is mostly caused by intrauterine growth retardation caused first by undernutrition and pregnancy morbidities, and then by prematurity.[20] In high-income countries, fetal growth and BW for GA show a normal distribution in VPT infants, and as a consequence VLBW is mostly associated with very preterm birth.[21] Only a small percentage of the infants are SGA. In several high-income countries proportions remains close to 10% of the infants.[22,23]

The etiology of SGA births remains partly unclear, however, fetal (chromosomal abnormalities), maternal (socio-economic status, maternal nutrition, smoking, alcohol consumption, pre-eclampsia, etc.), and environmental factors (placental infarction, infections) appear to affect birthweight.[24,25]

4. Mortality

Worldwide, preterm birth is the second most important cause of death, after pneumonia, in children under 5 years old. In 2018, this encountered 2.5 million newborn deaths.[26] However, in high income and middle-income countries, preterm birth is the principal cause of death.[27]

Preterm neonatal mortality rates correlate with BW and GA. Decreasing BW and GA increases the risk of death. Across 11 European countries, the risk-adjusted regional mortality rates for very preterm infants (28-31 weeks GA) ranged from 1.4% to 6.0% (unadjusted 1.5% to 7.5%). For extremely preterm infants (<28 weeks GA), this ranged from 19.4% to 45.4% (unadjusted 17.0% to 43.8%).[28]

Remarkably differences exists between countries and hospitals.[29] This is particularly the case in the periviable infants, born between 23 and 24 weeks GA.[30,31] This variability among countries and units, may indicate variations in practices and policies of initiating active resuscitation and treatment, as well as for withholding and withdrawing of intensive care in case of severe neonatal morbidities.[32]

4.1. Causes of death

Neonatal mortality has several causes. The most important cause is complications related to preterm birth, followed by intrapartum-related events, sepsis/meningitis, congenital abnormalities and pneumonia. Neonatal death due to tetanus, diarrhea or other conditions are less frequent.[27] The immediate cause of death in VPT/EPT infants differs by GA. It has been reported that in infants with GA 22-25 weeks, acute respiratory illnesses is the most common cause of death, whereas in infants born between 26-28 weeks GA and between 29-31 weeks GA, major intraventricular hemorrhage and perinatal asphyxia were the most important causes of death, respectively.[33]

4.2. Trends over time

4.2.1. Decrease in mortality

Advances in neonatal care (Table 4), such as routine use of antenatal steroids along with improvements in respiratory and nutritional support, have led to substantial improvements in the neonatal survival rates of preterm born infants and infants with low BW, throughout the past decades. This is especially the case of neonates with BW less than 500g[34-36] and less than 28 weeks GA.[37]

Table 4. Innovations in perinatal care

Innovation	Time
CPAP, mechanical ventilation	1980s
Exogenous surfactant	Early 1990s
Antenatal steroids	Mid/late 1990s
Avoiding postnatal steroids	Early 2000s
Targeted oxygen therapy	Mid 2000s
Systematic care/experience	continuous

Adapted from glass et al. 2015[38]

The EPICURE study in England showed that the survival rate to discharge from hospital in infants born between 22 and 26 weeks gestation, rose from 40% in 1995 to 53% in 2006.[39] This increasing tendency continued even after this period. Another study in England in very preterm infants, showed also an improvement in survival rate between 2008 and 2014 (88% in 2008 to 91.3% in 2014), with the greatest improvement in infants with the lowest GA (between 22+0 and 23+6 weeks GA).[40] This constantly improving survival trend is consistently reported in different studies effectuated in high-income countries.[41-43]

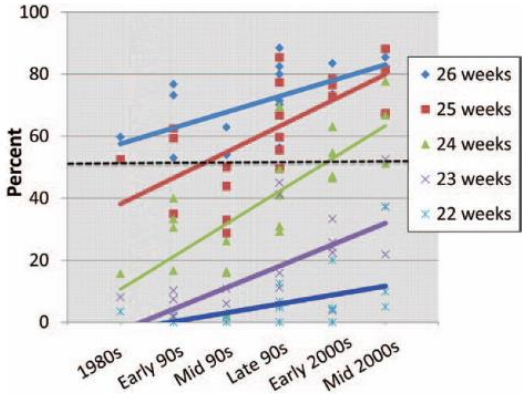

Figure 1.

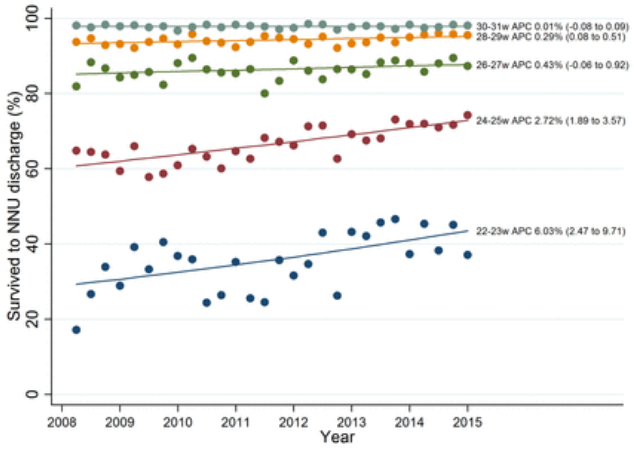

Figure 2.

Figure 1. This figure shows increasing survival rates between the 1990s to the mid-2000s. This represents pooled data from different cohort studies. *From Glass et al. 2015*[38]

Figure 2. This figure shows an increasing survival rate, especially for infants with the lowest GA between 2008 and 2014 for infants born in England. Joinpoint regression analysis for crude rates of survival to discharge for admitted infants born at 22+0–31+6 weeks' GA by birth year (2008–2014). *From Santhakumaran et al. 2017*[40]

4.2.2. Changes in etiology

Also etiology of death has changed over time. A large population based study in the United Kingdom examined causes of death across different time epochs (between 1988 and 2008) in very preterm infants (24-31 weeks GA).[44] The study showed a dramatic decrease of respiratory mortality. On the other hand, other causes of death, in particular infection and necrotizing enterocolitis, did not decrease over time in their cohort. Another study in extremely preterm infants in the US, confirmed the decrease of pulmonary-related deaths over time between 2000 and 2011.[45] On the contrary, they found that deaths caused by immaturity and infection and central nervous system injuries declined as well.

5. Outcome

Infants born preterm are at greater risk for developing perinatal and longer term problems.[7,37,46,47]

5.1. Perinatal morbidities

What makes preterm infants so vulnerable is their immaturity. Many organ systems are not yet sufficiently developed to function independently. The lower the GA, the less organs are able to function maturely outside the uterus. This can lead to severe problems with the respiratory function, blood circulation, oxygen supply to the brain and other organs, infection due to insufficient immunity, nutritional problems due to gastrointestinal immaturity and hypothermia because the body temperature cannot be kept constant.

As such, increased survival among VPT, and especially EPT infants, may lead to higher risks of neonatal morbidity among survivors.[46,48,49]

Based on data (1993-2012) from the neonatal research network, the percentage of infants without severe perinatal morbidities rangs from 0% at 22 weeks GA to 54% at 28 weeks GA among the surviving babies. Overall, of EPT infants only 39% survive to discharge without severe morbidity.[37] In France, rates are higher, with 70% of the infants born between 23 and 28 weeks, leaving the hospital without severe morbidity.[50] This can mainly be explained by the lower incidence of bronchopulmonary dysplasia, probably because of differently used definitions and lower survival rates among the infants born at 22-24 weeks GA. Another study by Edstedy Bonamy et al.[28], explored rates of severe morbidity in VPT infants across 11 European countries. Overall, 13.8% of the survivors had a severe neonatal morbidity, with regional rates ranging from 6.4% to 23.5%.

The most common and serious comorbidities among preterm infants are[51]: respiratory distress syndrome, bronchopulmonary dysplasia, infection, necrotizing enterocolitis, retinopathy of prematurity and brain injuries.

Within the context of this doctoral thesis, only brain injury of the preterm brain will be discussed in more detail.

5.1.1. Brain injury in the preterm brain

The development of the human brain starts shortly after conception and progresses until early adulthood.[52] During this process complex organizational changes occur.[53] A key factor in the pattern of brain damage, including regional and cell-specific susceptibility, is the brain's maturation stage at the time of injury.[54,55]

5.1.1.1. An outline of early brain development

Brain development begins in the first weeks after conception.[56] During the embryonic period (the first eight weeks after fertilization) most of the brain's structural features emerge, which then continue to grow and mature during the remainder of the gestation.[57] Neural tube formation is the first key event of brain development. The transformation from the neural plate to a neural tube is usually completed by four weeks after conception. This neural tube keeps developing, eventually becoming the brain and spinal cord. The first neurons and synapses begin to develop in the spinal cord around seven weeks after conception.[57] This cortical neurogenesis will continue and will predominantly take place during the first and second trimester. Cortical neurogenesis is defined as a complex process of proliferation, migration and organization of neuronal precursor cells to finally generate cortical neurons.[58] Gyri and sulci start to be visible on the brain's surface early in the second trimester and this process is nearly completed by the end of this trimester, however, for the frontal cortex it will go on in the first months postnatally.[59] The cerebral cortex is growing in thickness and complexity and the formation of synapse in this area is starting. Also, by the end of the second trimester, the brain stem is almost entirely developed, which controls heart rate, breathing and blood pressure.[57] In this stage, genetic or external environmental factors could lead to disorders of proliferation, migration and organization, leading to brain maldevelopments.[58]

From the 3th trimester, the foundations and important brain structures are established and from then on growth and differentiation will dominate.[56,57] Neuronal organization and myelination starts early in the third trimester and continues well after birth. Those are the main processes that contributes to the rapid brain growth and maturation.[55]

Events disturbing the brain development, mainly caused by ischemia and/or infection, at this stage will result in lesions.[60] As the infant matures, the area most vulnerable to hypoxia/ischemia differs, by changing location of intervascular boundary zones ("watershed regions"). Therefore, the immature brain of preterm infants reacts differently compared to term born infants to hypoxia-ischemia. During the early third trimester the white matter is mostly involved, whereas near the term born age the cortical or deep grey matter is prominent involved (Figure 3).[55] This includes the cerebral neocortex, hippocampus, basal ganglia-thalamus, and deep nuclear-brainstem.[61]

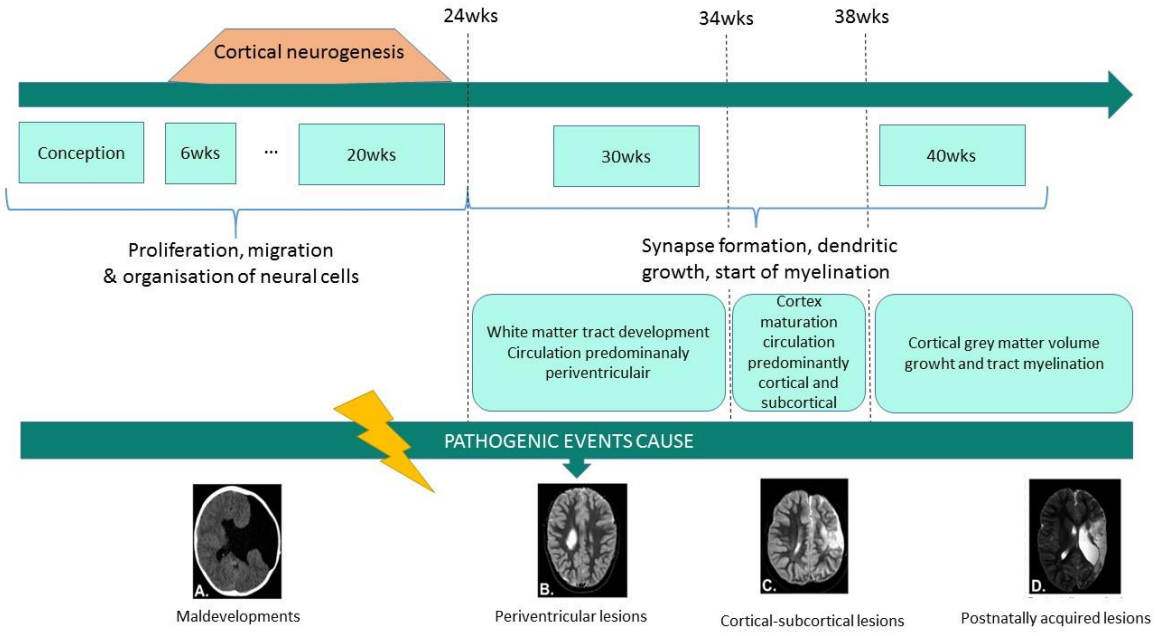

Figure 3. Overview of brain development, pathogenic pattern and timing. *Adapted from Himmelman et al. 2017[62]; Krägeloh-Mann et al., 2007[63] and Jaspers et al. 2015[64].*

5.1.1.2. Patterns of the preterm brain injury

The main lesional pattern in preterm infants are 1) germinal matrix and intraventricular hemorrhage 2) periventricular venous hemorrhagic infarction (PVHI) and 3) periventricular leukomalacia (PVL) with a focal necrotic and a diffuse component.[55]

5.1.1.2.1. Germinal matrix-intraventricular hemorrhage

The germinal matrix (GM) is a richly vascularized, transient layer near the ventricles. It produces neurons and glial cells, and is present in the foetal brain between 8 and 36 weeks of gestation.[65] The germinal matrix is vulnerable to hemorrhage in preterm infants, because of the increased vessel fragility and immature autoregulation of cerebral blood flow.[66]

Intraventricular hemorrhage (IVH) typically initiates in the GM and may be limited to the GM or extend into the ventricle and develop ventricular dilatation.[67] Severity of GMH-IVH is commonly described according to the modified Papile classification[56,68]:

- Grade I: bleeding confined to periventricular area (germinal matrix)
- Grade II: intraventricular bleeding without ventricular dilation (≤50% of lateral ventricular area)
- Grade III: intraventricular bleeding with ventricular dilation(>50% of ventricular area, usually leading to distension and dilation of the ventricles)
- PVHI: this represents a venous infarction in the area ipsilateral to IVH, associated with any of the former grades, however most frequently with grade III. It was often referred as grade IV.

The prevalence of IVH ranges between 15% and 45% in VPT/VLBW infants, with a significant higher occurrence in EPT infants.[69-71] However, GMH-IVH associated with PVHI occurs in 4-5% of VLBW infants, but the incidence increase remarkably to 20-30% in infants born between 24-26 weeks GA or with a BW below 750 gram.[72-74] This severe form of GMH-IVH, which is mostly unilateral or grossly asymmetric, accounts therefore for the most neurological disability among the entire spectrum of GMH-IVH.[55]

Previously, it was believed that mild GMH-IVH (grade I and II), did not increase the likehood of neurodevelopmental injury beyond the risk associated with prematurity alone.[75] Lately, there has been less clarity about this, as some have raised the contrary[69,71], while other studies continue to support the benign nature of mild IVH, having still shown that this has hardly any consequences on later development.[76] Those conflicting findings could partly be explained by two important factors. First, the inclusion criteria and gestational ages of the study population might be important confounding factors, as it has been reported that infants below 28 weeks of GA with IVH I and II showed a significantly worse outcome when compared to infants with IVH I and II born above 28 weeks of GA.[70] Secondly, most of those studies did not take into account other brain lesions, for instance IVH I-II in combination with PVL, which might influence the overall outcome results.[77]

In contrary to this, no doubt exists about the consequences of grade III IVH and/or PVHI, as it is well known to be associated with high rates of mortality and neurodevelopmental impairments.[72,78,79] For instance, in children with grade III IVH, 28% develop CP, whereas in GMH-IVH with PHI (grade IV) 60% of the infants develop CP.[80]

Overall, a meta-analytic review has reported that increasing grades of GMH-IVH are associated with adverse neurodevelopmental outcome.[81] Mild GMH-IVH was associated with higher odds of moderate-severe neurodevelopmental impairment (NDI) compared with no IVH among those who survived to discharge (unadjusted OR 1.75, 95% CI 1.40–2.20; adjusted OR 1.39, 95% CI 1.09–1.77). The overall unadjusted pooled odds ratio for death or moderate-severe neurodevelopmental impairment after severe PVHI is 4.72 (95% CI 4.21–5.31).[81]

5.1.1.2.2. White matter injury of prematurity

The main reasons for the predominant cerebral white matter injury in preterm infants is a selective vulnerability of premyelinating oligodendrocytes to oxidative stress and the cerebral vascular anatomical character of the white matter.[82] In addition, preterm infants may have reduced brain blood flow autoregulation.[83] The periventricular white matter of the preterm infant lies in an end-zone of the watershed zone, where changes in blood flow can lead to cell injury. This is why from 24 to 34 weeks gestational, the highest risk occurs for white matter injury (WMI) and the most common form of brain injury in preterm infants.[84,85]

WMI is related to various clinical factors, before or after birth, affecting the hemodynamic stability and preterm fetal inflammatory status, such as postnatal infections, hypoxia-ischemia, hypoxemia, hypocarbia, metabolic acidosis, hypotension and hypoglycemia.[86]

For a long time, cranial ultrasound (cUS) images were scored using the 4-grade classification of periventricular leukomalacia (PVL) by de Vries et al.[87] (1992).

- Grade I: areas of increased periventricular echogenicity without any cyst formation persisting for more than 7 days
- Grade II: the echogenicity has resolved into small periventricular cysts
- Grade III: areas of increased periventricular echogenicity, evolving into extensive periventricular cysts in the occipital and frontoparietal white matter
- Grade IV: areas of increased periventricular echogenicity in the deep white matter developing into extensive subcortical cysts

Increased use of MRI in recent years has shown that the spectrum of WMI is wider and includes more subtle lesions not so easily identified by cUS. Therefore, recently, a different

WMI-scoring system has been established.[88-90] A commonly used scoring system is based on the MRI-classification by Kidokoro et al.[88] (2013) combining measures of injury and impaired growth.

The spectrum of WMI includes three major forms of pathology: focal cystic or microscopic necrosis and diffuse non-necrotic lesions.[85] Grade II to IV are referred to as cystic PVL. As an aside, it is a common error to refer to non-cystic PVL as "diffuse PVL" with the purpose of differentiating it from cystic PVL, because both cystic PVL and non-cystic PVL have a component with "diffuse" astrogliosis, microglial activation.[91]

The incidence of focal cystic lesions, both macroscopic and microscopic, decreased dramatically in the last few years, and is found in less than 5% of the VPT infants.[92-94] Cystic WMI is highly associated with adverse neurodevelopmental outcome. A systematic review by Hielkema et al. 2016[95], showed that the rates of CP varied between 52 and 100%, with an overall median of 86%. Intellectual disability was diagnosed in 47% of the infants with cystic WMI (range 25-100%, median 50%).

On the other hand, diffuse WMI is now the most common form of injury in preterm infants and is found in 50% to 80% of the extremely and very preterm infants.[94,96,97] Whereas in cystic WMI there is axonal damage, in diffuse WMI axons are mostly spared but there is selective degeneration of pre-oligodendrocytes.[96] Those pre-oligodendrocytes are at the basis for forming pre-myelinating oligodendrocytes (OL) (Figure 4).[85] They are particularly sensitive for hypoxia and susceptible for oxidative damage resulting in cell death, resulting in disturbing in myelination. Premyelinating immature OLs and mature myelinating OLs are much more resistant to oxidative stress, and as a consequence, as the white matter matures, it becomes more resistant to hypoxia-ischemia events.[98]

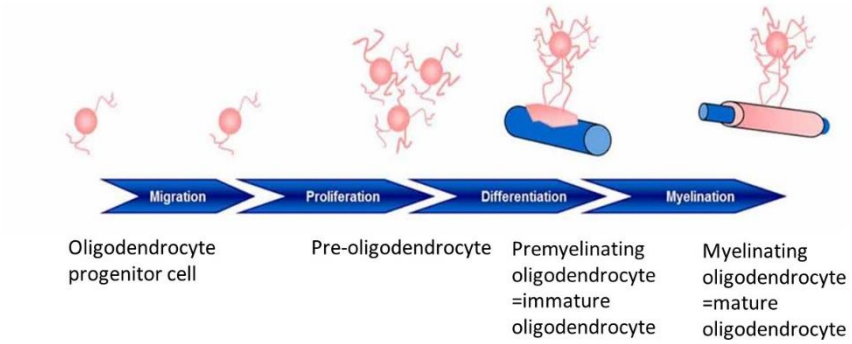

Figure 4. Diagram of the oligodendrocytic lineage progression: from early oligodendrocyte precursor cell to functioning mature myelinating oligodendrocyte. *Adapted from Marinelli et al. 2016.*[99]

As a result, impaired white matter maturation that appears as altered brain structures and connectivity, is frequently associated with adverse long-term neurodevelopmental outcomes.[100-103]

Motor and/or cognitive disabilities are frequently associated with mild-to moderate WMI, or non-cystic WMI.[89,104-107] Concerning WMI, there is a linear relationship between the presence and severity of adverse neurodevelopmental outcome.[89,106,107]

In a VPT/VLBW cohort(<30wks GA and/or BW<1250g) it was found that mild WMI (versus no WMI) increased the odds of moderate to severe motor impairment by over fivefold (odds ratio [OR] 5.6; 95% confidence interval [CI] 1.9–16.1; p=0.002) and mild to severe impairment by twofold (OR 2.2; 95% CI 1.1–4.2; p=0.02).[106] The volume of non-cystic WMI (defined by punctate lesion load and quantified by manual segmentation) has also a positive association with lower motor scores at 18–22 months.[108] Especially, lesions extending in the frontal lobes are key to predicting adverse cognitive and motor outcomes.[108]

Furthermore, infants with mild WMI are 1.7–3.0 times more likely to show a delay and 1.8–3.6 times more likely to exhibit severe delay on measures of IQ, language, and executive functioning.[107]

5.1.2. Cerebellar lesions

Abnormalities of the cerebellum are increasingly recognized as complications of VPT birth and important cause of neurodevelopmental disability. The cerebellar abnormalities constitute on primarily destructive conditions such as hemorrhage or infarction, and primarily underdevelopment.[109] Cerebellar damage varies greatly in severity going from minute focal, unilateral lesions to lesions that damage the entire cerebellum.[110-112]

Cerebellar hemorrhage is the most common destructive form of cerebellar lesions in preterm infants and also the best studied. It is mainly observed in the smallest infants with an incidence of 9% in infants <750g and in infants with BW >750g is it rarely observed, i.e. in 2-3% of the cases.[111] There is often a prominent hemorrhagic component, and often, but not always, supratentorial injury such as IVH, PVHI, PVL or posthemorrhagic hydrocephalus is accompanied with a cerebellar injury.[109,111]

Meta-analysis has revealed that GA, BW, intubation at birth, hypotension, patent ductus arteriosus, IVH, sepsis, necrotizing enterocolitis and bronchopulmonary dysplasia are significant risk factors for cerebellar hemorrhage.[113]

Neurodevelopmental outcome is highly associated with cerebellar hemorrhage. It was long thought that the cerebellum was particularly involved in motor function, but the cerebellum also plays a major role in several cognitive and affective functions, including for instance executive functions, working memory and emotional regulation.[114] A recent meta-analytic review reported increased odds ratios for delayed mental development (6 studies, OR2.95, 95% CI 1.21 to 7.20), psychomotor development (6 studies, OR 3.62, 95% CI 1.34 to 9.76) and higher cerebral palsy rates (4 studies, OR 3.09, 95% CI 1.55to 6.19).[113] Also severe language and/or behavioral development have been related to cerebellar hemorrhage with an incidence of 41%, and 38%, respectively.[115]

Most of what is known about cerebellar infarction is based on neuroimaging studies in infants with diagnosed CP, and some postmortem case reports. Nevertheless studies about it are sparse.[109,111]

5.1.3. Brain development

There is growing evidence, that even in the absence of brain injury, brain development is affected by preterm delivery. At term equivalent age (TEA), preterm infants show smaller cerebral and cerebellar volume, altered cortical surface area and microstructural organization and impaired functional connectivity, compared to term infants.[116,117] Moreover, those findings persist into infancy, childhood and even adolescence.[118] These changes have been attributed to prematurity itself, as well as to the presence of both cerebral and cerebellar injury.[119-122]

Cerebellar dysmaturation plays a role in the high incidence of long-term cognitive, language and behavioral dysfunctions in VPT infants.[118,123,124]

5.2. Long-term neurodevelopmental outcome

Impaired neurodevelopmental outcome is a major long-term complication observed in surviving premature infants which often require additional health care and educational services.. Though infants of any GA may have a neurodevelopmental deficit, impairment rates increase with decreasingly birth weight and GA.[47,125]

Outcome studies primarily from North America and Western Europe have demonstrated an increased prevalence of the following neurodevelopmental disabilities in survivors of premature birth compared to individuals who were born full term:

- Motor deficits, including mild fine or gross motor dysfunctions, and CP.
- Impaired cognitive skills.
- Behavioral and psychological problems.
- Sensory impairment including vision and hearing losses*.

*This item will not be discussed in further detail.

5.2.1. Motor deficits

5.2.1.1. Mild motor dysfunctions

While many preterm infants demonstrate a neuromotor delay on examination, most do not develop CP. Most preterm children experience a minor motor dysfunction, including fine or gross motor delay or deficit, issues with motor coordination and/or sensorimotor control that contribute to functional impairments, educational challenges, and social-emotional problems.[78,126,127]

The Bayley Scales of Infant Development (BSID) is the most commonly used assessment tool for the evaluation of cognitive, language and motor development in young infants and toddlers.[128] The second edition (BSID-II) comprised a total Mental and Psychomotor Developmental Index. The third edition (Bayley-III) consists of a cognitive, language and motor scale, each represented as a total composite score. Mild delay on the cognitive, language or motor scale is mostly defined as score between 1 and 2 standard deviations (SD) below the mean of the reference group of the standardized assessment tool, i.e. a score between 70 and 85.[129] Moderate-to-severe delay is generally defined as 2 SD below the mean (score <70)..

Children born very preterm and VLBW children have significantly poorer motor scores on the BSID compared to the normative sample, as indicated by the combined random effect size of −0.88 (95% CI, −0.96 to −0.80, P<.001), evaluated by the meta-analytic review of De Kieviet et al. (2009).[130]

In EPT infants, mild motor delay was found in 8 to 18% of the children[131,132]. Moderate to severe delay is reported in 7 to 13% of the EPT infants.[131-133] In VPT and VLBW infants only 4-5% of the infants were scored with a moderate to severe delay.[134,135]

Motor deficits perceived through school-age might be classified as DCD, if the child meets four criteria according to the DSM-V, including: a) motor coordination and performance are below that expected for the child's chronological age and intelligence level; (b) the motor

disorder interferes with activities of daily living or academic achievement; (c) it is not due to general medical or neurological condition; and (d) if intellectual disability is present, the motor difficulties are in excess of those associated with it.[138]

It includes difficulties with balance, gross and fine motor control and visual-motor integration, which manifest as lack of agility, clumsiness in running , jumping and climbing, as well as in actions requiring competence with objects such as ball games.[138] Manipulation of writing , drawing, and small objects may be affected, along with self-care skills including autonomous feeding and dressing.[139,140] DCD has also been related with learning difficulties, psychosocial problems, lower cognitive functions and an increased risk for mental and physical issues.[141-144]

DCD affects approximately 5%-6% of typically developing school-age children, however, VPT infants are 6-8 times more likely to develop DCD.[145,146] A large Danish study found that a decline in gestational age by a week was associated with a 19% [95% CI 14%-25%] increased risk of DCD screening positive among children delivered before 40 weeks.[147] In preterm populations the reported prevalences vary between less than 10% up to more than 50%. This variation can be explained by different used definitions, sample size and the sample composition.[145]

The Movement Assessment Battery for Children–Second Edition (MABC-2) is the most commonly used and recommended test for detecting DCD.[138] The most used definition is a motor performance below the fifth percentile or lower on the MABC-2. However, several studies have used a cutoff point of the 15th percentile, as children with scores in the sixth to 15th percentile interval are also at risk for developing DCD.[140,146] Parental questionnaires designed to detect motor problems, have a low sensitivity for detecting DCD, compared with the MABC.[148,149]

Even though some early signs might be present[150], it is generally not recommended to diagnose DCD before the age of 5 years.[138] This is also reflected by the fact that different studies highlighted the poor predictive value of the motor score on the BSID around 2 years CA for later motor difficulties, often assessed with the Movement-ABC (MABC).[135-137] The results on the MABC indicate greater deficit with increasing age during elementary school and early adolescence. Those results suggests that there is catch up effect in early childhood years in reaching important motor milestones, and that less subtle motor problems appear to increase when these vulnerable children are imposed to greater demands at elementary school and later on in life.[135]

Just as described with cognition, the influence of perinatal factors such as GA and BW is decreasing at later stages of development, since less robust relations between BW, GA, and motor scores are obtained for the MABC.[130]

5.2.1.2. Cerebral palsy

CP is the most common cause of physical disability in childhood[151] and is also the most common severe long-term neurodevelopmental disability associated with preterm birth.[152]

In 2000, the Surveillance of cerebral palsy in Europe (SCPE) did the first attempt to standardize the definition of CP.[153] In 2004, an international workshop was created to reconsider the definition and classification of CP.[154] The most recent definition of CP is: "CP describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception and behavior, by epilepsy, and by secondary musculoskeletal problems".

The incidence of CP decreases significantly with increasing GA [80,155], which makes preterm birth the most important risk factor for CP. CP occurs in 8-9% of the infants with GA between 22 and 32 weeks GA [80,156,157], and in 14% of infants with GA between 22 and 25 weeks [157]. A meta-analytic review, estimated the pooled prevalence of CP at 2.11 per 1000 live births.[158]

Table 5. Subtypes of CP. *Adapted from SCPE*

		Neurologic findings in all the CP subtypes
		Abnormal pattern of movement and posture
Subtypes of CP		**Neurologic findings by subtype**
Spastic CP	Bilateral spastic Unilateral spastic	Increased tone Pathological reflexes: -increased reflexes, e.g. hyperreflexia -pyramidal signs, e.g. Babinski response → resulting in abnormal pattern of movement and posture
Dyskinetic CP	Dystonic Choreo-athetotic	Involuntary, uncontrolled recurring, occasionally, stereotyped movements, primitive reflex patterns predominate, muscle tone is varying.
Ataxic CP		Loss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy.

The large heterogeneity of CP has led to several classification systems. The SCPE created well-defined categories and has classified CP based on clinical signs and symptoms into three main subtypes: spastic, ataxic and dyskinetic CP (Table 5). The spastic form of CP can further be

classified based on the localization of the impairment, which can be either unilateral or bilateral. Bilateral spastic CP, includes diplegia (two limbs are affected) and quadriplegia (four limbs are affected). In unilateral spastic CP (USCP) predominantly only one side of the body is affected.

The spastic type of CP is the most common form in preterm and term infants and is predominantly bilateral.[80,155] However, distribution of CP types changed and USCP in term infants increased significantly over recent years. A recent cohort study in Sweden found USCP to be now the most prevalent form of CP, with 44% compared to 39% of bilateral spastic CP.[159] USCP is more present in term infants. The non-spastic forms are more frequent in term compared to preterm infants, because of the timing and localization of the brain injury.[155] In late preterm and term infants the cortical and deep grey matter are the most vulnerable for injury, which is more related to non-spastic types of CP.[160]

The severity of CP can be categorized based on several assessment tools. The gross motor function can be classified into different levels using the 'Gross motor function classification system (GMFCS)'.[161] Based on different movements, such as sitting and walking and the use of mobility devices a score can be given from 1 to 5, where 1 is the most functional score and a score of 5 means wheelchair dependent in all settings.

CP results from an injury in the developing central nervous system, which can occur in utero, during the peri- or neonatal period or in the first year of life, and can be multifactorial. Congenital brain malformations are the most common antenatal cause of CP. Other known antenatal causes of CP are vascular events, as well as maternal infections during the first and second trimesters of pregnancy. Less common causes of CP include metabolic disorders, maternal ingestion of toxins and rare genetic syndromes.[162] Perinatal and neonatal causes are asphyxia, infection and/or sepsis.[159] Post-neonatal acquired CP is caused by a brain insult, independent of antenatal and perinatal factors, that occurred after day 28 and before 24 months.[163]

In a large recent cohort in Sweden, the etiology of CP is considered prenatal in 38%, peri/neonatal in 38% and unclassified in 24%.[159] Based on the large database of the SCPE, it can be assumed that post-neonatal CP is rare and occurs in approximately 5% of cases.[163]

Brain imaging can predict CP to a considerable extent. In approximately 80% of the children with CP abnormal findings are observed on neuroimaging.[63,164] Normal or nonspecific findings on MRI are particularly associated with ataxic CP.[164] In USCP, abnormal MRI findings have been reported in 90% of the cases. This includes: brain maldevelopments (16%),

periventricular white matter lesions (36%), cortical or deep grey matter lesions (31% and 7% were miscellaneous.[63] .

WMI is the most common imaging pattern in children with CP.[63] White matter changes are the result of either venous infarction (with GMH-IVH) and/or primary white matter injury (WMI, former leukomalacia), two different lesions which produce similar permanent imaging effects. In preterm infants (<37 weeks) WMI is diagnosed in 31 to 71%, with even higher rates in infants born before 34 weeks gestation (67-79%), whereas in term born infants this is less present (12-32%). In term born infants brain patterns are different. Compared to preterm infants, they are more likely to have grey matter injury (21%), focal vascular insults (12%) and malformations (13%).[164]

5.2.2. Cognitive impairment

Cognitive impairment in the VPT or VLBW population is by far the most common neurological sequel.[165,166] In cohort studies of VPT infants, 30 % have mild cognitive delay[90] and 17% have a moderate-severe cognitive delay around 2 years corrected age.[90,167] In an Australian cohort of VPT infants born before 30 weeks GA, language was mildly delayed in 39% and moderate to severely delayed in 14% of the infants.[168] In EPT infants the rates of cognitive delay are higher, and approximately one third of the population has some moderate to severe cognitive delay at the age of 2 to 3 years[169-171], and they are -1.7 standard deviations (SD) behind their term-born peers on the cognitive scale.[172]

At preschool age (4 years), 33% of EPT and 36% of the VPT infants have a cognitive delay, and between a quarter and a third demonstrate a delayed receptive or expressive language development (both defined as an IQ score >1 SD below the mean for the full term group).[23] Even in later childhood, EPT infants shows similar rates of cognitive impairment. A long-term follow-up was performed of the EPT infants enrolled in het ELGAN study. At 10 years of age, 28% of the boys and 21% of the girls exhibited moderate to severe impairment on summary measures of cognitive abilities.[173] Another large population-based study examined the cognitive trajectories in EPT infants from 2.5 to 19 years and found small but negligible improvement over time, with no evidence of a substantial 'catch-up' with term-born infants.[174] This excessive burden of cognitive deficits in later childhood is also reported in other EPT cohort studies.[175-177]

A recent meta-analytic review in VPT infants aged between 4 and 17, reported that VPT infants lag behind their term born controls with 0.82 SD (95% CI 0.74-0.90; p<0.001) on intelligence

tests, 0.51 SDs (95% CI 0.44-0.58; p<0.001) on measures of executive functioning, and 0.49 SDs (95% CI 0.39-0.60; p<0.001) on measures of processing speed.[178]

However, it is important to notice that the influence of perinatal risk factors on the cognitive development of VPT or VLBW children diminishes over time as environmental factors become more important. Linsell et al.[165] found evidence that male sex, nonwhite race/ethnicity, lower level of parental education, and lower BW were predictive of global cognitive impairment in children younger than 5 years. Only the impact of parental education has been maintained for older children.

5.2.3. Behavioral and psychological problems

It has been reported that VPT/VLBW infants are at increased risk of social, emotional attentional and internalizing problems (anxiety/depression) compared to their term born peers.[179,180] Based on screening questionnaires it is estimated that 13% to 46% of VPT/VLBW children show significant behavioral problems.[181]

Research identified an increase of attention deficit/hyperactivity disorders (ADHDs), autism spectrum disorders (ASDs) and psychiatric disorders compared to term infants.[182,183] A recent meta-analytic review reported that the odds for ADHD were three-fold higher in VPT infants (OR: 3.3; 95% CI: 2.0–5.6) compared to their peers[184], and has been reported in 16 to 19% of the VPT/VLBW infants.[183] Studies reporting the rates of ASD in VPT/VLBW are sparse. One study reported a prevalence of 3.6% in ELBW infants[185] and 8% in EPT infants, which is higher than the estimated prevalence of 0.6% in the general population.[186]

Studies have showed that behavioral problems persist into adolescence and early adulthood, which have a significant impact on daily life.[187-189] Furthermore, VPT/VLBW are more at risk to be diagnosed with psychiatric disorders in adulthood.[190,191] A longitudinal study in EPT infants (<26weeks GA) has showed that behavioral problems at 2.5 years and moderate/severe cognitive impairment were associated with behavioral problems in later childhood until adult age, i.e. from 6 until 19 years.[180]

Low cognitive performance of the child, hospitalizations of the child, young maternal age and low motherly emotional well-being is found to be correlated with behavioral problems in VPT/VLBW infants.[192,193] Even after correction for cognitive performance and all other variables, it was found that VPT infants were still at higher risk of behavioral problems compared to term infants.[192]

5.2.4. Trends over time

Advances in perinatal and neonatal care, are major contributors to both improved survival and a reduction of neonatal morbidities. However, since the limit of viability has declined, concerns exist about the overall rate of neurodevelopmental impairment.

An overall trend being observed is the decrease of CP and severe motor impairment,[131,194-198] with the biggest improvement in infants with VLBW [197] or the most periviable infants at a low GA.[159,199] Rates of CP among children born at term remained stable.[159,200] Furthermore, the large cohort study of the Neonatal Research Network in EPT infants <28weeks, revealed a switch in the severity of CP. Between 2011 and 2015, rates of severe CP decreased with 43% whereas mild CP increased with 13%.[131] This could be related to the changes in pattern of WMI, taken into account the decrease of severe cystic PVL along with the increasing evidence of diffuse white matter damage[201]

On the other hand, no improvement in cognitive outcome or behavioral problems is been observed over time.[194,202]

PART II: Perinatal stroke

1. Definition

Perinatal stroke is an acute neurologic event, occurring between 20 weeks gestation and 28 days postnatal life.[203] The diagnosis must be confirmed by neuroimaging or neuropathological studies.[204]

Perinatal stroke can be classified using 3 characteristics[205,206]: (1) Type of lesion: ischemic or hemorrhagic; (2) Localization of the lesion: blood vessel affected – artery or vein; (3) Timing of the lesion: fetal, neonatal or presumed fetal or neonatal.

1.1. Type of lesion

1.1.1. Ischemic stroke

Perinatal ischemic stroke is defined as 'a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of foetal life through 28th post-natal day, and confirmed by neuroimaging or neuropathological studies'.[206]

The most common subtypes of neonatal ischemic stroke include[205,207]:

- arterial ischemic stroke (AIS), which is defined by documented vessel occlusion in relation to a focal brain lesion or documented lesion pattern on imaging that can only be explained by occlusion of a specific brain vessel
- cerebral sinus venous thrombosis (CSVT), defined as presence of thrombus with partial or complete occlusion in a cranial venous sinus, large deep brain vein, or smaller cortical or deep vein.

Other forms of vaso-occlusive ischemic stroke include[205]:

- periventricular venous infarction (PVI), which is more common in premature infants and may occur with or without germinal matrix and/or intraventricular hemorrhage
- presumed fetal or neonatal stroke, which may be considered when neuroimaging after the perinatal period shows chronic changes suggestive of earlier stroke in a neurologically normal infant without symptoms of acute stroke.

1.1.2. Hemorrhagic stroke

Hemorrhagic stroke (HS) is characterized by rupture of normal or abnormal intracranial blood vessels and is defined as an intracranial hemorrhagic lesion in the intraventricular, intraparenchymal, or subarachnoid compartment.[205]

1.2. Localization

Classification is primarily focused on the vascular territory of specific named arteries and veins, as described by Govaert et al.[205].

This can be diagnosed if a partial or complete occlusion of the vessel is observed, or if the occlusion is not recorded but the lesion pattern can only be clarified by occlusion of a particular brain vessel.[205]

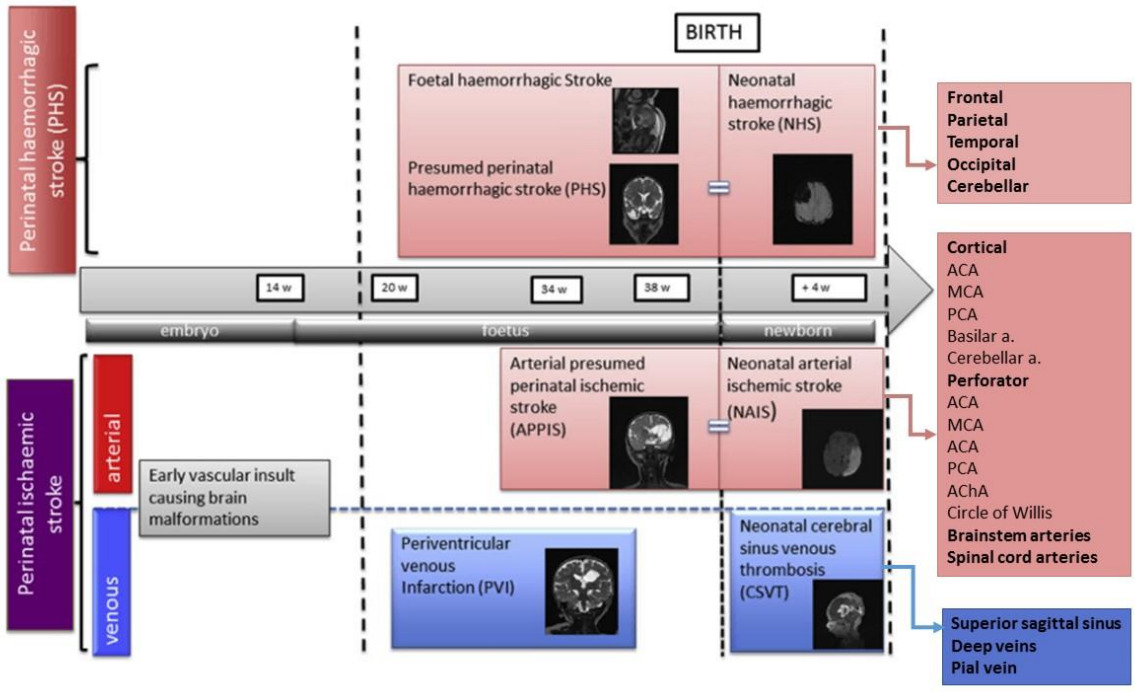

Figure 5. The patterns of perinatal stroke according to timing and vascular mechanism, as well as the major types of large vessel occlusions. *Adapted from Fluss et al. 2019[208] and Govaert et al. 2009[207]*

1.3. Timing of the lesion

Subcategories based on timing include[206]:

- fetal ischemic stroke: diagnosed before birth by fetal imaging methods or in stillbirths based on neuropathologic examination
- neonatal ischemic stroke: diagnosed after birth in infant ≤ 28 postnatal days old (including in preterm infants)
- presumed perinatal ischemic stroke: diagnosed in infants > 28 days old in whom it is presumed (but not certain) that an ischemic event occurred between the 20th week of fetal life and the 28th postnatal day

2. Incidence

The incidence of perinatal stroke across studies remains inconsistent because of variation in - terminology, evaluation and diagnosis. Reported rates of perinatal stroke range from 20 to 44 per 100 000 live births[205,206,209], and, as reported by Dunbar et al. 2019[210], the overall combined incidence is approximately 1:1600-1:2300 live births.

Perinatal AIS is described as the most common type of perinatal stroke and is reported in 1/2000 to 1/5000 live births.[211-215] In both term and premature newborns, perinatal AIS is more common in the middle cerebral artery territories due to the large size of the territory and the direct flow from internal carotid artery into the middle cerebral artery, providing the easiest path for thromboembolism.[207] Moreover, in some studies it has been reported to be slightly more common on the left side.[207] This might be declared the velocity differences in the carotid circulation and the direct branching of the left common carotid artery from the aorta.[216-218]

The prevalence of perinatal CVST is remarkably lower, ranging from 1 to 12 in 100 000 live births.[219,220] It seems that boys are more affected with AIS as well as CSVT.[221]

Perinatal HS is reported in 6 to 16 per 100 000.[222,223] However, those numbers do not include isolated subdural or subarachnoid hemorrhage, neither germinal-matrix related bleeding occurring in preterm newborns.[208]

3. Pathophysiology

Assigning a conclusive causative mechanism in perinatal stroke is very complicated, because the occurrence is rare. In addition, perinatal stroke coexists with several different disease conditions and is possibly multifactorial. Several possible risk factors are reported by different

studies, but none of those risk factors can be considered as the unique and direct cause of the infarction.[211]

Some risk factors associated with AIS include placenta disorders[224], thrombophilias[225,226], maternal factors (i.e. primiparity, infertility, pre-eclampsia, intra uterine growth retardation, prolonged rupture of membranes, and chorioamnionitis)[211,227], neonatal factors (low Apgar scores, cord pH<7.0, neonatal resuscitation, and hypoxic-ischemic encephalopathy can co-occur)[211,228], infection[207,229], congenital heart disease[214,230] and some genetic predisposition may interfere[231,232].

Risk factors for CSVT are less well described. Some of the reported risk factors are similar such as thrombophilia, hypoxic-ischemic encephalopathy, sepsis and other infections.[233,234]

Just as in ischemic perinatal stroke, the pathophysiology of HS is poorly understood and only sparse research exists on this topic. In only 25% of the cases specific causes such as thrombocytopenia and cavernous malformations could be defined in a large cohort study of intraparenchymal and subarachnoid hemorrhages across preterm and term infants.[222] Other significant associated clinical variables in multivariate analysis were fetal distress and postmaturity. In addition, genetic defects are also linked to perinatal HS.[232]

4. Mortality

Death is uncommon after perinatal stroke (3%).[226] However, mortality is often correlated to other comorbidities, such as sepsis, meningitis, severe prothrombotic disorder and severe congenital heart disease, and is not directly associated with the stroke itself. [208,235-237]

5. Outcome

5.1. Clinical presentation of perinatal stroke

The clinical presentation of perinatal stroke might be acute or delayed. Acute presentation accounts for approximately 50% of the cases.. The presentation is mostly during the first days of life, with symptoms including focal seizures (in 75% of the case[238]), apnea, chewing or bicycling movements, and persistent feeding difficulties.[228,239] A variable percentage of neonates will have focal findings such as differences in tone or an asymmetric Moro reflex.[239]

The remaining 50% will be categorized as presumed perinatal stroke, since delayed presentation will occur, and exact timing of the brain injury is difficult to determine.[210] In this case, diagnosis occurs retrospectively when symptoms such as hemiparesis, seizures or other neurological deficits manifest later in infancy. Typically, motor asymmetry and early hand

preference at 4 to 6 months are the first signs[215,240], however, assessments and final diagnosis are mostly postponed until the second year of life.[241]

5.2. Long term neurodevelopmental outcome

Perinatal stroke is widespread and causes substantial morbidity and long-term neurological and cognitive impairment, including CP, seizures, neurodevelopmental disabilities, behavioral disorder and impaired vision and language function.[204,226,242] A systematic review combining results over a 30 year period found that 57% of infants had motor and/or cognitive deficits at follow-up.[226] However, a large heterogeneity between studies was found in relation to stroke type, duration of follow-up and functional measurements.

Up to 60% of perinatal stroke cases results in long-term motor and neurological deficits, with USCP being the most frequent adverse motor outcome.[211,243,244] On the other hand, perinatal stroke is a leading known cause for CP, accounting for 30% of children affected with USCP.[206]

The relative proportion of motor deficit varies across the different types of perinatal stroke, the location and the severity of the brain damage. Motor deficits after perinatal AIS are generally less common compared to other perinatal stroke patterns.[228,245] Involvement of the CST (Posterior Limb of the Internal Capsule [PLIC], cerebral peduncles, basis pontis and the medullary pyramids) and deep grey matter structures (basal ganglia and thalamus) are highly associated with the development of CP.[246-248] If more CST segments are affected, the rates of CP increases.[236,243,249] In addition, neonates without CST involvement were reported to have a very low rate of CP.[247,250] Furthermore, the extent of the stroke also matters. A recent study showed that the stroke volumes were significantly larger in NAIS survivors with CP.[250] A cut-off of 3.3% stroke volume, calculated as stroke volume divided by whole brain volume, is considered as an optimal balance of sensitivity and specificity to classify neonates in high- and low-risk-group for CP.[250]

6. Early detection of unilateral spastic cerebral palsy

CP is already well described on page 30 to 32. The focus of this dissertation in the second chapter is in particular on USCP, because this is the most common motor problem after perinatal stroke. USCP is characterized by a predominantly one-sided motor movement disorder, where the upper limb is often more functionally impaired then the lower limb.[251] This

can be declared by the amount of motor cortex dedicated to a body part. This is related to the complexity of movement possible with that body part and is reflected in the familiar motor homunculus described in neuroanatomy, with a larger area of cortex related to hand movement than to leg.[252] In contrast, in USCP resulting after PVHI in preterm infants, the legs could be more affected than the upper limb because the fibers contributing to the motor function of the lower limb are located more medially, which is closer to the severe periventricular brain injury. [56,253]

There is a wide range of upper limb deficits in children with USCP. This could vary from only minor deficiencies in fine motor skills to children who are not even able to grasp or hold a pen. However, the vast majority (99%) of the children with USCP walks, and has a GMFCS level I to III.[254]

Historically, CP is diagnosed around 12 to 24 months of age, with many clinicians adopting a "wait and see" approach.[255] However, early detection is becoming an increased focus of research and clinical practice. In the meantime, different tools exists for earlier detection of CP or high risk of developing CP.[256] Early diagnosis is now considered best practice, since it allows diagnostic-related specific early intervention, when the brain plasticity is the highest and the most functional improvement can be achieved.[257,258]

It is now largely accepted that neonatal brain imaging can recognize the type of injury that may lead to CP in terms of the type and timing of the brain lesions typical of the different forms of CP.[63] The most severe forms of CP can be predicted by a combination of cranial ultrasound and MRI at term age in most of the cases.[259] Further sophisticated brain imaging techniques, such as for instance functional MRI and diffusion tensor imaging (DTI) can enhance the prognosis for the more subtle brain lesions that will eventually lead to less severe forms of CP.[260] However, brain imaging has its limitations and is not able to provide information on the functional status of the nervous system. This is why, in addition to other reasons, clinical assessment remains necessary in infants at high-risk of neurodevelopmental impairment.

It is advised that an early, accurate diagnosis of CP can be made using a combination of patient background, neuroimaging, and structured motor and neurological tests.[257] For clinical assessment, the most extensively validated tools for predicting CP in young preterm and full term infants, are the Hammersmith Infant Neurologic Examination (HINE) and the Prechtl General Movement Assessment (GMA).[257,258,260] The HINE, in contrary to GMA, is not included into this doctoral thesis and will not be discussed in further detail.

GMA evaluates spontaneous whole body movements (=general movements [GMs]) according to age-specific characteristics and is thus a non-invasive diagnostic tool. The quality of the infants spontaneous movements reflects the central nervous system integrity, and is therefore an excellent marker of brain lesion.[261,262] GMs are present from early fetal life and disappear around 4 months post term age, when goal-directed movements emerges.[263] Different types of GMs can be observed such as writhing (appearing from preterm age to 6–9 weeks of postterm age) and fidgety movements, which are best observed between 9 and 20 weeks of postterm age.

Writing movements are characterized by GMs with small-to-moderate amplitude and by slow- to moderate speed.[263] They are typically presented in an elliptical form, which is why it refer to writing movements.

Fidgety movements (FMs) are defined as movements with small amplitudes and moderate speed observed from the whole body including the neck, trunk, and proximal and distal limb segments. These movements have variable acceleration and directions and continue in the awake infant except during fussing and crying. FMs can be classified as normal, absent or abnormal (defined as FMs with exaggerated movement amplitudes, speed and jerkiness).[261,263] The validity and reliability of the GMA have been extensively reported throughout the years, in particular for prediction of CP. Different studies have showed that the absence of FMs is the most predictive sign for CP.[261,264-270] A meta-analysis reported sensitivity and specificity of 98% (95% CI 74-100%) and 91% (95% CI 83-93%) respectively, to detect CP.[260] Nevertheless, in infants with USCP prediction based on the GMs might be more challenging. It has been reported in different studies that some of the infants with later diagnosed USCP showed normal FM, resulting in a lower sensitivity for detecting USCP (75% to 100%).[265,271-273] However, asymmetrical segmental movements, are, on the other hand, strongly associated with USCP and should be further explored in future research.[265,272,273]

In recent years, GMA also has been evaluated for the prediction of minor neurological disorders[274-277], cognitive development[278,279] and autistic spectrum disorder[280].

To identify infants at high risk of USCP at an early age, it is important to detect early indicators of deviant and asymmetrical hand use, which is usually the first clinical sign, but often misinterpreted as an early hand preference.[257,273]

A study group in Pisa demonstrated that early signs of asymmetry could already be observed during the GMA, that are related to later USCP.[271-273] Segmental movements, defined as

isolated finger and toe movements, are reduced or even absent in the contralateral body side of the lesion, regardless of the head position.

Recently, a criterion-referenced assessment tool diagnostic tool has been implemented for early detection of USCP. The research group of the Karolinska institute in Sweden, has developed the 'Hand assessment for infants' (HAI). The test has been validated[281] and age referenced normative values have been published lately.[282] The HAI is an assessment tool to quantify the quality of goal-directed unimanual and bimanual actions, in infants aged between 3 and 12 months.[281] A video recording of a semi-structured play session of 10-15 minutes allows to score the 17 items, of which 12 are unilateral and 5 bimanual. Each item is scored on a 3-point scales, providing a total sum score between 0 and 58. The sum of all of the items, the "both hands Measure, HAI-units", is converted and expressed on a scale from 0 to 100. An asymmetry index, which makes a quantification possible of differences between hands, is calculated from the unimanual sum scores of the better- and the lesser-functioning hands, respectively, and is reported as percentage.

So far, only two studies have investigated the predictive value of the HAI for detecting of USCP. One study found excellent accuracy for USCP prediction of the unilateral HAI scores of the affected hand, in combination with GA and gender before 5 months of age (0.93, 95% CI 0.86–1.00).[283] Another study used the asymmetry index in the prediction model.[284] Before 5 months the asymmetry index had a sensitivity of 77% and specificity of 83% to detect later USCP. It was found that the sensitivity of the asymmetry index increased up to 100% after the age of 5 months.

7. Early intervention

In recent years there has been a high level of interest on early intervention, with the aim of improving the neurodevelopmental outcome of infants at high risk of developing CP. Early intervention is generally defined as "multidisciplinary services provided to children from birth to 5 years of age to promote child health and well-being, enhance emerging competencies, minimize developmental delays, remediate existing or emerging disabilities, prevent functional deterioration and promote adaptive parenting and overall family function".[258]

Meta-analysis indicated a positive effect of general developmental programs or early interventions on cognitive development until the age of 3 years.[285] No effect was obtained at

school age or into adulthood. Smaller but a significant effect was found on motor outcomes during infancy.[285] Only few reported outcomes on the longer term, with contradictory findings.

This little evidence on the effect on motor outcome, is mainly due to underpowered studies or insufficient differentiation between the study and control group.[285,286] Even though there is limited evidence so far, it is recommended that therapy approaches should include active parent engagement, environmental enrichment and the principles of motor learning, including task-specific training.[258,286] It is also advised that early intervention programs should be adapted to the type and topography of CP and the parental goals. [258]

Considering that this manuscript focuses only on children with USCP in chapter 3 and 4, only the specific therapy approaches for this type of CP will be further discussed. Before going into further detail about early intervention options, it is important to describe the main underlying mechanisms important for upper limb function and the potential to adapt and reorganize after brain lesions.

Neuroplasticity, or brain plasticity, is the ability of the brain to adapt and reorganize itself, by forming new neural networks throughout an individual life. This ability ensures physiological learning, but makes it also able to recover from brain injury.[287] Neuroplasticity involves a broad spectrum of changes at different levels of organization. There are mainly two types of neuroplasticity, including (1) functional plasticity, which is the ability of the brain to move functions from a damaged area of the brain to other undamaged areas and (2) structural plasticity which actually changes its physical structure as a result of learning.[287]

The CST is the primary conduit for neural signals that control voluntary movements, which starts by the trunk and ends with the limbs. Functional ipsilateral (same side) as well as contralateral (the other side) CST projections, are already established prenatally.[288] After birth, in children with a typical development, some CST axons will grow and others will be eliminated, which takes place to refine motor function. During this refinement process, myelination takes place.[289] Already present at birth, the ipsilateral and contralateral axonal projections start to withdraw in response to activity-dependent competition. Withdrawal of the ipsilateral projections already starts after a few months and continue over the first 24 postnatal months whereas the contralateral projections will become more dominant (Figure 6).[288-291]

However, in pathological conditions such as after perinatal stroke, the CST may develop differently due to poor activity and sensory input of the affected side.[292] It could be that due

to an unilateral brain lesion, the contralateral and/or ipsilateral CST may be preserved. However, the type of reorganization, referred to as the "re-wiring or wiring pattern", will mainly depend on the brain lesion characteristics such as the timing, the type and the extent of the brain lesion.[293]

Timing and type of brain lesions are correlated. Early brain lesions results in periventricular brain injury, such as PVHI, whereas lesions occurring near term, affect the cortical and deep-grey matter, e.g. as a result of PAIS. Previous studies exploring the effect of lesion timing on the upper limb (UL) function, have delineated that early brain lesions results in better motor and sensory UL function compared to lesions near term age.[294-296]

Furthermore, the affected brain location and extent are of major importance to further UL function. Brain imaging studies have demonstrated that when the posterior limb of the internal capsule (PLIC) and the basal ganglia are affected, as well as larger lesions, worse UL motor and sensory functions are observed.[294,296,297]

CST wiring is the main factor determining the UL sensorymotor function in infants with USCP.[297] Three wiring patterns are recognized (Figure 6): (1) "contralateral" (the affected hand receives input from the crossed CST, originating in the lesioned hemisphere), (2) "ipsilateral" (contralateral projections might become afunctional and withdraw, resulting in an ipsilateral reorganizing of the non-affected hemisphere, so the affected hand receives input from the uncrossed CST, originating in the nonlesioned hemisphere), and (3) in some cases, this activity-dependent competition pursue in both tracts, leads to a mixed reorganization, referred to as "bilateral" (the affected hand receives input from both the crossed and uncrossed CSTs, originating in the lesioned and nonlesioned hemispheres, respectively).[64]

There is evidence that a contralateral wiring pattern is more functional on motor and sensorial level, compared to the ipsilateral and bilateral wiring patterns.[297-300]

Considering the importance of brain plasticity at a young age, possible early intervention deserves attention in order to possibly influence the organization of the CST. This is the reason why researchers are now focusing on exploring options and modalities of early interventions for children with CP, and in particular children with USCP.

CST reorganization with abnormal ipsilateral projections can not access to the cortical and subcortical networks, which are necessary for effective arm and hand control and are therefore less functional.[303] Consequently, the excessive control by the ipsilateral (i.e.non-lesioned) hemisphere is considered as maladaptive developmental plasticity after perinatal stroke.[299,303,304]

As a result, interventions have been developed that may prevent or discourage such rewiring, by intensifying movements with the affected hand.

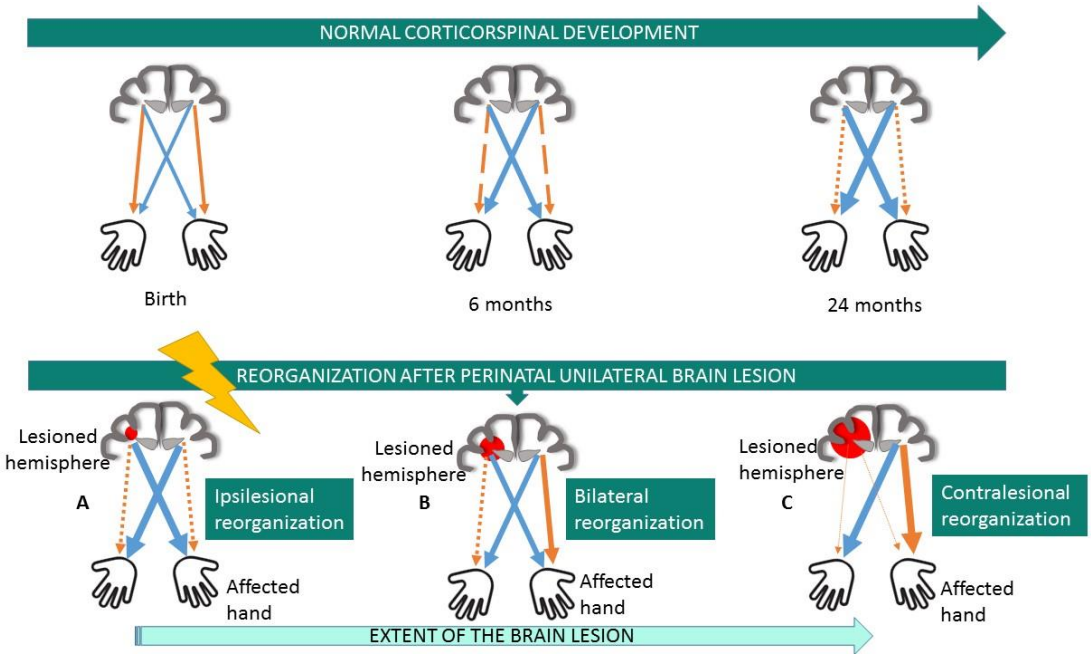

Figure 6. Graphic representation of the normal corticospinal development and reorganization after a unilateral brain lesion. *(Adapted from Staudt et al. 2007[301] and Fiori et al. 2015[302])*

In the last decades, growing number of clinical trials and subsequent reviews and meta-analysis of upper limb rehabilitation therapy have been published.[305,306] The most investigated and efficient non-invasive treatment has been identified as "Constraint-induced movement therapy (CIMT)", followed by bimanual training or "Hand-arm bimanual intensive training (HABIT)".

CIMT was developed as a therapeutic treatment for adult stroke patients.[307] CIMT aims to increase the use of the more affected upper limb and to improve bimanual efficiency, and is built on two main principles, namely the restraint of the less affected limb by using for example a splint, mitt or sling, and, secondly, intensive therapeutic training of the more affected limb. Traditional CIMT requires a restraint of the unaffected arm for approximately 90% of waking hours to facilitate the use of the affected arm throughout the day.[307] However, for the pediatric population the CIMT has been modified, by using shorter time limits over longer time spans, while preserving the CIMT concept of shaping and repeating.[308]

In older children with USCP, evidence has been found for the effectiveness of CIMT in order to improve UL function.[306,309] Explorative studies exist on the implementation of CIMT in early infancy and provides likewise promising results.[310-313] A baby-CIMT program has been compared to baby-massage in infants aged between 3 and 8 months at high risk for USCP, with asymmetric hand use, confirmed by MRI and the HAI evaluation. The baby-CIMT group revealed a better development of the affected hand during the program compared to the control group receiving baby-massage[310] and showed favorable future longitudinal development of hand function until the age of two.[312]

Another effective therapy approach is HABIT.[314] HABIT was introduced with the aim to address the limitations of CIMT, i.e. a failure to address bimanual coordination impairments, which directly relates to their limitations in functional independence and quality of life.[314] HABIT consists of bimanual activities with focuses on: "(1) provision of structured practice increasing in complexity; (2) provision of functional activities that necessitate bimanual hand use; and (3) remaining a child-friendly intervention protocol that takes into account children's goals and parental involvement."[314] HABIT has been effective for improving both unimanual and bimanual upper limb functioning of children with USCP.[305,315] However, in young infants sparse studies exists about HABIT. A protocol has been published to investigate CIMT versus bimanual training in infants aged between 3 and 6 months. [316] At this moment, already 100 infants have been recruited and data collection is still going on.

Both CIMT and HABIT are equivalently effective if performed with an equal dose.[315]

At the same time, other therapy approaches are investigated in young infants. For instance, the UP-beat protocol relies on the principles of action-observation training (AOT).[317] AOT is characterized by learning through imitation which relies on the mirror neuron system.[317] However, this approach should be considered as more experimental since less evidence is available for this approach.[315]

Early intervention for infants at risk of developing USCP is considered to be very important due to important activity-dependent cortical plasticity predominantly occurring early in life. Nevertheless, intervention programs generally start from early childhood onwards, due to delayed detection. Considering that the activity-dependent reorganization of the motor-projection pattern to the hand occurs before 1 year of age, this has been showed to be a critical period for motor plasticity in animals.[318,319] Accordingly, it should be considered to start before the first year of life to benefit the most from the brain reorganization.

Background and aims of this dissertation

The quality of care for infants born preterm, with a VLBW, or with other conditions of high neurological risk, such as hypoxic-ischaemic damage, has dramatically improved over the past decades. This has led to increased survival rates and decreased morbidities since the late 1960s. As a result, the interest for follow-up studies started and since then, over the past few decades much of the literature focuses on the neurodevelopmental outcome of VPT/VLBW and other high-risk infants. This has demonstrated that those fragile infants remain at high risk for neurological damage and long term neurodevelopmental impairments. The incidence of CP has historically been an excellent marker of quality of care, as a clear definition and diagnosis is well defined and easier to compare throughout different studies. Nonetheless, other neurodevelopmental impairments such as cognitive and behavior problems are far more common and are important for participation and quality of life of the children.

Follow-up studies are considered valuable for a variety of reasons. First, they are a reflection of the quality of care, so quality control and benchmarking are possible between NICU centers. Secondly, outcome studies can investigate the long term effects of certain therapies and may correspondingly improve healthcare. Third, understanding the spectrum of impairment is important for end-of life decision making and parental counseling. Lastly, adequate follow-up and early diagnosis might lead to early intervention, eventually resulting in better outcomes.

The constant evolution of neonatal care and changing limits in viability, ensures that this is a domain that is constantly evolving. Therefore, there is a constant need for recent and up to date information.

The core aim of this dissertation is to expand our knowledge on the long-term neurodevelopmental outcome in two different groups of high-risk infants that show similarities but also strikingly different features and clinical symptoms. Furthermore, early prediction of adverse motor outcome is of high importance to be able to provide early intervention therapy. The next important aims of this dissertation are to explore early prediction and early intervention in a particular group of high-risk infants, namely in infants with perinatal stroke.

More specific, the above outlined aims are divided into two major parts.

PART I: VPT/VLBW

The **first aim** of this doctoral dissertation is to provide a recent overview of neurodevelopmental outcome in VPT and/or VLBW infants and to explore the relation between GA and BW and the neurodevelopmental outcome

A first step towards gaining more insight in the light of the current situation is to summarize the available literature about neurodevelopmental outcome in VPT/VLBW infants. A wide range of literature describes neurodevelopmental outcome of EPT and VPT infants, however only few articles provide unified data through global meta-analysis. Furthermore, no clear overview about the separate outcome motor and cognitive outcome is present. Therefore, **Chapter 1** includes a meta-analytic review about 30 studies, providing the overall neurodevelopmental outcome, as well as separate motor, cognitive and CP outcome, at two years of age in VPT and/or VLBW infants born over the last decade. However, global and regional variations exists in the degree of initial care provided to infants at the threshold of viability. In infants born at 22 to 25 weeks gestation, these variations among clinical practice impact survival and ultimately neurodevelopmental outcome. As a consequence, comparing survival and neurodevelopmental outcomes from studies that may vary in their approach to resuscitation of EPT infants is challenging. Especially, in the light of individual parental counseling. Therefore, it is important to rely on national population-based data. **Chapter 2** therefore includes a large population-based cohort study of VPT and/or VLBW infants admitted to one of seven Flemish neonatal care units in Belgium. This study had as aim to investigate mortality and neurodevelopmental outcome at 2 years of age.

PART II: Perinatal stroke

Perinatal stroke is a second important cause of neurodevelopmental impairment.. Outcome studies after perinatal stroke are currently limited, especially studies including all types of perinatal stroke.

The **second aim** of the present thesis is to gain better insight in the neurological outcome of infants with perinatal stroke, based on the different subtypes of perinatal stroke and to possibility predict this at an early age.

Chapter 3 includes a prospective cohort study in infants with perinatal stroke. Stroke classifications are related to neurological outcome. Furthermore, the predictability of CP on the basis of the GMA and HAI is evaluated.

The **last aim** of this dissertation is to explore the feasibility of an early intervention program.

Although there are several studies that discuss the effectiveness of pediatric CIMT, the evidence on using modified CIMT with children less than one year old is sparse. Nevertheless, there is growing recognition that inventions at an earlier age need to be examined. A single-blind randomized trial comparing modified CIMT with baby massage for infants aged between 3 and 8 months with unilateral brain lesions was the first study of its kind. To our knowledge, HABIT has only been investigated in one study enrolling infants between 8 and 15 months, but so far has never been investigated in even younger infants. **Chapter 4** includes a protocol of an early intervention program for children at risk for USCP comparing baby-CIMT and baby-HABIT in infants with perinatal stroke, as well as the points of improvements of this protocol based on the experience gained by performing this intervention study in a preliminary small group of infants.

The most important findings are described and addressed in the general discussion. Clinical implications are established on the basis of these results. Further, the study shortcomings and weaknesses are discussed, offering recommendations for further research. Finally, a general conclusion is provided.

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PART I: Very preterm / very-low-birthweight infants

CHAPTER I

CHAPTER 1

Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review

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ABSTRACT

AIMS

The purpose of this systematic review was to provide an up-to-date global overview of the separate prevalences of motor and cognitive delays and cerebral palsy (CP) in very preterm (VPT) and very-low-birthweight (VLBW) infants.

METHODS

A comprehensive search was conducted across four databases. Cohort studies reporting the prevalence of CP and motor or cognitive outcome from 18 months corrected age until 6 years of VPT or VLBW infants born after 2006 were included. Pooled prevalences were calculated with random-effects models.

RESULTS

Thirty studies were retained, which included a total of 10 293 infants. The pooled prevalence of cognitive and motor delays, evaluated with developmental tests, was estimated at 16.9% (95% confidence interval [CI] 10.4–26.3) and 20.6% (95% CI 13.9–29.4%) respectively. Mild delays were more frequent than moderate-to-severe delays. Pooled prevalence of CP was estimated to be 6.8% (95% CI 5.5–8.4). Decreasing gestational age and birthweight resulted in higher prevalences. Lower pooled prevalences were found with the third edition of the Bayley Scales of Infant Development than with the second edition.

CONCLUSION

Even though neonatal intensive care has improved over recent decades, there is still a wide range of neurodevelopmental disabilities resulting from VPT and VLBW births. However, pooled prevalences of CP have diminished over the years.

KEYWORDS

Very preterm infants; very low birthweight infants; neurodevelopmental outcome, meta-analysis.

INTRODUCTION

It is estimated that preterm birth occurs in 11.1% of all worldwide deliveries, of which 10% are very preterm (VPT) infants (28–31wks gestational age) and 5% extremely preterm (EPT) (<28wks gestational age). This represents almost 15 million babies annually and the number keeps rising.[1,2] Such trends could be explained by enhanced reproductive technology, which is commonly associated with multiple gestations, increased age of the mother, and changes in clinical practice as an increase in Cesarean sections before term age.[3] With the more prevalent use of antenatal steroids, surfactants, advanced ventilator techniques, and a drastic reduction in postnatal steroid use over the past two decades,[4] not only have survival rates of VPT, especially EPT, infants increased, but neonatal morbidity has also decreased.[5,6] Furthermore, the frequency and severity of adverse outcomes seem to be related to a decreased gestational age, birthweight, and structural brain changes.[7–9] At present, a considerable number of infants born before 25 weeks gestational age do survive. Nevertheless, fewer than half of those infants survive without neurodevelopmental impairment around 2 years corrected age (20% for infants born at 22–24wks' gestation,[10] and 34–48.5% for infants born at 22–26wks' gestation).[11–13] Proportionally, the prevalence of EPT is low; however, on the basis of their high rate of mortality and morbidity, this may affect the overall impairment rates in the wider VPT population group.

A wide range of neurodevelopmental outcomes of EPT and VPT infants have been described in the literature; however, just a few articles have provided unified data through a global meta-analysis.[7,14–16] Neurodevelopmental outcomes, often defined as a combination of cognitive delays, motor delays, cerebral palsy (CP), blindness, and/or hearing impairment, have been the historical results of interest as they are the most commonly reported disabilities of infants born preterm. A recent meta-analysis by Blencowe et al.[14] was based on articles with a median birth year of 2000 or later and estimated that worldwide 52% and 24% of EPT and VPT infants respectively develop a certain degree of neurodevelopmental impairment. Yet this provides no detailed information on specific outcomes. In the past decade, two meta-analyses provided data on separate outcomes. One was performed by Mwaniki et al.,[16] which included articles from 1966 until 2011. They reported a median prevalence for CP and motor, cognitive, and overall neurodevelopmental impairment in 11.6%, 18.9%, 20.7%, and 27.9% of preterm infants respectively (<37wks gestational age). The other meta-analysis was performed by Oskoui et al.,[15] which featured articles published from 1985 until 2011; they revealed that the pooled prevalence of CP was 14.5% and 11.2% in EPT and VPT infants respectively.

On the basis of continuous advances in obstetric and neonatal care, which has affected the morbidities and neurodevelopmental outcomes of those VPT or very-low-birthweight (VLBW) infants, it is important to collect and unify recent data. Accurate prognostic information is valuable for clinicians and families who are exposed to VPT infants or those with a VLBW, as well as for benchmarking hospitals. The purpose of this systematic review is to provide an up-to-date overview of the separate prevalences of motor and cognitive delay and CP in relation to gestational age and birthweight.

METHODS

Search strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] A systematic literature search was conducted with the Embase, MEDLINE, Web of Science, and CINAHL databases in August 2016. The search strategy comprised free keywords combined with Medical Subject Headings (MeSH) terms or Emtree terms, as detailed in Appendix S1 (online supporting information). Searches were restricted to English, French, or Dutch publications (i.e. languages understood by the review authors) and strictly human studies. Only consecutive cohort studies (prospective and retrospective) investigating and reporting the prevalence of CP and motor or cognitive outcomes from 18 months, or if started earlier going up to at least 20 months, until the age of 6 years of VPT or VLBW infants were included. The participants had to be born within the past decade (2006 or after, or at least two-thirds of the total cohort born after 2006) and before 32 weeks gestational age (or mean gestational age <30.5wks), and/or have a VLBW (<1500g). Follow-ups had to be performed in at least 50 eligible infants by professionals. Outcomes based exclusively on questionnaires for parents or parental interviews were excluded. We also decided to dismiss studies with only outcomes for working memory, language, behavior, or executive functioning. If different papers were based on the same cohort, only the article representing the largest population or reporting most data was retained. The titles and abstracts of the studies were screened by two authors (AP and CVdB) to identify all potentially eligible studies. Full texts of the remaining articles were read and assessed thoroughly to exclude articles that did not meet our inclusion criteria. Any discrepancy in the suitability for inclusion of a study was resolved by discussion among the authors. A flowchart, summarizing the article selection process and the reasons for exclusion, is presented in Figure 1.

Quality assessment

Each study was evaluated by two independent authors (AP and CVdB) for methodological quality. As only cohort studies were included, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used for all studies. A total score was generated by summation of all criteria that were fulfilled and this score was transformed into a percentage. The limit to be included in the meta-analytic review was set at 50%. The results are found in Appendix S2 (online supporting information).

Data extraction and processing

Study characteristics (see Appendix S3, online supporting information) and outcome measurements of each included article were collected using our data extraction form, which included (1) first author, year of publication, country, neonatal death rate, and prevalences of active neonatal care; (2) participant characteristics (birth year, inclusion criteria, mean and range of gestational age and birthweight, exclusion criteria and sample size); (3) outcomes (number of patients at follow-up, mean age at follow-up, outcome measurements, and cut-off values). Outcome measurements were divided into developmental scales, as well as motor and cognitive tests.

Mild delays were considered to be scores between one and two units of standard deviation (SD) and moderate-to-severe delays had a score of two SD below standard norms or the comparison group. If other cut-off values were used, the described criteria were adopted.

Statistical analyses

Prevalence calculations were consistently based on the number of infants with a certain degree of mild or moderate-to-severe delays divided by the total number of infants assessed during the same follow-up period with the same outcome measures. The confidence intervals of the prevalences were calculated by using a logit transformation (with back-transformation). The overall pooled prevalences, with their 95% confidence limits, were estimated with a random-effects model that accounted for between-study heterogeneity. Using a random-effects model allows a higher generalization of the results than a fixed-effects model.[18] Heterogeneity between studies was evaluated with a χ^2 test (Cochran Q statistic) and quantified with the I^2 statistic, which represents the percentage of between-study variation that emanates from heterogeneity rather than from chance. A value of 0% indicated no observed heterogeneity, whereas I^2 values greater than or equal to 50% suggested a substantial level of heterogeneity, and a value greater than 75% was interpreted as high heterogeneity.[19] It is known that this test

has low power for the purposes of detecting heterogeneity and, therefore, it is advised to use a *p* value of 0.10 as a cut-off for significance.[19]

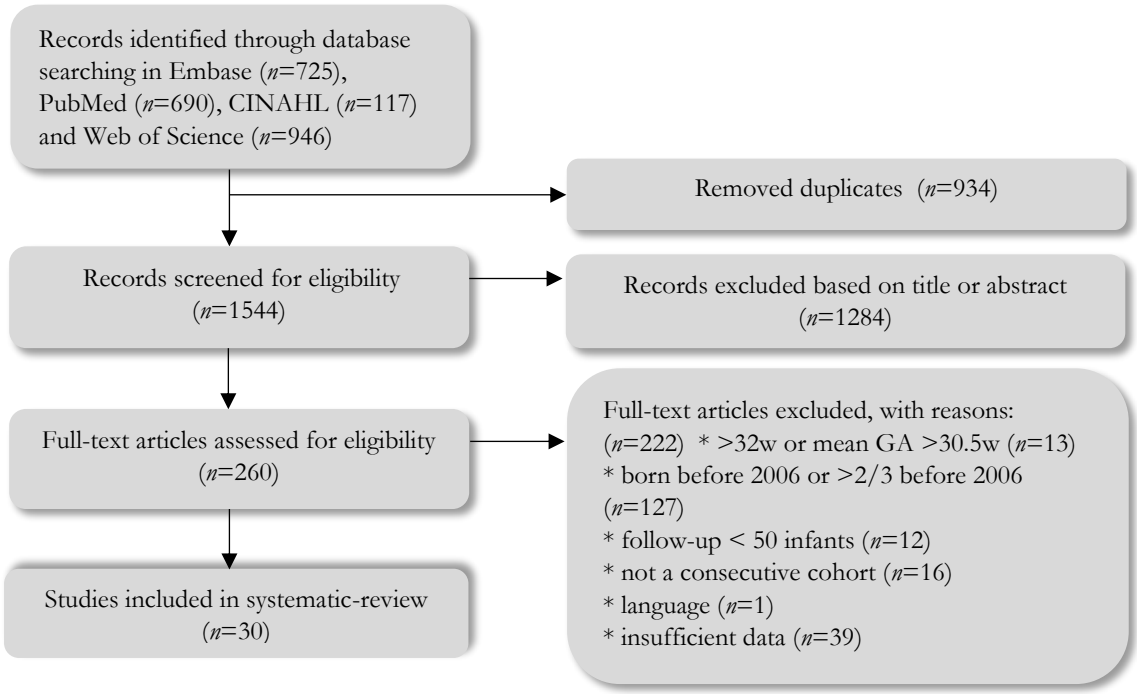
The potential sources of heterogeneity were investigated by stratification of the studies according to potentially relevant characteristics. Subgroup analyses were performed on the basis of the mean gestational age, mean birthweight, follow-up ratio, sample size, outcome measures and cut-off values, country income level, and geographical region. The significance threshold was set at 0.05 for variability in terms of prevalences. The prevalence of CP in relation to gestational age and birthweight was evaluated by meta-regression using weighted-linear regression. All statistical analyses were conducted with the Comprehensive Meta-Analysis program (Biostat, Inc., Englewood, NJ, USA), version 3.3.070.

RESULTS

Study selection process

A total of 2478 publications were initially identified (Fig. 1). After removing duplicates, 1284 citations were excluded on the basis of the screening of titles and abstracts, and 222 citations after detailed assessment of the full text. In total, 44 articles met our inclusion criteria. Cohort information was carefully verified and 14 studies were excluded as their results were based on the same cohort. Finally, 30 studies were retained for the work featured herein.[20–49]

Figure 1. Flowchart outlining literature selection process.



Study characteristics and population

All included articles had a level of evidence B. The quality of the articles varied between 58.3% and 92.3%. No articles were dismissed as a result of the quality assessment.

The characteristics of the included articles are listed in Appendix S2. There were 20 prospective,[20,21,23–26,29–31,33,34,37,40–42,44–48] and 10 retrospective cohort studies. [,22,27,28,32,35,36,38,39,43,49] Altogether, 10 293 infants were included for the follow-up, representing different continents. Eleven studies were conducted in Europe,[20,24,25,29,33,37,40,45–48] nine in North America,[23,30,32,34,35,39,41–43] five in Asia,[27,28,31,44,49] two each in Africa[21,36] and Oceania,[22,38] and one in South America.[26]

Six articles featured exclusively EPT infants.[23,24,32–34,38] Twelve articles used VLBW as an inclusion criterion.[21,25–28,31,37–39,42,44,49] Eleven articles reported a study sample with a mean gestational age of less than 28 weeks,[23,24,28,30,32–35,38,41,43] and 17 articles between 28 and 32 weeks.[20–22,25,26,28,29,31,37,39,42,44–49] Three articles reported no mean gestational age.[27,36,40] The mean birthweight was lower than 1000g in 11 articles,[23,24,28,30–32,34,35,38,41,43] and between 1000g and 1501g in 15 studies.[20–22,25,26,29,37,39,42,44–49] Four articles did not report a mean birthweight.[27,33,36,40]

Neonatal mortality and active neonatal care

The reported prevalences of neonatal mortality and active neonatal care are given in Appendix S3. Of the 30 included articles, just 19 (63.3%) reported the number of infants who died before discharge[21–26,34–38,41,43,44,46,49] or exclusively during the neonatal period, the first 28 days of life.[20,47,48] Four articles featured a subdivision between the period of death (0–7d, 7–28d, and after 28d[22,34,49] or ≤12h and >12h–3d[23]). Administration of antenatal and/or postnatal corticosteroids was described in, 21 articles[20,21,23,24,26,29–33,35–37,39–41,43–45,47,49] and eight articles[20,29,33,37–39,44,46] respectively and varied between 41% and 95% versus 5% and 29%. Only two articles noted specific limitations for active reanimation, which was set at a minimum of 900g in the study by Ballot et al.,[21] and a minimum of 26 weeks gestational age in the work of Besnard et al.[22]

Outcome measurements

The length of follow-up varied between 18 months and 5 years 6 months, except for one study where the authors started follow-up at 8 months up to 22 months.[21] Only five articles reported longer-term outcomes, in particular between 3 and 6 years.[22,24,27,29,33] The most commonly used outcome measure was the Bayley Scales of Infant Development (BSID). The Bayley Scales of Infant Development, second edition (BSID-II) and Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) were used in four studies[26,28,33,49] and 18 studies[21,23,29–

[35,38,39,41–43,45–48] respectively. Other developmental tests used were the Griffiths Development Scales[25,29,37] and Brunet–Lézine test.[40]

The Movement Assessment Battery for Children (M-ABC),[27,29] as a motor outcome measure, was used in two studies. As cognitive assessment tools, the Wechsler Preschool and Primary Scale of Intelligence Test, revised[27] and third editions, were used. The Amiel-Tison and Hempel neurological examinations were performed in six studies[20,24,32,37,39,44] and one study[45] respectively. The remaining investigations featured standard neurological examinations.

Cognitive outcomes

Prevalences

Cognitive outcomes were divided into developmental scales with a cognitive subscore and proper cognitive tests.

The cognitive subscore of the BSID was reported in 20 of the included studies. Five studies did not distinguish between any level of delay,[26,29,32,45,47] and six studies strictly described the prevalence of moderate-to-severe cognitive delay.[23,30,33,35,43,49] Age at follow-up varied between 8 months and 3 years, with most evaluating cognitive outcomes around 2 years corrected age.

Overall, few studies[29,35,37,48] described very low prevalences (<5%) of cognitive delay, whereas Rogers et al.[41] reported the highest prevalence, with nearly 70% of those infants demonstrating a cognitive delay.

Three studies reported the outcome of cognitive tests (Wechsler Preschool and Primary Scale of Intelligence Test) at a later age (27mo to 5y 6mo; see Table 1). Mild cognitive delay (<1 SD), as reported by Keunen et al.,[29] was present in 25% of those infants, while moderate-to-severe delay (<2 SD) was present in 11.9% to 16.3% of the infants.[27,33]

Table 1. Pooled prevalences of motor and cognitive delay at preschool age

Article	Outcome measures	Cut-off	Age at follow-up	Event rate (%)	95% CI	Heterogeneity I^2 (%), p
			Motor outcome			
Howe et al.[27]	M-ABC	<5th centile	5y	33.8 (52/154)	26.7–41.6	
Keunen et al.[29]	M-ABC	<1 SD	5y 6mo	40.0 (34/85)	30.2–50.7	
			Total	36.0 (86/239)	30.2–42.3	0.0 (p=0.337)
			Cognitive outcome			
Keunen et al.[29]	WPPSI-III	<1 SD	5y 6mo	25.0 (10/40)	14.0–40.5	
Howe et al.[27]	WPPSI-R	<2 SD	5y	11.9 (19/160)	7.7–17.9	
Moore et al.[33]	WPPSI-III	<2 SD	27–48mo	16.3 (94/576)	13.5–19.6	
			Total <2 SD	14.7 (113/736)	10.9–19.5	47.0 (p=0.170)

Random-effects analysis. CI, confidence interval; M-ABC, Movement Assessment Battery for Children; WPPSI (-III, -R), Wechsler Preschool and Primary Scale of Intelligence Test (third edition, revised edition).

Meta-analysis

Figure 2 illustrates the individual and pooled prevalences. The random-effects pooled prevalence of overall cognitive delay among VPT/VLBW infants on the basis of the developmental scales was estimated at 16.9% (95% CI 10.4–26.3, I^2=94.22, p<0.001). The pooled prevalence of mild cognitive delay was higher than moderate-to-severe cognitive delay a(95% CI 5.5–12.0, I^2=92.20, p<0.001; Table 4) respectively.

On the basis of cognitive tests at a later age, only the pooled prevalences of moderate-to-severe delay could be calculated. This was estimated at 14.7% (95% CI 10.9–19.5, I^2=46.99, p=0.170), on the basis of just two studies.[27,33]

Subgroup analysis

Table 2 summarizes the prevalence rate calculations and 95% CIs based on mean birthweight and gestational age for the cognitive score of the developmental scales. The prevalence of overall cognitive delay increased with a decreasing mean gestational age, although this was not found to be statistically significant (p=0.305). The estimated pooled prevalence of cognitive delay was higher in EPT infants than VPT infants, at 29.4% (95% CI 7.5–68.0, I^2=96.91, p<0.001) and 14.3% (95% CI 8.2–23.7%, I^2=93.75, p<0.001) respectively. ELBW infants had higher prevalences of cognitive delay than VLBW infants (22.4%, 95% CI 9.7–43.6, I^2=94.88 vs 14.3, 95% CI 7.3–25.4, I^2=94.32, p=0.368). Moderate-to-severe cognitive delay was also found to be higher in EPT and ELBW infants than VPT and VLBW infants. Other subgroup analyses are represented in Table 3. Sample sizes and follow-up ratios were not significant moderators for prevalence variability, whereas geographical region, country income, and age at follow-up were observed to be significant.

Table 4 offers a summary of the pooled prevalences by different outcome measures and the cut-off values used. The results indicate that studies making use of the BSID-II are associated with reports of higher, but not statistically significant (p=0.104), overall cognitive delay prevalence compared with the Bayley-III, when using the same standard cut-off values.

Motor outcomes

Prevalences

Motor outcomes were divided into developmental scales with a motor (sub)score and proper motor tests at a preschool age. Five studies[26,29,32,45,47] did not discriminate between any level of

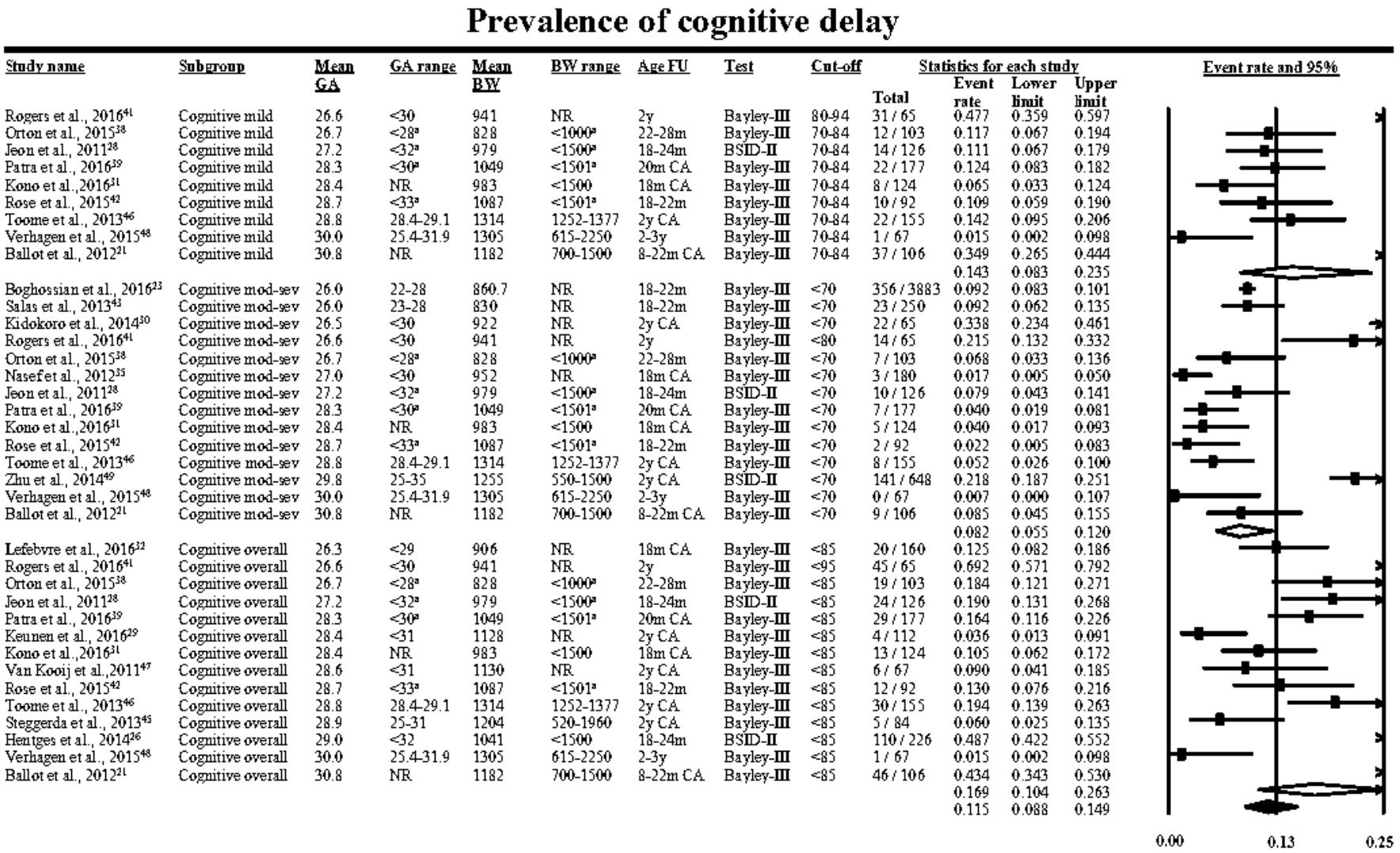


Figure 2: Prevalences of cognitive delays. Forest plot depicting the random-effects proportion meta-analysis for cognitive delays, on the basis of developmental scales (cognitive subscore of the Bayley Scales of Infant Development [2nd and 3rd editions]). Studies are ordered on mean gestation. Black squares denote the reported prevalence of each study and the horizontal line represents the 95% confidence interval (CI). The pooled prevalence estimate is marked with a diamond. [a]Birthweight range and/or gestational age range. GA, gestational age; BW, birthweight; FU, follow-up; NR, not reported; CA, corrected age; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; BSID-II, Bayley Scales of Infant Development, second edition.

Table 2. Pooled prevalences of cerebral palsy and cognitive and motor delays (based on developmental tests) by mean birthweight and gestational age

Subgroup	Categories	Number of studies	Event rate	Pooled prevalence (%)	95% CI (%)	Heterogeneity I^2 (%), p	p value for difference[a]
			Overall cognitive delay				
Mean gestational age	<28wks (26–27wks)	3	84/328	29.4	7.5–68.0	96.91 (p<0.001)	
	28–32wks	11	280/1336	14.3	8.2–23.7	93.75 (p<0.001)	0.305
Mean birthweight	<1000g	5	121/578	22.4	9.7–43.6	94.88 (p<0.001)	
	1000–1500g	9	243/1086	14.1	7.3–25.4	94.32 (p<0.001)	0.368
			Moderate-to-severe cognitive delay				
Mean gestational age	<28wks (26–27wks)	6	425/4546	10.9	6.1–18.6	91.30 (p <0.001)	
	28–32wks	8	182/1495	5.8	2.7–12.0	91.10 (p <0.001)	0.184
Mean birthweight	<1000g	8	440/4796	9.5	5.9–15.0	88.74 (p <0.001)	
	1000–1500g	6	167/1245	5.6	2.1–14.1	91.84 (p <0.001)	0.372
			Overall motor delay				
Mean gestational age	<28wks (26–27wks)	3	120/327	44.5	14.2–79.5	96.70 (p<0.001)	
	28–32wks	10	236/1181	16.4	11.1–23.7	85.92 (p<0.001)	0.093
Mean birthweight	<1000g	5	177/577	34.4	18.5–54.6	94.12 (p<0.001)	
	1000–1500g	8	179/931	13.3	7.6–22.2	88.79 (p<0.001)	0.021
			Moderate-to-severe motor delay				
Mean gestational age	<28wks	6	394/3340	11.2	7.0–17.4	89.82 (p<0.001)	
	<26wks	1	45/576	7.8	5.9–10.3	0.0	
	26–27wks	5	349/2764	12.0	6.5–21.1	89.15 (p<0.001)	
	28–32wks	6	41/692	6.3	4.3–9.3	34.87 (p=0.175)	0.227[a]
Mean birthweight	<1000g	7	368/3014	10.6	6.5–16.7	86.44 (p<0.001)	
	1000–1500g	4	22/442	5.5	3.3–9.1	23.53 (p=0.270)	0.185
	Not reported	1	45/576	7.8	5.9–10.3	0.0	
			Cerebral palsy				
Mean gestational age	<28wks	9	603/5416	10.0	8.1–12.2	61.76 (p=0.007)	
	<26wks	3	103/769	13.2	10.6–16.4	12.1 (p=0.320)	
	26–27wks	6	500/4647	8.6	6.4–11.6	64.8 (p=0.014)	
	28–32wks	15	117/2373	4.5	3.3–6.3	57.4 (p=0.003)	<0.001[a]
	Not reported	1	8/60	13.3	6.8–24.5	0.0	
Mean birthweight	<1000g	10	534/5090	8.4	6.6–10.7	58.5 (p=0.10)	
	1000–1500g	13	103/2123	4.2	2.9–6.2	62.2 (p=0.002)	<0.001
	Not reported	2	91/636	14.3	11.8–17.3	0.0 (p=0.821)	

Random-effects analysis. [a]p value for the mean gestational age is based on the three categories (<26wks, 26–27wks, and 28–32wks gestational age); the category 'not reported' is not included for the calculations of the p value. CI, confidence interval.

Table 3. Pooled prevalences of cerebral palsy and motor and cognitive delay (based on developmental tests) by subgroup analysis

Subgroup	Categories	Num-ber of studies	Event rate	Pooled preva-lence	95% CI	Heterogeneity I^2 (%), p	p value for differen
			Overall cognitive delay				
Age at follow-	18–24mo	11	298/138	16.8	9.5–28.0	94.89 (p<0.001)	
	24–36mo	1	1/67	1.5	0.2–9.8	0.0	
	8–22mo	1	46/106	43.4	34.3–53.0	0.0	
	22–28mo	1	19/103	18.4	12.1–27.1	0.0	<0.001
Follow-up	<40%	1	24/126	19.0	13.1–26.8	0.0	
	40–70%	2	48/280	17.2	13.2–22.0	<0.001	
	70–100%	10	279/113	17.0	8.8–30.5	95.16 (p<0.001)	
	Not reported	1	13/124	10.5	6.2–17.2	0.0	0.276
Sample size	<100	5	69/375	12.3	2.6–42.4	95.44 (p<0.001)	
	100–500	9	295/128	18.7	11.2–29.5	94.17 (p<0.001)	0.581
Geographical	Africa	1	46/106	43.4	34.3–53.0	0.0	
	Asia	2	37/150	14.5	7.9–25.2	71.77 (p=0.060)	
	Europe	5	46/485	6.9	2.9–15.5	82.11 (p<0.001)	
	North America	4	106/494	23.7	8.4–51.5	96.01 (p<0.001)	
	Oceania	1	19/103	18.4	12.1–27.1	0.0	
	South America	1	110/226	48.7	42.2–55.2	0.0	<0.001
Country	High-income economy	12	208//13	13.8	8.5–21.5	90.42 (p<0.001)	
	Upper-middle-income	2	156/332	47.0	41.7–52.4	<0.001	<0.001
			Overall motor delay				
Age at follow-	18–24mo	10	296/123	21.2	13.4–31.9	91.98	
	24–36mo	1	1/67	1.5	0.2–9.8	0.0	
	8–22mo	1	40/106	37.7	29.0–47.3	0.0	
	22–28mo	1	19/102	18.6	12.2–27.4	0.0	<0.001
Follow-up	<40%	1	32/126	25.4	18.6–33.7	0.0	
	40–70%	2	63/279	22.4	16.9–29.0	30.00	
	70–100%	9	236/979	17.7	9.1–31.5	93.52	
	Not reported	1	25/124	20.2	14.0–28.1	0.0	0.664
Sample size	<100	5	80/375	12.1	1.8–51.0	95.99	
	100–500	8	276/113	24.1	18.8–30.4	78.38	0.423
Geographical	Africa	1	40/106	37.7	29.0–47.3	0.0	
	Asia	2	55/250	22.9	18.1–28.5	<0.001	
	Europe	4	11/330	3.0	1.0–8.5	57.67	
	North America	4	160/494	37.8	17.6–63.4	95.44	
	Oceania	1	19/102	18.6	12.2–27.4	0.0	
	South America	1	69/226	30.5	24.9–36.8	0.0	<0.001
Country	High-income economy	11	247/117	17.4	10.4–27.7	91.68	
	Upper-middle-income	2	109/332	33.4	26.9–40.6	40.92	0.012
			Cerebral palsy				
Age at follow-	18–24mo	19	622/674	6.7	5.2–8.5	74.56	
	22–28mo	2	8/273	2.4	0.2–20.3	80.13	
	24–48mo	3	94/721	10.6	5.7–18.6	66.47	
	8–22mo	1	4/106	3.8	1.4–9.6	0.0	0.224
Follow-up	<40%	2	12/205	6.1	3.5–10.4	0.0 (p=0.328)	
	40–70%	5	111/988	9.1	5.3–15.3	77.5 (p=0.001)	
	70–100%	17	600/653	6.3	4.8–8.3	76.5 (p<0.001)	
	Not reported	1	5/124	4.0	1.7–9.3	0.0	0.423
Sample size	<100	8	40/570	7.7	4.8–12.0	51.3 (p=0.045)	
	100–500	14	113/217	5.4	4.0–7.2	56.5 (p=0.005)	
	>500	3	575/510	10.9	8.1–14.4	86.8 (p=0.001)	0.003
Geographical	Africa	2	12/166	7.5	2.1–23.6	78.4 (p=0.032)	
	Asia	4	65/953	6.9	5.5–8.7	0.0 (p=0.574)	
	Europe	8	121/138	5.9	3.2–10.5	80.4 (p<0.001)	
	North America	8	513/493	7.6	5.4–10.5	74.2 (p<0.001)	
	Oceania	2	10/188	5.5	3.0–9.9	0.0 (p<0.001)	
	South America	1	7/226	3.1	1.5–6.4	0.0	0.345
Country	High-income economy	20	658/675	7.0	5.5–8.9	75.1 (p<0.001)	
	Upper-middle-income	3	59/980	4.9	2.5–9.1	67.8 (p=0.045)	
	Lower-middle-income	2	11/115	9.5	3.9–21.1	48.4 (p=0.164)	0.419

Random-effects analysis. CI, confidence interval.

delay, and another four studies just described the prevalence of moderate-to-severe motor delay.[23,30,33,35]

Most of the articles reported motor outcomes at approximately 2 years corrected age. The prevalence of motor delays, based on developmental tests, varied considerably between the included studies. Moderate-to-severe delays were observed to be less than 5% in four of 17 studies,[31,35,42,48] and reached as high as 34% in the work of Rogers et al.,[41] where higher cut-off values for the motor scale of the Bayley-III were applied.

The prevalence of motor delays evaluated with the M-ABC increased until 33% or 40% at the age of 5 to 5 years 6 months, investigated by Howe et al.[27] and Keunen et al[29] respectively.

Meta-analysis

Pooled prevalences and a corresponding forest plot are featured in Figure 3. An overall motor delay, based on developmental scales, was documented at 20.6% (95% CI 13.9–29.4, I^2=90.91, p<0.001) among all VPT or VLBW infants. Mild delays (18.0%, 95% CI 11.1–27.8, I^2=88.53, p<0.001) were more common than moderate-to-severe motor delays (8.6%, 95% CI 6.0–12.1, I^2=84.77, p<0.001; Fig. 3).

At preschool age, a pooled prevalence of 36.0% (95% CI 30.2–42.3) was estimated for motor delay, established with the M-ABC (Table 1).

Subgroup analysis

Subgroup analyses based on the results of developmental tests are presented in Tables 2-4. The prevalence of motor delays among EPT infants was considerably higher than in VPT infants (44.5%, 95% CI 14.2–79.5, I^2=96.70 vs 16.4%, 95% CI 11.1–23.7, I^2=85.92), although this was not statistically significant (p=0.093). Motor delays were also significantly (p=0.021) more present in ELBW infants than in VLBW infants (34.4%, 95% CI 18.5–54.6, I^2=94.12 vs 13.3%, 95% CI 7.6–22.2, I^2=88.79).

Country income, geographical region, and age at follow-up were identified as significant moderators of prevalence variability (p<0.05). On the other hand, the variability in prevalence estimates was not explained by follow-up rate and sample size (p>0.05).

Stratification by outcome measure (see Table 4) showed that studies using the BSID-II had significantly (p=0.010) higher prevalence rates than studies using the Bayley-III, when using the same cut-off values.

Prevalence of motor delay

Study name	Subgroup	Mean GA	GA	Mean BW	BW range	Age FU	Test	Cut-off	Statistics for each study			
									Total	Event rate	Lower limit	Upper limit
Rogers et al., 2016[41]	Motor mild	26.6	<30	941	NR	2y	Bayley-III	80-94	34 / 65	0.523	0.403	0.641
Orton et al., 2015[38]	Motor mild	26.7	<28[a]	828	<1000[a]	22-28m CA	Bayley-III	70-84	11 / 102	0.108	0.061	0.184
Jeon et al., 2011[28]	Motor mild	27.2	<32[a]	979	<1500[a]	18-24m CA	BSID-II	70-84	19 / 126	0.151	0.098	0.224
Patra et al., 2016[39]	Motor mild	28.3	<30[a]	1049	<1501[a]	20m CA	Bayley-III	70-84	33 / 177	0.186	0.136	0.251
Kono et al.,2016[31]	Motor mild	28.4	NR	983	<1500	18m CA	Bayley-III	70-84	19 / 124	0.153	0.100	0.228
Rose et al., 2015[42]	Motor mild	28.7	<33[a]	1087	<1501[a]	18-22m CA	Bayley-III	70-84	12 / 92	0.130	0.076	0.216
Verhagen et al., 2015[48]	Motor mild	30.0	25.4-31.9	1305	615-2250	2-3y	Bayley-III	SS 4-7	1 / 67	0.015	0.002	0.098
Ballot et al., 2012[21]	Motor mild	30.8	NR	1182	700-1500	8-22m CA	Bayley-III	70-84	32 / 106	0.302	0.222	0.396
										0.180	0.111	0.278
Moore et al., 2012[33]	Motor mod-sev	25.6	22-26	NR	NR	27-48m	Bayley-III	<70	45 / 576	0.078	0.059	0.103
Boghossian et al., 2016[23]	Motor mod-sev	26.0	22-28	860.7	NR	18-22m CA	Bayley-III	<70	304 / 2352	0.129	0.116	0.143
Kidokoro et al., 2014[30]	Motor mod-sev	26.5	<30	922	NR	2y CA	Bayley-III	<70	9 / 65	0.138	0.074	0.245
Rogers et al., 2016[41]	Motor mod-sev	26.6	<30	941	NR	2y	Bayley-III	<80	22 / 65	0.338	0.234	0.461
Orton et al., 2015[38]	Motor mod-sev	26.7	<28[a]	828	<1000[a]	22-28m CA	Bayley-III	<70	8 / 102	0.078	0.040	0.149
Nasef et al., 2012[35]	Motor mod-sev	27.0	<30	952	NR	18m CA	Bayley-III	<70	6 / 180	0.033	0.015	0.072
Jeon et al., 2011[28]	Motor mod-sev	27.2	<32[a]	979	<1500[a]	18-24m CA	BSID-II	<70	13 / 126	0.103	0.061	0.170
Patra et al., 2016[39]	Motor mod-sev	28.3	<30[a]	1049	<1501[a]	20m CA	Bayley-III	<70	11 / 177	0.062	0.035	0.109
Kono et al.,2016[31]	Motor mod-sev	28.4	NR	983	<1500	18m CA	Bayley-III	<70	6 / 124	0.048	0.022	0.104
Rose et al., 2015[42]	Motor mod-sev	28.7	<33[a]	1087	<1501[a]	18-22m CA	Bayley-III	<70	3 / 92	0.033	0.011	0.096
Verhagen et al., 2015[48]	Motor mod-sev	30.0	25.4-31.9	1305	615-2250	2-3y	Bayley-III	SS<4	0 / 67	0.007	0.000	0.107
Ballot et al., 2012[21]	Motor mod-sev	30.8	NR	1182	700-1500	8-22m CA	Bayley-III	<70	8 / 106	0.075	0.038	0.144
										0.086	0.060	0.121
Lefebvre et al., 2016[32]	Motor overall	26.3	<29	906	NR	18m CA	Bayley-III	<85	45 / 160	0.281	0.217	0.356
Rogers et al., 2016[41]	Motor overall	26.6	<30	941	NR	2y	Bayley-III	<95	56 / 65	0.862	0.755	0.926
Orton et al., 2015[38]	Motor overall	26.7	<28[a]	828	<1000[a]	22-28m CA	Bayley-III	<85	19 / 102	0.186	0.122	0.274
Jeon et al., 2011[28]	Motor overall	27.2	<32[a]	979	<1500[a]	18-24m CA	BSID-II	<85	32 / 126	0.254	0.186	0.337
Patra et al., 2016[39]	Motor overall	28.3	<30[a]	1049	<1501[a]	20m CA	Bayley-III	<85	44 / 177	0.249	0.190	0.317
Keunen et al., 2016[29]	Motor overall	28.4	<31	1128	NR	2y	Bayley-III	<85	2 / 112	0.018	0.004	0.069
Kono et al.,2016[31]	Motor overall	28.4	NR	983	<1500	18m CA	Bayley-III	<85	25 / 124	0.202	0.140	0.281
Van Kooij et al.,2011[47]	Motor overall	28.6	<31	1130	NR	2y CA	Bayley-III	<85	1 / 67	0.015	0.002	0.098
Rose et al., 2015[42]	Motor overall	28.7	<33[a]	1087	<1501[a]	18-22m CA	Bayley-III	<85	15 / 92	0.163	0.101	0.253
Steggerda et al., 2013[45]	Motor overall	28.9	25-31	1204	520-1960	2y CA	Bayley-III	<85	7 / 84	0.083	0.040	0.165
Hentges et al., 2014[26]	Motor overall	29.0	<32	1041	<1500	18-24m CA	BSID-II	<85	69 / 226	0.305	0.249	0.368
Verhagen et al., 2015[48]	Motor overall	30.0	25.4-31.9	1305	615-2250	2-3y	Bayley-III	SS<8	1 / 67	0.015	0.002	0.098
Ballot et al., 2012[21]	Motor overall	30.8	NR	1182	700-1500	8-22m CA	Bayley-III	<85	40 / 106	0.377	0.290	0.473
										0.206	0.139	0.294
										0.134	0.107	0.168

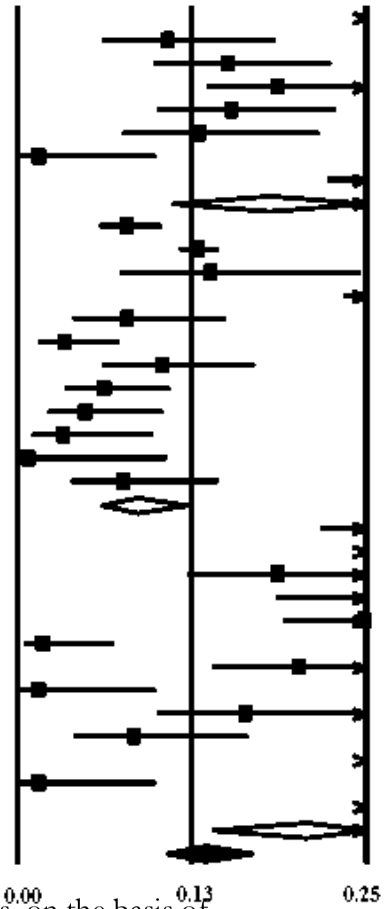


Figure 3. Prevalences of motor delays. Forest plot depicting the random-effects proportion meta-analysis for motor delays, on the basis of developmental scales (motor subscore of the BSID-II and Bayley-III). Studies are ordered on mean gestation. Black squares denote the reported prevalence of each study and the horizontal line represents the 95% confidence interval. The pooled prevalence estimate is marked with a diamond. [a]Birthweight range and/or gestational age range. GA, gestational age; BW, birthweight; FU, follow-up ; CI, confidence interval; NR, not reported; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; CA, corrected age; BSID-II, Bayley Scales of Infant Development, second edition; SS, scaled scores.

Table 4. Pooled prevalences of motor, cognitive, and general developmental delay (based on developmental tests) by outcome measures and cut-off values

Cut-off value	Cut-off value	Outcome measures	Number of studies	Event rate	Pooled prevalence (%)	95% CI	Heterogeneity I^2 (%), p	p value for difference	
				Cognitive delay					
Mild delay	Index/CS 70–84	BSID-II	1	14/126	11.1	6.7–17.9	0.0	}0.817	
		Bayley-III	7	112/824	12.1	7.0–20.2	86.69 (p<0.001)		}<0.001
		BSID-II + Bayley-III	8	126/950	12.1	7.5–19.0	85.07 (p<0.001)		
	CS 80–94	Bayley-III	1	31/65	47.7	35.9–59.7	0.0		
	Total	BSID-II + Bayley-III	9	157/1015	14.3	8.3–23.5	90.49 (p<0.001)		
Moderate-to-severe delay	Index/CS <70	BSID-II	2	151/774	13.9	4.9–33.7	91.42 (p=0.001)	}0.185	
		Bayley-III	11	442/5202	6.5	4.9–10.9	85.36 (p<0.001)		}<0.001
		BSID-II + Bayley-III	13	593/5976	7.5	4.9–11.2	92.49 (p<0.001)		
	CS <80	Bayley-III	1	14/65	21.5	13.2–33.2	0.0		
	Total	BSID-II + Bayley-III	14	607/6041	8.2	5.5–12.0	92.20 (p<0.001)		
Overall delay	Index/CS <85	BSID-II	2	134/352	32.3	10.9–65.2	96.44 (p<0.001)	}0.104	
		Bayley-III	11	185/1247	12.6	8.1–19.0	87.56 (p<0.001)		}<0.001
		BSID-II + Bayley-III	13	319/1599	14.6	9.1–22.6	93.11 (p<0.001)		
	CS <95	Bayley-III	1	45/65	69.2	57.1–79.2	0.0		
	Total	BSID-II + Bayley-III	14	364/1664	16.9	10.4–26.3	94.22 (p<0.001)		
				Motor delay					
Mild delay	Index/CS 70–84	BSID-II	1	19/126	15.1	9.8–22.4	0.0	}0.633	
		Bayley-III	5	107/601	17.2	11.9–24.3	74.67 (p=0.003)		
		BSID-II + Bayley-III	6	126/727	16.9	12.4–22.7	69.97 (p=0.005)		}<0.001
	CS 80–94	Bayley-III	1	34/65	52.3	40.3–64.1	0.0		
	Scaled score 4–7	Bayley-III	1	1/67	1.5	0.2–9.8	0.0		
	Total	BSID-II + Bayley-III + PDMS-II	8	161/859	18.0	11.1–27.8	88.53 (p<0.001)		
Moderate-to-severe delay	Index/CS <70	BSID-II	1	13/126	10.3	6.1–17.0	0.0	}0.291	
		Bayley-III	9	400/3774	7.4	5.2–10.4	80.18 (p<0.001)		
		BSID-II + Bayley-III	10	413/3900	7.7	5.6–10.5	77.76 (p<0.001)		}<0.001
	CS <80	Bayley-III	1	22/65	33.8	23.4–46.1	0.0		
	Scaled score <4	Bayley-III	1	0/67	0.7	0.0–10.7	0.0		
	Total	BSID-II + Bayley-III + PDMS-II	12	435/4032	8.6	6.0–12.1	84.77 (p<0.001)		

Table 4. Continued.

Overall delay	Index/CS <85	BSID-II	2	101/352	28.7	24.1–33.8	3.82 (p=0.308)	}0.010	
		Bayley-III	9	198/1024	17.0	11.5–24.4	84.72 (p<0.001)		
		BSID-II + Bayley-III	11	299/1376	19.8	14.9–25.9	82.64 (p<0.001)		}<0.001
	CS <95	Bayley-III	1	56/65	86.2	75.5–92.6	0.0		
	Scaled score ≤7	Bayley-III	1	1/67	1.5	0.2–9.8	0.0		
	Total	BSID-II + Bayley-III + PDMS-II	13	356/1508	20.6	13.9–29.4	90.91 (p<0.001)		
General development									
Mild delay	GQ < 1 SD > 2 SD	GDS	2	58/432	7.8	0.9–42.6	94.35 (p<0.001)		
Moderate-to-severe delay	GQ < 2 SD	GDS	2	33/432	4.3	0.5–29.3	89.53 (p=0.002)		
Overall delay	GQ < 1 SD	GDS	3	100/530	11.2	2.7–36.4	95.25 (p<0.001)		
		BL	1	101/968	10.4	8.7–12.5	0.0		
	Total	GDS + BL	4	201/1498	11.2	4.7–24.6	96.30 (p<0.001)		

Random-effects analysis. CI, confidence interval; CS, composite score; BSID-II, Bayley Scales of Infant Development, second edition; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; PDMS-II, Peabody Developmental Motor Scales, second edition; GQ, general quotient; GDS, Griffith Developmental scale; BL, Brunet–Lézine test.

General developmental quotient

Some developmental scales only provide an overall general developmental quotient, such as the Griffith's developmental scales, which was used in three studies,[25,29,37] and the Brunet–Lézine test used in the study of Perivier et al.[40]

The estimated pooled prevalence for a general developmental quotient less than 1 SD is 11.2% (I^2=96.30, p<0.001) and is reported in Table 4. The 95% prediction interval ranged from 4.7% to 24.6%, reflecting the between-study heterogeneity.

CP

Prevalences

In total, 25 of the included studies reported prevalences of CP.[20–24,26,28–39,42–47,49] Only six studies made a distinction between mild and moderate-to-severe CP, on the basis of the Gross Motor Function Classification System.[23,32,37,38,45,46] As a consequence of the small number of articles reporting the degree of disability and the differences in classification (moderate-to-severe Gross Motor Function Classification System >2 or ≥2), no separated pooled prevalences were calculated. Neurological assessment was completed between 18 months and 3 years.

Three investigations found a CP prevalence lower than 1%,[20,29,47] while five others observed it to be more than 10%.[23,24,30,33,36]

Meta-analysis

The overall prevalence of CP in the 25 retrieved studies was 6.8% (95% CI 5.5–8.4, I^2=76.1%, p<0.001; see Fig. 4).

Subgroup analysis and meta-regression

Significant differences (p<0.001) in the overall prevalence rates were documented according to the mean gestational age, being significant higher for EPT infants (10.0%, 95% CI 8.1–12.2, I^2=61.7, p=0.007) than for VPT infants (4.5%, 95% CI 3.3–6.3, I^2=57.4, p=0.003), and to the mean birthweight, being greater for ELBW infants (8.4%, 95% CI 6.6–10.7, I^2=58.5, p=0.10) than for VLBW infants (4.2%, 95% CI 2.9–6.2, I^2=62.2, p=0.002). The pooled differences in prevalence rates following the possible comparisons within studies were all non-significant (p<0.05) except for sample size (p=0.003) (Table 3).

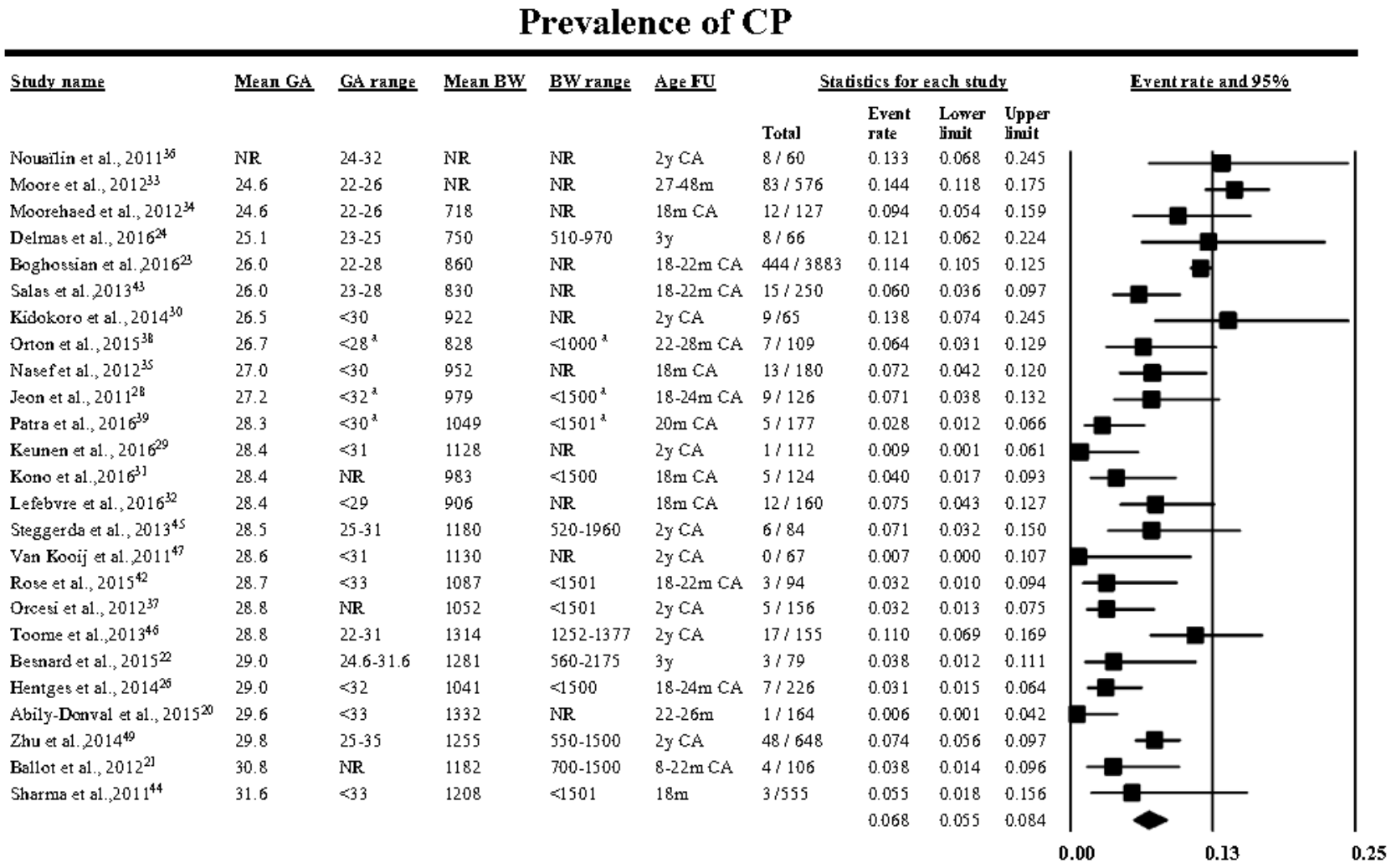


Figure 4. Prevalences of cerebral palsy (CP). Forest plot depicting the random-effects proportion meta-analysis for CP. Studies are ordered on mean gestation. Black squares denote the reported prevalence of each study and the horizontal line represents the 95% confidence interval. The pooled prevalence estimate is marked with a diamond. [a]Birthweight range and/or gestational age range. GA, gestational age; BW, birthweight; FU, follow-up; NR, not reported.

The results of random-effects meta-regression analyses that assessed the relationship between the selected covariates and the observed prevalences in each single study are presented in Figures 5 and 6. There was a statistically significant linear trend that explained prevalence variation by mean birthweight and mean gestational age (p<0.001) with 33% and 35% respectively, of variance accounted for.

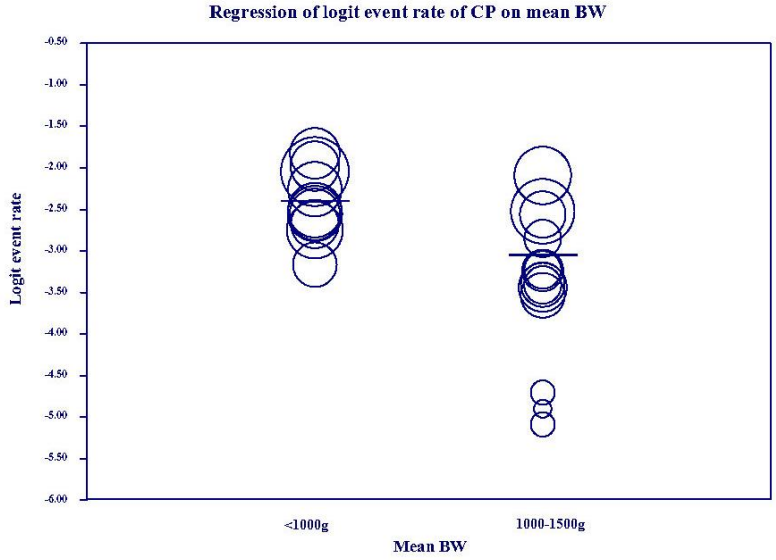


Figure 5. Regression of mean birthweight (BW) on logit event rate of cerebral palsy (CP). Scatter-plot representation of the relationship between gestational age and the prevalence of CP. Each circle represents the results of a study.

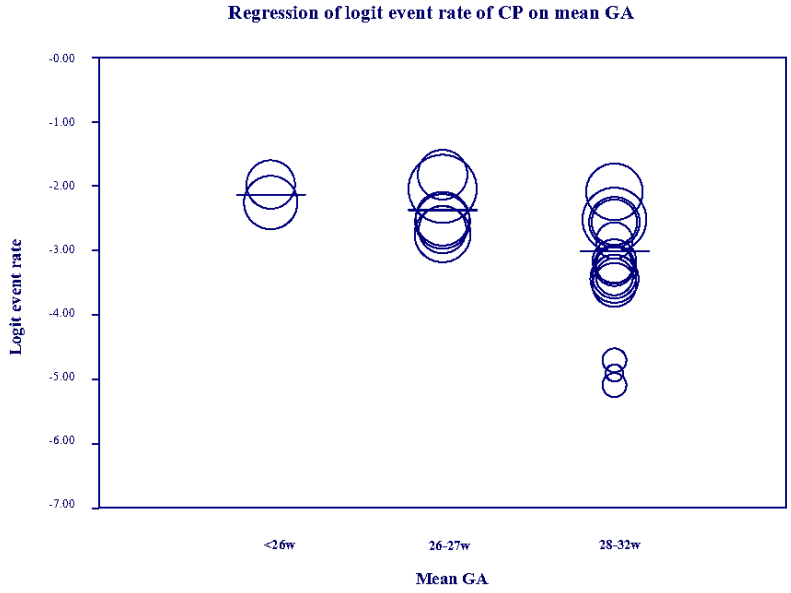


Figure 6. Regression of mean gestational age (GA) on logit event rate of cerebral palsy (CP). Scatter-plot representation of the relationship between birthweight and the prevalence of CP. Each circle represents the results of a study.

DISCUSSION

Main findings

This systematic review and meta-analysis was performed to supply an overview of separate prevalences of CP, as well as motor and cognitive delays in VPT and VLBW infants born in the past decade, and to evaluate the influence of gestational age and VLBW on these prevalences. Most of the included studies assessed motor and cognitive development near the age of 2 years corrected age. At this age, there is still a high proportion of parents motivated to attend follow-up visits and this is also the age where neurological problems can be reliably detected and most children with CP are diagnosed.[50]

Herein, it was estimated that 20.6% (95% CI 13.9–29.4) and 16.9% (95% CI 10.4–26.3) of VPT or VLBW infants respectively, developed a certain degree of motor or cognitive delay, on the basis of developmental scales at approximately 2 years corrected age. As expected, mild motor or cognitive delays were more frequent than moderate-to-severe delays (18.0% vs 8.6% and 14.3% vs 8.2% respectively).

Contrary to the definition of motor or cognitive delay, which varied considerably between articles, CP is a clearly defined criterion used as a touchstone for neurodevelopmental outcomes after preterm births and the quality of neonatal care. The overall estimated pooled prevalences for CP was 6.8% (95% CI 5.5–8.4) for all included articles. Since the heterogeneity of the articles was substantial (I^2>50), the specific rates should be interpreted with care.

A secondary objective of this study was to perform meta-regression to discern potential associations between the prevalence of CP, as well as motor and cognitive delays and mean birthweight and gestational age. Although overall prevalences of CP along with motor and cognitive delays were higher in ELBW infants than VLBW infants, this variability was only statically significant for CP (p<0.001) and motor delays (p=0.012). On the other hand, the subgroup analyses clearly indicated that the overall prevalence of CP and motor and cognitive delays rose with decreasing gestational age. However, this was only statistically significant for CP (p<0.001). These findings are in line with the results of a considerable number of studies where EPT and ELBW infants exhibited greater neurodevelopmental impairment than their older peers.[8,14,51,52]

As the prevalence of CP was elevated with decreasing gestational age[7] and more EPT infants survived to discharge, this could be proportionally the most concerning group. In this systematic review, three of the included articles had a mean gestational age of less than 26 weeks in their cohort,[24,33,34] which also included infants born at 22 to 23 weeks' gestation and reported prevalences varying between 9.4% and 14.4%. In total, the overall pooled prevalence

rate of CP in EPT was 10.0% (95% CI 8.1–12.2). Himpens et al.[7] reported a weighted prevalence of 14.4% in EPT infants, on the basis of all articles with a birth year earlier than 2006. An update of this meta-analysis by Oskoui et al.[15] included articles from 1985 until 2011 and showed that the overall rate remained constant. As such, our meta-analysis, which only included recent articles, could verify the decreasing trend of CP over recent years in EPT infants as a direct consequence of improved neonatal care.[53–56]

Only five articles fulfilling our inclusion criteria reported longer-term outcomes up to the age of 6 years. Large differences in prevalences were seen between articles reporting motor delays based on developmental scales, such as the BSID-II and Bayley-III tests, and motor tests such as the M-ABC. Motor delays assessed by those developmental scales were estimated to be 20.6% (95% CI 13.9–29.4) and rose to between 34% and 40% of motor delays when evaluated with the M-ABC at a preschool age.[27,29] This corresponds to the study of Spittle et al.,[57] which concluded that the Bayley-III underestimates later rates of motor performance delays evaluated with the M-ABC. This could be understood by the fact that the Bayley-III assesses current levels of motor development rather than basic milestones whereas the M-ABC focuses on specific motor function tasks in various categories (e.g. manual dexterity, aiming and catching, balance tasks). The previous literature has suggested that motor milestones could be more easily attained than advanced motor skills.[58] The same underestimation with the BSID-II was observed for later cognitive delays.[59] In accordance with this, we found that the pooled prevalences of moderate-to-severe cognitive delay evaluated with the BSID-II and Bayley-III were considerably lower than moderate-to-severe delay determined with the Wechsler Preschool and Primary Scale of Intelligence Test, third edition (8.2%, 95% CI 5.5–12.0 vs 14.7%, 95% CI 10.9–19.5).

It seems that as VPT and VLBW infants get older, more cognitive and motor delays become apparent as a result of increasing functional demands in daily life and school activities and because of the use of more specific function-related assessment tools instead of developmental outcome measurements. Therefore the results of developmental tests performed before or around 2 years of age should be treated with caution as the predictive value for later motor or cognitive delays is limited.[60]

To our knowledge, no similar previously unified data on separate motor or cognitive outcome prevalences in VPT or VLBW infants exist. Consequently, no possible evolution in time can be reported.

Study strengths and limitations

The major strength of this systematic review is that a literature search was performed in four different databases to identify all relevant articles. Articles were included on the basis of birthweight and gestational age, which may have caused more heterogeneity between studies but ensured that more pertinent publications were included. Certain groups within the preterm population are at greater risk of developing neurodevelopmental delays; therefore only sequential total cohort studies of VPT and/or VLBW infants were included, which reduced sampling bias. Additionally, because the sample size was set at a minimum of 50 infants, less representative studies were left out.

This systematic review also had several limitations that need to be considered when interpreting our findings. As our review featured clinically and methodologically very diverse studies, it is not surprising that high heterogeneity (I^2>75) was found for each individual outcome. This heterogeneity could have arisen from many different factors such as inclusion and exclusion criteria, length of follow-up, outcome measures used, etc. An example worth mentioning in this regard is the fact that just a few studies excluded infants with congenital malformations and genetic disorders. Some of those disorders could be associated with an increased risk of an adverse neurodevelopmental outcome, skewing the results towards higher prevalences of neurodevelopmental delay.

Several other sources of heterogeneity were explored into more detail, although this could never explain the entirety of the variance in the outcomes.

First, our review featured articles from all over the world, varying between low- and high-income countries and representative of important differences in religions, health systems, and norms surrounding active neonatology care. Most of the included articles originated from high-income countries where, in general, the prevalence of preterm infants was lower and the survival rate was higher.[1] Upper-middle-income countries reported significant (p<0.001) higher pooled prevalences of cognitive and motor delays than high-income countries. Stratification by region resulted in a significant variance for motor and cognitive delays (p<0.001). The reported prevalences were systematically the lowest in Europe and the highest in South America for cognitive delay, and North America and Africa for motor delay. No consistent results could be determined for income level and geographical region with respect to the prevalence of CP. Nevertheless, the number of studies or the sample size, in particular covariate subgroups, may be too sparse to arrive at robust conclusions.

Second, different outcome measurements and cut-off values were used, creating a serious challenge for this review in terms of cataloguing all outcome data into mild-to-severe

developmental delays. Even with the most widely used assessment tool, the BSID, inequity is often observed between the second and third editions. Recent studies have reported higher scores for the Bayley-III than the BSID-II.[13,61] Consequently, fewer infants were classified as moderately and severely impaired. Our results were consistent with these observations. It was found that pooled prevalences for moderate-to-severe motor and cognitive delays were higher when evaluated using the BSID-II than the Bayley-III, while the opposite was observed within the mild category. It is unclear whether the BSID-II underestimates or the Bayley-III overestimates development. To correct for this, it is advised to increase the cut-off values for the Bayley-III.[62] Only one study followed this advice and applied higher cut-off values for the Bayley-III, specifically composite scores of 80 and 65 instead of the 70 and 55 values generally used respectively.[41] This could explain why this study exhibited the highest prevalence of all the included studies on the subscales of motor and cognitive delays of the Bayley-III. Moreover, as described in a recent systematic review of the cross-cultural validity of assessment tools, the use of standardized norms should be used and interpreted with caution across varying cultures versus the initial samples.[63] For example, one included study was based on an Australian sample,[37] and used standardized American Bayley-III norms, although it is suggested that this would considerably underestimate developmental delays.[64]

Third, the follow-up rate and sample size varied considerably between the studies. The mean follow-up rate was 77.7%, meaning that nearly one out of five infants was not seen at follow-up. Furthermore, two of the 28 articles reporting the number of eligible infants for follow-up had a follow-up rate of less than 50%.[22,28] However, subgroup analyses based on the percentage of eligible infants that had follow-up were not statistically different for CP or motor and cognitive delays ($p>0.005$). Only the prevalence of CP was significantly influenced by the sample size ($p=0.003$), but no linear trend could be observed. Of all included articles, only 12 reported information about statistics between the infants followed up and the groups lost to follow-up. Six articles found no significant differences in neonatal characteristics,[20,28,29,32,37,47] and one reported no difference in maternal characteristics.[32] In contrast, six articles noted significant differences between both groups.[24,25,29,38–40] Infants included in the follow-up had significantly ($p<0.05$) lower mean birthweight[25,29,38] and gestational age,[25,38,40] and were more severely ill (days on mechanical ventilation,[25,29] sepsis,[25,29,38] infection,[24,40] bronchopulmonary dysplasia,[25,39] chorioamnionitis,[24] chronic lung disease,[38] and inferior neuromotor examination at discharge).[40] Two studies observed differences in maternal characteristics.[24,39] Delmas et al.[24] found non-significant differences between both groups with respect to higher maternal education (60% in the follow-up group and 35.3% for the lost-to-follow-up group, $p=0.074$);

and in the study of Patra et al.,[39] mothers were slightly younger in the lost-to-follow-up group (not significant). One investigation noted that, in the follow-up group, significantly more parents living in metropolitan areas were represented (p=0.02) compared with parents living in rural areas.[38] This could validate the hypothesis that infants with no or mild disabilities may be more likely to be lost to follow-up as parents determine there is less of a benefit from returning for it. Further, this could potentially have biased the results towards a greater prevalence of more severe delays.

Implications for future research

In line with a recent paper,[65] this systematic review has highlighted the strong need for uniformization of the used assessment tools and cut-off values to be able to compare studies more accurately. Recent large epidemiological studies such as EXPRESS,[66] EPICure,[33] and EPIPAGE[67] have demonstrated how this is necessary to reach solid conclusions. Finally, more long-term follow-up is required at preschool ages, since other difficulties can be observed, such as visual–motor integration or coordination problems.

CONCLUSIONS

To our knowledge, this is the first systematic review and meta-analysis to separately demarcate the prevalence of both motor and of cognitive delays in VPT or VLBW infants born over the past decade. Even though neonatal intensive care has improved over the previous few decades, the data from this meta-analysis suggest that, overall, nearly one out of six and one out of five VPT or VLBW infants had a cognitive or motor delay respectively, assessed with developmental scales at approximately 2 years corrected age and roughly one out of fifteen developed CP. Decreasing birthweight and gestational age led to higher prevalences of CP, as well as motor and cognitive delays. It was also shown that overall prevalences of CP diminished over the years in EPT infants. As a result of the notable heterogeneity between the articles and the wide confidence intervals, the results should be interpreted with care.

ACKNOWLEDGEMENTS

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPLEMENTARY INFORMATION

The following additional materials may be found in appendix:

Appendix S1: Search strategy (8 August 2016).

Appendix S2: Quality assessment of the included studies.

Appendix S3: Characteristics of the included studies.

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Appendix 1. Search strategy (08/08/2016)

Nr	Search strategy	Number of hits
	Pubmed	
# 1	Premature infants [tiab] OR preterm infants [tiab] OR preterm babies [tiab] OR premature babies[tiab] OR very low birth weight infants [tiab] OR VLBW [tiab]	35362
# 2	"Developmental disabilities"[Mesh]OR "psychomotor disorders" [Mesh] OR "cognition disorders" [Mesh] OR "intellectual disability" [Mesh] OR "cerebral palsy" [Mesh] OR "Motor Skills Disorders" [Mesh]	195764
# 3	"neurodevelopment disabilities"[tiab] OR "neurodevelopment outcome"[tiab] OR "neurodevelopment impairment" [tiab] OR "development outcome"[tiab] OR "development disorders" [tiab] OR "development disabilities"[tiab] OR "cognitive outcome"[tiab] OR "cognitive function"[tiab] OR "cognitive impairment"[tiab]) OR "motor function"[tiab] OR "motor impairment"[tiab] OR "motor disorder"[tiab] OR "motor outcome"[tiab] OR "motor development" [tiab] OR "neuromotor development"[tiab] OR "neuromotor outcome" [tiab] OR "neuromotor impairment" [tiab] OR "neuromotor disorder"[tiab] OR "cerebral palsy" [tiab]	96100
# 4	#2 OR #3	252717
# 5	# 1 AND # 4	2424
# 6	# 5 NOT "drug therapy" [MeSH Terms] OR "surgery" [Subheading])	2313
# 7	# 6 AND "humans"[MeSH Terms]	2151
# 8	#7 AND (("2006/01/01"[PDAT] : "3000/12/31"[PDAT])	1082
# 9	# 8 AND (French[lang] OR Dutch[lang] OR English[lang]))	1018
# 10	#9 NOT ((Comment[sb] OR Letter[ptyp] OR Review[ptyp] OR (systematic[sb] OR Case Reports[ptyp]) OR Randomized Controlled Trial[ptyp] OR Controlled Clinical Trial[ptyp]))	690
	Embase	
# 1	'premature infants':ab,ti OR 'preterm infants':ab,ti OR 'preterm babies':ab,ti OR 'premature babies':ab,ti OR 'very low birth weight infants':ab,ti OR 'vlbw':ab,ti	43660
# 2	'developmental disorder'/exp OR 'psychomotor retardation'/exp OR 'motor retardation'/exp OR 'developmental coordination disorder'/exp OR 'cerebral palsy'/exp OR 'motor performance'/exp OR 'mild cognitive impairment'/exp OR 'cognitive development'/exp	138216
# 3	'neurodevelopment disabilities':ab,ti OR 'neurodevelopment outcome':ab,ti OR 'neurodevelopment impairment':ab,ti OR 'development outcome':ab,ti OR 'development disorders':ab,ti OR 'development disabilities':ab,ti OR 'cognitive outcome':ab,ti OR 'cognitive function':ab,ti OR 'cognitive impairment':ab,ti OR 'motor function':ab,ti OR 'motor impairment':ab,ti OR 'motor disorder':ab,ti OR 'motor outcome':ab,ti OR 'motor development':ab,ti OR 'neuromotor development':ab,ti OR 'neuromotor outcome':ab,ti OR 'neuromotor impairment':ab,ti OR 'neuromotor disorder':ab,ti OR 'cerebral palsy':ab,ti	134363
# 4	#2 OR #3	222965
# 5	#4 AND #1	3020
# 6	# 5 NOT 'drug therapy'/exp OR 'surgery'/exp	2714
# 7	# 6 AND [humans]/lim	2502
# 8	#7 AND [2006-2016]/py	1550
# 9	# 8 AND ('article'/it OR 'article in press'/it)	912
# 10	# 9 NOT ('controlled clinical trial'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de OR 'case report'/de OR 'practice guideline'/de))	799
#11	# 10 AND ([dutch]/lim OR [english]/lim OR [french]/lim)	725
	Web of Science	
# 1	(Premature infants OR preterm infants OR preterm babies OR premature babies OR very low birth weight infants OR VLBW): title	26272
# 2	'neurodevelopment disabilities' OR 'neurodevelopment outcome' OR 'neurodevelopment impairment' OR 'development outcome' OR 'development disorders' OR 'development disabilities' OR 'cognitive outcome' OR 'cognitive function' OR 'cognitive impairment' OR 'motor function' OR 'motor	564956

	impairment' OR 'motor disorder' OR 'motor outcome' OR 'motor development' OR 'neuromotor development' OR 'neuromotor outcome' OR 'neuromotor impairment' OR 'neuromotor disorder' OR 'cerebral palsy'	
# 3	#1 AND #2	2240
# 4	#3 NOT drug therapy OR surgery	2189
#5	#4 NOT (randomized controlled trial)	1864
# 5	TYPES: (ARTICLE)	1589
# 6	PUBLICATION YEARS: (2015 OR 2007 OR 2014 OR 2006 OR 2012 OR 2013 OR 2011 OR 2009 OR 2010 OR 2008 OR 2001 OR 2016)	997
# 7	Languages: (English or French or Dutch)	973
# 8	Exclude CATEGORIES: (surgery OR pharmacology pharmacy OR engineering OR anesthesiology OR urology nephrology OR telecommunications OR computer science OR otorhinolaryngology OR oncology OR music or mathematics OR mathematical computational biology OR genetics heredity or biophysics)	946
	CINAHL	
# 1	(Premature infants OR preterm infants OR preterm babies OR premature babies OR very low birth weight infants OR VLBW):tittle	4987
# 2	'neurodevelopment disabilities' OR 'neurodevelopment outcome' OR 'neurodevelopment impairment' OR 'development outcome' OR 'development disorders' OR 'development disabilities' OR 'cognitive outcome' OR 'cognitive function' OR 'cognitive impairment' OR 'motor function' OR 'motor impairment' OR 'motor disorder' OR 'motor outcome' OR 'motor development' OR 'neuromotor development' OR 'neuromotor outcome' OR 'neuromotor impairment' OR 'neuromotor disorder' OR 'cerebral palsy' : abstract	21113
# 3	#1 AND # 2	456
#4	#3 NOT randomized controlled trials	216
# 4	Publication date : 2006-2016	146
# 5	Academic journals	121
# 6	Language : English	117

Appendix 2. Quality assessment included studies

Author, year	Design	LOE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total	%
Abily-Donval, 2015	→ cohort study	B	+	+	+	+	-	+	+	-	+	/	+	?	+	-	9/13	69.2
Ballot, 2012	→ cohort study	B	+	+	+	+	-	+	+	+	+	/	-	+	-	+	10/13	76.9
Besnard, 2015	← cohort study	B	+	+	+	+	-	+	+	+	+	/	-	?	?	+	9/13	69.2
Boghossian, 2016	→ cohort study	B	+	+	+	+	-	+	+	+	-	/	+	?	+	+	10/13	76.9
Delmas, 2016	→ cohort study	B	+	+	+	+	-	+	+	-	+	/	+	?	-	+	9/13	69.2
Fairchild, 2014	→ cohort study	B	+	+	+	+	-	+	+	-	+	+	+	+	-	+	11/14	78.6
Gibertoni, 2015	→ cohort study	B	+	+	+	-	-	+	+	+	-	/	+	+	-	+	9/13	69.2
Hentges, 2014	→ cohort study	B	+	+	+	+	+	+	+	+	+	/	+	+	-	+	12/13	92.3
Howe, 2011	← case-control study	B	+	+	?	+	-	+	+	/	+	/	+	?	+	-	8/12	66.7
Jeon, 2011	← cohort study	B	+	+	+	+	-	+	+	/	+	/	+	+	-	+	10/13	76.9
Keunen, 2016	→ cohort study	B	+	+	+	+	-	+	+	+	+	/	+	?	+	+	11/13	84.6
Kidokoro, 2014	→ cohort study	B	+	+	+	-	-	+	+	+	-	/	-	+	+	+	9/13	69.2
Kono,2016	→ cohort study	B	+	+	+	+	-	+	+	+	+	/	+	?	?	+	10/13	76.9
Lefebvre, 2016	← cohort study	B	+	+	+	+	-	+	+	+	+	/	+	+	-	-	10/13	76.9
Moore, 2012	→ cohort study	B	+	+	+	-	-	+	+	+	-	/	-	+	-	+	8/13	61.5
Moorehaed, 2012	→ cohort study	B	+	+	?	+	-	+	+	+	+	/	+	?	-	-	8/13	61.5
Nasef, 2012	← cohort study	B	+	+	+	+	-	+	+	+	+	/	+	?	+	+	11/13	84.6
Nouaïli, 2011	← cohort study	B	+	+	+	+	-	+	+	/	+	/	-	?	-	-	7/12	58.3
Orcesi, 2012	→ cohort study	B	+	+	+	+	-	+	+	+	+	/	+	+	+	-	11/13	84.6
Orton, 2015	← cohort study	B	+	+	+	+	-	+	+	-	+	/	+	-	-	-	8/13	61.5
Patra, 2016	← cohort study	B	+	+	+	+	-	+	+	+	+	/	+	?	+	+	11/13	84.6
Perivier,2016	→ cohort study	B	+	+	+	+	-	+	+	+	-	+	+	?	+	+	11/14	78.6
Rogers, 2016	→ cohort study	B	+	+	+	+	-	+	+	+	+	+	+	+	+	+	13/14	92.5
Rose, 2015	→ cohort study	B	+	+	+	-	-	+	+	+	+	+	+	+	+	+	12/14	85.7
Salas,2013	← cohort study	B	+	+	+	+	+	+	+	+	+	+	+	?	+	+	13/14	92.5
Sharma,2011	→ cohort study	B	+	+	+	+	-	+	+	+	+	/	+	?	+	-	10/13	76.9
Steggerda, 2013	→ cohort study	B	+	+	+	+	-	+	+	/	+	/	+	+	+	+	11/12	91.7
Toome,2013	→ cohort study	B	+	+	+	+	-	+	+	+	+	+	+	?	+	+	12/14	85.7
Van Kooij,2011	→ cohort study	B	+	+	+	+	-	+	+	+	+	/	+	+	+	+	12/13	92.3
Verhagen, 2015	→ cohort study	B	+	+	+	+	-	+	+	+	+	+	+	?	+	+	12/14	85.7
Zhu,2014	← case-control study	B	+	+	+	+	-	+	+	/	-	/	+	?	+	+	9/12	75.0

→ prospective; ← retrospective; + yes; - no; / not applicable; ? not reported; LOE: level of evidence

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?

14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Level of evidence

A1 - Systematic review of at least two independently conducted A2 level studies
A2 - Randomized, blinded comparative clinical trial of good quality and sufficient size.
B - Comparative study, but not with all the features listed under A2 (including the patient control study and cohort).
C - Non-comparative study
D - Expert opinion

Appendix 3. Characteristic of the included articles

First author, year	City Country	Birth year	Inclusion criteria Mean GA ±SD Mean BW ±SD (*)	Exclusion criteria and reasons dropout analysis(**)	Active neonatal care	Neonatal Death/Live births Period	Outcome age Mean age/*Me-dian* age	n FU/N % FU (***)	Reasons lost-to-follow-up	Outcome	Cut-off/definitions
Abily-Donval, 2015	Rouen, France	2010	< 33w 29.6w±2.2 1332.3g±391.7	NR	Antenatal CCS 84% Postnatal CCS 8% Magnesium sulfate 61%	14/193 Neonatal period (0-28d)	22-26m Chr.A 24.9±2.5m	164/179 91.6%	NR	ATNE	-
Ballot, 2012	Johannesburg, South Africa	01/06/2006 - 28/2/2007	VLBW 30.8w±2.67 1182g±198 (700-1500gr)	transferred to step-down facilities before discharge, babies who were put up for adoption or relocated	All infants were resuscitated at birth if needed, regardless to BW. BW <900gr all other care but no ventilation provided Resuscitation 34% Surfactant 15.1% Antenatal CCS 42.4% Ventilatory support 22.6%	92/314 Before DC	8-22m CA *16.48m*	106/143 74.2%	Parents Relocated, parents cannot get-off from work, transport and hospital strikes, returned wrong day of visit	Bayley-III NE	Mild delay: 70-85 (≤-1SD - ≥-2SD) Mod-severe delay: <70 (<-2SD)
Besnard, 2014	Tahiti, Polynésie française	01/01/2007-31/12/2011	< 32 w 29w (24.6-31.6) 1281g (560g–2175g)	NR	Active reanimation from 26w GA Surfactant 38% Intubation 43%	19/204 7 before d7 1 d7-d28 11 after d28-179	3y 21m	79/204 38.7%	Geographical remoteness	NR NE	NR
Boghossian, 2016	NRN centers, USA	01/2006-31/12/2011	22-28w 26.0±1.6; 26.3±1.7; *26.0* 25.7±1.8; 841±240; 903±262; 838±247; *860.7*	NR	Antenatal CSS 82.4%	2847/10752 Before DC 1169 ≤12h 327 >12h-3d	18-22m CA	3883/4292 90.5%	NR	BSID-III NE	Mod-severe delay: <70 (<-2SD) Mod-severe CP: ?
Delmas, 2016	Marseille, France	01/01/2007-31/12/2011	23-25w5d 25.1w (23.6-25.4) 750g (510-970)	NR	Antenatal CSS 95%	61/162 Before DC	3y	66/101 67.3%	Social difficulties, no close by physician transferring the children to the FU center, exhaustion of the parents	ATNE	Mild-mod. Motor delay: monoplegia or diplegia or motor delay but the infant is able to walk independently Severe motor delay: tetraparaplegia or

First author, year	City Country	Birth year	Inclusion criteria Mean GA ±SD Mean BW ±SD (*)	Exclusion criteria and reasons dropout analysis(**)	Active neonatal care	Neonatal Death/Live births Period	Outcome age Mean age/*Median* age	n FU/N % FU (***)	Reasons lost-to-follow-up	Outcome	Cut-off/definitions
											diplegia without independent walking Mild-mod cognitive delay: not able to perform 1 or 2 subtest (in total 6) Severe cognitive delay: not able to perform ≥3 subtests
Gibertoni, 2015	Bologna, Italy	1/1/2005-30/6/2011	V<1500g and/or ≤32w 29.0w±2.3 1149g±341	severe cong. Malformations / outliers with at least 4 NICU complications and > 150 d of hospitalization	Mechanical ventilation 25.3%	40/511 Before DC	224m CA	276/462 59.7%	mainly because they were living far from the center or for parents' unavailability to attend visits	GMDS	Mild delay: GQ 88.6–76.9 Moderate delay: GQ 76.8–65.1 Severe delay: GQ ≤65
Hentges, 2013	Porto Alegre, Brazil	11/2003-5/2010	< 1500 g and <32w 29w±2.2 1041g±281	cong. malformations, genetic syndromes, cong. infection by HIV, cong. infection (STORCH), early-onset sepsis, >1 pathogen growth in blood cultures	Antenatal CSS 60.8%	114/411 Before DC	18-24m CA	226/291 77.7%	NR	BSID-II	Mild-mod-severe delay: <85 (<-1 SD)
Howe, 2011	Taiwan	8/2007-7/2009	≤1500g and ≤37w NR NR	major cardiac, gastrointestinal, neurologic, cong. impairments	NR	NR	5y (58-71m) 59.97±5.1	160/NR (retrospective, only infants seen at FU were	NR	M-ABC WPPSI-RNE	Mild-moderate-severe motor delay: <5th Pc Moderate-severe cognitive delay: FSIQ < 70

First author, year	City Country	Birth year	Inclusion criteria Mean GA ±SD Mean BW ±SD (*)	Exclusion criteria and reasons dropout analysis(**)	Active neonatal care	Neonatal Death/Live births Period	Outcome age Mean age/*Me-dian* age	n FU/N % FU (***)	Reasons lost-to-follow-up	Outcome	Cut-off/definitions
								contacted)			
Jeon, 2012	Seoul, Korea	11/2004-04/2008	< 32w or <1500g 27.8±2.7 26.6±2.9 *27.2* 1036.5±270.2 922.1±267.7 *979*	metabolic disorder, cong. malformation, cong. Infection/MRI after 44w GA	NR	NR	18-24m CA	127/377 33.7%	NR	BSID-II NE	Mild delay: 70-84 (<-1SD - ≥-2SD) Mod-severe delay: < 70 (<-2SD)
Keunen, 2016	Utrecht, The Netherlands	10/2006-3/2008	<31 w 28.4w±1.7 1128g±324	cong. anomalies, genetic disorders, inborn errors of metabolism, cong. infections of the CNS / motion artifacts, MRI in coronal plane, MRI beyond 44w GA , unsuccessful segmentation	Antenatal CSS 71% Postnatal CSS 14%	NR	2 y CA 3.5 y Chr.A 5.5 y Chr.A	112/112 100% 98/112 87.5% 85/112 75.9%	NR	BAYLEY-III GMDS MABC-2 WPPSI-III	Mild-mod-severe delay: <1 SD
Kidokoro, 2014	St Louis, USA	2007-2010	<30 w 26.5w±1.7 922g±238	Cong., chromosomal abnormalities, no TEA MRI	Antenatal CSS 77%	NR	2y CA	65/81 80.2%	NR	BAYLEY-III NE	Mod-severe delay: Cognition <80, Motor < 70
Kono, 2016	Japan	11/2012-1/2014	VLBW 28.4w±2.9 983g±308	NR	Antenatal CSS 41.1%	NR	18m CA 18.2±0.9m	124/NR	NR	BAYLEY-III	Mild delay: 70-84 (<-1SD - ≥-2SD) Mod-severe delay: < 70 (<-2SD)
Lefebvre, 2016	Montréal, Canada	2009–2011	≤28w 26.3w±1.4 906g±207	Incomplete evaluation, moved out of the province or lived >600 km from FU-clinic, lost due to an error in gestational age computation	Antenatal CSS 93%	NR	18m CA 18.7±0.7m	194/222 87.4%	NR	BAYLEY-III ATNE	Mild-mod-severe delay: <85 (<-1 SD) Mod-severe CP: GMFCS ≥2
Moore, 2012	England	2006	22-26w 25.6w±0.92 NR	NR	Antenatal CSS 82.4% Postnatal CSS 15.4% Surfactant 99.1%	NR	27-48m *34m*	576/1031 55.8%	NR	BSID-II + BAYLEY-III WPPSI-III NE	Mod. Delay : (<-2SD - ≥-3SD) Severe delay: <-3SD
Moorehead, 2012	Ohio, USA	26/12/2004-13/8/2008	<27w (22-26w) 24.6w±1.1 718g±167	NR	Ventilation (IPPV or nCPAP) 83%	49/227 Before DC 25% by d8	118m±3m CA	127/178 71.3%	NR	BAYLEY-III NE	NR

First author, year	City Country	Birth year	Inclusion criteria Mean GA ±SD Mean BW ±SD (*)	Exclusion criteria and reasons dropout analysis(**)	Active neonatal care	Neonatal Death/Live births Period	Outcome age Mean age/*Median* age	n FU/N % FU (***)	Reasons lost-to-follow-up	Outcome	Cut-off/definitions
						50% by d 21 75% by d 47 90% by d 73					
Nasef, 2013	Toronto, Canada	01/2007-12/2008	<30w 27w±1.6 952g±269	NR	Antenatal CSS 84.7%	44/274 Before DC	18m CA	180/230 78.2%	NR	BAYLEY-III NE	Mod-severe delay: < 70 (<-2SD)
Nouaïli, 2011	Tunis, Tunesia	01/2005-31/12/2007	<33w (24-32w) NR NR	Live births due medical interruption of pregnancy	Antenatal CSS 68.5% Reanimation 59.5% Mechanical ventilation 55%	59/162 Before DC	2y CA	60/89 67.4%	NR	NE	-
Orcesi, 2012	Pavia, Italy	01/01/2005-31/12/2007	≤ 1500 g 28.8w±3.1 1052.6g±292	cong. malformations or genetic disorders	Antenatal CSS 85.8% Postnatal CSS 12.8% Surfactant 62.1% Assisted ventilation 65.4%	26/214 Before DC	2y CA	156/185 84.3%	NR	GMDS NE	Mild delay: GQ 76-87 Mod –severe delay: GQ ≤ 75 Mild CP: Non-disabling CP Mod-Severe CP: Disabling CP
Orton, 2015	Melbourne, Australia	01/01/2008-31/12/2009	<28 (81%) and/or <1000g (83%) or transferred to NICU 26.7w±1.7 828.5g±196	No exclusion criteria	Postnatal CSS 5%	43/262 Before DC	22–28 m CA 24.3±1.0m	109/219 49.8%	Lost contact (n=84), fail to attend (n=15), declined FU (n=10), withdrew (n=1)	BAYLEY-III NE	Mild delay: 70-84 (<-1SD - ≥-2SD) Mod-severe delay: <70 (<-2SD) Mod-severe CP: GMFCS >2
Patra, 2016	Chicago, USA	2008 -2010	≤ 1500g and/or ≤ 29w or multiple siblings 28.3w±2.5 1049g±307	Cong. malformations and/or genetic syndromes / Mothers for whom education level was unavailable	Antenatal CSS 88.7% Postnatal CSS 28.8%	NR	20m CA	177/NR 60%	NR	BAYLEY-III ATNE	Mild delay: 70-84 (<-1SD - ≥-2SD) Mod-severe delay: < 70 (<-2SD)
Périvier, 2016	Pays de La Loire, France	01/03/2003-31/12/2009	<32w NR NR	Genetic syndromes	Antenatal CSS 63.6% Intubation at birth 37.4%	NR	2y CA	1744/1954 89.2%	NR	Brunet–Lézine Test	Mild-mod-severe delay: DQ < 85

First author, year	City Country	Birth year	Inclusion criteria Mean GA ±SD Mean BW ±SD (*)	Exclusion criteria and reasons dropout analysis(**)	Active neonatal care	Neonatal Death/Live births Period	Outcome age Mean age/*Median* age	n FU/N % FU (***)	Reasons lost-to-follow-up	Outcome	Cut-off/definitions
Rogers, 2016	Missouri, USA	2007-2010	< 30w 26.6w±1.8 941g±246	chromosomal abnormalities, cong. infections	Antenatal CSS 85%	20/174 Before DC	2y	65/78 83.3%	NR	BAYLEY-III	Mild delay: <95 and ≥80 Moderate delay: <80 and ≥65 Severe delay: <65
Rose, 2015	Stanford, USA	1/2010–12/2011	≤1500g and ≤32w 28.7w±2.4 1087g±279	Genetic disorders, cong. brain abnormalities	NR	NR	18-22m CA	94/102 92.1%	NR	BAYLEY-III	Mild delay: 70-84 Mod-severe delay: < 70
Salas, 2013	Birmingham, USA	2006-2008	23-28w6d 26w 830g	Major cong. anomalies, without placental evaluation	Antenatal CSS 64%	97/347 NR	18-22m CA	347/399 87.0%	NR	BAYLEY-III NE	Mod-severe delay: < 70
Sharma, 2011	New Delhi, India	07/2006-06/2007	≤1500 g or ≤32 w 31.6w±2.4 1208g±365	major malformation, residence >20 km from the study site	Antenatal CSS 66% Postnatal CSS 7% Surfactant 13%	30/141 Before DC	18m 19.0±2.7m	55/59 93.2%	NR	ATNE	-
Steggerda, 2013	Leiden, The Netherlands	05/2006-11/2007	<32 w 28.9w (25-31) 1204g (520-1960)	cong. anomalies of the CNS, severe cong. anomalies, chromosomal disorders, metabolic disorders, neonatal meningitis./ infants without MRI and/or with large CBH from further analyses	Antenatal CSS 75%	NR	2y CA	84/108 78%	NR	BAYLEY-III NE (Hempel)	Mild-mod-severe delay: ≤ -1 SD Mod-severe CP: GMFCS ≥2
Toome, 2013	Estonia	01/2007-31/12/2007	22-31w6d 28.8w 1314g	NR	Surfactant 57% Postnatal CSS 5%	29/187 Before DC	2y CA	155/156 99.3%	moved abroad (n=1)	BAYLEY-III NE	Mild delay: -1 SD- -2SD) Moderate delay: -2SD – 3SD Severe delay: < -3SD Mod-severe CP: GMFCS ≥2
Van Kooij, 2011	Utrecht, The Netherlands	01/2007-07/2008	<31 w 28.6 w ± 1.8 1130g ± 349	dysmorphic features or an infection of their CNS/ examined on a 1.5-Tesla MRI	Antenatal CSS 80.6%	22/175 Neonatal period (0-28d)	2y CA 24.2±0.6m	67/69 97.1%	NR	BAYLEY-III NE	Mild-mod-severe delay: ≤ -1 SD

First author, year	City Country	Birth year	Inclusion criteria Mean GA ±SD Mean BW ±SD (*)	Exclusion criteria and reasons dropout analysis(**)	Active neonatal care	Neonatal Death/Live births Period	Outcome age Mean age/*Median* age	n FU/N % FU (***)	Reasons lost-to-follow-up	Outcome	Cut-off/definitions
Verhagen, 2015	Groningen, The Netherlands	05/2006-03/2008	<32 w 30.0 w (25.4-31.9) 1305g (615-2250g)	major chromosomal or cong. abnormalities	Mechanical ventilation 52%	11/83 Neonatal period (0-28d)	2-3y *30m*	67/68 98.5%	NR	BAYLEY-III NE	Mild delay: cognitive composite score 70-84 / total motor scaled score 4-7 Mod – severe delay: cognitive composite score <70 / total motor scaled score ≤3
Zhu, 2014	Zhejiang, China	01/2005-12/2009	≤1500 g 29.7±1.1 } *29.8* 29.8±1.2 (25-35w) 1247±168 1263±190.2 } *1255* (550-1500)	transported to other hospitals, surgical conditions, incomplete data	Antenatal CSS 54.8% Surfactant 47.0% Mechanical ventilation 29.0%	127/710 74 : 0-7d 21 : 7-28d 32 : after 28d	2y CA	648/710 91.3%	NR	BSID-II NE	Mod-severe delay: < 70 (<-2SD)

Abbreviations:

ATNE: Amiel-Tison neurological examination; Bayley-III: Bayley Scales of Infant Development, third edition; BSID-II: Bayley Scales of Infant Development, second edition; CA: corrected age for prematurity; CBH: cerebellar haemorrhage; CCS: corticosteroids; Chr.A.: chronological age; CNS: central nervous system; cong.: congenital; CUS: cranial ultrasound; d: days; DC: discharge; DQ: developmental quotient; g: gram; FU: follow-up; GMDS: Griffiths Mental Development Scale; GMFCS: Gross Motor Function Classification System; HIV: human immunodeficiency virus; m: months; IPPV: intermittent positive-pressure ventilation; MABC-2: Movement Assessment Battery for Children, Second Edition; MRI: magnetic resonance imaging; nCPAP: nasal continuous positive airway pressure; NE: neurological examination; NR: not reported; SD: standard deviation; TEA: term age equivalent; VLBW: very low birth weight; w: weeks ; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence, Third Edition; WPPSI-r: Wechsler Preschool and Primary Scale of Intelligence, revised; y: years

(*) When the mean GA and BW where only reported for the different subgroups, the arithmetical mean was calculated of those subgroups

(**): reasons drop-out analysis for follow-up: this refers to extra criteria that excluded infants afterwards. Infants that died before discharge or before or during the follow-up period are an obvious reason for exclusion for the analysis and is applicable for all articles and therefore not reported in this table

(***) n: number of infants eligible for FU (excluding infants that died before discharge and before or during the follow-up period and the ones that were excluded for other reasons)

n FU : number of infants assessed for follow-up

% FU : number of infants assessed for follow-up / number of infants eligible for FU (=follow-up rate)

CHAPTER II

CHAPTER 2

Neurodevelopmental outcomes of very preterm and very-low-birthweight infants in a population-based clinical cohort with a definite perinatal treatment policy

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ABSTRACT

BACKGROUND

With constant changes in neonatal care practices, recent information is valuable for healthcare providers and for parental counselling. The aim of the study was to describe the neurodevelopmental outcome in a cohort of very preterm (VPT)/very-low-birthweight (VLBW) infants at 2 years corrected age (CA).

METHODS

This is a population-based cohort study of all infants born with a GA <31 weeks and/or BW <1500g between 2014-2016 admitted to the Flemish (Belgium) neonatal intensive care units. Infants had routine clinical follow-up around 2 years CA. The diagnosis of cerebral palsy (CP), visual and hearing impairments were recorded. Motor, cognitive and language outcomes were assessed using the Bayley-III. Neurodevelopmental impairment (NDI) was classified as mild (<1 standard deviation [SD]) or moderate-severe (<2SD) based on the defined categories of motor, cognitive, hearing, and vision impairments.

RESULTS

Of the 1941 admissions, 92% survived to discharge and follow-up data were available for 1089 infants (61.1%). Overall, 19.3%, 18.9% and 41.8% of infants had a motor, cognitive and language delay, respectively. CP was diagnosed in 4.3% of the infants. Mild and moderate-to-severe NDI was observed in 25.2% and 10.9% of the infants, respectively. The number of infants with a normal outcome increased from nearly 40% in the category of GA<26 weeks to 70% for infants in the category of 30─31 weeks GA.

CONCLUSION

At 2 years CA, 64% were free from NDI and 90% were free from moderate-to-severe NDI. However, a lower GA and BW are associated with higher rates of adverse neurodevelopmental outcomes at 2 years CA.

KEYWORDS

Cerebral palsy, neurodevelopmental outcome, very-low birthweight, very preterm infants.

1. INTRODUCTION[1]

The survival rate of very preterm (VPT) and very-low-birthweight (VLBW) infants has incrementally improved over the past decades, however, it is widely reported that these infants remain at higher risk of developing neurodevelopmental impairments (NDIs). [1] Population-based cohorts are considered the most ideal scenario for investigating exposure-outcome relations to answer epidemiological and healthcare-related questions, which can, subsequently, improve the quality of care. Furthermore, by reporting the results of outcomes based on standardised tests, international benchmarking, and trend analyses are facilitated over time. Several large populations-based cohort studies of preterm infants date back a few years. [2-6] With constant changes in neonatal care practices, up-to-date information is valuable for healthcare providers and for parental counselling. Accordingly, a high demand exists for more recent large population-based studies.[7]

Multidisciplinary routine follow-up programs for high-risk infants are highly recommended and implemented in different countries. [8] The Belgian government approved a royal decree in 2014, stating that all VPT/VLBW infants should benefit from a multidisciplinary, systematic, long-term follow-up program. The purpose of this study is to describe the perinatal mortality and neurodevelopmental outcomes at two years corrected age (CA) of VPT/VLBW infants based on routine follow-up and to describe the influence of gestational age (GA) and birthweight (BW) on neurodevelopmental outcome.

2. MATERIALS AND METHODS

2.1. Participants

This is a population-based cohort study of all VPT (<31 weeks GA) and/or VLBW (<1500 g) infants born between January 1, 2014 and December 31, 2016 and admitted to the eight Flemish neonatal intensive care units (NICUs) in Belgium. Stillbirths or infants who died in the delivery room were not included.

[1] Bayley-III: Bayley Scales of Infant and Toddler Development, third edition; BSID-II: Bayley Scales of Infant Development, second edition; BW: Birthweight; CA: Corrected age; CP: Cerebral palsy; ELBW: Extremely low birthweight; EPT: Extremely preterm; g: grams; GA: Gestational age; GMFCS: Gross Motor Function Classification System; NDI: Neurodevelopmental impairment; NICU: Neonatal intensive care unit; SD: Standard deviation; SGA: small for gestational age; VLBW: Very low birthweight; VPT: Very preterm

2.2. Perinatal treatment policy

In Belgium, after the EPIBEL study was released, presenting poor outcomes for the most periviable infants,[9, 10] the Flemish NICU centres decided in 2014 to pursue a similar policy in all centres, which has been set out in a consensus document based on international guidelines for early active treatment.[11, 12] This implies that no active resuscitation is performed at ≤23 weeks GA, unless on explicit demand of the parents. At 24 to 25 weeks, resuscitation is started in accordance with parental wishes. When parents choose for active treatment at 24 and 25 weeks GA, antenatal steroids are always given and fetal monitoring is started. When parents do not choose for active treatment, antenatal steroids are given at 25 weeks and 5 days and fetal monitoring is started at 26 weeks. At 26 weeks, active resuscitation is always started unless other serious complications are present. C-sections are indicated when severe foetal distress is diagnosed. Withholding or withdrawal of neonatal care is considered highly acceptable in case of absence of real survival chances and in infants with expected very poor quality of life.

2.3. Follow-up convention and data collection

In 2014, a Royal decree, named from here as the follow-up convention, was established between the Belgian healthcare system and some follow-up centres. As a result of the Belgian follow-up convention, a national standardised assessment was developed for preterm infants. This follow-up convention state that all VPT (<31 weeks GA) and/or VLBW (<1500 g) are eligible for follow-up assessments at four different ages: (1) 3─6 months CA, (2) 9─14 months CA, (3) 22─26 months CA and (4) 4.5─5.5 years old. Eligible infants were invited by the follow-up centre associated with the NICU where the infant was admitted. The Belgian health insurance fund covers practically the whole costs of the follow-up program. The personal contribution amounts to a small percentage of the total costs.

A database was created for prospectively recording perinatal parameters and follow-up outcomes, which are linked. The data were extracted anonymously from the database.

2.4. Ethical approval

The research related to the use of human subjects has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

2.5. Perinatal data definitions

Resuscitation was defined as the administration of at least one of the following resuscitative interventions: endotracheal ventilation, perfusion and/or drugs or chest compressions. Small for gestational age (SGA) was defined as a BW below the 10th percentile for the GA based on the Fenton Preterm Growth Chart.[14] The diagnosis of bronchopulmonary dysplasia was assessed at 36 weeks GA (±3 days) or at discharge, whichever came first. Definitions were used according to Kinsella et al. (2006).[15] Cerebral lesions were mostly diagnosed using a cranial ultrasound, which is standard care in Belgium. Intraventricular haemorrhage (IVH) was graded according to the Papile classification criteria[16], whereas periventricular leukomalacia (PVL) was scored using the four-grade classification by de Vries et al [17]. When an magnetic resonance imaging is performed, the results were used for the classification of brain damage according to the Surveillance of Cerebral Palsy in Europe classification criteria.[18] The presence of early (≤72 hours) or late-onset (>72 hours) sepsis was determined using clinical characteristics and/or positive microbiology.

2.6. Neurodevelopmental assessment

Routine clinical follow-up was performed around the CA of 2 years (22─26 months CA). Experienced paediatricians or paediatric neurologists performed the neurological assessment to identify hearing and vision impairments and cerebral palsy (CP), which was defined by the European Cerebral Palsy Network definition.[19] The Gross Motor Function Classification System (GMFCS) was used to describe the severity of CP. Data from hearing and ophthalmological assessments by otolaryngologists and ophthalmologists were also collected and consolidated for the vision and hearing classification. The definitions of vision and hearing impairments are in accordance with the report of the British Association of Perinatal Medicine[20]. Neurodevelopmental outcomes were assessed by trained physiotherapists and educational psychologists using the Bayley Scales of Infant and Toddler Development (Bayley-III-NL; Dutch version with norm values based on Flemish (Belgian) infants).[21] The motor and cognitive scales were implemented since the start of the Royal Decree for follow-up. The language scale, contrarily, was systematically implemented in all follow-up centres at a later stage and, therefore, less reported and not implemented into the overall definition of NDI. Overall neurodevelopmental outcomes were classified as normal, mild, moderate, or severe based on the defined categories of motor, cognitive, hearing, and vision impairments (Appendix 2). Infants who were not able to have a Bayley-III assessment because of severe

impairment, were classified as moderate-severe NDI. If an infant had multiple impairments of different severities, the infant was classified in the most severe category.

2.7. Statistical analysis

Categorical variables were presented as proportions and percentages, whereas continuous data were represented as the mean and standard deviation (SD). Comparisons of the continuous perinatal characteristics between groups were examined using *t* tests for normally distributed data and the Mann-Whitney rank-sum test for non-normally distributed data. Dichotomous variables were compared using the Fisher exact test. Rates of impairment in relation to GA and BW were compared using the chi-square test. *P* values <.05 were defined as statistically significant. Analyses were performed using SPSS Statistics for Windows (v24;IBM Corp., Armonk, N.Y., USA).

3. RESULTS

3.1. Neonatal mortality

Of the 1942 live-born VPT/VLBW infants admitted to the eight participating NICUs, 159 infants died, and 1783 survived to discharge (neonatal survival rate of 91.8%; Appendix 2). Mortality rates decreased with increasing GA, ranging from 31.3% at <26 weeks to 2.0% in the age group of 30─31 weeks. Of the infants who died before discharge, the mean GA was 26.5±2.7 weeks and the mean BW was 859.9±324.7 g, which was significantly lower than in the survival group with a mean GA of 28.9±2.4 weeks and BW of 1181.4±313.1 g. Overall, the infants who died before discharge had significantly more severe complications (Table 1). Care was given until death in 42.1% (*n*=67) of the infants, whereas a withholding or withdrawal of intensive care occurred in 12.6% (*n*=20) and 45.3% (*n*=72), respectively. Primary causes of death were respiratory insufficiency and immaturity defined as a GA<26 weeks or BW<750 g (both 39.9%), followed by infection and intracranial haemorrhage (both 25%).

3.2. Follow-up

Follow-up data were available for 1089 of the 1782 survivors at 2 years CA, providing an overall follow-up rate of 61.1%. However, this varied from 67.5% in infants at a GA<28 weeks to 54.7% in infants at ≥30 weeks. Median CA at follow-up was 24 months or 105 weeks (interquartile range 102-108 weeks CA; Appendix 3). The perinatal characteristics of the infants are presented in Table 1. The number of infants increased with increasing GA and BW, with the sole exception of the group of infants born at GA ≥32 weeks (range 32-36 weeks GA).

Table 1. Characteristics of the infants

	Died before discharge NICU (*n*=159)	**Survived to discharge NICU (*n*=1782)**	
	N (%) / Mean±SD	**N (%) / Mean±SD**	***p*-value**
Perinatal characteristics			
GA (wks)	26.45±2.66	28.87±2.36	<0.001
<26	73/233 (31.3)	160/233 (68.7)	<0.001
22	0/1 (0.0)	1/1 (100)	
23	5/9 (55.6)	4/9 (44.4)	
24	37/90 (41.1)	53/90 (58.9)	
25	31/133 (23.3)	102/133 (76.7)	
26-27	41/361 (11.4)	320/361 (88.6)	
26	23/190 (12.1)	167/190 (87.9)	
27	18/171 (10.5)	153/171 (89.5)	
28-29	26/573 (4.5)	547/573 (95.5)	
30-31	11/554 (2.0)	543/554 (98.0)	
≥32 (and <1500g)	8/220 (3.6)	212/220 (96.4)	
BW (g)	859.94±324.73	1181.41±313.06	<0.001
<1000	115/650 (17.7)	535/650 (82.3)	<0.001
1000-1499	38/1077 (3.5)	1039/1077 (96.5)	
>1500 (and <31wks)	6/214 (2.8)	208/214 (97.2)	
Gender (Boys)	85/159 (53.5)	904/1782 (50.7)	0.562
SGA (<10th pc)	33/159 (20.8)	233/1782 (13.1)	0.011
Multiple birth	49/159 (30.8)	572/1781 (32.1)	0.790
Apgar score <7 at 5 minutes	66/157 (42.0)	292/1772 (16.5)	<0.001
Outborn	24/159 (15.1)	212/1780 (11.9)	0.254
Age at admission (days)	0.40±3.30	0.90±8.33	0.445
Hospital stay (days)	18.96±41.68	45.73±392.27	0.390
Therapy			
Resuscitation	117/159 (73.6)	796/1764 (45.1)	<0.001
Nasal CPAP (days)	5.46±12.60	13.99±18.10	<0.001
Oxygen therapy (days)	13.04±21.21	23.56±32.64	<0.001
Endotracheal ventilation (days)	10.31±12.74	4.66±9.78	<0.001
Surfactant	128/159 (80.5)	959/1771 (54.2)	<0.001
Systemic corticotherapy	45/159 (28.3)	255/1768 (14.4)	<0.001
Number of blood transfusion(s)	2.83±3.00	1.67±2.80	<0.001
Thoracic surgery	7/157 (4.5)	50/1765 (2.8)	0.224
Abdominal surgery	18/159 (11.3)	86/1759 (4.9)	0.003
Neurosurgery	3/159 (1.9)	32/1769 (1.8)	0.763
Neonatal morbidity			
Intracranial Hemorrhage			
IVH grade I-II	32/158 (20.3)	292/1769 (16.5)	0.223
IVH grade III and PVHI	45/158 (28.5)	49/1769 (2.8)	<0.001
Other hemorrhage	12/158 (7.6)	20/1769 (1.1)	<0.001
White matter disease			
Periventricular echodense area>7days	12/129 (9.3)	186/1751 (10.6)	0.766
PVL grade II	4/129 (3.1)	37/1751 (2.1)	0.524
PVL grade III-IV	14/129 (10.9)	15/1751 (0.9)	<0.001
Airleak syndrome	18/159 (11.3)	58/1767 (3.3)	<0.001
BPD at 36wks GA	-	462/1419 (32.6)	-
PDA	58/159 (36.5)	305/1768 (17.3)	<0.001
Necrotizing enterocolitis	14/159 (8.8)	66/1774 (3.7)	0.005
Infection early onset (≤72hours)	33/135 (24.4)	136/1454 (9.4)	<0.001
Infection late onset (>72hours)	53/135 (39.3)	465/1454 (32.0)	0.102
ROP (≥ stadium 3)	-	89/1402 (6.3)	-
Congenital malformations	25/155 (16.1)	103/1756 (5.6)	<0.001

Table 1. Continued.

	Survivors without follow-up data (*n*=694)	Survivors with follow-up data (*n*=1089)	
	N (%) / Mean±SD	N (%) / Mean±SD	*p*-value
Perinatal characteristics			
GA (wks)	29.31±2.48	28.58±2.23	<0.001
<26	50/160 (31.3)	110/160 (68.8)	<0.001
22	0/1 (0.0)	1/1 (100)	
23	1/4 (25.0)	3/4 (75.0)	
24	18/53 (34.0)	35/53 (66.0)	
25	31/102 (29.4)	71/102 (69.6)	
26-27	106/320 (33.1)	214/320 (66.9)	
26	54/167 (32.3)	113/167 (67.7)	
27	52/153 (34.0)	101/153 (66.0)	
28-29	196/548 (35.8)	352/548 (64.2)	
30-31	219/543 (40.3)	324/543 (59.7)	
≥32 (and <1500g)	123/212 (58.0)	89/212 (42.0)	
BW (g)	1222.25±314.85	1155.44±309.12	<0.001
<1000	171/535 (32.0)	364/535 (68.0)	<0.001
1000-1499	443/1040 (42.6)	597/1040 (57.4)	
>1500 (and <31wks)	80/208 (38.5)	128/208 (61.5)	
Gender (Boys)	348/694 (50.1)	557/1089 (51.1)	0.698
SGA (<10th pc)	117/694 (16.9)	116/1089 (10.7)	<0.001
Multiple birth	223/694 (32.1)	349/1087 (32.1)	1.000
Apgar score <7 at 5 minutes	98/687 (14.3)	194/1085 (17.9)	0.049
Outborn	110/693 (15.9)	102/1087 (9.4)	<0.001
Age at admission (days)	1.61±10.59	0.46±6.45	0.010
Hospital stay (days)	50.15±43.85	42.88±500.64	0.703
Therapy			
Resuscitation	263/687 (38.3)	533/1077 (49.5)	<0.001
Nasal CPAP (days)	11.43±17.54	15.63±18.27	<0.001
Oxygen therapy (days)	20.23±32.39	25.62±32.64	0.001
Endotracheal ventilation (days)	4.67±10.18	4.65±9.53	0.964
Surfactant	330/692 (47.7)	629/1079 (58.3)	<0.001
Systemic corticotherapy	88/689 (12.8)	167/1079 (15.5)	0.127
Number of blood transfusion(s)	1.36±2.42	1.87±3.00	<0.001
Thoracic surgery	25/688 (3.6)	25/1077 (2.3)	0.108
Abdominal surgery	27/686 (3.9)	59/1073 (5.5)	0.143
Neurosurgery	12/691 (1.7)	20/1078 (1.9)	1.000
Neonatal morbidity			
Intracranial Hemorrhage			
IVH grade I-II	97/691 (14.0)	195/1078 (18.1)	0.026
IVH grade III and PVHI	24/691 (3.5)	25/1078 (2.3)	0.181
Other hemorrhage	12/691 (1.7)	8/1078 (0.7)	0.065
White matter disease			
Periventricular echodense area>7days	55/682 (8.1)	131/1069 (12.3)	0.005
PVL grade II	16/682 (2.3)	21/1069 (2.0)	0.612
PVL grade III-IV	9/682 (1.3)	6/1069 (0.6)	0.112
Airleak syndrome	20/689 (2.9)	38/1078 (3.5)	0.498
BPD at 36wks GA	151/555 (27.2)	311/864 (36.0)	0.001
PDA	102/690 (14.8)	203/1078 (18.8)	0.028
Necrotizing enterocolitis	32/691 (4.6)	34/1084 (3.1)	0.122
Infection early onset (≤72hours)	50/561 (8.9)	86/893 (9.6)	0.712
Infection late onset (>72hours)	158/561 (28.2)	307/893 (34.4)	0.015
ROP (≥ stadium 3)	23/503 (4.6)	66/899 (7.3)	0.052
Congenital malformations	46/686 (6.7)	57/1070 (5.3)	0.252

This category is the least represented (8.2% of the study population) because these are the infants at a GA ≥32 weeks but with a BW<1500 g. Consequently, 51% of the infants in this group are categorised as 'small for gestational age (SGA)', compared with ≤9% in the other groups. The mean GA and mean BW of the study patients were 28.6±2.2 weeks and 1155.4±309.1 g respectively, and 51% were boys.

3.2.1. Bayley scales

Of the 1089 infants at follow-up, 96.2% were assessed with the Bayley-III. The mean composite score for each subscale increased with an increasing GA and BW (Figure 1). The mean motor composite score was 95.6±16.5, which was the highest, with a disharmonic motor profile. Gross motor development was poorer than fine motor development (mean scaled score 8.4±2.9 versus 10.1±3.4, respectively). Similar mean scores were found for the cognition subscales (94.1±14.2). The mean language composite score (88.1±16.2), was the lowest, with a similar mean scaled score for expressive and receptive communication, 7.8±2.8 and 7.9±3.0, respectively. Overall, 19.3%, 18.9% and 41.8% of infants, respectively, had a motor, cognitive and language composite score of one SD below the reference population (<85) versus 6.2%, 3.9%, and 10.5% for subscale composite scores of <2 SD (<70; Table 2).

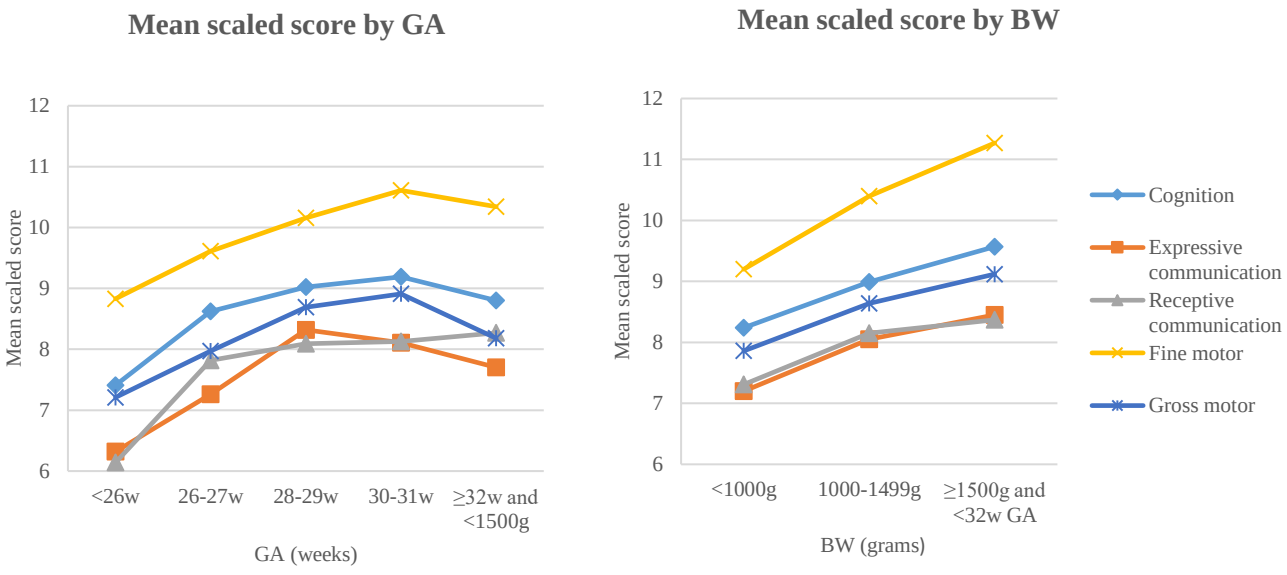

Figure 1. Mean scaled scores of the Bayley-III at 2 years corrected age based on gestational age (GA) and birthweight (BW).

3.2.2. Cerebral palsy

In total, 46 of 1072 children were diagnosed with CP (4.3%). A linear decrease occurred in the incidence of CP with increasing GA, starting at 6.4% in infants with a GA <26 weeks to 3.5% in infants born at 30─31 weeks. Forty-six percent were classified at a GMFCS level I, whereas the number of infants with GMFCS II was equal to that of infants at a GMFCS level III to V, representing 27% each. Infants with a lower GA tend to have a more severe classification of CP (GMFCS III─V), whereas GMFCS type I was most present in infants with a higher GA.

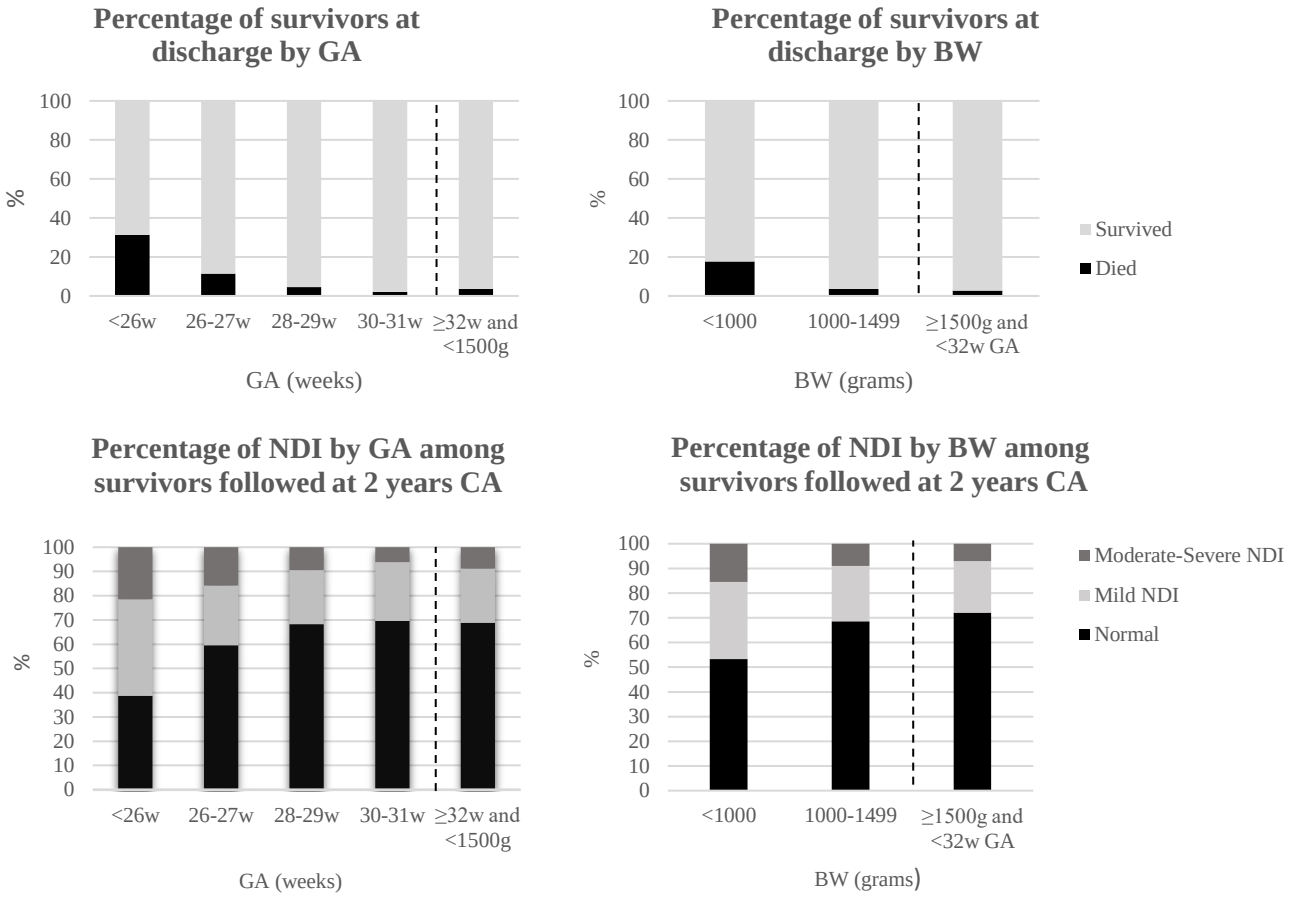

Figure 2. Distribution of survival rate and neurodevelopmental impairment (NDI) by gestational age (GA) and birthweight (BW), demonstrating a positive effect on the survival and NDI rates by an increasing GA and BW.

Table 2. Neurodevelopmental outcome based on GA and BW

	<26wks N (%)	**26-27wks N (%)**	**28-29wks N (%)**	**30-31wks N (%)**	**≥32wks (and BW<1500g) N (%)**
Motor Bayley-III					
≥85	65/96 (67.7)	143/186 (76.9)	244/306 (79.7)	248/283 (87.6)	63/75 (84.0)
70-84	16/96 (16.7)	25/186 (13.4)	47/306 (15.4)	29/283 (10.2)	7/75 (9.3)
55-69	10/96 (10.4)	14/186 (7.5)	11/306 (3.6)	5/283 (1.8)	2/75 (2.7)
<55	5/96 (5.2)	4/186 (2.2)	4/306 (1.3)	1/283 (0.4)	3/75 (4.0)
Cognition Bayley-III					
≥85	64/102 (62.7)	160/205 (78.0)	290/347 (83.6)	267/308 (86.7)	69/86 (80.2)
70-84	30/102 (29.4)	35/205 (17.1)	45/347 (13.0)	36/308 (11.7)	11/86 (12.8)
55-69	4/102 (3.9)	8/205 (3.9)	5/347 (1.4)	5/308 (1.6)	2/86 (2.3)
<55	4/102 (3.9)	2/205 (1.0)	7/347 (2.0)	0/308 (0.0)	4/86 (4.7)
Language Bayley-III					
≥85	17/58 (29.3)	70/124 (56.5)	136/220 (61.8)	128/205 (62.4)	35/57 (61.4)
70-84	25/58 (43.1)	37/124 (29.8)	65/220 (29.5)	61/205 (29.8)	20/57 (35.1)
55-69	10/58 (17.2)	13/124 (10.5)	18/220 (8.2)	15/205 (8.2)	2/57 (3.5)
<55	6/58 (10.3)	4/124 (3.2)	1/220 (0.5)	1/205 (0.5)	0/57 (0.0)
CP					
Overall CP	7/110 (6.4)	10/208 (4.8)	16/347 (4.6)	11/318 (3.5)	2/89 (2.2)
GMFCS I	3/7 (42.9)	4/10 (40.0)	5/16 (31.3)	7/11 (63.6)	2/2 (100.0)
GMFCS II	1/7 (14.3)	4/10 (40.0)	5/16 (31.3)	3/11 (27.3)	0/2 (0.0)
GMFCS III-IV	3/7 (42.9)	2/10 (20.0)	6/16 (37.5)	1/11 (9.1)	0/2 (0.0)
Vision					
Overall vision impairment	19/107 (17.8)	18/207 (8.7)	16/345 (4.6)	16/319 (5.0)	3/89 (3.4)
Mild impairment	18/107 (16.8)	18/207 (8.7)	15/345 (4.3)	14/319 (4.4)	3/89 (3.4)
Moderate impairment	1/107 (0.9)	0/207 (0.0)	1/345 (0.3)	2/319 (0.6)	0/89 (0.0)
Severe impairment	-	-	-	-	-
Hearing					
Overall hearing impairment	3/108 (3.1)	1/207 (0.5)	5/345 (1.5)	5/319 (1.6)	1/89 (1.1)
Mild impairment	1/108 (1.0)	0/207 (0.0)	1/345 (0.3)	3/319 (0.9)	0/89 (0.0)
Moderate impairment	2/108 (1.9))	1/207 (0.5)	2/345 (0.6)	2/319 (0.6)	1/89 (1.1)
Severe impairment	0/108 (0.0)	0/207 (0.0)	2/345 (0.6)	0/319 (0.0)	0/89 (0.0)
NDI					
Overall NDI	60/98 (61.2)	77/190 (40.5)	101/317 (31.9)	85/280 (30.4)	24/76 (31.6)
Mild NDI	39/98 (39.8)	47/190 (24.7)	71/317 (22.4)	68/280 (24.3)	17/76 (22.4)
Moderate NDI	13/98 (13.3)	23/190 (12.1)	16/317 (5.0)	16/280 (5.7)	2/76 (2.6)
Severe NDI	8/98 (8.2)	7/190 (3.7)	14/317 (4.4)	1/280 (0.4)	5/76 (6.6)

Abbreviations: Bayley-III= Bayley Scales of Infant and Toddler Development, third edition; CP=cerebral palsy; g=grams; GMFCS= Gross Motor Function Classification System; N=number; NDI=neurodevelopmental impairment; wks=weeks; *p-value: χ^2 for trend tests

Table 2. continued

P-value*	<1000g N (%)	1000-1499g N (%)	≥1500g (and GA<31wks) N (%)	P-value*	All N (%)
<0.001	229/318 (72.0)	432/515 (83.9)	102/113 (90.3)	<0.001	763/946 (80.7)
	54/318 (17.0)	63/515 (12.2)	7/113 (6.2)		124/946 (13.1)
	27/318 (8.5)	12/515 (2.3)	3/113 (2.7)		42/946 (4.4)
	8/318 (2.5)	8/515 (1.6)	1/113 (0.9)		17/946 (1.8)
<0.001	254/346 (73.4)	485/578 (83.9)	111/124 (89.5)	<0.001	850/1048 (81.1)
	76/346 (22.0)	69/578 (11.9)	12/124 (9.7)		157/1048 (15.0)
	10/346 (2.9)	14/578 (2.4)	0/124 (0.0)		24/1048 (2.3)
	6/346 (1.7)	10/578 (1.7)	1/124 (0.8)		17/1048 (1.6)
<0.001	100/207 (48.3)	231/373 (61.9)	55/84 (65.5)	0.001	386/664 (58.1)
	73/207 (35.3)	110/373 (29.5)	25/84 (29.8)		208/664 (31.3)
	24/207 (11.6)	30/373 (8.0)	4/84 (4.8)		58/664 (8.7)
	10/207 (4.8)	2/373 (0.5)	0/84 (0.0)		12/664 (1.8)
0.590	11/360 (3.1)	27/585 (4.6)	8/127 (6.3)	0.255	46/1072 (4.3)
	5/11 (45.5)	13/27 (48.1)	3/8 (37.5)		21/46 (45.7)
	1/11 (9.1)	11/27 (40.7)	1/8 (12.5)		13/46 (28.3)
	5/11 (45.5)	3/27 (11.1)	4/8 (50.0)		12/46 (26.1)
<0.001	37/355 (10.4)	27/587 (4.6)	8/126 (6.3)	0.001	72/1067 (6.7)
	35/355 (9.9)	27/587 (4.6)	6/126 (4.8)		68/1067 (6.4)
	2/355 (0.6)	0/587 (0.0)	2/126 (1.6)		4/1067 (0.4)
	-	-	-		-
0.601	6/356 (1.8)	7/586 (1.3)	2/126 (1.6)	0.984	15/1068 (1.4)
	2/356 (0.6)	2/586 (0.3)	1/126 (0.8)		5/1068 (0.5)
	3/356 (0.8)	4/586 (0.7)	1/126 (0.8)		8/1068 (0.7)
	1/356 (0.3)	1/586 (0.2)	0/126 (0.0)		2/1068 (0.2)
<0.001	151/324 (46.6)	164/522 (31.4)	32/115 (27.8)	<0.001	347/961 (36.1)
	101/324 (31.2)	117/522 (22.4)	24/115 (20.9)		242/961 (25.2)
	35/324 (10.8)	31/522 (5.9)	4/115 (3.5)		70/961 (7.3)
	15/324 (4.6)	16/522 (3.1)	4/115 (3.5)		35/961 (3.6)

3.2.3. Vision and hearing

Vision and hearing impairments were observed in 6.7% and 1.4% of the infants, respectively. The majority (*n*=68, 6.4%) had a mild vision impairment. Most of them had strabismus, whereas only four infants (0.4%) had moderately reduced vision. None were blind. Mild, moderate, and severe hearing impairment occurred in <1% (for each category) of the infants.

3.2.4. Neurodevelopmental impairment

The overall classification of NDI was evaluated in 961 infants. According to the defined overall disability criteria, 25.2% and 10.9% of the infants were considered to have a mild or moderate-to-severe NDI, respectively. An increasing BW and GA were associated with a lower incidence rate of NDI. The number of infants with a normal outcome rose from nearly 40% at GA<26 weeks to 70% in the age category 30─31 weeks (Figure 2).

4. DISCUSSION

4.1. Main findings

This Flemish large population-based cohort study presents recent information about the outcomes of VPT/VLBW at 2 years CA, which could help inform parents and healthcare professionals. This study revealed a 92% neonatal survival rate of infants admitted to a NICU. Nearly 65% of the survivors at 2 years CA had normal neurodevelopmental outcome. The GA had a clear influence on the prevalence of mild and moderate-to-severe NDIs. At GA<26 weeks, nearly 40% had a normal outcome, whereas this rose to 70% at 30─31 weeks. Mild and moderate-to-severe NDIs, were observed in 25.2% and 10.9% of the infants, respectively.

The Bayley-III provides standard scores and is the most widely used assessment tool in VPT/VLBW infants for early screening of neurodevelopmental delay. The VPT and extremely preterm (EPT) infants have significantly lower scores on the Bayley assessment than babies born at term.[22, 23] However, there is some inconsistency in the literature about which subscales score the highest. In our cohort, the development of language is the most precarious of all evaluated domains. This is consistent with previous VPT/EPT follow-up studies at 2 years CA[24, 25] and contrasts with other studies [23, 26]. Nearly 4 out of 10 infants of this cohort had a language composite score lower than 1 SD, and 1 out of 10 had a score of 2 SD below the reference population. Those results are comparable to an Australian (<30 weeks GA) and Estonian VPT cohort (<32 weeks), where 39%─33% had a score of <1 SD and 14%─10% had a score of ≤2 SD, respectively.[25, 27] The mean motor subscale was the highest of all

subscales, with better results on the fine motor skills scale than gross motor skills, which is also in line with previous studies.[24, 25, 28, 29]

In infants born at GA<26 weeks, mild motor delay (<1SD) was found in 17% of the infants, which is less than in other population-based cohort studies with inclusion criteria of ≤26 weeks GA, having rates of 27%—30%.[9, 26, 28] Moderate-to-severe delays were observed in 16%, which is comparable to the EXPRESS study[26], but is considerably lower than the 28% in the Belgium EPIBEL study [9]. The prevalence of mild cognitive delays (30%) is comparable to other population-based studies, all ranging from 24%—28% [9, 26, 28], whereas moderate-to-severe delays are substantially lower (8%) than the 12%—16% rates found in other studies [2, 26, 28], especially compared with the EPIBEL study (22%). This could possibly indicate a decrease in moderate-to-severe impairments over time, which has also been reported in other studies.[30] However, comparisons must be made with caution because the BSID-II is used in the EPIBEL study, and the EXPRESS study related their results to their own control group of full-term infants, resulting in higher mean composite scores. Moreover, the literature reveals concerns about the Bayley-III, which would possibly overestimate development, resulting in an underestimation of neurodevelopmental delay compared with the BSID-II.[31]

In our cohort, 4.3% of the VPT/VLBW infants were diagnosed with CP at 2 years CA. This is consistent with the most recent large cohort study, EPIPAGE-2, where a rate of 4.6% was found for infants born between 24 and 31 weeks GA.[3] However, it is lower than the pooled prevalence of 6.8% based on 25 papers assessing those with a birth year over the past decade.[32] In infants born at <26 weeks GA, a prevalence of 6.4% was observed, which is in line with the 7% prevalence found in the Swedish cohort study [26], but is significantly lower than the 12—14% in the cohort from England [2] and the USA [28]. This inconsistency could be explained by the substantial differences in active resuscitation procedures and provided perinatal care. For example, among the NICUs from the Neonatal Research Network[6], more active care is provided from 22 weeks GA, whereas, in France, the Netherlands and Belgium active care for the most periviable infants (<24 weeks GA) is more the exception than the rule[3, 33]. Furthermore, it must be acknowledged that, since 2014, as a consequence of the reflection originated by the results of the EPIBEL study[9, 10], the Flemish region has set out a consensus document about care-related decisions and practices for extremely preterm infants, as aforementioned. In combination with the advances in perinatal care, this could clarify the drastic decrease in CP (and NDI) over time, which can be observed by comparing our results to the EPIBEL study, which reported a CP prevalence of 25% in infants born between 1999

and 2001 and with a GA ≤26 weeks. However, this positive evolution has also been described in various previous cohort studies.[34]

The influence of GA and BW is observable in all neurodevelopmental domains, with an increase in GA and BW demonstrating a positive effect on the NDI rates. Nonetheless, infants born at ≥32 weeks but with a BW <1500 g, benefit less from an increased GA, because they tend to have comparable outcome rates to the category of infants born at 28─29 weeks GA. This could be because half of the infants are classified as SGA in this category, which could have a negative effect since it has been reported that SGA may be associated with an increased risk of perinatal mortality and morbidity.[35-37] Notwithstanding, there is no clear consensus about the impact of SGA on the neurodevelopmental outcome. Some studies found a relation between SGA and adverse outcomes[38, 39] whereas some studies did not found any significant effect on the neurodevelopmental outcome.[40-42]

Overall, it is important to take into consideration the specific perinatal treatment policy when interpreting the results. This includes, among other perinatal treatments, the particular resuscitation policy, which is more restrictive than some countries where infants at 22-23 weeks GA receive commonly active treatment.[26, 28] On the other hand, there is the end-of-life policy. It must be noted that half of the children with severe IVH did not survive discharge. This can be associated with a more progressive policy regarding withdrawing or withholding of care in infants with severe IVH brain lesions, which are known to have poor neurodevelopmental prognosis.[43] A recent survey in Flemish neonatologists and nurses emphasis that end-of-life decisions are generally very well supported, even for decisions that currently fall outside the Belgium legal framework.[44] Nevertheless, this was also described in several studies.[45-47] Consequently, all of this must be taken into account when comparing our results to other large cohort studies with a more active resuscitation policy in the most vulnerable infants and/or a more conservative end-of-life policy.

4.2. Limitations and strengths

Finally, several important limitations must be considered. First, although this is a national follow-up program, only half of the national cohort is represented in the results. Belgium has several official language areas and consequently different norm values for the Bayley-III are used (Flemish versus American norms). Numerous papers have highlighted the differences in outcomes based on population-specific outcomes compared with the US norms [29, 48], which is why the results from the different language communities were not combined. Consequently, it is not only a population-based but also a language-based cohort study. Second, just over half

of the children had available language outcome. A reason for this is that the language scale was implemented in a standard way in the follow-up program at a later stage. Another additional explanation, is that even though an additional scale was added to the follow-up program, the foreseen consultation time did not extend. This makes it sometimes difficult to complete all evaluation scales within a limited time. Moreover, as the language scale is often last to be completed, it often happens that the child is too tired to be correctly evaluated on language. Moreover, the general follow-up rate of 61% is moderately lower than other large follow-up studies, which achieved a follow-up range of 80% and higher [2, 4, 25], but are comparable to the follow-up rates of the EPICURE 2 and Vermont Oxford Network (55% and 59%, respectively)[2, 49]. To our knowledge, except for the Swiss[4], Estonian[25] and Vermont Oxford Network[49] studies, the other mentioned cohort studies were research-related, which could explain the higher follow-up rate.[50] It is assumed that more efforts are made in the context of research to maintain contact with parents, and, some incentives may exist[50]. Other reasons for this relatively lower follow-up rate is the fact infants seen outside the time-window of the convention are not registered into the database and therefore not taken into account for the follow-up rate. In addition, a small amount of children might also have been lost-to-follow up because of emigration or because they moved to the French speaking part of Belgium. Lastly, as described by previous studies the ethnicity and socio-economic status might be an important factor for compliance.[51] It turned out that the lowest follow-up rates have been reported in follow-up centres in the cities with the highest rates of migrants, which has been demonstrated to be a risk factor for drop-out.[52, 53] Last possible explaining factor is that the follow-up database was only implemented in 2016, which could also play its part in the lower follow-up rates. In general, it takes some time before everything is automated and everyone gets into the habit of immediately completing the database. This manuscript reported the outcome of the available data into the database, but it is possible that the actual follow-up rate is slightly higher. Third, according to the reports of the Neonatal Research Network[28], the study group had more morbidities and a significantly lower mean GA and BW than the infants without follow-up data, which could have potentially biased our results towards a slightly worse outcome.

The key strengths of this study are its population-based cohort design with the prospective registration of a large number of infants. In addition, broadly used validated assessment tools and standardised definitions are used, which is conducive to the quality of the follow-up program and facilitates the comparison with other population-based studies. Notwithstanding, an international standardization (content, age at follow-up and used definitions) of routine follow-up is highly needed. This will enhance conformity and

consequently, facilitate benchmarking and evaluating trends over time. In addition, this will simplify large-scale collaborative research projects on developmental disorders of high-risk infants, which could enhance the extrapolation of the results. Moreover, it will be important in the future to examine how the follow-up rate can be increased for a routine follow-up to avoid attrition bias in outcome studies of routine follow-up.

5. CONCLUSION

This study demonstrates that a total of 92% of infants born <31weeks and/or VLBW who were admitted to the NICU survived. Significantly improved survival was observed with increasing GA, going from nearly 70% survival rate in infants born before 26 weeks GA to 98% in infants with GA 30-31 weeks.

At 2 years CA, overall, 64% were free from NDI and nearly 90% from moderate-to-severe impairment. However, a lower GA and BW are associated with higher rates of adverse neurodevelopmental outcomes. In the most vulnerable infants (GA < 26 weeks) more than 60% were diagnosed with NDI at 2 years CA, whereas a significantly decrease (40% and less) is observed from 26 weeks GA onwards.

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The authors have no financial relationships relevant to this article to disclose.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

SUPLLEMENTARY INFORMATION

Appendix 1. Flow chart of all VPT (<31 weeks GA) and/or VLBW (<1500 g) infants born between January 1, 2014 and December 31, 2016 and admitted to one of the eight Flemish neonatal intensive care units (NICUs) in Belgium.

Appendix 2. Definitions of neurodevelopmental impairment (NDI)

Appendix 3. Supplementary information about the infants seen in follow-up

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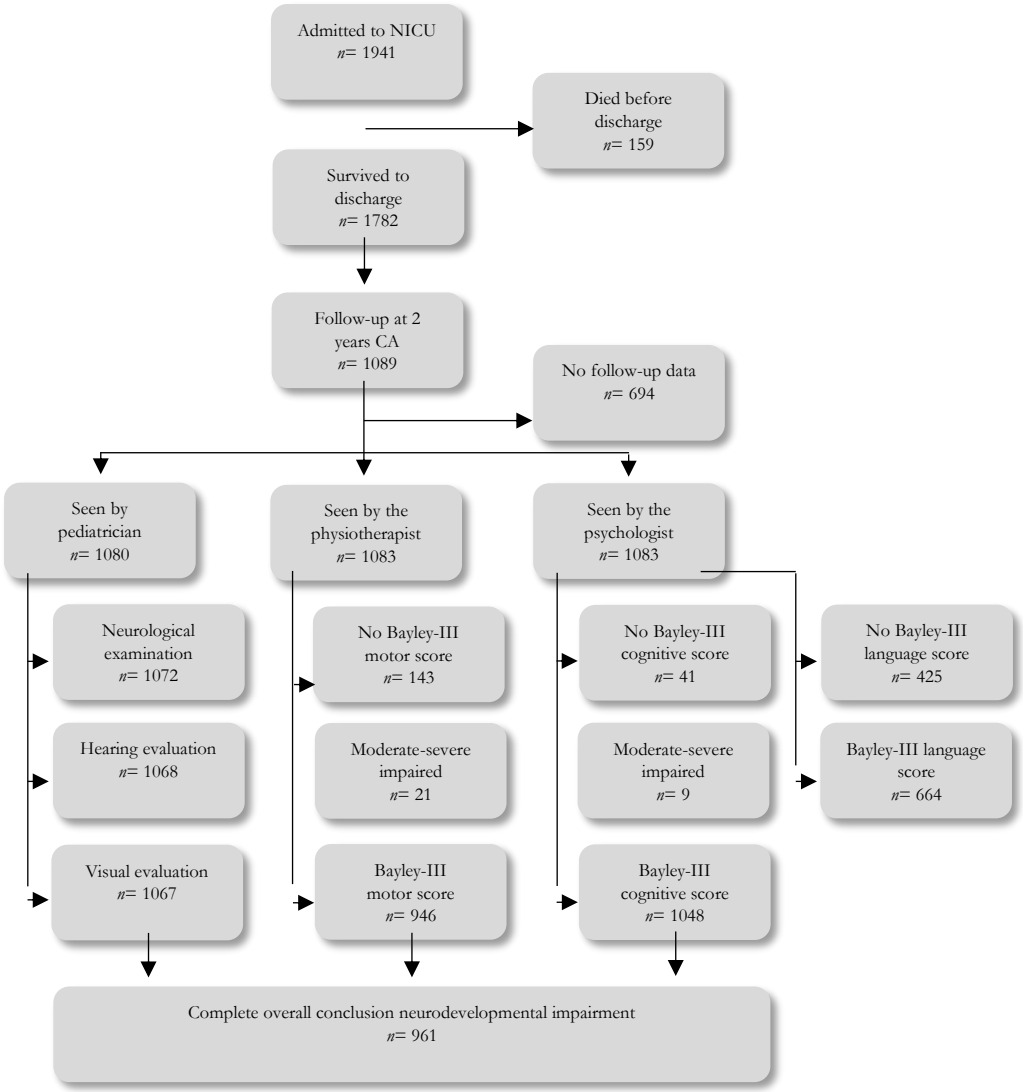
Appendix 1. Flow chart of all VPT (<31 weeks GA) and/or VLBW (<1500 g) infants born between January 1, 2014 and December 31, 2016 and admitted to one of the eight Flemish neonatal intensive care units (NICUs) in Belgium.



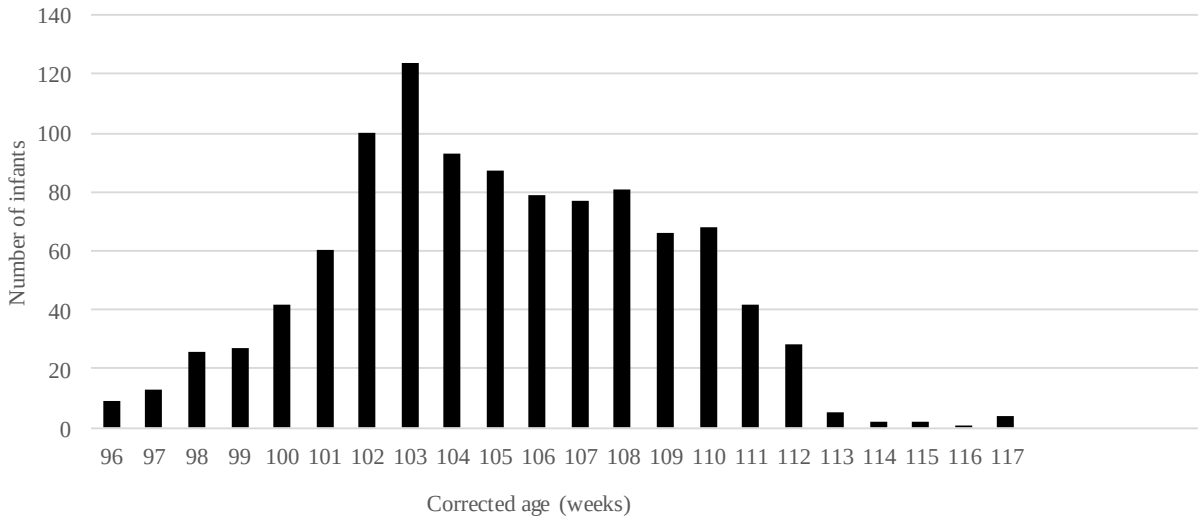
Appendix 2. Definitions of neurodevelopmental impairment (NDI)

Category	Mild NDI	Moderate NDI	Severe NDI
Motor	Motor composite score of 70-84 on Bayley-III	Motor composite score of <70 on Bayley-III	Motor composite score of <55 on Bayley-III
Cognition	Cognitive composite score 70-84 on Bayley-III	Cognitive composite score of <70 on Bayley-III	Cognitive composite score of <55 on Bayley-III
CP	CP GMFCS I	CP GMFCS II	CP GMFCS III-IV
Hearing	Hearing loss <40dBHL	Hearing loss corrected with aids (40-70dBHL) or some hearing loss but not corrected by aids (70-90dBHL)	Profound >90dBHL (no useful hearing even with aids)
Vision	Vision impaired but appears to have useful vision	Seems to have moderately reduced vision but better than severe impairment or blind in one eye with good vision in the contralateral eye	Blind or can only perceive light or light reflecting objects

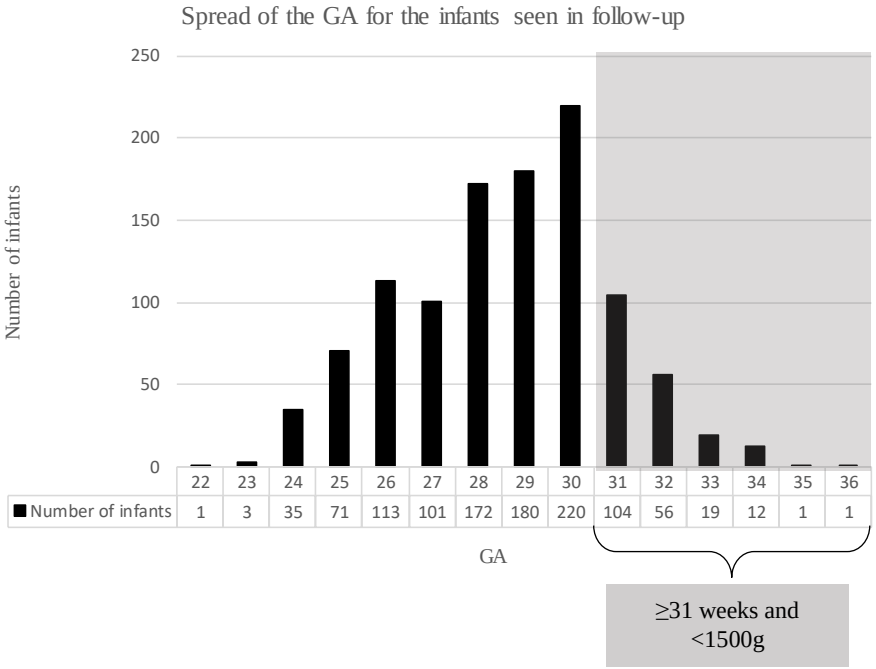
Abbreviations: Bayley-III=Bayley Scales of Infant and Toddler Development, third edition; CP=cerebral palsy; dBHL=Decibels Hearing Level; GMFCS=Gross Motor Function Classification System; NDI=neurodevelopmental impairment

Appendix 3: Supplementary information about the infants seen in follow-up

1) Spread of the corrected age at follow-up



2) Spread of the gestational age



3) Highest educational level of the mother

Educational level	N	%
No education	11	1.0
Primary education	35	3.2
Secondary education	344	31.6
Bachelor	272	25.0
Master	113	10.4
Unknown	314	28.8
TOTAL	1089	100%

4) Native language of the mother

Language	N	%
Dutch	708	65.0
French	36	3.3
Arabic	48	4.4
Turkish	25	2.3
English	11	1.0
Other European languages	25	2.3
Other non-European languages	65	6.0
Unknown	171	15.7
TOTAL	1089	100%

CHAPTER II
Additional data

ADDITIONAL RESEARCH DATA

The impact of Germinal Matrix-Intraventricular Hemorrhage and periventricular leukomalacia on neurodevelopmental outcome in very preterm and very-low-birthweight infants

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ABSTRACT

AIMS

Several studies have shown the negative impact of severe germinal matrix-intraventricular hemorrhage (GM-IVH) on neurodevelopmental outcome, however the impact of low-grade GM-IVH remain contradictory.[1-4] Periventricular leukomalacia (PVL) is the most common white matter brain injury in preterm infants and has been related to adverse neurodevelopmental outcome.[5-7] Limited large cohort studies have reported the impact of GM-IVH and PVL in a same cohort of very preterm (VPT) and very-low-birthweight (VLBW) infants. The aim was to survey the range of cerebral injury by gestational age (GA) and to report the impact of IVH and PVL on mortality and neurodevelopmental outcome in VPT/VLBW infants.

METHODS

This is a prospective population-based cohort study of VPT/VLBW infants born between 2014 and 2016 and admitted to the Flemish NICU's (Belgium). Infants underwent serial cranial ultrasound and MRI brain scan from birth until term-equivalent age. Standard follow-up assessment was at 2 years corrected age, with the Bayley Scales of Infant and Toddler Development-Third Edition and neurological assessment. All data were extracted from a national database.

RESULTS

Of the 1927 infants admitted to the NICU, the prevalence of GM-IVH grade I-II, GM-IVH grade III-IV, persistent echodensities and cystic PVL (grade II-IV) was respectively 16.8%, 4.9%, 10.5% and 3.7% (Table 1). The risk of IVH and PVL increased with decreasing GA. Severe IVH or PVL (grade III-IV) was related to neonatal death in 48% of the infants. This was less than 10% in low grades of GM-IVH and PVL (Table 2). Adverse outcomes were associated with IVH and PVL, and the prevalence increased with the severity of the brain lesions. Univariate logistic regression revealed that IVH grade III-IV did significantly increase the odds for CP, motor and cognitive delay (odds 15 [95% CI 6-38]; odds 3 [95% CI 1-7]; odds 3 [95% CI1-6]), whereas PVL grade III-IV was only significantly related to motor outcome (odds CP 12 [95% CI 2-69]; odds motor delay 17 [95% CI 2-155]) (Table 3).

CONCLUSION

The prevalence of IVH and PVL is high in VPT/VLBW infants and is strongly related to GA. Severe grade of IVH and PVL is highly related to neonatal death and later adverse neurodevelopmental outcome in VPT/VLBW infants.

Table 1. Brain lesions by gestational age of all infants admitted to the NICU and of the survivors to discharge

Brain lesion	22-23 weeks GA	24-25 weeks GA	26-27 weeks GA	28-29 weeks GA	30-31 weeks GA	≥32 weeks GA (and <1500g)	Overall
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
ALL INFANTS ADMITTED TO THE NICU							
Intracranial Hemorrhage							
IVH grade I-II	6/9 (66.6%)	62/223 (27.8%)	81/359 (22.6%)	106/569 (18.6%)	53/548 (9.7%)	16/219 (7.3%)	324/1927 (16.8%)
IVH grade III and PVHI	1/9 (11.1%)	41/223 (18.4%)	17/359 (4.7%)	26/569 (4.6%)	8/548 (1.5%)	1/219 (0.5%)	94/1927 (4.9%)
Other hemorrhage	0/9 (0%)	10/223 (4.5%)	7/359 (1.9%)	12/569 (2.1%)	2/548 (3.6%)	1/219 (0.5%)	32/1927 (1.7%)
All Hemorrhages	7/9 (77.8%)	113/223 (50.7%)	105/359 (29.2%)	144/569 (25.3%)	62/548 (11.3%)	18/219 (8.2%)	450/1927 (23.4%)
White matter disease							
Periventricular echodense area>7days (grade I)	1/6 (16.7%)	37/203 (18.2%)	54/354 (15.3%)	65/563 (11.5%)	33/541 (6.1%)	8/213 (3.8%)	198/1880 (10.5%)
PVL grade II	0/6 (0%)	11/203 (8.9%)	12/354 (3.4%)	9/563 (1.6%)	8/541 (1.5%)	1/213 (0.5%)	41/1880 (2.2%)
PVL grade III-IV	0/6 (0%)	9/203 (4.4%)	10/354 (2.8%)	6/563 (1.1%)	3/541 (0.6%)	1/213 (0.5%)	29/1880 (1.5%)
PVL grade I-IV	1/6 (16.7%)	57/203 (28.1%)	76/354 (21.5%)	80/563 (14.2%)	44/541 (8.1%)	10/213 (4.7%)	268/1880 (14.3%)
All brain lesions*	8/9 (88.9%)	170/223 (76.2%)	181/359 (50.4%)	224/569 (39.4%)	106/548 (19.3%)	28/219 (12.8%)	718/1927 (37.3%)
ALL SURVIVORS TO DISCHARGE							
Intracranial Hemorrhage							
IVH grade I-II	4/5 (80.0)	44/155 (28.4)	72/318 (22.6)	103/543 (19.0)	53/537 (9.9)	16/211 (7.6)	292/1769 (16.5)
IVH grade III and PVHI	1/5 (20.0)	11/155 (7.1)	9/318 (2.8)	20/543 (36.8)	7/537 (1.3)	1/211 (0.5)	49/1769 (2.8)
Other hemorrhage	0/5 (0.0)	4/155 (2.6)	4/318 (1.3)	10/543 (1.8)	2/537 (3.7)	0/211 (0.0)	20/1769 (1.1)
All Hemorrhages	5/5 (100.0)	59/155 (38.1)	85/318 (26.7)	133/543 (24.5)	62/537 (11.5)	17/211 (8.1)	361/1769 (20.4)
White matter disease							
Periventricular echodense area>7days (grade I)	1/4 (25.0)	30/151 (19.9)	51/316 (16.1)	64/539 (11.9)	32/533 (6.0)	8/208 (3.8)	186/1751 (10.6)
PVL grade II	0/4 (0.0)	8/151 (5.3)	13/316 (4.1)	8/539 (1.5)	8/533 (1.5)	1/208 (0.5)	37/1751 (2.1)
PVL grade III-IV	0/4 (0.0)	3/151 (2.0)	5/316 (1.6)	3/539 (5.6)	3/533 (5.6)	1/208 (0.5)	15/1751 (0.9)
PVL grade I-IV	1/4 (25.0)	41/151 (27.1)	69/316 (21.8)	75/539 (13.9)	43/533 (8.0)	10/208 (4.8)	238/1751 (13.6)
All brain lesions*	5/5 (100.0)	100/155 (64.5)	154/318 (48.4)	208/543 (38.3)	105/537 (19.6)	27/211 (12.8)	599/1769 (33.9)

*the sum of all lesions, however it is possible that infants have a combination of an hemorrhage and PVL

KEYWORDS very preterm infants, very low birthweight infants, Periventricular leukomalacia, intraventricular hemorrhage, neurodevelopmental outcome

Table 2. Neurodevelopmental outcomes at 2 years corrected age

	No brain hemorrhage or PVL	IVH grade I-II	IVH grade III-IV	Other hemorrhage	PVL grade I	PVL grade II	PVL grade III-IV
Mortality rate	46/1249 (3.7)	32/324 (9.9)	45/94 (47.9)	12/32 (37.5)	12/198 (6.1)	4/41 (9.8)	14/29 (48.3)
Motor							
Mean ± SD	88.42±15.6	93.3±17.8	88.0±20.6	88.0±16.9	94.6±18.4	93.7±17.2	65.8±17.9
<70	31/622 (5.0)	14/168 (8.3)	4/22 (18.2)	1/8 (12.5)	11/112 (9.8)	2/20 (10.0)	2/5 (40.0)
70-84	74/622 (11.9)	25/168 (14.9)	5/22 (22.7)	3/8 (37.5)	15/112 (13.4)	2/20 (10.0)	2/5 (40.0)
≥85	517/622 (83.1)	129/168 (76.8)	13/22 (59.1)	4/8 (50.0)	86/112 (76.8)	16/20 (80.0)	1/5 (20.0)
Cognition							
Mean ± SD	94.24±16.7	94.30±14.5	90.0±22.0	95.0±14.6	92.4±15.0	89.5±16.0	81.0±20.4
<70	24/689 (3.5)	7/188 (3.7)	4/24 (16.7)	0/8 (0.0)	7/124 (5.6)	2/21 (9.5)	2/5 (40.0)
70-84	96/689 (13.4)	30/188 (16.0)	5/24 (20.8)	2/8 (25.0)	23/124 (18.5)	4/21 (19.0)	0/5 (0.0)
≥85	569/689 (82.6)	151/188 (80.3)	15/24 (62.5)	6/8 (75.0)	94/124 (75.8)	15/21 (71.4)	3/5 (60.0)
CP	19/703 (2.7)	8/192 (4.2)	9/25 (36.0)	1/8 (12.5)	9/128 (7.0)	3/21 (14.3)	2/6 (33.3)
Overall NDI	206/626 (32.9)	69/170 (40.6)	17/23 (73.9)	5/8 (62.5)	51/118 (43.2)	9/21 (42.9)	5/6 (83.3)

CP: cerebral palsy; IVH: intraventricular hemorrhage; NDI: neurodevelopmental impairment; PVL: periventricular leukomalacia

Table 3. Univariate logistic regression

	Odds ratio	95% CI	p-value
Cognitive delay (<85)			
IVH 1-2	1.065	0.715-1.587	0.757
IVH 3-4	2.653	1.144-6.156	**0.023**
Other hemorrhage	1.436	0.288-7.717	0.659
Echodense area	1.453	0.931-2.266	0.100
PVL II	1.756	0.672-4.586	0.250
PVL III-IV	2.908	0.482-17.521	0.244
Motor delay (<85)			
IVH 1-2	1.323	0.886-1.978	0.171
IVH 3-4	2.969	1.249-7.058	**0.014**
Other hemorrhage	4.219	1.045-17.033	**0.043**
Echodense area	1.321	0.823-2.119	0.249
PVL II	1.055	0.348-3.194	0.925
PVL III-IV	17.218	1.913-155.009	**0.011**
CP			
IVH 1-2	0.978	0.448-2.134	0.955
IVH 3-4	15.625	6.470-37.736	**<0.001**
Other hemorrhage	3.276	0.394-27.209	0.272
Echodense area	1.980	0.927-4.230	0.078
PVL II	4.129	1.168-14.593	**0.028**
PVL III-IV	12.256	2.182-68.847	**0.004**
Overall NDI (excl. language)			
IVH 1-2	1.260	0.897-1.769	0.183
IVH 3-4	5.216	2.037-13.358	**0.001**
Other hemorrhage	2.974	0.706-12.523	0.137
Echodense area	1.412	0.955-2.088	0.084
PVL II	1.339	0.558-3.211	0.513
PVL III-IV	8.985	1.045-77.227	**0.045**

CP: cerebral palsy; IVH: intraventricular hemorrhage; NDI: neurodevelopmental impairment; PVL: periventricular leukomalacia

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PART II:
Perinatal stroke

CHAPTER III

CHAPTER 3

Motor outcome after perinatal stroke and early prediction of unilateral spastic cerebral palsy

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ABSTRACT

AIMS

Unilateral spastic cerebral palsy (USCP) occurs in 30% to 68% of infants with perinatal stroke. Early detection of USCP is essential for referring infants to early intervention. The aims of this study were to report motor outcomes after perinatal stroke, and to determine the predictive value of the General Movements Assessment (GMA) and Hand Assessment for Infants (HAI) for detection of USCP.

METHODS

This was a prospective observational study involving infants with perinatal stroke. GMA was conducted between 10 and 15 weeks post term-age (PTA). The HAI was performed between 3 and 5 months PTA. Motor outcome was collected between 12 and 36 months PTA.

RESULTS

The sample consisted of 45 infants. Fifteen children (32.6%) were diagnosed with CP, two children with bilateral CP and 13 with USCP. Abnormal GMA had a sensitivity of 85% (95% confidence interval [CI] 55-98%) and a specificity of 52% (95% CI 33-71%) to predict USCP. When asymmetrically presented FMs were also considered as abnormal, sensitivity increased to 100%, hence the specificity declined to 43%. A HAI asymmetry index cut-off of 23, had both a sensitivity and a specificity of 100% to detect USCP.

CONCLUSION

Using GMA and HAI can enable prediction of USCP before the age of 5 months in infants with perinatal stroke. Nevertheless, GMA must be interpreted with caution in this particular population. The HAI was found to be a very accurate screening tool for early detection of asymmetry and prediction of USCP.

KEYWORDS Perinatal stroke, cerebral palsy, general movements, motor development, hand assessment, early prediction

1. INTRODUCTION

Perinatal stroke is defined as a group of heterogeneous conditions in which a (multi)focal disruption of blood flow secondary to arterial (perinatal arterial ischemic stroke [PAIS]) or venous (cerebral sinovenous thrombosis [CSVT]) thrombosis or embolization occurred between 20 weeks postmenstrual age and the 28th postnatal day.[1] Hemorrhagic stroke (HS) is also included under the umbrella of perinatal stroke.[2] Primary HS tends to affect near-term and term infants, whereas periventricular hemorrhagic infarction (PVHI) is a lesion that primarily affects preterm infants and is a serious complication of germinal matrix-intraventricular hemorrhage.[3, 4] The overall incidence of perinatal stroke is approximately 1:1600-1:2300 live births.[5]

After perinatal stroke, 30-68% of the infants develop cerebral palsy (CP), of which unilateral spastic CP (USCP) is the most common form due to the focal nature of the brain injury.[6-9] However, large variations exist between studies and there remains some uncertainty about the outcome according to the type of brain lesion.

CP is typically diagnosed between the ages of 12 and 24 months.[10] However, due to significant activity-dependent cortical plasticity predominantly occurring early in life, it is important to diagnose CP as early as possible to benefit from intervention during this limited time-window.[11] Recently, it has been recommended to combine neonatal magnetic resonance imaging (MRI), a standardized neurological examination with the Prechtl General Movements Assessment (GMA) to predict CP before five months corrected age.[11] Regarding the GMA, in particular, the absence of fidgety movements (FMs) predicts CP with a sensitivity of 98% and a specificity of 94% in high-risk infants.[12] Moreover, other motor signs predictive for USCP may occur at an early age. For example, asymmetric hand function has been identified as one of the earliest clinical signs of USCP.[13] Recently, a new assessment tool was developed for detecting upper limb asymmetry in infants at risk of developing USCP. The Hand Assessment for Infants (HAI) quantifies hand function, both bimanually and for each hand separately, in infants between 3 and 12 months post-term age (PTA).[14] It has been demonstrated that a unilateral HAI score of the affected hand, in combination with gestational age and gender, predicts USCP before 5 months of age with an accuracy of 93% (95% CI 0.86-100).[15]
Numerous studies have reported outcomes after perinatal stroke or unilateral brain lesions, however, studies on early detection of USCP based on the GMA and HAI are few.[15-18] To our knowledge, no studies have yet compared both tests for early prediction of USCP.

The aims of this study were (1) to report on motor outcomes after perinatal stroke, taking into consideration brain lesion type and timing of injury; (2) to investigate whether there

is a difference in early spontaneous movements and motor patterns (as determined using GMA and HAI) between infants who later developed USCP and those who did not; and (3) to determine the predictive value of the GMA and HAI for detection of USCP.

2. MATERIALS AND METHODS

2.1. Patients

This was a prospective observational study involving infants with perinatal stroke. The study comprised newborns who were admitted to the neonatal intensive care unit (NICU) of hospitals in Flanders, Belgium (UZ Gent, AZ Sint-Jan Brugge, UZ Leuven, UZ Brussel, UZ Antwerpen and ZNA Middelheim), between October 2015 and October 2018. Inclusion criteria were a diagnosis of perinatal stroke confirmed by neonatal brain imaging and having a video recording for the GMA during the fidgety movements period (9-18 weeks PTA). All ethical committees of the participating hospitals approved the present study and all parents provided written informed consent.

2.2. Brain imaging

In all centres, MRI was performed on a 1.5 or 3 Tesla system in the acute stage or around term age. The scans were scored blinded by a senior neonatologist and expert in neonatal brain imaging (PG). All infants were classified based on the type and localization of their lesion and the most predominant stroke pattern. Definitions and classifications of the types of perinatal stroke described by Govaert et al. (2009) were applied.[2] Diffusion-weighted sequences were not available in most cases. Therefore, involvement of the corticospinal tract (CST) was estimated by locating the lesion in relation to the precentral and postcentral gyrus. When the precentral gyrus or subcortical white matter underlying this gyrus was clearly involved, the CST was judged affected. Cases in which the lesion bordered on the precentral gyrus or in which image resolution was insufficient were registered as inconclusive CST injury.

2.3. General Movements Assessment

The GMA based on Prechtl's method of observation of general movements is a widely used diagnostic tool for the functional assessment of the young nervous system and was used in this study.[11] Video recordings were performed once for each infant between 10 and 15 weeks PTA at the parents' home with a standardized video set-up. General movements were classified by two experienced and certified observers (LA and TF) who did not have any knowledge about the infant's clinical history. In cases of disagreement between the two observers, a third observer served as the tie-breaking observer. FMs were classified as normal if they were continuously (FM++) or intermittently (FM+) present, or as abnormal if absent (FM-),

sporadic (FM+/-; very short FMs interspersed with long pauses), or abnormal in nature (Fa; exaggerated with respect to speed and amplitude).[19] When FMs were observed asymmetrically, they were classified as normal with present FMs and a comment was noted about the observed asymmetry.

2.4. Hand Assessment for Infants

The HAI is an assessment tool that aims to quantify hand function between 3 and 12 months post-term.[14] A semi-structured video-recorded play session lasting 15 minutes was performed to evaluate upper limb movements, reaching and grasping. The assessment was performed in the natural habitat of the infant during a home visit when the infant was between 3 and 5 months PTA. In total, 17 items were scored, which included 12 unimanual items for each hand scored separately (Each hand sum score [EaHS]) and 5 bimanual items. Each item was scored on a 3-point rating scale. The EaHS values of the better-functioning hand and the lesser-functioning hand were used to calculate an asymmetry index (AI), in which a higher percentage indicates a larger asymmetry. The total score was converted into a score between 0-100, referred to as the Both Hands Measure (BoHM). Video recordings were scored by a certified researcher (AP).

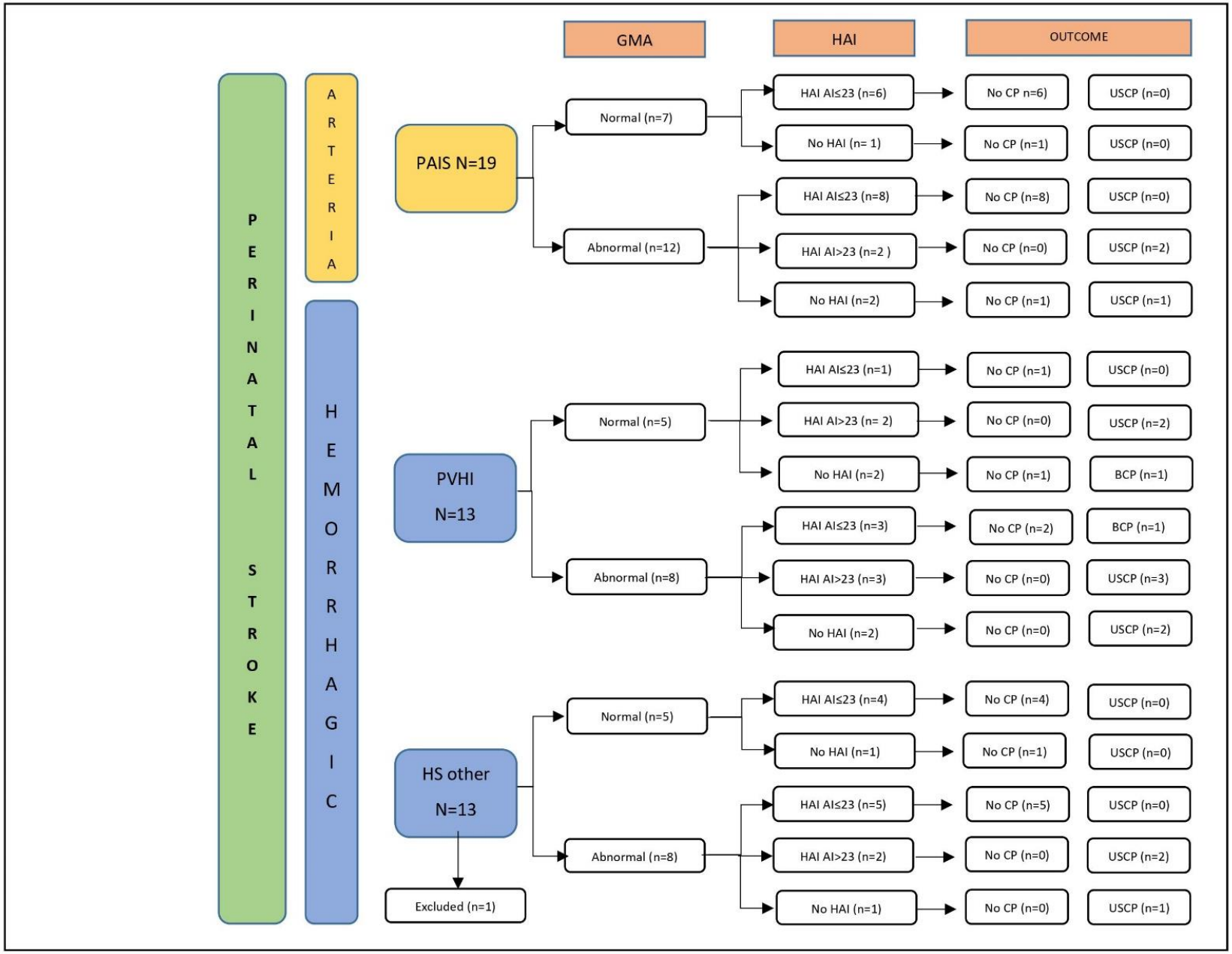
2.5. Outcomes

Infants had regular follow-up assessments at the follow-up centre associated with the NICU where they had been admitted. Neurological examinations were performed by experienced pediatric neurologists or by neonatologists with expertise in neonatal follow-up. CP was diagnosed according to the European guidelines and severity was classified using the Gross Motor Function Classification System (GMFCS).[20, 21] Motor outcomes were collected between 12 and 36 months PTA.

2.6. Statistics

Descriptive statistics were expressed as means with standard deviation, medians with interquartile ranges, or proportions, as appropriate. Differences between groups were evaluated with the two-sample Mann–Whitney test or the Fisher's exact test. Receiver operating characteristic (ROC) analysis was performed to find an optimal cut-off value for the HAI AI for the prediction of USCP. Prediction measures including sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and test accuracy, as well as the positive and negative likelihood ratios (+LR and –LR, respectively), were calculated for predicting USCP. Infants with bilateral CP (BCP) were not included in the analysis.

Figure 1. Flowchart



Abbreviations: AI: asymmetry index; BCP: bilateral cerebral palsy; FM: fidgety movements; GMA: General Movement Assessment; HAI: Hand Assessment for Infants; HS: hemorrhagic stroke; PAIS: Perinatal Arterial Ischemic Stroke ;PVHI: periventricular hemorrhagic infarction; USCP: unilateral spastic cerebral palsy Abnormal GMA= absent/sporadic/exaggerated fidgety movements; Normal GMA= intermittent or continuous fidgety movements

Furthermore, cases with exaggerated fidgety types of general movements were excluded from the analysis due to their low predictive accuracy for CP.[19]

P-values <0.05 were defined as statistically significant. Analyses were performed using SPSS Statistics for Windows (v25;IBM Corp., Armonk, N.Y., USA).

3. RESULTS

3.1. Patients and stroke characteristics

In total, 46 infants were enrolled in the study. Motor outcome was available for 45 infants, resulting in a sample of 45 infants. All infants had one video recording available for GMA and in 35 children, a HAI evaluation was also performed. However, one infant's HAI evaluation was performed at 27 weeks PTA (outside the time frame); thus, these results were not included. The flowchart is depicted in Figure 1 and the characteristics of the infants are shown in Table 1. Gestational age ranged from 24 to 41 weeks, with a mean of 35.0±5.4 weeks, and 21 (46%) infants were born preterm. Birthweight ranged from 740 to 4245 grams (mean 2451±1107).

PAIS was diagnosed in 19 infants, with the middle cerebral artery (MCA) territory the most frequently affected. HS was observed in 26 infants, of whom 13 had a PVHI and 13 received another diagnosis (haemorrhage in supratentorial parenchym [n=10], lobar cerebral haemorrhage [n=2] or haemorrhage in the cerebellum [n=1]). PVHI was significantly more common in preterm infants (92%, p<0.001) and PAIS was more common in term-born infants (68%), although this was not statistically significant (p=0.076). CST could be assessed in 37 cases, with 14 infants (38%) clearly exhibiting damage of the CST.

3.2. Outcomes

The majority of the infants (40/45, 89%) received a follow-up examination between 18 and 36 months of age, while in six infants motor outcome was available at 12 to 18 months. In total, 15 children (33%) were diagnosed with CP. Of these, two children had BCP and 13 had USCP. Of the two infants with BCP, one was classified at GMFCS level III and the other at GMFCS level IV. Of the infants with USCP, five had a very mild form and were classified at GMFCS level I and eight were classified at GMFCS level II.

Significantly more preterm (n=13) than term-born (n=2) infants developed CP (p<0.001), and more boys than girls developed CP (10 versus 5, p=0.290), however the latter result was not statistically significant.

Table 2 reports the outcomes in relation to the stroke type. Of the infants suffering from PAIS, 16% were diagnosed with CP. After HS, 46% of the children developed CP, thus,

Table 1. Characteristics of the infants

Characteristics	Type of stroke				
	All infants (n=45)	PAIS (n=19)	PVHI (n=13)	HS other (n=13)	P-value
	Mean±SD / N (%)	Mean±SD / N (%)	Mean±SD / N (%)	Mean±SD / N (%)	
Gestational age	35.0±5.4	36.4±4.7	30.2±4.4	37.8±4.4	<0.001
≥37	24/45 (53.3)	13/19 (68.4)	1/13 (7.7)	10/13 (76.9)	
32-36	8/46 (17.8)	2/19 (10.5)	4/13 (30.8)	2/13 (15.4)	
<32	13/45 (28.9)	4/19 (21.1)	8/13 (61.5)	1/13 (7.7)	
Birthweight	2451.3±1107	2681.6±974	1565.0±861	3001.2±1035	0.001
Small for gestational age	5/45 (10.6)	2/19 (10.5)	2/13 (15.4)	1/13 (7.7)	0.818
Sex, male (%)	27/45 (60.0)	10/19 (52.6)	9/13 (69.2)	8/13 (61.5)	0.636
Delivery mode					
Spontaneous vaginal	21/45 (44.7)	9/19 (47.4)	4/13 (30.8)	8/13 (61.5)	0.494
Instrumental vaginal	8/45 (17.0)	4/19 (21.1)	2/13 (15.4)	2/13 (15.4)	
Secondary cesarean	16/45 (34.0)	6/19 (31.6)	7/13 (53.8)	3/13 (23.1)	
Resuscitation	9/45 (19.1)	3/19 (15.8)	6/13 (46.2)	0/13 (0.0)	0.011
APGAR <7 at 5min	10/45 (21.3)	6/19 (31.6)	2/13 (15.4)	2/13 (15.4)	0.435
APGAR <7 at 10 min	2/45 (4.3)	1/19 (5.3)	0/13 (0.0)	1/13 (7.7)	0.620
Multiple pregnancy	7/45 (14.9)	2/19 (10.5)	3/13 (23.1)	2/13 (15.4)	0.629
Time of detection					
Within 48 hours after birth	30/45 (63.8)	14/19 (73.7)	10/13 (76.9)	6/13 (46.2)	0.092
After 48h but within first week after birth	13/45 (27.7)	3/19 (15.8)	3/13 (23.1)	7/13 (53.8)	
Within second week after birth	2/45 (4.3)	2/19 (10.5)	0/13 (0.0)	0/13 (0.0)	
Presentation					
Neonatal brain imaging	25/456 (55.6)	8/19 (42.1)	12/13 (92.3)	4/13 (30.8)	0.003
Seizures	16/45 (34.0)	11/19 (57.9)	0/13 (0.0)	5/13 (38.5)	
Other clinical presentation	4/45 (8.5)	0/19 (0.0)	1/13 (7.7)	3/13 (23.1)	
Corticospinal tract affected	14/37 (37.8)	5/15 (33.3)	8/11 (72.7)	1/11 (9.1)	0.028

HS: Hemorrhagic stroke; PAIS: perinatal arterial ischemic stroke; PVHI: periventricular hemorrhagic infarction

developed in 23.1% of the cases with haemorrhages in other brain regions. The CST was significantly more affected in infants with USCP than in infants who did not develop CP (64% versus 21%, p=0.022).

Table 2. Stroke type and outcome

Stroke type	No CP	CP
PAIS		
MCA anterior truncal	◐◐	
MCA posterior truncal	◐◐◐◐◑	◑
MCA complete proximal M1	◐	●
MCA complete distal M2	◐	
MCA other pial	◑	
Perforator PCA thalamus	◐◑	◑
Perforator PCoA thalamus	●	
Perforator ACA Heubner's	◑◑	
Other: multiple perforator strokes	●	
HS		
GM-IVH with a venous infarct (PVHI)	◐◐●●	◐◑◑◑◑◑◑●●
Parenchymal other supratentorial	◐◐◐◐◑◑◑	◑◑◑
Lobar cerebral	◐◑	
Cerebellum	◐	

ACA: arterial cerebral artery; CP: cerebral palsy; GM-IVH: Germinal Matrix-Intraventricular Hemorrhage; MCA: middle cerebral artery; PCA: posterior cerebral artery; PCoA: posterior communicating artery; PVHI: periventricular hemorrhagic infarction

Each bullet represents a child.

◐ : an infant with a brain lesion in the left hemisphere

◑ : an infant with a brain lesion in the right hemisphere

● : an infant with a bilateral brain lesion

3.3. General Movements Assessment and prediction of unilateral cerebral palsy

GMA was normal with intermittently present FMs in 18 (40%) infants. None of the infants had continuous FMs. Of the remaining 27 (60%) infants with abnormal GMA score, 13 (28%) had absent FMs, 12 (27%) had sporadic FMs, and two (4%) had exaggerated FMs. From these 28 abnormal cases, 12 (43%) developed CP (Table 3).

Of the two infants with BCP, one had absent FMs and the other had intermittent FMs. Of the 13 infants with USCP, absent, sporadic, and intermittent FMs were observed in seven, four and two infants, respectively. The two infants with intermittent FMs displayed asymmetrical FMs (observed only on the ipsilesional body side) and were later diagnosed with a mild form of USCP (GMFCS-I). Of the four infants with sporadic FMs and USCP, three were classified at GMFCS-I and one at GMFCS-II. All seven infants with absent FMs had GMFCS-II.

An abnormal GMA classification (combining absent and sporadic FMs) had a sensitivity of 85% (95% CI 58-68%) and specificity of 54% (95% CI 36-71%) to detect later USCP (Table 4). If the two infants with present but asymmetrical FMs were classified into the abnormal category, sensitivity increased to 100% (95% CI 77-100%), but specificity dropped to 43% (95% CI 27-61%), because not all infants with asymmetrical FMs were later diagnosed with CP. Of the six infants with asymmetrical FMs, three were diagnosed with USCP.

Table 3. General movements classification by motor outcome

	FM+	FM+/-	FM-	Fa	Total
bCP	1	0	1	0	2
USCP	2	4	7	0	13
Asymmetrical FM	2	1	-	-	3
No asymmetrical FM	0	3	-	-	3
No CP	15	8	5	2	30
Asymmetrical FM	3	0	-	0	3
No asymmetrical FM	12	8	-	2	22
TOTAL	18	12	13	2	45

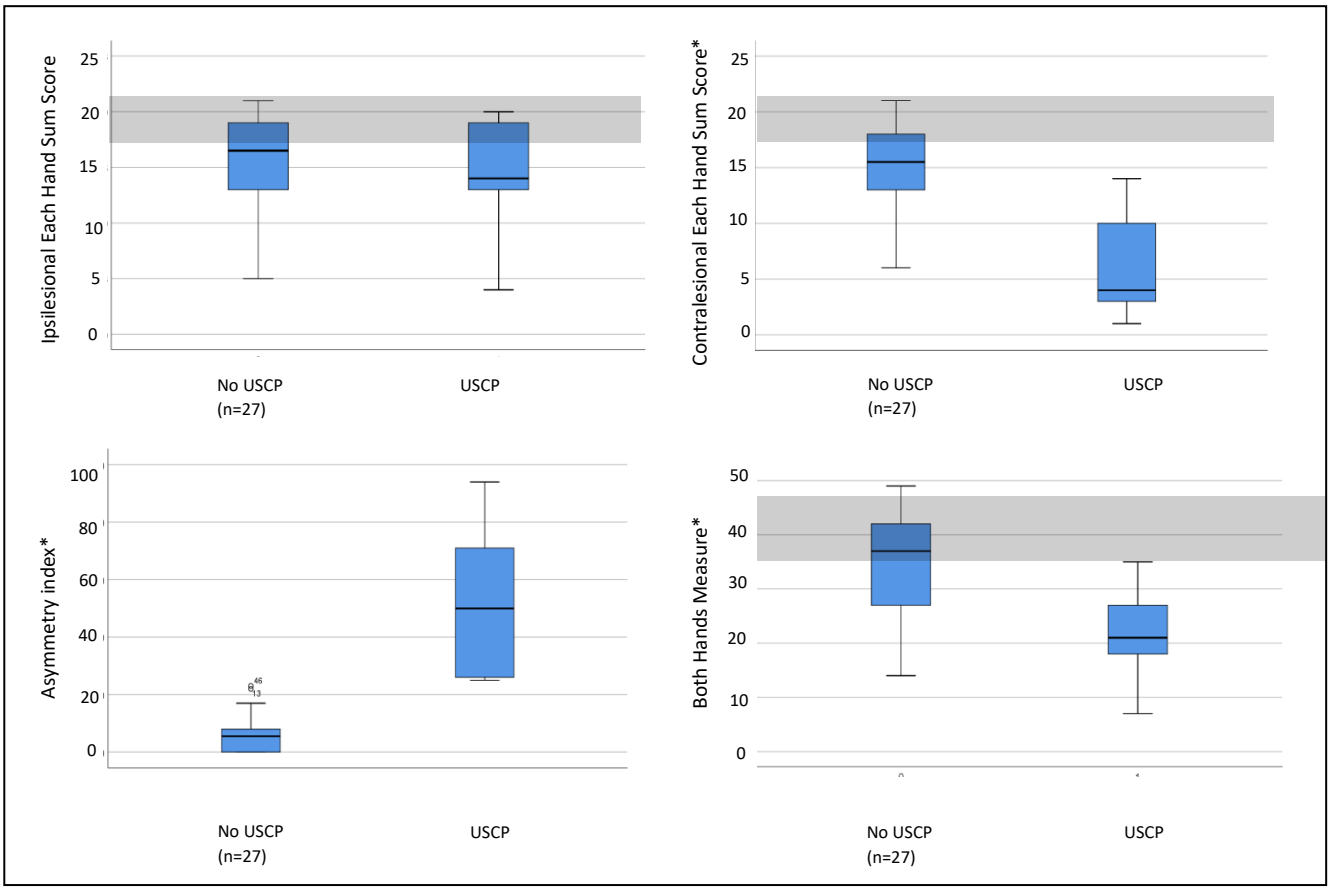
bCP: bilateral spastic cerebral palsy; FM: fidgety movements: FM+: intermittent FM; FM+/-: sporadic FM; FM-: absent FM; Fa: abnormal FM; USCP: unilateral spastic cerebral palsy.
None of the infants had continuous FM (FM++).

3.4. Hand Assessment for Infants and prediction of unilateral cerebral palsy

The majority of the infants (n=25) had a HAI evaluation at 4 months PTA, and only a small number had a HAI at 3 months (n=5) or at 5 months PTA (n=5). The mean PTA was 19±2.1 weeks. Boxplots of the HAI values are presented in Figure 2. The contralesional EaHS and BoHM were significantly lower ($p<0.005$) and the AI significantly higher ($p<0.001$) in the infants with USCP compared to the infants without CP. In children with USCP, the ipsilesional and contralesional EaHS were significantly different ($p=0.008$), in contrast to the infants without CP ($p=0.085$). In infants who did not develop CP, no significant differences on any HAI items were found between the preterm and term born infants ($p>0.05$).

Of the 13 infants with USCP, nine infants had a HAI assessment, and all nine had an AI of more than 23. In contrast, all infants without CP had an AI≤23. One infant without CP had a HAI AI of exactly 23 and another of 22, but all other infants without CP had scores under 17. Thus, using ROC analysis a cut-off of 23 on the AI of the HAI was identified as having the best sensitivity to specificity ratio to classify infants at high risk for USCP, with a sensitivity of 100% (95% CI 66.4-100) and a specificity and 100% (95% CI 87.7-100) (Supplement 1).

Figure 2. Boxplots of the Hand Assessment for Infants (HAI)



HAI: Hand Assessment for Infants; USCP: unilateral spastic cerebral palsy

The grey zone provides the normative mean values of the HAI for infants age 3-5 months (Ek et al. 2019). The two infants with bilateral spastic cerebral palsy were excluded from this analysis.

*p-value <0.005

Table 4. Predictive values for USCP

	USCP		No USCP								
	TP	**FN**	**FP**	**TN**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Accuracy (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**
Absent FM	7	6	5	23	53.9% (25.1% - 80.8%)	82.1% (63.1% - 923.9%)	58.3% (35.3% - 78.2%)	79.3% (67.5% - 88.0%)	73.2% (57.1% - 85.8%)	3.02 (1.2-7.7)	0.56 (0.3-1.0)
Absent/sporadic FM	11	2	13	15	84.6% (54.6% - 98.1%)	53.6% (33.9% - 72.5%)	45.8% (34.8% - 57.3%)	88.2% (66.7% - 96.6%)	63.4% (46.9% - 77.9%)	1.82 (1.2-2.9)	0.29 (0.1-1.1)
Absent FM or asymmetrical FM	10	3	8	20	76.9% (46.2% - 95.0%)	71.4% (51.3% - 86.8%)	55.6% (39.2% - 70.7%)	87.0% (70.6% - 94.9%)	73.2% (57.1% - 85.8%)	2.69 (1.4-5.2)	0.32 (0.1-0.9)
Absent/sporadic/asymmetrical FM	13	0	16	12	100% (75.3% - 100%)	42.9% (24.5% - 62.8%)	44.8% (37.91- 52.8%)	100%	60.98% (44.5% - 75.8%)	1.75 (1.3-2.4)	0.00
HAI AI > 23	9	0	0	26	100% (66.4% - 100%)	100% (86.8% - 100%)	100.0%	100%	100% (90.0% - 100%)	∞	0.00

AI: asymmetry index; FM: fidgety movements; FN: false negative; FP: false positive; GMA: general movement assessment; HAI: hand assessment for infants; +LR: positive likelihood ratio; -LR: negative likelihood ratio ; NPV: negative predictive value ; PPV: positive predictive value; TN: true negative ; TP: true positive; USCP: unilateral spastic cerebral palsy; ∞: infinite

4. DISCUSSION

4.1. General findings

The present study explored the outcome of perinatal stroke and the possibly early diagnosis of USCP in high-risk infants. To our knowledge, this is the first study to evaluate the predictive value of the GMA and HAI in a sample of patients at high risk of USCP. Our results showed that GMA (absent/sporadic FMs) and the HAI had a good predictive value (≥85% sensitivity) for detecting USCP.

The first aim of this article was to the report motor outcomes after perinatal stroke. Overall, 33% of the infants with perinatal stroke in our sample developed USCP. Literature reveals that in infants with PAIS, 30-50% develop USCP[6, 9, 22], whereas this increases to 50-70% after PVHI[23, 24]. Our results confirm those findings, showing that USCP is more common after PVHI (69%) than after PAIS (16%), however, the incidence of USCP after PAIS is lower compared to that observed in other studies without apparent reason. According to the literature, the MCA territory is the most frequently affected.[25] Other types of PAIS, including perforator strokes, resulted in CP in only a minority of the infants, which is consistent with previous studies.[25-27] Nevertheless, the numbers by each subgroup are relatively small, so incidence rates of CP should be interpreted with caution.

The second and third aims of this study were to investigate the motor outcome in infants with perinatal stroke and to explore the predictive value of the GMA and HAI for later USCP. In our study of infants with perinatal stroke, absent FMs alone had poor sensitivity (54%) compared to what has been reported in the literature (98% CI 74-100%). In contrast, the specificity for absent FMs was high, which is in line with previous findings in high-risk populations.[28, 29]

The appearance of sporadic FMs was more frequent than has been described in previous cohorts of high-risk infants.[29, 31] Sporadic FMs have low predictive values for CP, however this is not very well documented.[29] In this study, combining sporadic and absent FMs increased the sensitivity to 85%, but considerably decreased the specificity to 54%, making the GMA less accurate for predicting USCP. However, when asymmetrical FMs were also considered abnormal, the sensitivity to predict USCP increased to 100% to predict USCP, however due to numerous false positives the specificity dropped below 50%. The two infants with USCP and intermittent asymmetrical FMs had very discrete USCP and were classified as GMFCS-I. This is in agreement with recent GMA studies that showed that FMs could be

observed in infants with mild forms of USCP.[13, 31] However, it must be noted that not all infants with observed asymmetry later developed USCP. These findings suggest that infants with perinatal stroke differ in GMA observations from previously described high-risk populations and therefore constitute a highly interesting group to further investigate the GMA at fidgety age.

Furthermore, although our sample is too small to draw definitive conclusions, our results suggest that absent FMs may be a predictor of more severe USCP, based on the GMFCS classification, in contrast to sporadic and present asymmetrical FMs. This is somewhat inconsistent with the conclusion made by Einspieler et al.[32], who suggested in their study that no differences were found in GMFCS levels between the group with sporadic and absent FMs. However, they observed slightly better (although not normal) concurrent movement repertoire.

Altogether, GMA is a useful screening tool in this population group for early detecting of USCP especially when sporadic and asymmetrical FMs are also taken into account. Nevertheless, due to considerable high false positives rates, our results might suggest some cautions using GMA in infants with perinatal stroke, especially within clinical practice.

The HAI helped us assess asymmetric hand function in infants as early as three months of age.[14] A closer inspection of the normal references for 3- to 5-month-old infants, revealed that the infants with perinatal stroke who did not develop USCP had a score of approximately one standard deviation below the normal references.[33] This could indicate that, despite these children not developing USCP, there might still be some delay in upper limb development compared to typically developing children without brain lesions. Delay in reaching was also reported previously in a small sample of infants with perinatal stroke.[34] Furthermore, in the reference population, the vast majority of the infants (98%) had no or only a small difference in the EaHS between both hands (0- to 2-point difference in raw scores between their hands).[33] In contrast, our data indicate that 32% of the infants with perinatal stroke had a difference of more than 2 points (8/9 [89%] USCP versus 4/26 [15%] without USCP). The fact that, even in children without USCP, a larger difference is found between the contra and ipsilesional side, compared to children without brain injuries, could possibly be explained by the cortical reorganization after the brain injury, specifically the competition between the ipsi- and contralesional CSTs, which should be peaking at that time.[35]

Our results showed that the HAI AI between 3 and 5 months PTA has excellent predictive values for USCP. This is in line with the studies by Ryll et al.[15] and Wagenaar et al.[16],

who both evaluated the predictive value of the HAI in combination with MRI. Based on the ROC analysis, we identified the cut-off of 23 on the HAI AI to have the best balance between sensitivity and specificity to classify infants with USCP. Coincidently, all infants with USCP had a score higher than 23 and all infants without USCP had a score ≤23, without any outliers, resulting in an area under the curve (AUC) of the ROC-curve of 1. This cut-off of 23 is in line with the findings of Sakzewski et al.[36], who reported that the median AI in USCP infants was 25.5 (interquartile range [IQR] 22-39) in high-functioning infants, and was increased to 61 (IQR 38-83) in low- functioning children with USCP. Moreover, in an intervention study conducted by Eliasson and colleagues, a HAI AI cut-off of 15 was used as an inclusion criterion.[37] This cut-off was shown to be too low because some infants with an AI of >15 developed either bilateral CP or no CP at all. However, our results and cut-off value should be interpreted with caution because it is based on only 9 infants with USCP and 27 without USCP. In a larger sample, there is a higher probability of outliers, which will consequently decrease the AUC and have an impact on the sensitivity and specificity.

4.2. Strengths and limitations

The key strengths of this study are its highly skilled assessors and that the assessment were conducted in a blinded fashion. However, some limitations must be considered. First, brain imaging information was collected at different care centres in a clinical setting according to their standard procedures, resulting in substantial variation of the image quality. Moreover, only the type of perinatal stroke was reported with the associated motor outcome. Additional brain lesions, such as intraventricular haemorrhage, and the severity of the brain lesions, were not taken into account. It could be expected that more severe brain lesions are more related to adverse motor outcome.

Furthermore, the GMA classifications were based on a single video recording. A recent large study suggested that FMs are still maturing in some infants and might show temporal changes within the 12-16-week period, implying that FMs might emerge later.[38] Accordingly, it is possible to sufficient identify present FMs with a single observation, but in cases of abnormal GMA, particularly sporadic FMs, repeated observation could have increased the predictive value of the GMA. Moreover, the Motor Optimality Score has not been used, which might have led to a more detailed assessment of the GMA and possibly a better prediction of the motor outcome.

Lastly, we have investigated a relatively small sample with heterogeneous brain lesions. This limitation is common in the field: because perinatal stroke is a rare disease, most studies

about perinatal stroke are multicentre and involve limited sample sizes and, often, heterogeneous lesion types.

4.3. Further research

Future research directions include detailed observation of the GMA, refining classifications related to the type of brain lesion and reorganization of motor tracts, and performance of longer-term neurodevelopmental follow-up examinations, preferably in a larger and homogenous sample. Another important next step would be to validate or possibly refine the clinical threshold for the AI of the HAI between 3 and 5 months of age for early detection of USCP so that this could eventually be implemented in clinical practice.

5. CONCLUSION

Early diagnosis of CP is important and can lead to early intervention. This study emphasizes that early detection of USCP is possible before the age of 5 months PTA. GMA is feasible in a population with perinatal stroke for early prediction of USCP. However, it is important to note that normal GMA must be interpreted with caution in this particular population, considering the high rates of false positive cases. Furthermore, asymmetrical FMs might be observed, which could be an indicator for later mild USCP. The HAI was found to be a highly accurate screening tool for early detection of asymmetry and prediction of USCP. Nevertheless, the current study is based on a small sample and further research is needed to confirm and expand on these findings.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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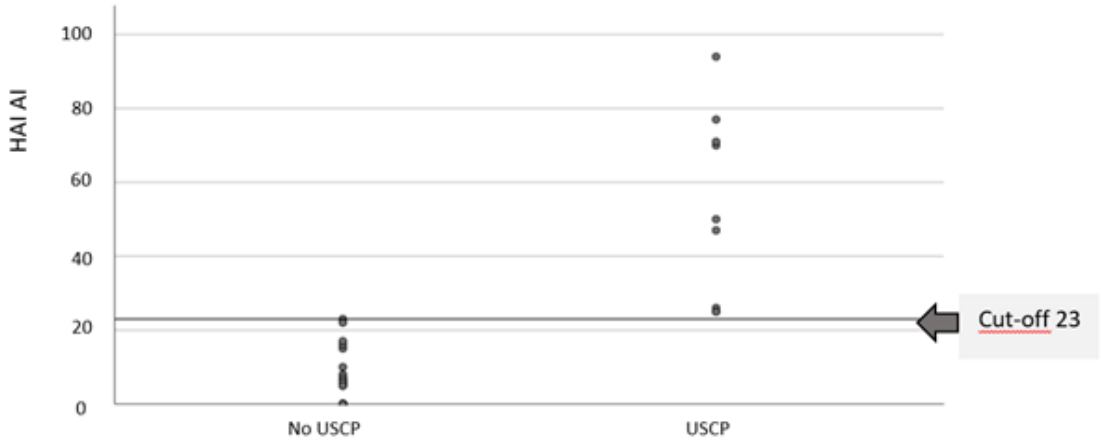
Appendix 1. Scatterplot and ROC curve of the Asymmetry index of the Hand Assessment for Infants



Test Result Variable(s):

Asymmetry Index

Area
1,000

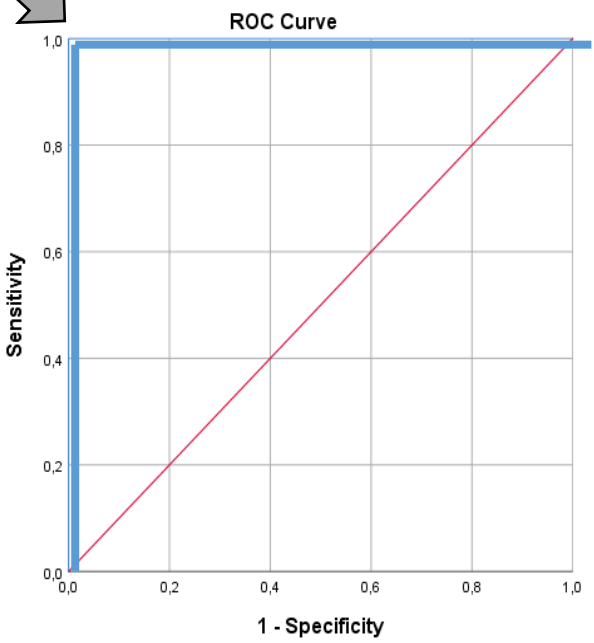
Cut-off 23

Coordinates of the Curve

Test Result Variable(s): Asymmetry Index

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
-1,00	1,000	1,000
2,50	1,000	,593
5,50	1,000	,481
6,50	1,000	,370
7,50	1,000	,296
9,00	1,000	,222
12,50	1,000	,185
15,50	1,000	,148
16,50	1,000	,111
19,50	1,000	,074
22,50	1,000	,037
24,00	1,000	,000
25,50	,778	,000
36,50	,667	,000
48,50	,556	,000
60,00	,444	,000
70,50	,333	,000
74,00	,222	,000
85,50	,111	,000
95,00	,000	,000

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.



CHAPTER IV

CHAPTER 4

Home-based early intervention for infants at high risk for unilateral spastic cerebral palsy: a feasibility study

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ABSTRACT

AIMS

Perinatal stroke exposes infants to be at high-risk for developing unilateral cerebral palsy (USCP). Early intervention programs could significantly impact and improve long-term motor outcome. This feasibility study was conducted to determine acceptability and suitability of a randomized controlled trial (RCT) aimed to evaluate the efficacy of constraint-induced movement therapy (CIMT) versus Hand-arm bimanual intensive training (HABIT) in infants at high risk for developing USCP.

METHODS

Infants with perinatal stroke and abnormal general movements and/or clear asymmetric hand use observed by the 'hand assessment for infants (HAI)' between 4 and 6 months corrected age, were enrolled in the study. A 18 weeks a home-based intervention program was carried out. Parents were educated and coached to deliver the therapy. During the intervention weeks parents performed CIMT or HABIT, for 30 minutes, 6 days a week. Parental satisfaction with the intervention was evaluated with a questionnaire and the therapist perspectives by an interview.

RESULTS

Of the 16 recruited infants, seven were eligible children for the intervention study and they were all enrolled in the feasibility study. Four infants received HABIT and three CIMT. Parental compliance and satisfaction with the intervention was high.

CONCLUSION

This pilot study revealed that this program is feasible, however, some adjustments might need to be considered, before implementing this protocol into a larger sample. Overall, parents were satisfied with the early intervention program and were compliant to the therapy program.

KEYWORDS

Perinatal stroke; constraint-induced movement therapy; Hand-arm bimanual intensive training; hand assessment for infants; early intervention; cerebral palsy

INTRODUCTION

Perinatal stroke is defined as a cerebrovascular event characterized by focal disruption of cerebral blood flow due to arterial or cerebral venous thrombosis or embolization, occurring between 20 weeks of gestation and 28 days postnatal age.[1,2] The incidence of perinatal stroke has been estimated at 1 in 1600 to 5000 births.[3] Perinatal stroke is the most common cause of unilateral spastic cerebral palsy (USCP), and can be found in up to 68% of the infants with perinatal stroke.[4,5] Infants with USCP present motor and sensory impairments mainly on one side of the body, which are typically more prominent in the upper limb. These sensorimotor impairments typically lead to difficulties to execute activities in daily life, reducing their participation and quality of life.[6]

Interest in early intervention programs for infants at high risk of developing cerebral palsy (CP) is growing over the past few years. Meta-analysis indicated a positive effect of general developmental programs or early interventions on cognitive development until the age of 3 years.[7] However, there is little evidence on the effect on motor outcome, mainly due to underpowered studies or insufficient differentiation between the study and control group.[7,8] On the contrary, more evidence is available about specific therapy approaches. Research into upper limb treatments for children with USCP has grown exponentially over the last decade. Different therapeutical approaches exist aiming at improving upper limb performance in adults and children with established USCP. Currently, the two most popular non-invasive treatment modalities for children with USCP are: constraint induced movement therapy (CIMT) and Hand-arm bimanual intensive training (HABIT).[7] Those current therapy approaches fundamentally comprise repeated practice of desired movements based on motor learning principles with the adult/child as an active participant. CIMT involves restraint of the non-involved upper extremity with intensive targeted practice of the involved extremity, while HABIT has a bimanual approach and is oriented at tasks that are progressed bimanually.[8] Both therapies, in adults and in children with established USCP are effective and show similar improvements if the dosage of therapy is similar.[9-11] In contrast, the feasibility and the effects of both therapy approaches in young infants, between brain insult and one year, has barely been investigated, even though it has extensively been demonstrated that this is a critical period of motor system plasticity, occurring as activity-dependent reorganization of the motor-projection pattern to the hand.[12,13]

An early intervention program with baby-CIMT has been demonstrated to be feasible in children less than 12 months of age[14] and had promising positive results compared to the control group who received baby-massage[15]. Another study, whose protocol has been published, is currently carried out comparing baby-CIMT and baby-HABIT.[16] As far as we know, those are the only studies investigating the effect of CIMT or HABIT in young infants, so more research is needed to explore those interventions in young infants.

The objective of this exploratory study was to determine acceptability and suitability of the two most used therapies 'CIMT' and 'HABIT', in young infants with perinatal stroke and with a high risk to develop USCP. Our first hypothesis was that parent would consider the program acceptable and that the intervention program would be feasible. We hypothesized that this intervention study, after some fine-tuning revisions would be ready for use in a controlled study. Our second hypothesis regarding the therapy, was that infants with perinatal stroke would increase in unimanual and bimanual ability of the affected hand in bimanual activities, just as much in the CIMT as in the HABIT group, after each intervention block.[10,19] Nevertheless, this second hypothesis has not been investigated in this feasibility study.

METHODS

Design

This is a feasibility study of an evaluator-blinded, randomized controlled clinical trial.

Study population

Infants born between January 2016 and February 2018 at one of the 6 collaborating NICU's (UZ Ghent, AZ Sint-Jan Bruges, UZ Brussels, UZ Antwerp, ZNA Middelheim Antwerp, UZ Leuven) in Flanders, Belgium, with perinatal stroke confirmed on neonatal imaging and from who the parents speak Dutch, were eligible for the study. Infants with severe genetic abnormalities or malformations, with severe visual impairments or with refractory seizures were excluded. Parents were informed about the study and recruited by the neonatologist at discharge.

Stratification was according to the period of which the perinatal stroke occurred (<37weeks GA or >37 weeks GA). The randomization, based on sealed numbered envelopes, occurred after the first assessment. The infants were randomly assigned to either the CIMT or HABIT.

Screening

General movements assessment

The observation of the *General movements* (GMs) based on the Prechtl's method is considered as a very reliable and accurate, diagnostic tool for neurological issues.[17] Generally considered GMs are very sensitive (95-100%) and specific 94-98% to predict CP (24-27).[18] In particular, the absence of fidgety movements, described as circular movements of small amplitude, moderate speed and variable acceleration, between 2 and 4 months are the most predictive for CP (28).[19] Video recordings of GMs were performed at fidgety age, between 10 and 15 weeks post term age at the parent's home. A standardized video set up was used. Infants were recorded for 5 minutes in an awake and active condition, approximately 30 minutes after feeding. The infants were positioned in supine position only wearing a bodysuit. The GMs were classified following Prechtl's GMA methodology by two experienced and certified observers (AL and TF). In case of disagreement between the two observers, a third observer (TVR) was the tie-breaking observer. GMs were classified as normal (continuously or intermittent presence of fidgety movements) or abnormal (absent, sporadic or exaggerated fidgety movements).

Hand assessment for infants

Upper limb function was evaluated with the hand assessment for infants (HAI). The HAI is a new assessment tool to evaluate the hand function and asymmetry in infants aged 3 to 12 months post term.[20] The HAI consists of a semi-structured video-recorded play session lasting 10-15 minutes to evaluate the upper limb movements, reaching and grasping. The HAI assessment was performed between 4 and 6 months corrected age and scored afterwards on video by a certified pediatric physiotherapist. The HAI scores consists of 12 items for each individual hand (score 0–24 for each hand) and 5 bimanual items creating a total score for both hands combined (Both hand measure, score 0–100) and an asymmetry index (0-100). Infants with abnormal GM and/or clear asymmetric hand function during the HAI were enrolled in the intervention study.

Intervention

A schematic overview of the study is presented in Figure 1. The whole intervention period lasted 18 weeks, separated into 3 blocks of 4 weeks intervention and 2 blocks of 3 weeks of rest (Figure 2). Parents were trained and guided by an experienced physiotherapist to perform

the intervention at home, in the natural habitat of the infant. In addition, a box with adapted toys was offered during the whole intervention program. Parents were instructed to use those toys only for therapy moments and not throughout the day, to keep the infants triggered during training sessions. During the intervention weeks parents performed CIMT or HABIT, consequently to their group allocation, for 30 minutes, 6 days a week. Altogether, parents needed to administer 30 minutes of therapy every day, but this could be split up in blocks of 10 or 15 minutes, depending on the attention span of the infant. Parents were asked to keep a diary with the treatment duration. During the rest weeks, no therapy was effectuated.

Before the start of each intervention block, a home visit was performed, during which adjustment and additional advice was supplied. In between, every two weeks parents were contacted by telephone by the same therapist. Questions were answered and parents were supported and motivated to continue with the therapy. If parents had an urgent problem or question during the study, they could always contact the therapist by phone. If a child received additional usual care, the frequency, intensity as well as the content was registered.

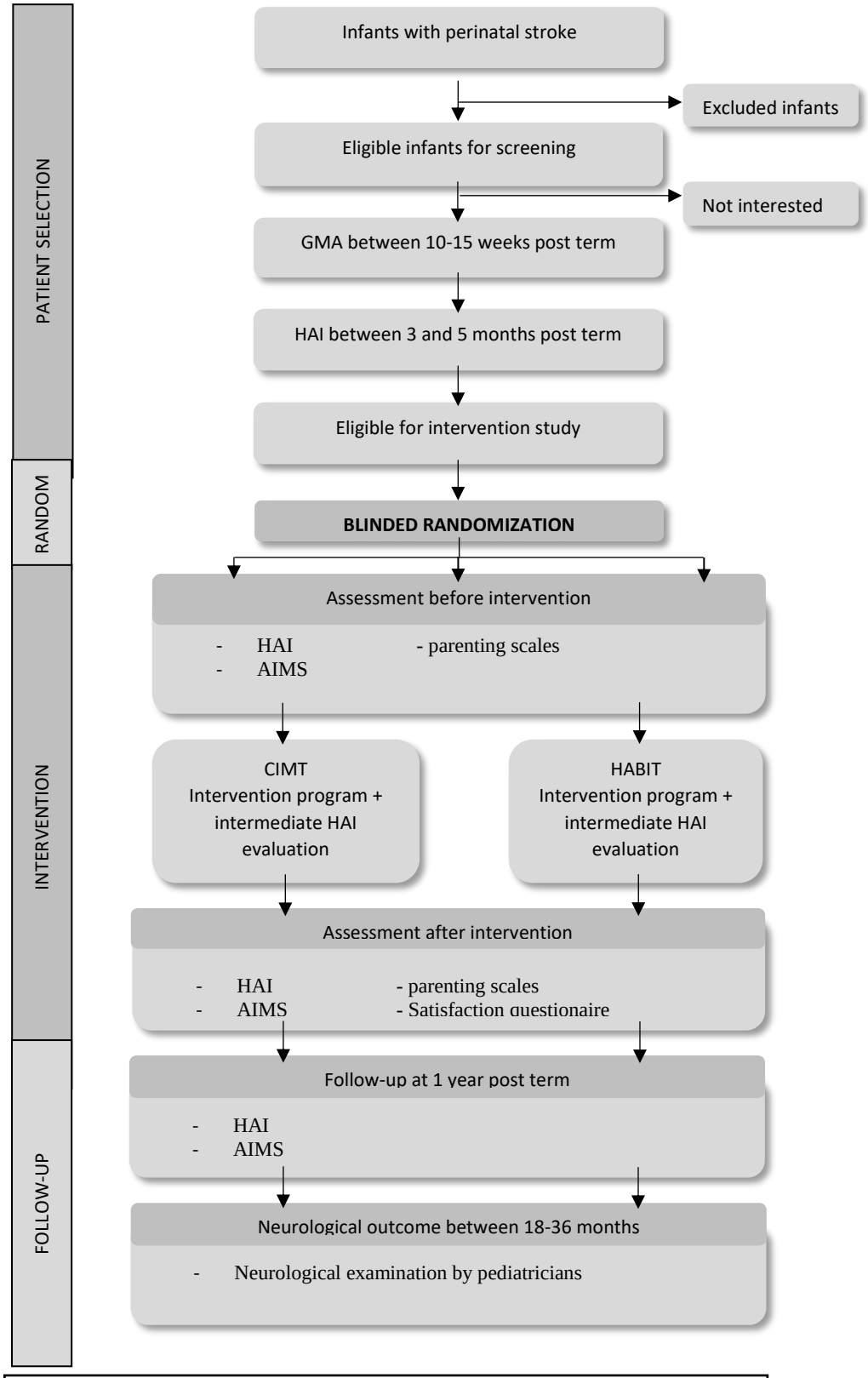
Baby-CIMT

A soft splint or restraint was used for the best functioning hand of the infant only during the therapy session. During the therapy session, all distraction needed to be avoided and parents tried to keep the child's attention by holding on direct eye contact with their infants and actively focus on the toys. A good child-caregiver interaction was indispensable for a successful therapy session.

Baby-HABIT

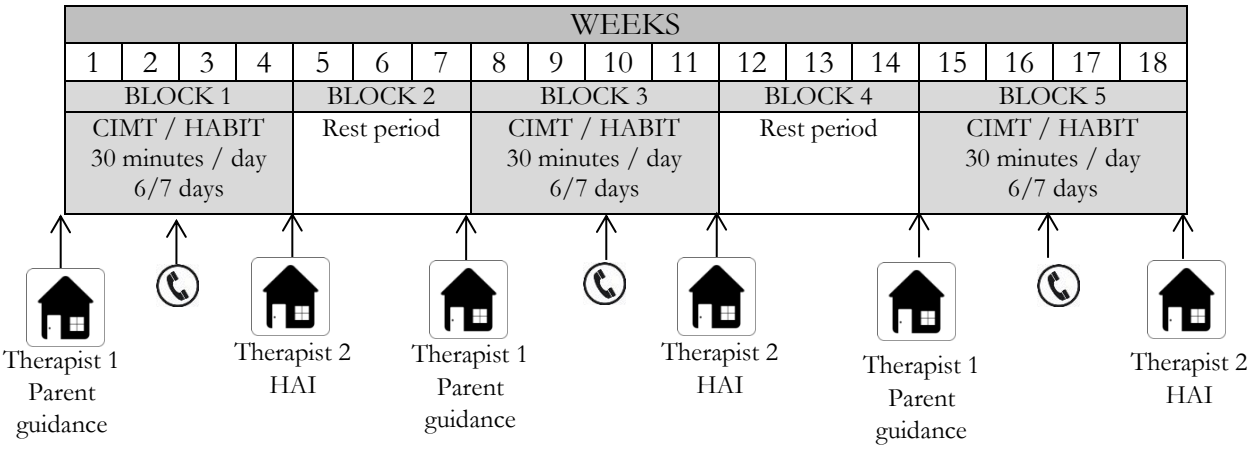
HABIT differs from CIMT in the way that no restraint was implemented and instead of promoting unilateral grasping, bimanual grasping was stimulated. Toys were precisely selected to stimulate progressed bimanual grasping. The approach of the therapist and parents remained equal to the baby-CIMT.

Figure 1. Flow-chart study



Abbrevations : AIMS : Alberta infant motor scale; CIMT: constraint-induced movement therapy ; GMA: general movements assessment; HABIT: hand arm bimanual training ;HAI: hand assessment for infants

Figure 2. Intervention program



Usual care

Infants with perinatal care receive systematic follow-up at the hospital. The first screening is mostly between 4 and 6 months post term age. Possibly, physiotherapy could be prescribed. Infants with the early diagnosis of CP have access to unlimited number of physiotherapy sessions for the first three year after approval of the status (E-pathology). Infants without the official diagnosis of CP (at that age) but with developmental delay have access to maximum 60 session during one year (F-pathology). In practice, we notice that only children with very clear symptoms or developmental delay are referred to early intervention, but in other cases there is often a wait-and-see attitude.

Outcome measures

The primary outcome measure was the HAI. This was performed during a home visit before and after the whole intervention program, as wel as intermediately after each intervention bloc. Video scoring was done by a certified physiotherapist who was blinded to the group allocation.

The secondary outcome measures were the *Alberta infant motor scale (AIMS)* and several questionnaires. The AIMS is a standardized observational scale to assess the gross motor development from birth till independent walking around 18 months of age.[21] Spontaneous movements are observed in four positions: prone, supine, sitting and standing. The test is easy and quick to administer and can detect a delayed and abnormal motor development, due to the focus on the achievement of motor milestones and quality of posture and movement outcomes. The AIMS was evaluated before and after the intervention and at follow-up at one year.

The *parenting Sense of Competence scale* is a 16-item Likert-scale questionnaire to measure parent's sense of confidence and satisfaction. The questionnaire exists of two subscales,

satisfaction and efficacy, and every item is scored in six levels ranging from strongly agree to strongly disagree. . The internal consistency reliability of the total PSOC scale has been evaluated in different samples and is between 0.71 and 0.87.[25-28] Parents were asked to complete the questionnaire before and after the intervention program.

At the end of the intervention program, parents were asked to complete a *satisfaction questionnaire*. This questionnaire consisted of open and closed questions regarding the satisfaction and the feasibility of the intervention program. .

The *neurological information* (hearing or vision impairment; diagnosis of CP and the Gross Motor Function Classification System (GMFCS) scores; or other diagnosis) was collected through the infant's medical follow-up file, when the child was aged between 18 and 36 months post term age.

Ethics approval

Full ethical approval has been obtained by the Medical Ethics Committee of The University of Ghent as a central Committee as well as by the local ethical committees. Written informed consent was obtained from all parents before entering the trial. The Belgian trial registration number is NCT02720432.

Statistics

Descriptive statistics were used to document general and clinical characteristics. Differences between groups were determined by the independent t-test for continues variables and chi-square test for categorical variables.

RESULTS

Patients

Enrollment for the feasibility study started in June 2016 and the study was completed in February 2018. Sixteen infants were screened and eight met the inclusion criteria. All of them agreed to participate for the intervention study. However, one infant, which was allocated to the CIMT-group was soon disregarded for the feasibility study because this infant did not show sufficient asymmetric hand use during the third home visit. Consequently, parents were no longer convinced that the CIMT program was necessary for their child and also the therapist decided that it would be better to renounce the program.

Table 1 shows the demographic and clinical characteristics for each group of the remaining seven infants. At two years, only four were diagnosed with USCP. Four infants were allocated to the HABIT and three to the CIMT group.

Table 1. Demographic and clinical characteristics of each group

	Baby-CIMT			Baby-HABIT				
Infant	**1**	**2**	**3**	**1**	**2**	**3**	**4**	**p-value***
GA (weeks)	34	40	32	40	29	41	36	0.771
BW (grams)	1990	3350	1990	4245	1390	3668	2960	0.484
SGA	No	No	No	No	No	No	No	1.000
Type of perinatal stroke (side)	PVHI (Left)	PAIS (Left)	PVHI (Left)	HS (Left)	PVHI (Right)	HS (Left)	PVHI (Left)	0.233
Absent fidgety movements	No	No	No	No	No	No	Yes	1.000
Gender	Boy	Boy	Boy	Boy	Boy	Girl	Girl	0.429
HAI age (months)	4	4	5	5	4	4	4	0.724
HAI AI (%)	94	16	47	15	77	7	70	0.480
Cerebral palsy	USCP	No	USCP	No	USCP	No	USCP	1.000

AI: asymmetry index; BW: birthweight; CIMT: constraint-induced movement therapy; GA: gestational age; HABIT: Hand-arm bimanual intensive training; HAI: hand assessment for infants; HS: hemorrhagic stroke; PAIS: Perinatal Arterial Ischemic Stroke; PVHI: Periventricular hemorrhagic infarction; SD: standard deviation

Therapy compliance

Of the seven enrolled infants, six parents were very compliant with the study and finished the whole protocol. In one infant, the therapy had to be stopped prematurely because parents were not compliant to the protocol and did not fill out the documents as requested. This family had a low socio-economic status and only the father spoke Dutch. Furthermore, the daily logbook was not completed by all parents.

Parents' perspective

Parental satisfaction with the intervention was evaluated with a questionnaire, comprising open and closed questions. The results of the closed questions are presented in Table 2. In general, parents were very positive about the offered therapy program. They all had the feeling that the motor development of their child improved by the therapy program. They felt capable of delivering the intervention. Furthermore, all parents indicated that by participating in this study, they became more aware of the motor development and asymmetric hand function of

their child. As a result, they indicated that they did not only pay attention to the more impaired hand during the practice moment, but also throughout the day. This can of course influence the final results and must be taken into consideration, however, this is difficult to measure. Moreover, they considered the box with adapted toys an important added value. As a result, they had a better understanding of appropriate toys for their child's current motor and cognitive development. There was no negative feedback about the frequency of the therapy sessions. In contrast, the duration of the intervention sessions was often perceived as too long. A block of 30 consecutive minutes can be long, especially in young children, so this had often to be split up in different blocks.

Table 2. Satisfaction questionnaire

	Decreased	**Did not change**	**Somewhat improved**	**Made good progression**
Do you have the feeling that the motor development improved by the therapy?			●●●	●●●
Due to contact with the therapist, something has changed in the way you approached your child?			●●●●●	●
Has contact with the therapist clarified your view of your child's development? Do you have more insight into your child's problems?		●	●●	●●●
	Absolutely not	**Maybe**	**Absolutely**	**/**
Suppose family or acquaintances would experience the same problem with one of their children, would you recommend this form of treatment to them?		●	●●●●	
	Insufficient	**Sufficient**	**Very good**	**/**
What did you think of the guidance you received during the treatment period?		●	●●●●●	
	Very unsatisfied	**Unsatisfied**	**Satisfied**	**Very satisfied**
Are you generally satisfied with your participation in the study?			●●	●●●●

Each bullet represents the answers of the parents of one child.

Therapists' perspective

The physiotherapist who performed the home visits for training and assisting the parents, appreciated the approach. She felt that the therapy would lead to better outcomes. The toy box was really viewed as an added value for the parents and infants and helped her for providing clear instructions. She had the feeling that the infants and especially the parents, were really looking forward to receive new toys at the start of every therapy block. Maintaining

the communication with the parents was essential to support families and keep them motivated. She gained the impression that without the intermediate home visits and phone calls, therapy compliance would be much lower.

The therapist who carried out the assessments, had no specific remarks about the used assessment tools. The chosen outcome measures were useful and easy to perform in a home setting.

DISCUSSION

The aim of this feasibility study was to examine the workability of the protocol and receive feedback of the parents and therapists. Overall, parents were satisfied with the early intervention program and were compliant to the therapy program. They had the feeling that the hand function of their child improved, however, the efficacy of the therapy was not examined and as a result, this cannot be confirmed yet. Based on this feasibility study we have gained some insights and also a few concerns are raised about this intervention study if this protocol would be carried out on a larger-scale basis. Some topics are addressed below.

Recruitment

In reference to this feasibility study, it is expected that the inclusion might be problematic. Based on the baby-CIMT protocol, a sample size of 16 infants per group is required to achieve a significance level of 0.05 and 80% power.[22] If a dropout rate of 10% is taken into consideration, a minimum of 54 infants (18 in each group) is required. A rough estimation was made that between 50 and 100 children per year would be diagnosed with perinatal stroke in Flanders. However, it took more than two years to reach 50 infants with perinatal stroke. Of them if was found that only 32% developed USCP. If this study wants to be conducted in a large group, and the predetermined sample size wants to be reached within a limited period, more attention will have to be paid to the recruitment. First, there was most likely an overestimation of the number of cases in Flanders, but it is also probable that some cases were missed and that not all parents were informed about the study. To reach a large enough sample size, it could also be appropriate to expand the number of cooperating NICU centers. However, currently, the study was only available in Dutch and consequently only Flemish NICU's participated in the study. Since this study has already been carried out in collaboration with the largest NICU's in Flanders, the options for recruiting more children via other Dutch-speaking NICUs are limited. Alternatively, it is possible to collaborate with the Netherlands or to translate the study into French for collaboration with the remaining Belgian NICU's.

Inclusion criteria

The inclusion criteria comprised the diagnosis of perinatal stroke and abnormal GM and/or asymmetrical signs on the HAI, however no explicit cut-off was determined for the HAI. When this feasibility study was executed, the prospective cohort study (described in chapter 3) in infants with perinatal stroke was still ongoing and the results unknown. Now the results are established, it could be suggested to implement the cut-off value of 23 on the asymmetry index of the HAI, because this was found to have a sensitivity and specificity of 100% to predict USCP. In addition, in case of delayed presentation, the HAI should be repeated a few weeks later if the first test did not show asymmetry. On the other hand, we also found (chapter 3) that even in infants who will not develop USCP, in some infants more asymmetry is noted between both hands on the HAI compared to a healthy norm group. Therefore, it could be that some asymmetry is observed during the first weeks or months after the brain lesion, that could spontaneously disappear. Therefore, it should be important that when an asymmetry is noted, this should be noted repeatedly and confirmed by the parents.

Control group

Even though, for this feasibility study no infants were recruited for the control group, in the final study it would add value if a control group would be implemented. However, a few concerns have come to mind. When recruiting for an intervention study, a placebo is usually offered for the control group, however this might be challenging in this case. In the study of Eliasson et al.[15] the control group received baby-massage, but it was found to also have some positive effects on the development. Therefore, it would be important to find out what could serve as an alternative and valuable placebo training with less effect on the motor development. Alternatively, the control group could only consist of usual care without adding any additional training. Nevertheless, this could make it uninteresting for the parents of the control group to further participate. To address this issue, it may be appropriate to randomize only for the CIMT and HABIT. Moreover, a prospective cohort study, could be conducted in which the same measurements are performed following the same protocol without additional CIMT or HABIT. This way you ensure that parents do not feel disadvantaged when participating to the study. However, it might be methodologically less rigorous to compare the CIMT and HABIT group to this control group, since there might be a time period bias. Another option would be to perform a retrospective study and compare the outcome to a 'historic group' of infants who did not receive any additional therapy. This allows that all infants could start with the

intervention. Given the promising results based on the results of the study of Eliasson et al.[17],it could be argued whether it is still justified to form a control group.

Intervention

The fact that this whole study program is home-based, results in some practical and methodological disadvantages. First, it is time-consuming for the therapists to drive around Flanders and Brussels to visit the patients. Furthermore, the quality of the intervention program might vary between families because of their home environment and this cannot be controlled for. On the other hand, the advantages outweigh the disadvantages for the families. They do not have to visit the hospital or some therapy center, which is more convenient for them and might enhance compliance. In addition, the infant is always in a his/her home environment during the evaluation moments, which could enhance the representability of the test results.

Engagement is a complex and crucial component of effective treatment that increases retention. Parents are no longer observers of the therapy, but they were the most important person during the intervention. They felt involved into the motor therapy of their child and had the feeling they could perform the program and that it fitted into their everyday lives. The frequency of 6 days a week during the intervention blocks seems plausible. The intensity is remarkably reduced to 30 minutes a day, instead of mostly a few hours a day in older children and adults.[22] A well-targeted dosage of CIMT is necessary to minimize the potential risk of damage to the immature brain because of restraining the use of a healthy limb in a young child.[23] Even though this dosage was decreased considerably compared to older infants, it was sometimes difficult to complete a full session of 30 minutes. Therefore, it would be important to keep the possibility to split up the session in case it is not possible to have a complete session in one time, as long as the 30 minutes are reached at the end of the day. Furthermore, it seems that the daily logbook requires a lot of energy and punctuality from the parents. Repeated reminders will be needed to enhance compliance for the logbook. The regular communication with the parents was essential. Eventually, even a phone call once a week instead of one every two weeks, could be considered to enhance compliance and reinforce the importance of the therapy program.

CONCLUSION

This study outlines the protocol of an RCT with two different treatment groups, comparing the effect of CIMT versus HABIT. To the best of our knowledge, this is the first study to investigate the effect of baby-HABIT and to compare it to baby-CIMT. A feasibility study in seven infants revealed that this program is achievable, however, some adjustments in the recruitment process and protocol need to be considered, before implementing this study protocol into two larger groups. If these therapy approaches would also found to be effective in young children with a high risk of developing USCP, this study offers significant added value. Not only might even small improvements be of great importance to the participating infants, it will also help to further fine-tune these therapies in young infants. Further research will have to investigate which therapy modalities are most suitable for young infants.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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DISCUSSION

GENERAL DISCUSSION

Although, the quality of care has drastically improved over the past few decades, infants with perinatal insults, caused by very premature birth or brain lesions, remain at high risk for early death or later neurodevelopmental impairments compared to their term born and/or healthy peers. The general aim of this dissertation was to contribute to the field of knowledge about mortality, neurodevelopmental outcome, early diagnosis and early intervention in high-risk infants. This aim was subdivided into two major parts; each addressing one specific topic and specific group of high-risk infants. In **part 1**, existing literature regarding the overall neurodevelopmental outcome at two years corrected age in VPT/VLBW infants born over the last decade was reviewed and reported in a meta-analytic review **(chapter 1**). Additionally, the neonatal mortality and neurodevelopmental outcome in a national population-based prospective cohort was investigated **(chapter 2). Part 2**, focused on the neurodevelopmental outcome, early diagnosis and early intervention in infants with perinatal stroke. More specifically, the neurological outcome was reported in infants with perinatal stroke as well as the predictability of two motor evaluation tools for early detection of USCP **(chapter 3)**. Finally, a feasibility study of an early intervention program was evaluated for infants at high risk of USCP **(chapter 4)**. The general discussion of this dissertation will summarize the most important findings as well as the translation of science to practice for each part, the overall strengths and limitations and future research perspectives. The general discussion is closed with the main conclusions of the current dissertation.

PART 1: VPT/VLBW infants

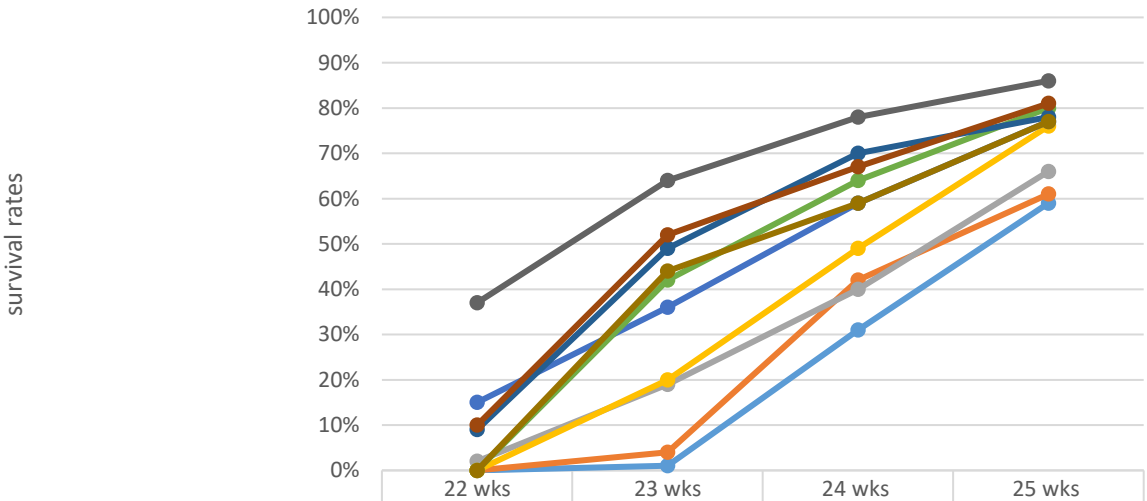
1. Summary and discussion of the results

1.1. Preterm birth and mortality

Up to date in-hospital mortality and morbidity rates among VPT infants are essential for family counseling and evaluation of innovative approaches to enhance outcomes. Therefore, a population-based cohort study based on Flemish infants was undertaken and reported in **chapter 2**. This large sample sized recent cohort provides a detailed picture of the birth and survival of infants of VPT/VLBW infants in Flanders. All infants admitted to the 8 Flemish NICUs were included and data were uploaded into a database. The number of stillbirths and deaths in the delivery room were not registered into the database, which makes it not possible

to provide a complete overview of mortality rates in VPT/VLBW infants but only of the infants who did receive active care.

Our results display an overall neonatal survival rate of 92% in all VPT/VLBW infants admitted to a NICU. Infants with the lowest GA had remarkably higher mortality rates. Whereas only 59% of all infants admitted to the NICU at 24 weeks GA survived, 99% of the infants born at 32 weeks gestation survived. When comparing our data to other large cohort studies in VPT/VLBW infants, it can be concluded that Flanders has survival rates close to the average of all large cohort studies (Figure 1). However, interpretation of these results must be made with caution, because definitions of neonatal survival may vary among studies and this might have some impact on the rates. More specific the denominator could be different, i.e. all births, live births or infants admitted to the NICU. For instance, the EPIPAGE study reported an overall difference in survival rates according to whether the denominator was all births or live births of 8% for the whole sample of VPT infants but about 20% for the lower GA groups (EPT infants).[1]



	22 wks	23 wks	24 wks	25 wks
EPIPAGE 2 (France, 2011)	0%	1%	31%	59%
SNN (Switzerland, 1997-2013)	0	4%	42%	61%
EPIcure (UK,2006)	2%	19%	40%	66%
Victoria (Australia, 2010-2011)	0%	20%	49%	76%
Peditraix (US, 1997-2013)	15%	36%	59%	77%
CNN (Canada, 2010-2011)	0	42%	64%	80%
NIDCHD NRN (US, 2013-2015)	9%	49%	70%	78%
EXPRESS (Sweden, 2004-2007)	10%	52%	67%	81%
Japan NRN (Japan, 2003-2005)	37%	64%	78%	86%
PRESENT COHORT (2014-2016)	0	44%	59%	77%

Figure 1. Survival rates for different large population-based cohorts in the most periviable infants. *Adapted from Patel 2017*[2]

The existing evidence has demonstrated a rise of survival rate of periviable infants over the past two decades. [3-7] In order to investigate a possible evolution over time, our results were compared to the Belgium EPIBEL study in EPT infants. This confirmed the improving survival trends, as it was found that the neonatal survival rate of the 2014-2016 cohort, increased by 19% (58% to 77%) over a time period of 15 years in Flanders (Figure 2). The factors underlying the improved outcomes in our study are not investigated and therefore uncertain, but there are a number of possible contributing factors.

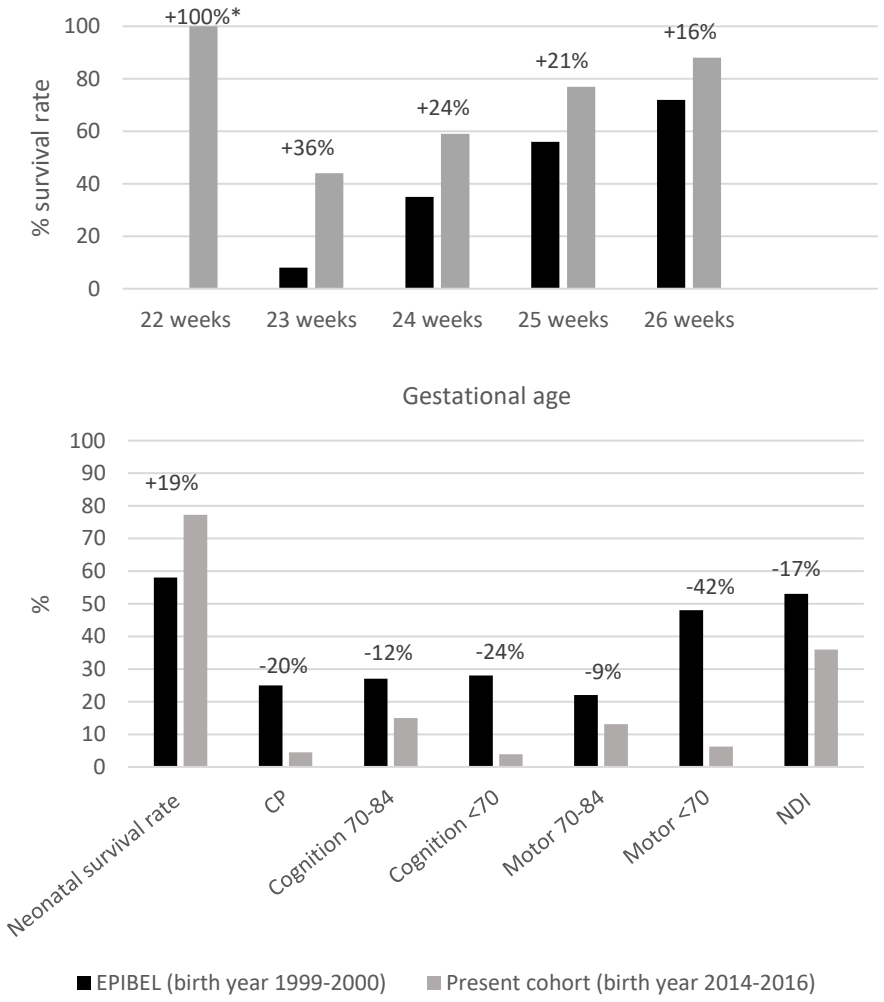


Figure 2. Comparison between two Flemish cohort studies with 15 year intervals in infants with gestational age <27 weeks, showing an improvement in survival rate and a reduction of adverse outcomes. Motor and cognitive outcomes were based on BSID-II (EPIBEL) and Bayley-III (this cohort). Nevertheless, it is important to note that NDI is based on different formulated definitions, i.e. Bayley scores <70 in the EPIBEL study versus <85 in the present cohort.

*In the EPIBEL study no infants survived at 22 weeks GA whereas in this present cohort only 1 surviving infant was reported, which declares the 100% increase at 22 weeks GA.

Mortality rates are closely related to local resuscitation policies and perinatal care. In high income countries, the limit of viability has been decreased from about 32 weeks of gestation, first to 28 weeks, and in recent decades, neonates born after the 24th week of GA or weighing at least 500g at birth have been considered candidates for active care in the NICU. However, recommendations on the management of extremely preterm births continue to vary and international consensus is lacking. Most guidelines still advocate comfort care at 22 weeks' GA and active care at 25weeks' GA, whereas there is a wide variation in recommendations regarding deliveries at 23 and 24 weeks' GA.[8] In Belgium, after the EPIBEL study was released, presenting poor outcomes for the most periviable infants, the Flemish NICUs decided in 2014 to pursue a similar policy in all centers, stating that no active resuscitation is performed at <24 weeks GA, unless on explicit demand of the parents.[9, 10] At 24 to 25 weeks, resuscitation is started in accordance with parental wishes. At 26 weeks, active resuscitation is always started unless other serious complications are present. As a result, this stricter resuscitation policy may have influenced the overall survival rates. However, for comparisons over time and between studies, survival rates by week of GA are more informative than global mortality. When looking at our results, survival rate also increased by each GA, demonstrating that not only the limit of viability is important but also a number of quality improvement efforts and practice changes over time may have contributed to the improved outcomes.

Changes in delivery room and neonatal unit policies have been reported over the past two decades in European centers.[7] Key points in the quality improvement is the widespread use of prenatal steroid prophylaxis, which is one of the most effective interventions, and the more aggressive use of prenatal antibiotics, in an attempt to decrease the complications arising from vaginal or intrauterine infection.[6, 11, 12] Maternity units reports a more active obstetrical management, for instance in the case of fetal distress and caesarean section is performed at earlier GA. Furthermore, neonatologists are more present in the delivery room at earlier gestations, which results in more frequent involvement in resuscitation decisions.[7] Also changes in respiratory care is reported over time, including less aggressive ventilation and decreased intubation in the delivery room in combination with increased surfactant use in order to improve postnatal respiratory function.[6]

Moreover, prenatal diagnostics techniques (genetic techniques, prenatal imaging techniques) have also evolved considerably, leading to an increased number of congenital malformations being diagnosed prenatally instead of after birth, which could also play a role in the mortality trends.

To summarize, it can be stated that:

Currently, in Flanders, the overall survival rate to discharge was 92% of the VPT/VLBW infants admitted to intensive care, however chances of survival among those infants vary greatly according to the GA. Mortality rates increased significantly with decreasing GA. Compared to the Belgian EPIBEL study 15 years ago, survival rate increased with nearly 20% in EPT infants.

1.2. Preterm birth and perinatal morbidities

Challenges in the care of preterm infants are represented by high mortality rates and as well as significant morbidity.[13] Preterm born infants are at high risk of injury to the developing and immature brain, which is crucial for their development. Such injury can lead to motor, cognitive or behavioural problems extending into adult life.[14] There is not only a lack of recent information regarding mortality but also regarding the morbidity within VPT/VLBW infants. In **chapter 2**, comorbidities are described for all infants admitted to the NICU, consisting of a sample of 1941 infants.

As described in the introduction of this dissertation, the focus will only be on the most common brain injuries in preterm infants. Neonatal intracranial hemorrhage is characteristic for the preterm infant.[15] It was found that germinal matrix-IVH was the most common variety of neonatal intracranial hemorrhage, with mild lesions more prevalent than severe IVH, which is consistent with the literature.[16] In infants who died before discharge more than half of them had some form of intracranial hemorrhage, whereas in the survivors intracranial hemorrhage was observed in one out of five infants.

PVL is the second common brain lesion in preterm infants, which is also coherent with our findings.[14] Approximately in one out of ten VPT/VLBW infants transient periventricular densities were observed for more than 7 days (PVL grade I), and this in the whole population (survivors and non-survivors). This allowed us to confirm that PVL grade I, or also defined as non-cystic PVL, is commonly identified in VPT/VLBW infants and is not related to mortality. Cystic PVL, referred as grade II to IV, was rather uncommon and was observed in 3% of the whole VPT/VLBW population. This confirms previous findings that cystic PVL is seen more rarely.[17-19]

Since the survival rate of the most periviable infants increased over the past decade and since they are at higher risk of complications, it is believed that it would be clinically relevant to further explore the influence of GA on the brain lesions. Thus, **additional data analyses** were performed including the sample of chapter 2. Not surprisingly, this shows that lower GA was associated with an increased risk of developing brain lesions, whether it was intracranial hemorrhage or PVL. This is in line with the expectation, as it is know that EPT infants have a limited hemostatic capacity. In addition, the highly vascularized germinal matrix in the immature brain, which is surrounding the ventricular system, is exceptionally vulnerable to hemorrhage.[16] Germinal matrix volume (and fragility) peaks around 25 weeks and declines until little matrix is left over around 34 weeks.[14, 20] Involvement of white matter associated with GM-IVH is almost invariably due to venous infarction, caused by compression of medullary veins coalescing near the matrix area.[21] Primary injury to white matter, in the absence of GM-IVH, has a different mechanistic character. Selective vulnerability of pre-oligodendrocytes peaks between 28 and 34 weeks GA, and this injury typically affects subrolandic white matter bilaterally.[22]

Overall, when comparing the rates of cystic PVL in the survivors at discharge to other large cohort studies in VPT/VLBW infants, it can be concluded that this is in line with other large studies, with an incidence between 2% to 6%. [19] On the contrary, severe IVH (grade ≥3) was found to be less prevalent in our cohort compared to other international studies.[19] This may be explained by the considerable higher mortality in infants with severe IVH. Half of the children with severe IVH did not survive discharge. Furthermore, severe forms of IVH are often combined with cystic PVL, which makes the prognosis even worse.[17, 23] This might indicate a more progressive policy regarding withdrawing or withholding of care in infants with severe IVH brain lesions, which are known to have a poor neurodevelopmental prognosis.[15, 24, 25] This was recently also described in different studies.[26-28] Moreover, a recent nationwide survey in Flanders (Belgium) of neonatologists and nurses emphasises that end-of-life decisions are generally very well supported, even for decisions that currently fall outside the Belgium legal framework.[29]

When comparing the prevalence of severe brain lesions in the EPIBEL and MOSAIC study it is expected that the presence of cystic PVL and severe IVH decreased over time in Belgium as well.[30, 31] A reduced incidence of cystic PVL has also been recorded by others.[17, 32, 33] The two principal mechanisms in the pathogenesis of periventricular white matter injury are systemic hypoxia/ischemia and infection/inflammation.[18, 22, 34] Changes in management can explain the decreasing occurrence of preterm cystic PVL. Firstly, there is an increased antenatal

use of antibiotics and which have been proven to decrease the prevalence of cystic PVL.[35] Secondly, prolonged exposure to mechanical ventilation has also been reported to be significantly associated with cystic PVL.[18, 36, 37] Therefore, the more frequent use of nasal CPAP and less mechanical ventilation could have contributed to a decrease of hypocapnia, causing a reduction in cerebral blood flow, which also might play an important role in the decrease of cystic PVL.[34, 38]

The pathophysiological mechanisms for GM-IVH are, aside from prolonged mechanical ventilation, slightly different from PVL. Profound hypoxic-ischemic events and pneumothorax, mostly occurring during the first days of life, causing acute hemodynamic disturbances in patients with often a disturbed autoregulation, are related to the occurrence of IVH.[23, 39, 40] The reduction of the incidence of IVH over time has been related to improved perinatal management including timely intra uterine transport to a specialized center and efforts that are being made to a better hemodynamic stabilization. In addition, the use of antenatal glucocorticoids and antibiotics have been related to a decrease of IVH incidence.[41, 42] However, although advances in perinatal care have led to a significant decrease of GM-IVH, the overall incidence of GM-IVH remains high and continues to be a significant problem. The major cause is the fact that the incidence of birth and survival of the smallest preterm infants, which are at highest risk for acquiring GM-IVH, has clearly increased over the past decade.

To summarize, it can be stated that:

Severe brain lesions are correlated with higher mortality rates. Intracranial hemorrhages are more common than PVL. The prevalence of brain lesions increases with decreasing GA. The prevalence of severe brain lesions has decreased over time due to improved perinatal management.

1.3. Preterm birth and neurodevelopmental outcome

Survival is not the only goal in perinatal medicine while trying to set a lower viability limit, but outcome and quality of life are the main priorities. Updated information on outcomes of those preterm infants at different gestational ages is needed for guiding health policy, informing physicians for perinatal management, offering comprehensive information for enabling parents in shared decisions making and for benchmarking outcomes. To be able to compare data, it is necessary to have a general overview. Therefore, in **chapter 1**, a thorough literature screening was conducted to provide overall pooled prevalence of neurodevelopmental

impairments in VPT/VLBW infants in a meta-analytic review. Cohort studies about VPT/VLBW infants born over the past decade were searched throughout four different databases. A total of thirty papers were included into this meta-analysis, of which most studies reported outcome at 2 years of age. Herein, it was estimated that approximately one in five of VPT or VLBW infants respectively developed a certain degree of motor or cognitive delay, based on developmental scales at approximately 2 years corrected age. CP was found to be present in approximately one out of 14 VPT/VLBW infants. The comparisons with previous meta-analytic reviews by Himpens et al.[43] and Oskoui et al.[44] showed a decreasing trend of overall rates of CP. This trend has also been reported by separate cohort-studies evaluating outcome over time.[45-49]

However, as commented by Marlow on our systematic review it is dangerous to compare different studies due to the large heterogeneity within studies.[50] Probably, the most important factor is the local resuscitation policy. Most of the studies did not even report the limits of resuscitation, and if they did, a large variety was observed. The fact that resuscitation policy is at the lower or upper boundary of the 'grey zone' in some countries may have an impact on the overall outcome of these children, since it has been clearly demonstrated that a lower GA is associated with higher complications and consequently, with a higher risk of developmental disabilities. These pooled results can only give a picture of the current situation but these generalized results should not be used for individual counseling. In **chapter 2,** the presence of neuromotor impairments among a Flemish population-based cohort of VPT/VLBW infants was investigated, including nearly 2000 infants. It could be demonstrated that at 2 years CA, 64% were free from neurodevelopmental impairment and 90% were free from moderate-to-severe impairment. The diagnosis of CP was made in 4.3% of all VPT/VLBW infants. By calculating the rate for CP infants with a GA ≤26 weeks, it made it possible to compare our results to the Belgian EPIBEL study to evaluate a possible evolution over time. It could be concluded, comparable to the global prevalence, that a drastic decrease of CP is occurring over time, ranging from 25% to 5% in our cohort. The main risk factors for CP are known to be severe intracranial hemorrhage and PVL grade ≥3.[51, 52] As a result of the decreasing prevalence of severe brain lesions by changing and improving perinatal management, as already mentioned above, the decreasing trend of CP is a direct consequence of this.

1.3.1. Relation between GA/BW and neurodevelopmental outcome

Overall, both low BW and GA at delivery can be considered as some of the strongest predictors for postnatal clinical outcomes in premature infants.[53-55] In **chapter 1 and 2,** results of neurodevelopmental outcome were categorized for infants with different GA and BW. As expected, subgroup analyses clearly indicated that the overall prevalence of CP and motor and cognitive delays rose with decreasing GA and BW. An overview of the overall and national neurodevelopmental outcomes by GA are presented in Figure 3. This reveals that Flemish EPT (<28 weeks) infants showed better motor outcomes (motor delay and CP) compared to overall global pooled prevalences of motor delay and CP. However, cognitive delay was comparable to the overall prevelances.

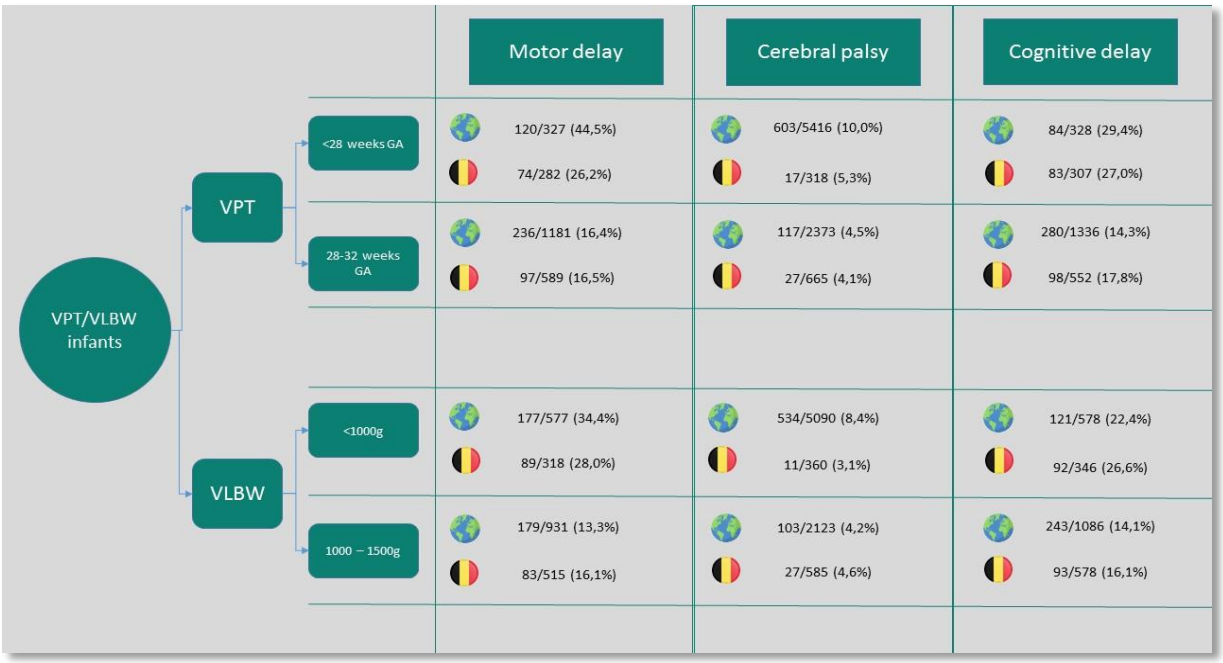


Figure 3. Overview of global (chapter 1) and national data (chapter 2) on neurodevelopmental impairment by GA.

The fact that motor delay and CP is less prevalent in our cohort of EPT infants compared to worldwide pooled prevalences can be explained by previously stated findings. This includes that the prevalence of severe brain lesions in the infants who survived to discharge was lower compared to other studies in VPT/VLBW infants.[19]

On the contrary, the prevalence of cognitive delay in EPT infants is comparable to the overall global pooled prevalences. This can be attributed to the fact that the relation between brain lesions and cognitive outcome remains unclear.[56] The occurrence of cognitive delay is more complex and multifactorial. Consequently, it can be assumed that possible risk factors were not different from other large studies, even though this is only an assumption.

In infants born between 28-32 weeks the prevalences of CP, motor and cognitive delay are very similar between the Flemish population and the worldwide-pooled prevalences. This can be explained by the fact that resuscitation policy and the presence of brain lesions have less influence on the overall outcome in infants with higher gestational ages. Moreover, the proportion of infants raises with increasing GA, as a result, only noticeable differences in perinatal care would effectively have an impact on the outcome rates.

1.3.2. Relation between brain lesions and neurodevelopmental outcome

Brain injuries detected by cerebral imaging including IVH and PVL have been demonstrated to be strong predictors for adverse motor outcomes, especially affecting gross motor function.[24, 52, 56, 61] Accordingly, brain lesions and neurodevelopmental outcomes were recorded in a large VPT/VLBW Belgian cohort. Analyses based on the sample of chapter 2 were reported in the **additional data analyses.** It could be confirmed that IVH grade III-IV was significantly related to motor and cognitive delay as well as CP. PVL increased remarkably the chances for motor developmental problems (motor delay and CP) and somewhat the odds for cognitive delay, however, it was not found to be statistically significant.

Those findings are generally in agreement whit previous research. It is generally accepted that severe brain lesions, such as IVH and PVL are the main risk factors for adverse motor outcome.[52] This is not surprising as it is known that the predominant location of the damage within the white matter in the preterm infants, is around the CST in their descent into the internal capsule and somewhat less commonly, in the centrum semiovale and the corona radiata.[22] Since these regions control motor function it is not surprising that severe IVH and PVL are related to adverse motor outcomes.

Literature remains ambiguous about the effect of PVL on cognition. Some have reported higher prevalences of cognitive disability in infants with PVL, with increasing rates according to the severity of PVL.[62-65] On the opposite, persisting echodensities are not associated with adverse outcomes.[66-68] This association, between PVL and adverse outcome,

might also be related to the fact that it has been shown that PVL is often accompanied by neuronal abnormalities affecting not only the cerebral white matter but also the thalamus, basal ganglia, cerebral cortex, brainstem and cerebellum, that together constitute a complex amalgam of 'encephalopathy of prematurity'.[22]

To summarize, it can be stated that:

Neurodevelopmental impairments are common in VPT/VLBW infants. Nearly one in five VPT/VLBW infants show some adverse neurodevelopment. GA and BW are negatively related to outcomes. A drastic decrease of CP is observed globally as well as nationally. The presence of severe brain lesions increases the chances of motor and cognitive impairment.

2. Clinical relevance and implications

Based on the presented research in this first part of this dissertation, some clinical implications are worth mentioning.

Based on the results of our studies in chapter 1 and 2, it can be inferred that very preterm birth is closely related to an adverse neurodevelopmental outcome. Our results showed that on average nearly 1 in 5 VPT/VLBW infants develop some kind of delay on motor, cognition or sensory domain at 2 years of age. Moreover, 1 out of 15 infants develops CP. If this data is further extended to the entire Belgian population, and it is known that in recent years approximately 120 000 children are born in Belgium every year, of which 1.2% are very preterm, this could indicate that each year nearly 300 VPT/VLBW children will probably have some of the above mentioned neurodevelopmental delay. Moreover, this number does not even take into account behavioral or psychological problems. Considering that behavioral problems are a common problem in VPT/VLBW infants, this would result in annually even higher numbers of infants with neurodevelopmental impairments if this would be counted in the overall rates.

Therefore, it can be recommended that the early and systematic follow-up of those patients be of highly importance considering the high absolute number of infants with neurodevelopmental impairments. Nevertheless, it should be mentioned the outcomes are evaluated on a group level and may differ substantially at the individual patient level. Follow-up assessment should clearly observe and assess the neurological, motor-cognitive, language and behavioral outcome for each individual patient to make sure all aspects of the development are observed.

It is already generally accepted that infants who are at high risk should be enrolled in a follow-up clinic that specializes in the neurodevelopmental assessment of high-risk infants, which is standard implemented in increasingly more high-income countries.[69-71] In line with the recommendations, the Belgian government approved already a Royal Decree stating that all VPT/VLBW infants should benefit from a long-term follow-up program. Therefore, our results are crucial for demonstrating the importance of the national follow-up program offered by the Belgian government, at is it recommended that this follow-up program remains operational. Furthermore, the fact that it is mandatory to register the data into a national database has great value for scientific research, and this is highly recommended to sustain.

On the other hand, our prospective population-based cohort study revealed that only 61% of the infants were seen at the follow-up assessment near the age of 2 years old. Although loss to follow-up is actually a common problem in cohort studies[72-76], it enlightened the fact that concerted efforts must be made to improve the follow-up rate to make sure that as many infants as possible can benefit from a professional follow-up and if necessary be referred to early intervention.

Furthermore, an important contribution of our study is that it elucidated the positive trends over time in the most periviable infants. Despite the fact that specific obstetric or perinatal interventions are not analyzed or taken into account, this can provide feedback to the involved NICUs. It provides evidence that the progress they have made over the last 15 years had also a direct or indirect impact on the improved survival rate and neurodevelopmental outcome of those infants. This should be a reason to continue with the current approaches or even continue to improve it. Additionally, by providing an overview of the outcome by each GA, this report also distressed the importance of GA on the prevalence of neurodevelopmental impairments. This could be important for clinicians, both in counseling and early-care decision-making. Our results could be an argument and motivation for the gynecologists and neonatologists to preserve the current resuscitation policy and certainly not shift the limit of resuscitation towards lower gestational ages.

PART 2: Perinatal stroke

1. Summary and discussion of the results

The second group of high-risk infants discussed in this dissertation are infants with perinatal stroke. Perinatal stroke comprises a diverse but specific group of cerebrovascular diseases that occur between 20 weeks of fetal life and 28 days postnatal life. Perinatal stroke might not be as common as preterm birth, hence it is still an important group of infants. It is known that more than a quart of the children with perinatal stroke demonstrate important neurological deficits. However the exact number varies considerable between studies.[77]

1.1. Perinatal stroke and neurological outcome

Well-powered, population-based studies about perinatal stroke are limited. There is need to have a better understanding of the presentations, potential risk factors, strategies for treatment, and long-term results. Furthermore, limited studies reported outcomes of the whole umbrella of perinatal stroke together into one study. Since the pathology and consequences of perinatal stroke remain underinvestigated, a prospective cohort study in infants with perinatal stroke was undertaken and reported in **chapter 3**. A total of 47 infants with perinatal stroke were enrolled from different NICUs in Flanders and the infants were assessed at different time moments. It was found that one third of these infants developed CP, and in the majority of the infants it was unilateral (USCP). Since perinatal stroke comprises different type of brain lesions, outcomes were reported by stroke type. Nevertheless, none of the infants had a CSVT, which is not unexpected given that the incidence of CSVT is very low[78] and that this was a relatively small sample. Hence, only the outcome after hemorrhagic and arterial stroke were reported.

PVHI, resulted in CP in more than half of the children, and is therefore far more related to adverse outcome compared to other types of stroke. Our findings are in the range of what has been reported in previous research. Taking into account that PVHI is a complication of a germinal matrix hemorrhage that develops due to impaired venous drainage of the medullary veins in the periventricular white matter, it is not surprising that this serious brain lesions lead to CP in the majority of the infants.[14] Furthermore, PVHI may have adverse effects on the CST, which is well-known to be associated with CP.[79] The location of PVHI is important and will mainly determine whether CP will develop or not. Parietal and temporal

PVHI may lead to CP, whereas frontal PVHI mainly results in cognitive, behavioral or visual problems.[80] Nevertheless, the specific location of PVHI was not further investigated in our cohort.

Other types of perinatal stroke, including AIS were less associated with CP. In our cohort, only one out of six infants with PAIS developed CP, whereas in literature the prevalence has been reported twice as high.[81, 82] To our knowledge, there is not a particular reason that could explain this finding. However, it must be acknowledged that only 13 infants demonstrated AIS, which means that the sample is too small to draw strong conclusions from this.

Since the pathophysiological mechanisms are quite different between the different types of perinatal stroke, also the presentation and timing of detection were different. PVHI was mainly observed within 48 hours after birth and by brain imaging. PVHI is a complication of GM-IVH, which occurs mainly during the first days of life, and this progression is often very rapid because in most cases the severe IVH and the PVHI are detected simultaneously.[22] And since cranial ultrasound is performed immediately after admission to the NICU and regularly during the first week of life, this declares why most PVHI are observed within the first days after birth.

The occurrence of HS (other than PVHI) and PAIS was mostly observed within the first week of birth but PAIS was also observed after the first week in a few cases. Late neonatal stroke is more likely to be related to disorders of the late neonatal period, including cardiac disease, extracorporeal membrane oxygenation, venous thrombosis with embolism, post-natal infection or other events after birth, whereas early stroke are mostly related to the labor and birth.[83]

With regard to the timing of detection, it is also important to note the difference in monitoring between infants admitted to the NICU, where any manifestation will mostly be observed immediately, versus low-risk term born infants staying at the maternity unit.

The average length of postnatal stay has decreased over the last decades in western countries.[84, 85] Nowadays, the typical length of stay for mothers who had un uncomplicated delivery without complications is 2-3 days.[85, 86] Nevertheless, the number of mothers that are discharged on the date of delivery significantly increases over time.[87, 88] Some concerns are arisen about whether early discharge of mothers and their babies is safe.[89, 90] Early discharges can be detrimental for early detection of infants and maternal morbidities.

The majority of infants with perinatal stroke manifest during the perinatal period. The most common presenting feature of AIS are seizures, which has been reported to occur within the first 3 days of life in the majority of the cases.[91] It is often the case that subtle symptoms of perinatal stroke, i.e. short-lasting-fits, happen to be noticed by caregivers the first days after birth. Due to increased early discharge from maternity, it is a concern that more infants with perinatal stroke may go undetected because early presentation signs might not be recognizable by the parents at home, especially the mild symptoms. Nevertheless, in line with the trend for early discharge from the hospital, other safety netting are facilitated. In Belgium, this includes the newborn screening program by 'Kind and Gezin' as well as referral to community midwifery services. Notwithstanding, it is still expected that a lot of cases are missed. Consequently, in the missed cases, the infant is not treated, early follow-up is not designated which will lead in most cases to a later diagnosis of possible motor sequels. In the end, this will often result in a later start of therapy and missing the critical period for brain reorganization.

To summarize, it can be stated that:

CP is observed in approximately one third of the infants with perinatal stroke. PVHI, associated with very preterm birth, resulted in higher prevalences of CP compared to other types of perinatal stroke. PVHI was always observed during the first days after birth, mainly by brain imaging, whereas other types of HS and PAIS manifested by seizures in some cases and by neonatal brain imaging in others.

1.2. Perinatal stroke and early prediction of neurological outcome

Perinatal stroke is the most common cause of USCP. This lifelong condition has consequences for performance in everyday activities, quality of life and self-esteem.[92]

Nowadays, infants with perinatal stroke are referred to therapy services when focal neurological symptoms are detected. Mostly this is when parents or caregivers observes a preference for using one hand over the other, decreased movement or weakness on one side of the body or when there is a delay in reaching motor milestones.[93] However, early detection and referral of infants at risk for intervention, rather than referral of children with known CP has been recommended.[94] Delays in diagnosis of CP are correlated with worse long-term

function and participation of the infants and parental dissatisfaction, as well as higher rates of mental health conditions, including depression.[95, 96]

Nonetheless, diagnosing CP is not a straightforward process. It requires careful monitoring in the first months of development and this requires appropriate early diagnostic tools. So far, the prediction of motor and other neurological outcomes after perinatal stroke tend to mainly focus on neuroimaging characteristics. Besides the extend of the brain lesion, the lesion topography and combined involvement of structures including the motor cortex, basal ganglia or internal capsule on MRI may help predict motor outcomes.[97, 98] Furthermore, certain clinical features, such as the severity of early seizures or neurologic abnormalities at discharge, have shown to be related to the outcome.[77, 99] Despite these factors all being linked to the outcome, they can predict likelihood of USCP with insufficient certainty.

In a general high-risk population, literature describes the use of MRI in combination with the GMA and an accurate neurological examination as the best predictor for CP during the first months after birth.[100] Even though GMA has extensively been investigated as a prediction tool in high-risk populations, limited research is available for the use of GMA in a particular population with unilateral brain lesions or perinatal stroke (also most occurring as unilateral brain lesions).[101, 102] Therefore, GMA was implemented in our study. Besides the GMA, another new assessment tool has been elaborated for the evaluation of upper limb movement between 3 and 12 months, namely HAI. Since this is a relatively new assessment tool, it has not been investigated in depth.

These two background ideas formed the basis for our research described in **chapter 3**. In our sample of infants with perinatal stroke, the GMA and HAI were both evaluated and explored as prediction tools for CP, and more particular USCP. Both assessment tools had good predictive values, with a sensitivity of ≥85% to predict USCP. However, in our study of infants with perinatal stroke, absent FMs alone had poor sensitivity compared to what has been reported in the literature.[103, 104] Combining absent and sporadic FMs had a sensitivity of 85% (95% CI 55-98%) and specificity of 52% (95% CI 33-71%). Nevertheless, when asymmetrical FMs were classified into the abnormal category, sensitivity increased to 100%, but specificity dropped to 48% (95% CI 30-68%). This can be explained by the fact that not all infants with asymmetrical FMs were later diagnosed with CP. Of the six infants with asymmetrical FMs, three were diagnosed with USCP. This has also been reported by the recent paper from the GM trust, stating that mild, usually unilateral CP (GMFCS I or II) were exceptionally reported in infants who had shown normal fidgety movements.[105] Altogether,

this implies that GMA is feasible in a population with perinatal stroke for early prediction of USCP, but normal GMA must be interpreted with caution, considering the high rates of false positive cases.

Our study is also a confirmation of previous findings about possible asymmetry observed during GMA. An Italian research group described previously that a reduction of segmental movements on the contralesional side is related to later USCP.[101, 102, 106] Those fine distal movements may be regulated by corticospinal fibers, emanating from the contralesional frontal and parietal cortex and descend laterally to the spinal cord, which results in delicate, graceful wrist and finger movements.[101] Thus, these early asymmetries could be attributed to the latent ipsilateral corticospinal projections regression.[107]

Another interesting finding in our cohort is that the appearance of exaggerated FM were present in two infants out of 46, which is four times higher than the general 1% that is find in large cohorts of high-risk infants.[105] As described before, exaggerated FM are not predictive for later CP but are often associated with later coordination difficulties, fine manipulative disabilities, as well as autism spectrum disorder.[105, 108, 109] Those two infants in our sample did not develop CP, and other disabilities could not been confirmed yet as the infants in our study did not reach preschool age yet. Moreover, sporadic FM occurred also more frequently compared to other high-risk populations, which were found to have low predictability for CP in a large sample of high-risk infants, but has further not been very well documented.[104] Those findings might suggest that infants with perinatal stroke might differ in GMA observations from the mostly described high-risk populations and is a highly interesting group to further investigate the GMA.

Additionally, the predictive value of the HAI was evaluated. A cut-off value was calculated for the asymmetry index, which was found to have the maximal values of sensitivity and specificity of 100%. The HAI is a relatively new assessment tool, so research about it is sparse. To our knowledge, only two studies have preceded us on investigating the predictive value of the HAI for later USCP.[98, 110] They have also declared HAI to be a good predictive tool, however, they found that DTI had still higher prognostic value before the age of 5 months compared to the combination of conventional MRI and HAI.[98] The other study built a prediction model combining MRI, HAI, GA and sex founding a very good area under the curve with this model.[110]

Studies have revealed that the CST wiring patters is the most important predictor for upper limb function, with ipsilateral CST wiring pattern leading to poorer upper limb

function.[111, 112] It is established that the timing of brain lesion as well as the brain lesion type, is highly correlated with the type of wiring.[112] Lesions in the cortical and/or subcortical structures, mostly occurring in the late preterm/full term infants, reduces the ability of the CST to evolve according to its usual contralateral wiring pattern, mostly resulting in worse performance.[111, 113-115] In infants with white matter lesions, contralateral wiring pattern is predominantly observed.[111] Therefore, typically preterm lesions, such as PVHI results generally in milder USCP compared to lesions in the grey matter as in the cortex, subcortical area and basal ganglia, observed in PAIS.[111] Nevertheless, brain lesion extent must also be taken into account. Large periventricular brain lesions might also result in poor hand function.[111, 112]

Consequently, it would be expected that overall the preterm infants would have better hand function compared to the term born infants with USCP. Therefore, HAI values were evaluated of the infants with USCP and compared the preterm and term born infants, but no statistical differences were found. A possible explanation could be that the groups were too small to make any significant conclusions. Of the 13 infants with USCP only 9 of them had an HAI evaluation, of which six were preterm and three with a GA of 37 weeks or more. As a result, the predictive value for the HAI was similar in both groups. In contrast to our study, Wagenaar et al. (2019) found that hand function asymmetry was highly predictive before 5 months of corrected age in term infants, while it was not in preterm infants.[98]

To summarize, it can be stated that:

Early detection of USCP is possible before the age of 6 months, by using adequate assessment tools. GMA had good predictive values and showed possible early asymmetry, whereas the asymmetry index of the HAI provides excellent predictive values for later USCP.

1.3. Perinatal stroke and early intervention

In infants with perinatal stroke, most intervention studies focused on motor function, most likely because this is the most prevalent neurologic outcome after perinatal stroke and also the most amenable to clinical evaluation. The literature on established and experimental approaches for the treatment of upper limb function USCP in older children is comprehensive.[116] However, in young infants this remain practically unexplored, despite

evidence of a critical time limit for activity-dependent plasticity to influence the corticospinal tract development during the first years of life, especially in the first months after birth.[107, 117] Given the shortage of early intervention studies, very little is known about the feasibility of such intervention programs in very young infants. Therefore, in **chapter 4**, a study was undertaken to investigate the feasibility of a parent-delivered home-based early intervention program comparing baby-CIMT to baby-HABIT and to address potential obstacles for further implementation. Eight infants were recruited and seven infants reached the end of the protocol. Based on the satisfaction questionnaire, it can be concluded that parents were satisfied about the intervention program as they felt that the program enabled them to make a positive contribution to the motor development of their child. This was true for both the CIMT and HABIT-group. This is in line with the findings of a previous study about baby-CIMT, where it was reported that most parents found it easy to perform the baby-CIMT and that they had the impression that the treatment had an effect on the child's hand function and general development.[118] Another early parent-delivered homebased therapy intervention (E-tips) for infants with perinatal stroke was evaluated in a small sample and was reported to be feasible as well.[119] However, this program has a slight initial different approach. The E-tips promote activity of the potentially affected side through early environmental manipulation during daily activities and do not add some additional delimited therapy moment such as with the Baby-CIMT or baby-HABIT. Nevertheless, if could be questioned if with our parent-training similar effect might be achieved. This in view of the fact that parents affirmed that they were much more aware of the motor asymmetry and therefrom paid more attention to stimulate the affected side throughout the day, for instance during feeding or playing, and not just during the intervention blocks.

It is well documented that receiving the diagnosis of a child's disability evokes a range of emotions. Feelings such as grief, disbelief, helplessness and anger can be overwhelming.[120, 121] Nevertheless, even during this vulnerable period in their lives, this overall positive response suggests that parents are happy and comfortable with being the training provider. By enrolling in the study they feel they can make a difference for their child and it gives them the feeling that they make sure that they had done everything they could to help their child's future.

In addition, the therapists who conducted the study had no substantive comments about the program. However, the recruitment of infants with perinatal stroke (chapter 3 and 4) was more time-consuming then expected, raising some concerns if this study would like to be repeated in a larger sample. It might indicate that additional NICUs are needed for sufficient recruitment along with extra efforts that should be made to make sure all infants are addressed

to enroll in the intervention study. Furthermore, based on the results of chapter 3, it can be assumed that the inclusions criteria must be refined. More specifically, an HAI cut-off value must be considered to increase the chances to address the infants who will develop USCP with almost certainty.

To summarize, it can be stated that:

An early home-based intervention program, consisting of baby-CIMT and baby-HABIT is feasible in young infants with perinatal stroke.

2. Clinical relevance and implications

Perinatal cerebrovascular disorders are a major cause of permanent morbidity in infants and are an emerging field for clinical research. Perinatal stroke encompasses distinct brain injuries, not only in term of causality, but also in terms of timing, risk factor and most of all, their implications for the further brain development and neurological outcome.[77] **Chapter 3** contributes to the knowledge of perinatal stroke by reporting the neurological outcome by each different subtype of perinatal stroke. The overview by the specific brain lesions should allow clinicians to better understand the variety of perinatal stroke-labeled lesions.

Poor outcome across the whole cohort suggests that all infants who have suffered perinatal stroke are at risk of neurodevelopmental impairments. It is therefore advised that all infants with perinatal stroke should benefit from standard long-term follow-up. Early diagnosis of CP is important as such might lead to earlier referral to therapeutic services, family support and a better outcome for the future.

As reported by international guidelines for early diagnosis, it is advised to combine different assessment tools to enhance the capability to diagnose CP at an early age. It has been determined that before the age of 5 months the combination of MRI, GMA and neurological examination, such as the Hammersmith infants neurological examination (HINE) have to best possible prediction.[100] Therefore, it should be encouraged that those assessment tools are implemented into clinical care.

Even though MRI is performed in most cases, this imaging technique may not be available at all times and in all places. Therefore, when neuroimaging is not available, observation becomes even more important. The advantage of clinical neurological and

neuromotor assessments is that they are relatively cheap instruments, and therefore, may be applied in many settings across the world.

Standardized developmental assessment tools are valuable, but domain-specific assessment methods are more worthwhile. As it is know that early hand preference is often observed as the first sign of USCP, there should be more focus on the detection of early asymmetry. This could be done by observing asymmetry during GMA or evaluated with the HAI.

To our knowledge, this is the first outcome study to report the predictability of GMA and HAI together in a high-risk population for USCP. By demonstrating that HAI has even better predictive values than GMA in infants with perinatal stroke, it can be advised that the HAI should be used in combination with GMA for accurate early detection of USCP in this population group. Furthermore, an optimal cut-off value for the HAI asymmetry index was identified, which had a maximal sensitivity and specificity of 100%. Therefore, it is recommended that HAI should be implemented into standard follow-up of infants with perinatal stroke, which can be of added value for diagnosing USCP between 3 and 5 months of age. However, implementing the HAI into standard clinical care requires a trained assessor to perform the assessment (10-15 minutes testing + scoring). As this might be too time-consuming and in order to keep the balance between costs and benefits, it would be advised to only perform the HAI in a clinical setting in infants at high risk of USCP based on the MRI findings. Furthermore, it can be recommended using the HAI as a screening and assessment tool in any early intervention study focusing on the upper limb in with infants perinatal stroke or unilateral brain lesions.

Neurophysiological interventions that modulate cortical excitability, and treatment approaches, such as CIMT, have been shown to affect movement performance following stroke, even in older infants and adults. However, co-morbidity such as a delayed development, may become more important over time in USCP. The sooner on intervention is started, the more secondary morbidity will hopefully be dissuaded. Furthermore, early intervention is also of high importance to take advance of the neuroplasticity in infancy. Even though this is generally accepted, no standard therapy is available yet. It is not yet known which therapy is most efficient in young children with USCP and at which intensity and frequency it is best offered. By demonstrating the feasibility of an early intervention program in **chapter 4** this might be of clinical relevance to support further research of early intervention programs.

However, more clinical research is needed to be able to provide the best patient-tailored therapy program.

Therefore, based on the literature and our findings it can be advised that all infants with perinatal stroke observed on neuroimaging, with absent fidgety movements and/or the asymmetry of segmental movements of fingers and wrists, and/or an HAI AI ≥23 or with persistent asymmetry before the age of 5 months should definitely be transferred for early intervention, regardless of the underlying type of brain lesions or timing of occurrence.[105] This early intervention should focus on increased usage of the affected side, before the learned non-usage of the affected side has occurred, whether this is by bimanual or by a constraint approach, or general adapting the daily life activities. Moreover, in order to reach a sufficient daily training, it is useful to have parents perform the therapy; it has turned out that this is certainly feasible and that parents are satisfied with this.

STRENGTHS AND LIMITATIONS

For each chapter comprehensive considerations have already been listed. A basic overview and expanded perspective on the most critical shortcomings and strengths across chapters will be given in this section, which is necessary for a correct interpretation of the general discussion of this dissertation.

Strengths

Some strengths from **chapter 1** are worth mentioning. Meta-analytic reviews are considered at the top of evidence-hierarchy.[122] The screening was performed in four different relevant search engines, which ensures that a large amount of literature has been investigated and consequently the chances that relevant research has been overlooked is minimal. Moreover, two independent researchers performed the screening on in-and exclusion criteria, as well as the risk of bias. A limit of 50% for the quality checklist was set as inclusion criteria, consequently, only relative high quality research papers were included into the analysis.

A major strength of **chapter 1 and 2** is that those studies included a large sample size. The meta-analytic review included 30 papers representing in total 10 293 infants. The population-based cohort study in chapter 2 comprised a sample of 1941 infants. Furthermore, the fact that it was a population-based cohort study results in great external validity, meaning that the results can be applicability to a defined population, in this case to Flanders on a whole.

The study samples of **chapter 2, 3 and 4** are multicenter. Multicenter research confers many distinct advantages over single-center studies. The benefits of multicenter studies include a larger number of participants, different geographic locations, the possibility of inclusion of a wider range of population groups, and the ability to compare results among centers, all of which increase the generalizability of the study.

Another strength of **chapter 1 and 2** was its inclusion criteria including VPT as well as VLBW infants, on the contrary to many studies who restrict their inclusion criteria based on rather GA or BW. This ensured more relevant studies in chapter 1 and a larger sample in chapter 2. However, some might considerer as a limitation since this enhanced heterogeneity. Nevertheless, noticing that the results were represented by different GA and BW categories this should not be considered as a limitation but rather as a strength.

To the best of our knowledge, **chapter 3,** comprised the first study to evaluate GM and HAI together in a sample at high risk of USCP, which contribute to the understanding of early assessment and prediction. Furthermore, a main strength was that the GM videos were

scored blinded by two or three experienced raters, which have improved the quality of the research and makes the results more reliable to interpret.

Finally, the main strength of **chapter 4**, is the novelty of this research. So far, baby-CIMT has only been investigated by one research group, and, on the other hand, the implementation of baby-HABIT has not been investigated yet by others.

Limitations

Next to the strengths, some methodological considerations and limitations need to be taken into account as well when interpreting these results.

Some limitations are inherent to the presented meta-analytic review in **chapter 1**. Due to different included patients, and the used methodology, there was a considerable high heterogeneity of the included papers, including inclusion criteria, used assessment tools and cut-off values. Therefore, the results should be interpreted with care.

Also some limitations regarding study samples need be considered in **chapter 2,3 and 4**. In chapter 2, the main limitation is that only 61% of the survivors were seen at follow-up clinic at 2 years. Moreover, perinatal characteristics and comorbidities were compared between the follow-up and non-follow-up group, which highlighted that the follow-up group had significant lower mean GA and BW and more comorbidities. Those findings could have potentially influenced the outcome rates towards higher prevalences of adverse outcome[74] and refrains somewhat generalization into the whole population of VPT/VLBW infants. In addition, the study in chapter 3, comprises only 47 infants. Nevertheless, many research studies in the domain of perinatal stroke are limited by small sample sizes, due to the relatively rare appearance of this disease. Thereafter, the feasibility study in chapter 4 comprised a sample size of seven infants, which is a relatively modest sample size.

In **chapter 3 and 4**, GMA were used as a prediction tool or early screening tool for the eligibility for the intervention study. The original instructions state that GMA must be filmed for 30 minutes to one hour so that three sufficiently long examples of GMs could be identified.[123, 124] Also more than one observation is recommended during the fidgety period. In our sample, GMA were observed and recorded only once and only during 5 to 10 minutes when the infant was in an awake situation. This could have resulted in less long sequences of GMs being observed. Nevertheless, our videos were scored blinded by extremely experienced observers, wherefore this should not have an impact on the scorings.

Lastly, the focus of this dissertation was not on psychological outcomes or behavior, so this was never taken into consideration, although these important features could had influence the observed outcomes. Furthermore, neurodevelopmental impairment is a complex multifactorial situation that varies considerable between infants. Confounding factors such as for instance, education level of the mother, the psychosocial and economical child environment were not controlled for.

FUTURE DIRECTIONS

The present dissertation answers some questions but it also raises several new ideas and research questions, which could lead to further development of scientific knowledge.

1. Further research directions regarding neurodevelopmental outcome studies

This dissertation focused mainly on relatively short term outcomes of VPT/VLBW infants and infants with perinatal stroke till 2 years of age. Literature indicates that a reliable developmental examination can be performed at the age of 18-22 months, and that neurological examination at that age will detect the overwhelming majority of children with CP, definitely all those with moderate and severe CP. However, evaluations of early childhood developmental and neurological outcomes should only be viewed as a first step in systematic follow-up. Evaluations at school age, adolescence and adulthood are critical for understanding the longer term functional and social consequences of preterm birth and its complications, nonetheless longer-term follow up studies are limited.[125] Moreover, some studies have showed that developmental evaluation tools used at young ages, such as the Bayley Scales, have poor predictive for later school-age have[126-129]. The lack of association between early Bayley scores and achievement tests at school age may reflect the challenges that preterm infants have with increasing age.[130] Nevertheless, this is in contrast to the longitudinal study by Linsell et al. who reported that cognitive test at age 2.5 years reflected cognitive outcome in adulthood in EPT infants.[58] Taken together, this highlights the strong need for further follow-up into school years and adolescent age.

Additionally, it has been reported that the impact of perinatal risk factors on the cognitive development of preterm infants is likely to decrease over time, whereas the effects of environmental factors become more prominent.[56, 58] It emphasizes the importance of evaluating the interaction of biologic and environmental factors on outcome over time.

Behavior problems in VPT/VLBW have not been investigated in this cohort, although it is one of the most common problems in preterm infants, which has been shown to remain throughout adolescence and adulthood and has a great impact on daily life.[131] The causes of these behavioral issues in this vulnerable population, remain a great challenge to understand. Research should examine perinatal and structural factors influencing the child's behavior in order to gain a better understanding of those behavioral problems in preterm infants.

In order to plan meaningful management, as well as preventive and neuroprotective strategies, clinical and epidemiological studies remain critical to better elucidate the multiple

predictive and prognostics factors and their corresponding contributions within the distinct entities. Preterm birth as well as perinatal stroke etiology is multifactorial and incompletely understood which reduces preventive and therapeutic options. Well-powered, population-based, case-control data are required to explore potential risk factors for preterm infants and different subtypes of stroke.

2. Further research directions regarding early detection of CP in infants with perinatal stroke

The high prevalence of USCP among children with perinatal stroke highlights the need to further improve early diagnostics, which might detect the infants who could most benefit from early interventions. Prediction is improved by using multiple tools, such as neuroimaging, neurological and neuromotor examinations and neurophysiological evaluations. Predictions often significantly improves with longitudinal sequence of evaluations. Therefore, the next important step will be to combine the data from GMA, HAI and MRI to optimize early detection of USCP.

Furthermore, opportunities exist to further explore the GMA in infants with perinatal stroke. It is now confirmed that asymmetry can occur during fidgety age, whether or not with present FM. The asymmetry of segmental movements should be further explored, instead on focusing only on the presence or absence of FM, in order to be able to increase predictability of the GMA in a specific group of infants at high risk of USCP. It would also be interesting to analyze the motor optimality score in that group of infants to provide a more detailed picture of early signs of USCP observed during GMA.

Moreover, the established cut-off value of the HAI asymmetry index in our study should be further confirmed by covering larger and adequately powered studies before this could eventually be implemented into clinical practice.

Lastly, future studies are necessary to investigate the distinctive effects of brain lesion type and consequently the timing of injury on asymmetric hand function in young infants. If a large difference is observed, this might indicate the need for specific norm values and cut-off values by GA.

3. *Further research directions regarding early intervention in infants with perinatal stroke*

During the first 2 years of life, CST projections mature significantly and ipsilateral projections are slowly removed in favor of contralateral hemispheric regulation.[107] Such findings support the need for improved treatment of both CST in perinatal stroke, utilizing clinical, radiological and neurophysiological inventions.[132] Therefore, interventional approaches should be focused on this, with the objective of improving and reorienting the CST reorganization in the best possible way to enhance functional outcome. Some studies did some attempts to evaluate different approaches in young infants[118, 119, 133, 134] however, it is still unclear which therapy approach has the best results and at what age, frequency and intensity this should be administrated to obtain the best results and to avoid overstimulation. Therefore, there is still a great need for more research about early intervention program in infants with unilateral brain lesions at high risk for USCP.

Since the implementation of baby-CIMT and baby-HABIT was found to be feasible in young infants, a first step would be to carry out this early intervention study in a larger multicenter randomized controlled trial. Subsequently, further exploration can be carried out with a combination of different therapy approaches (for instance a combination of CIMT or HABIT). Possibly, also the baby-CIMT and/or baby-HABIT could be compared to the promising E-tips intervention as well.

In the following steps, it will be important to find out which children benefit the most from a particular therapy approach with the objective to be able to provide a patient-tailored treatment planning in the future. In older infants it has been unraveled that the brain lesion characteristics and the CST wiring pattern is of high influence for the motor and sensory functional capacity of the upper limb.[111, 132, 135] It has been revealed that periventricular lesions will mostly preserve the contralesional CST, with more preservation of upper limb function, while term cortical-subcortical lesions will mainly result in ipsilateral reorganization, which has been demonstrated to be less functional [111, 136] More recently, some attempts have been made to find out which children would most benefit from CIMT according to their type of brain lesion or CST wiring pattern, however not all studies have yielded consistent results. Two studies found evidence in older infants that CIMT is more beneficial in infants with early brain lesions, namely after PVHI, in comparisons to infants with later and consequently cortical–subcortical brain lesions such as after PAIS.[133, 137] Nevertheless, it is important to note that significant baseline differences of hand function were found in the study by Chamudot et

al.(2018)[133], which could be possibly be explained by underlying different trajectory of hand function.[138] On the contrary, Islam et al. (2014)[139] and Simon-Martinez et al. (2020)[140] could not find a significant relation between the training-induced changes of motor function and the type of brain lesions or the CST wiring patterns. Nevertheless, it was demonstrated that CIMT was more beneficial for children with poor sensory function.[140] Also the effectiveness of HABIT was found to be independent of the CST connectivity pattern.[141] This suggests that in order to increase correct prediction of treatment response after intensive UL training, not only the CST wiring pattern must be taken into account, but multiple neurological characteristics should be included in the model.[142] However, those findings need to be further explored in younger infants. To gain more knowledge in the brain plasticity of those young infants, it could offer enormous added value if the reorganization of the CST after early intervention programs could be objectively determined based on functional neuroimaging, such as DTI or fMRI, such as been already repeatedly performed in older infants with USCP. This could allow to investigate the therapy-induced neuroplasticity on micro level and to determine possible influence of the type of brain lesion in relation to the possible therapy effect. Nonetheless, even though this might be greatly interesting, performing MRI's in a pediatric population is generally only carried out if it is deemed necessary due to the often necessary use of anesthesia to ensure the image quality. Moreover, extensive MRI post-processing techniques such as DTI tractography assumes strict scanning protocols without movement artifacts, which is the reason why anesthesia should mostly be considered. However, some animal studies showed potentially deleterious effects of sedation and anesthesia on central nervous system development in immature laboratory animals.[143-145] Therefore, despite this adverse effects not being confirmed in a human infant population and some attempts are made to minimize sedation, parents and ethical committees are not keen on performing repeated DTI or fMRI in very young infants for the only purpose of research. As a result, it is uncertain if the therapy-induced neuroplasticity might be investigated via brain imaging in the near future in young infants. Nevertheless, alternative protocols and further imaging progress could offer the solution in the long term.[146]

As these neuroimaging assessments are not always possible in young children, there is a necessity to find tools that are more applicable to daily practice than neurophysiological techniques. For long a time, there was no non-invasive assessment tool that could provide an objective score of the hand function before the age of 12 months, and consequently, it was difficult to investigate effectiveness of early interventions with infants below 12 months with high risk of unilateral CP in a non-invasive way. Nevertheless, the recent implemented HAI

changed this. For the time being, this is the only objective method that is available and has been validated. However, for some time now exploring studies exists on wearable sensors that could detect movements and asymmetry providing a large amount of quantitative data.[147] Nevertheless, to our knowledge, none if those devices have been validated to use as screening or assessment tool into a larger public. However, this is worthwhile considering further exploration.

Furthermore, it would be important to consider long-term follow-up to investigate the potential long-term effects of early interventions.

Another research area that needs further investigation is transcranial magnetic stimulation (TMS). Favorable and reassuring results have been reported of TMS as a tool to evaluate and modulating neuroplasticity in older children with USCP.[148] Until a few years ago, it was not known whether TMS would be safe in young infants and vigilance was indicated in a pediatric population.[149] A research group originating from Minneapolis (USA), were the first to perform TMS in a small sample of 3-to 12 month old infants with perinatal stroke or intracranial hemorrhage.[150, 151] No adverse events were reported and TMS was well tolerated by the six infants, so it was concluded that TMS could be performed safely in young infants.[151] In a subsequent study, it was found that TMS may contribute diagnostic and prognostic information in infants with perinatal stroke during the first year of life.[152] It was found that the absence of TMS-induced motor evoked potentials from the most-affected hemisphere, is indicative of an atypical CST organization and corresponds with reduced hand function in infants with USCP. However, research on the use of TMS in young infants with perinatal stroke has just been launched and offer many opportunities for further research.

GENERAL CONCLUSION

This dissertation focused on two specific groups of high-risk infants and improved our insight into neurodevelopmental outcome, early diagnosis and early intervention of those infants.

The first part of this dissertation focused on the neurodevelopmental outcome of VPT/VLBW infants. The care for preterm infants has improved considerably in the last decades, however, these infants continue to face complex medical and neurodevelopmental problems. In the last few decades preterm births increased and the survival of VPT/VLBW has improved, and this is not accompanied by increased morbidity. Although most preterm born infants do not develop major impairments, they are at higher risk to develop CP, motor and/or cognitive impairments and the risk increases with decreasing GA and BW. An overview was provided of the current prevalence of neurodevelopmental impairment, globally as well as for our local population. Furthermore, the decreasing trend of mortality and severe impairments in EPT infants could be confirmed.

In the second part, early screening and early intervention in infants with perinatal stroke was highlighted. Neurological outcome for each specific type of stroke lesion was reported. This revealed that that infants with preterm type of perinatal stroke have the highest changes to develop USCP. Furthermore, it was demonstrated that USCP could be predicted as early as between 3 and 5 months based on two different screening tools, namely the GMA and the HAI. Lastly, the feasibility of an early intervention program , focusing on the upper limb function, for infants with perinatal stroke at high risk of developing USCP could be demonstrated, making it now ready to conduct into a larger sample in the form of an RCT.

In conclusion, this dissertation provided some useful insight on the outcome of those high-risk infants as well as some newfound knowledge about early predictions tools and early intervention for infants with perinatal stroke. However, more research is needed in order to fully understand the impact of very preterm birth and perinatal stroke on the longer term and how early diagnosis and early intervention can be improved in high-risk infants.

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SUMMARY

ENGLISH SUMMARY

Developmental disability is a broad term encompassing many different diagnoses. These conditions, predominantly associated with the functioning of the neurological system and brain, manifest during infancy or childhood and usually last throughout a person's lifetime. These are marked by delayed development or functional limitations in cognition, language, communication, behavior socialization or motor function, and are defined as 'neurodevelopmental disorders'.

Most neurodevelopmental disorders are caused by a complex mix of factors, that may affect neurological function. This might be due to genetics, due to conditions occurring during pregnancy, such as malnutrition, infection or parental behavior (i.e. smoking, drugs and/or drinking alcohol during pregnancy,…) or due to perinatal and neonatal complications.

Neurodevelopmental problems due to injury that has occurred during the perinatal period can mainly be subdivided in 3 groups:

- Infants with congenital malformations, including syndromes, chromosomal and genetic defects and inborn errors of metabolism
- Infants that are born preterm and/or with low birthweight
- Infants with a hypoxic-ischemic insult and/or perinatal stroke

This doctoral thesis focused on preterm birth and perinatal stroke, two main perinatal causes of neurodevelopmental disorders and improved our insight about the neurodevelopmental outcome, early diagnosis and early intervention of those high-risk infants.

PART I of this dissertation focused on very preterm (VPT)/very-low-birthweight (VLBW) infants. The care for preterm infants has improved considerably in the last decades, however, they continue to face complex medical and neurodevelopmental problems. In the last few decades preterm births increased and the survival of VPT/VLBW have improved, however this is not accompanied by increased morbidity. Although most preterm born infants do not develop major impairments, they are at higher risk to develop cerebral palsy (CP), motor and/or cognitive impairments and the risk increases with decreasing gestational age (GA) and birthweight (BW). Recent actual mortality, morbidity and neurodevelopmental outcome rates among VPT/VLBW infants is essential for family counseling and evaluation of innovative approaches to enhance outcomes.

The first part of this dissertation comprises two chapters, providing an overview of the current prevalences of neurodevelopmental impairment, globally as well as for our local population.

In **chapter 1,** existing literature regarding the overall neurodevelopmental outcome at two years corrected age in VLB/VLBW infants born over the last decade was reviewed and reported in a meta-analytic review. In **chapter 2**, the neonatal mortality and neurodevelopmental outcome in a national population-based cohort was investigated. The following summarizes the findings of both chapters.

- Preterm birth and mortality

Currently, in Flanders, the overall survival rate to discharge was 92% of the VPT/VLBW infants admitted to intensive care, however chances of survival among those infants vary greatly according to the GA. Mortality rates increased significantly with decreasing GA. Compared to the Belgian EPIBEL study, survival rate increased by nearly 20% in extremely preterm infants, over the past 15 years.

- Preterm birth and short-term morbidities

Severe brain lesions leads to significant higher mortality rates. Intracranial hemorrhages are more common than periventricular leucomalacia. The prevalence of brain lesions increases with decreasing GA. The prevalence of severe brain lesions has decreased over time due to improved perinatal management.

- Preterm birth and neurodevelopmental outcome

Neurodevelopmental impairments are common in VPT/VLBW infants. Nearly one in five VPT/VLBW infants show some adverse neurodevelopment. GA and BW are negatively related to outcomes. A drastic decrease of CP is observed globally as well as nationally. The presence of severe brain lesions increases the chances of motor and cognitive impairment.

PART II of this dissertation focused on infants with perinatal stroke. Perinatal stroke might not be as common as preterm birth, it is still an important group of infants because it is know that more than quart of the children with perinatal results in neurological deficits, however the exact number varies considerably between studies. Early detection and referral of infants at risk for intervention, rather than referral children with known CP has been called for. Nonetheless, this requires careful monitoring in the first months of development and appropriate early diagnostic tools. The literature on established and experimental approaches for the treatment of upper limb function unilateral spastic CP (USCP) in older children is comprehensive, however, in young infants this remain practically unexplored, despite evidence of a critical time limit for activity-dependent plasticity to influence the corticospinal tract

development during the first years of life. Given the shortage of early intervention studies, very little is known about the feasibility of such intervention programs in very young infants.

Part II is composed of two chapters, describing two original research articles. In **chapter 3,** the neurological outcome was for each specific type of stroke lesion reported in infants with perinatal stroke as well as the predictability of two motor evaluation tools ('General movement assessment [GMA]' and the 'Hand assessment for infants [HAI]') for early detection of USCP. Lastly, in **chapter 4,** a study was undertaken in infants with perinatal stroke at high risk of USCP to investigate the feasibility of a parent-delivered home-based early intervention program, comparing two therapy approaches, namely 'Constraint-induced movement therapy (baby-CIMT)' and 'hand–arm bimanual training (baby-HABIT)' and to address potential obstacles for further implementation. The following summarizes the findings of this second part of the doctoral thesis.

- Perinatal stroke and motor outcome

CP is observed in approximately one third of the infants with perinatal stroke. Periventricular hemorrhagic infarction (PVHI), associated with very preterm birth, resulted in higher prevalences of CP compared to other types of perinatal stroke. PVHI was always observed during the days after birth, mainly by brain imaging, whereas other types of hemorrhagic stroke and perinatal arterial ischemic stroke were manifested by seizures in some cases and others by neonatal brain imaging.

- Perinatal stroke and early prediction of unilateral spastic cerebral palsy

Early detection of USCP is possible before the age of 6 months, by using adequate assessment tools. The GMA had good predictive values and showed possible early asymmetry, whereas the asymmetry index of the HAI provides excellent predictive values for later USCP.

- Perinatal stroke and early intervention

An early home-based intervention program, consisting of baby-CIMT and baby-HABIT is feasible in young infants with perinatal stroke.

In conclusion, this dissertation provided some useful insight on the outcome of those high-risk infants as well as some newfound knowledge about early predictions tools and early intervention for infants with perinatal stroke. However, more research is needed in order to fully understand the impact of very preterm birth and perinatal stroke on the longer term and how early diagnosis and early intervention can be improved in high-risk infants.

SAMENVATTING

NEDERLANDSTALIGE SAMENVATTING

Het brede begrip 'ontwikkelingsstoornissen' omvat veel verschillende diagnoses. Deze aandoeningen, die voornamelijk verband houden met het functioneren van het centraal zenuwstelsel, manifesteren zich tijdens de kindertijd en duren meestal een heel leven lang. Deze worden gekenmerkt door een vertraagde ontwikkeling of functionele beperkingen in cognitie, taal, communicatie, socialisatie, gedrag of de motorische functie, en worden gedefinieerd als 'neurologische ontwikkelingsstoornissen'.

De meeste neurologische ontwikkelingsstoornissen worden veroorzaakt door een complexe mix van factoren, die de neurologische functie kunnen beïnvloeden. Dit kan te wijten zijn aan de genetica, door omstandigheden die zich voordoen tijdens de zwangerschap; zoals ondervoeding, infectie of ouderlijk gedrag (d.w.z. roken, drugs en/of het drinken van alcohol tijdens de zwangerschap, ...) of door perinatale en neonatale complicaties.

De neurologische ontwikkelingsproblemen als gevolg van de schade die zich in de perinatale periode heeft voorgedaan, kunnen voornamelijk worden onderverdeeld in 3 groepen:

- Zuigelingen met aangeboren afwijkingen, waaronder syndromen, chromosomale en genetische afwijkingen en aangeboren stofwisselingsfouten
- Zuigelingen die te vroeg geboren zijn en/of een laag geboortegewicht hebben
- Zuigelingen met een hypoxisch-ischemische letsel en/of een perinatale beroerte

Dit proefschrift richtte zich op vroeggeboorte en perinatale beroerte, twee belangrijke perinatale oorzaken van neurologische ontwikkelingsstoornissen. Het verbeterde het inzicht in de neurologische uitkomst, vroege diagnose en vroegtijdige interventie van deze risicovolle zuigelingen.

DEEL I van dit proefschrift richtte zich op kinderen die ernstig vroeg geboren zijn of kinderen met een zeer laag geboortegewicht, voortaan genoemd als "VPT/VLBW" kinderen. De zorg voor premature baby's is de laatste decennia aanzienlijk verbeterd, maar zij hebben nog steeds te maken met complexe medische en neurologische ontwikkelingsproblemen. In de laatste decennia zijn de vroeggeboorten toegenomen en is de overleving van VPT/VLBW kinderen verbeterd, en dit gaat niet gepaard met een verhoogde morbiditeit. Hoewel de meerderheid van de VPT/VLBW baby's geen grote beperkingen ontwikkelen, lopen ze een hoger risico op cerebrale parese (CP), motorische en/of cognitieve beperkingen te ontwikkelen en het risico neemt toe met afnemende zwangerschapsduur en geboortegewicht. De recente prevalentie van sterfte, morbiditeit en neurologische ontwikkelingsstoornissen van

VPT/VLBW zuigelingen is essentieel voor gezinsbegeleiding en voor de evaluatie van de huidige neonatale zorg.

Het eerste deel van dit proefschrift bestaat uit twee hoofdstukken, die een overzicht geven van de huidige ontwikkelingen op het gebied van neurologische ontwikkelingsstoornissen, zowel wereldwijd als voor onze lokale Vlaamse bevolking. In hoofdstuk 1 wordt de bestaande literatuur over de neurologische ontwikkelingsuitkomst op twee jaar gecorrigeerde leeftijd bij VLB/VLBW zuigelingen die in het laatste decennium zijn geboren, bekeken en gerapporteerd in een meta-analytische review. In hoofdstuk 2 wordt de neonatale sterfte en de neurologische ontwikkelingsuitkomst onderzocht in een nationaal populatie-gebaseerd cohort. Hieronder volgt een samenvatting van de bevindingen van beide hoofdstukken.

- VPT/VLBW kinderen en sterfte

Op dit moment is in Vlaanderen de overlevingskans 92% van de VPT/VLBW zuigelingen die opgenomen werden op de neonatale intensieve zorgen, maar de overlevingskansen van deze kinderen variëren sterk volgens de zwangerschapsduur. De sterftecijfers namen aanzienlijk toe met een dalende zwangerschapsduur en geboortegewicht. In vergelijking met de Belgische EPIBEL-studie steeg de overlevingskans bij extreem prematuur geboren kinderen met bijna 20% in de afgelopen 15 jaar.

- VPT/VLBW kinderen en morbiditeiten op korte termijn

Ernstige hersenletsels leiden tot aanzienlijk hogere sterftecijfers. Intracraniale bloedingen komen vaker voor dan periventriculaire leukomalacie. De prevalentie van hersenletsels neemt toe met afnemende zwangerschapsduur. De prevalentie van ernstige hersenletsels is in de loop van de tijd afgenomen als gevolg van een verbeterde perinatale zorg.

- VPT/VLBW kinderen en neurologische ontwikkeling

Neurologische ontwikkelingsstoornissen komen vaak voor bij VPT/VLBW-kinderen. Bijna één op de vijf VPT/VLBW baby's vertoont enige verstoorde neurologische ontwikkeling. Zwangerschapsduur en geboortegewicht zijn negatief gerelateerd aan de uitkomsten. Een drastische afname van CP wordt zowel wereldwijd als nationaal waargenomen. De aanwezigheid van ernstige hersenletsels verhoogt de kansen van de motorische en cognitieve stoornissen.

DEEL II van dit proefschrift richtte zich op zuigelingen met een perinatale beroerte. Perinatale beroerte komt misschien niet zo vaak voor als vroeggeboorte, maar het is nog steeds een belangrijke groep van zuigelingen omdat meer dan een kwart van de kinderen met een perinatale beroerte leidt tot neurologische problemen, zoals onder meer CP, maar het exacte aantal varieert aanzienlijk tussen de studies. Tegenwoordig wordt er aangespoord om kinderen op hoog risico voor ontwikkelingsstoornissen reeds door te verwijzen naar vroegtijdige interventie, in plaatst van te wachten op een definitieve diagnose op latere leeftijd. Dit vereist een zorgvuldige controle in de eerste maanden van de ontwikkeling en geschikte meetinstrumenten voor vroegtijdige diagnose. De literatuur over de behandeling van de bovenste ledematenfunctie bij oudere kinderen met CP is uitgebreid, maar bij jonge kinderen is er weinig onderzoek gedaan, ondanks het bewijs van een kritische tijdslimiet voor activiteits-afhankelijke plasticiteit om de ontwikkeling van de corticospinale banen tijdens de eerste levensjaren te beïnvloeden. Gezien het tekort aan vroege interventiestudies is er weinig bekend over de haalbaarheid van dergelijke interventieprogramma's bij zeer jonge kinderen.

Deel II bestaat uit twee hoofdstukken, waarin twee originele onderzoeksartikelen worden beschreven. In hoofdstuk 3 wordt de neurologische uitkomst voor elk specifiek type beroerte beschreven bij zuigelingen, evenals de voorspelbaarheid van twee motorische meetinstrumenten ('general movement assessment' [GMA] en de 'hand assessment for infants [HAI]) voor de vroege detectie van CP. Ten slotte wordt in hoofdstuk 4 een studie beschreven waarbij de haalbaarheid wordt onderzocht van een vroegtijdige interventie bij zuigelingen met een perinatale beroerte en met een hoog risico op unilaterale spastische CP (USCP). Deze wordt door de ouders uitgevoerd in hun thuisomgeving, waarbij baby-CIMT wordt vergeleken met baby-HABIT. Hieronder volgt een samenvatting van de bevindingen van dit tweede deel van het proefschrift.

- Perinatale beroerte en motorische uitkomst

CP werd bij ongeveer een derde van de zuigelingen met een perinatale beroerte waargenomen. PVHI resulteerde in een hogere prevalentie van CP in vergelijking met andere types van perinatale beroerte. PVHI werd altijd waargenomen in de eerste dagen na de geboorte, voornamelijk door de beeldvorming, terwijl andere soorten perinatale beroertes werden waargenomen door neonatale beeldvorming of in sommige gevallen door epilepsie aanvallen.

- Perinatale beroerte en vroege voorspelling van USCP

Vroegtijdige opsporing van USCP is mogelijk vóór de leeftijd van 6 maanden, door gebruik te maken van adequate meetinstrumenten. De GMA had goede voorspellende waarden en toonde mogelijke vroege asymmetrie, terwijl de asymmetrie-index van de HAI uitstekende voorspellende waarden biedt voor latere USCP.

- Perinatale beroerte en vroegtijdige interventie

Het vroeg interventieprogramma, aangeboden door ouders in de huiselijke omgeving, bestaande uit baby-CIMT en baby-HABIT, is haalbaar bij jonge kinderen met een perinatale beroerte.

Tot besluit biedt dit proefschrift enig nuttig inzicht in de uitkomst van deze risicovolle zuigelingen, evenals nieuw verworven kennis over vroegtijdige voorspellende instrumenten en vroegtijdige interventie voor zuigelingen met een perinatale beroerte. Echter zal verder onderzoek onontbeerlijk zijn om de huidige bevindingen te bevestigen alsook om de impact van ernstige vroeggeboorte en perinatale beroerte op de langere termijn volledig te begrijpen, en ten slotte om na te gaan hoe vroegtijdige diagnose en vroegtijdige interventie bij hoog-risico-kinderen kan worden verbeterd.

DANKWOORD

DANKWOORD

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Aurelie

- Life is a journey, make the most out of it -

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Publications

Master thesis

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Pascal A, Naulaers G, Ortibus E, Oostra A, De Coen K, Sonnaert M, Cloet E, Casaer A, D'Haese J, Laroche S, Jonckheere A, Plaskie K, Van Mol C, Delanghe G, Bruneel E, Van Hoestenberghe MR, Samijn B, Govaert P, Van den Broeck C, in name of the Flemish very preterm infants study group. Neurodevelopmental outcomes of very preterm and very-low-birthweight infants in a population-based clinical cohort with a definite perinatal treatment policy. European Journal of Paediatric Neurology, 2020, in press.

Pascal A, Govaert P, Ortibus E, Naulaers G, Lars A, Fjørtoft T, Oostra A, Zecic A, Cools F, Cloet E, Casaer A, Cornette L, Laroche S, Samijn B, Van den Broeck C. Motor outcome after perinatal stroke and early prediction of unilateral spastic cerebral palsy. Submitted to "European Journal of Paediatric Neurology"

Samijn B, Christine Van den Broeck C, Plasschaert F; **Pascal A**, Descheppere E, Hoebeke P, Van Laecke E. Incontinence training in children with cerebral palsy: a prospective controlled trial. Submitted to "Neurology and urodynamics".

Adde L, Brown A, Eriksen B, Fjørtoft T, Groos D, Ihlen E, Osland S, **Pascal A,** Paulsen H, Sivertsen W, Skog OM, Van den Broeck C, Støen R. The In-Motion for remote General Movement Assessment: A multi-site observational study. Submitted to "BMJ Open".

Peyton C, **Pascal A,** Boswell L, deRegnier R, Fjørtoft T, Støen R, Adde L. Interrater reliability of the General Movement Assessment at 10-15 weeks of age. Under preparation for submission.

Boswell L, Adde L, Fjortoft T, Naranjan T, **Pascal A**, Stoen R, Van den Broeck C, de Regnier A. The Development of Movement and Postural Patterns in Healthy Low Risk Infants from Four Countries at 10-16 weeks of age. Under preparation for submission.

Presentations

Oral presentations

Pascal A, Govaert P, Van den Broeck C. From nosology of perinatal stroke to early intervention.
National symposium of CP centers, Brussels, 2017.

Pascal A, Govaert P, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome of very preterm or very low birth weight infants born in the last decade: a systematic review.
European Academy of Childhood Disability, Amsterdam 2017.

Samijn B, Van Laecke E Plasschaert F, Hoebeke P, Van Tittelboom V, **Pascal A**, Van den Broeck C. The effectiveness of urotherapy in incontinent children with cerebral palsy.
European Academy of Childhood Disability, Paris 2019.

Pascal A. Uitkomsten na extreme vroeggeboorte op tweejarige leeftijd in België.
Infertiliteit, Gynaecologie en Obstetrie doelencongres, Rotterdam, 2019.

Pascal A. & Dehaene I. Interactieve sessie: Ernstige vroeggeboorte: van foetus tot kleuter
Jaarcongres Vlaamse Vereniging voor Obstetrie en Gynaecologie), Antwerp, 2019.

Pascal A. Ernstige vroeggeboorte: van foetus tot kleuter
Studiedag wereldprematurendag, Leuven, 2019

Poster presentations

Pascal A, Adde L, Stoen R, Fjortoft T, Naulaers G, Govaert P, Ortibus E, Van den Broeck C. Children with unilateral cerebral palsy after perinatal stroke commonly show presence of fidgety movements in some body parts.
European Academy of Childhood Disability, 2019

deRegnier R, Adde L, Fjortoft T, **Pascal A**, Thomas N, Weck M, Russow A, Van den Broeck C, Stoen R, Boswell L. The development of general movements at 3-5 months of age is similar in low risk infants from Belgium, India, Norway and the United States.
European Academy of Childhood Disability, 2019.

Boswell L, Fjortoft T, Adde L, **Pascal A,** Thomas N, Russow A, Van den Broeck C, Weck M, Stoen R, deRegnier R. Prevalence of Abnormal Movement and Postural Patterns in Healthy Low Risk Infants from Belgium, India, Norway, and the United States.
American Academy for Cerebral Palsy & Developmental Medicine, 2019.

Attended conferences

Conference	Symposium for Neurodevelopmental disabilities
Location	Leuven, Belgium
Date	6 February 2015
Conference	Early intervention
Location	Groningen, The Netherlands
Date	4 – 9 April 2016
Conference	Belgian National Symposium of CP centers
Location	Brussels & Gent, Belgium
Date	27 January 2017 & 18 February 2019
Conference	Symposium Dyskinesia
Location	Bruges, Belgium
Date	17 March 2018
Conference	European Academy of Childhood Disability
Location	Copenhagen, Stockholm, Amsterdam, Tbilisi, Paris
Dates	May 2015, 2016, 2017, 2018, 2019

Additional courses and training

Course	General Movements Assessment - Basic course
Location	Pisa, Italy
Date	6 – 8 June 2016
Course	Hand Assessment for infants
Location	Milan, Italy
Date	13 – 15 October 2016

Course	General Movements Assessment - Advanced course
Location	London, UK
Date	7 – 9 December 2016
Course	Bobath course – Early intervention and assessment in baby's and young children
Location	London, UK
Date	15 – 20 October 2018
Course	Summer School Evidence based medicine and research in rehabilitation of childhood disabilities
Location	Pisa, Italy
Date	15 – 19 July 2019
Courses	How to give feedback? - March 2015
Doctoral	Statistics (basic and advanced course) - October-November 2016
Schools	Effective slide design - May 2017
	Advanced English Academic writing - October- December 2017
	Communication skills - January 2017
	Leadership course - November 2018
	Project management - November 2019

Reviewer for medical journals

Pediatrics
BMJ Open

Languages

Dutch	Native speaker
French	Bilingual proficiency
English	Full professional proficiency

International experience

2007	3 months student job animator in Turkey (Jetair-TUI)
2010-2011	1 year of work and travel to Canada & USA
2012	5 months of travel to Southeast Asia
2013	3 months of travel to India
2016-ongoing	International travel tour leader for 'Joker' (travels to Southeast Asia & Africa)

Other interests

Photography
Graphic design (Illustrator, Photoshop, InDesign)