# Neurological signs in infancy

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*DOI:*
10.33612/diss.256570186

# Neurological signs in infancy

prevalence, pathophysiology and neurodevelopmental outcome

**Lilian Straathof**

Printing of this thesis was financially supported by:
the University of Groningen, University Medical Center Groningen, Graduate School of Medical Sciences, Research Institute SHARE, Stichting Beatrixoord Noord-Nederland, Phelps Stichting voor spastici, Noord Negentig and Chipsoft.





Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
Layout and design: Leo Orth, persoonlijkproefschrift.nl

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**Proefschrift**

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 14 december 2022 om 16.15 uur

door

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geboren op 7 september 1994
te Haarlem

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# 1

# General introduction

This thesis addresses neurological signs in infancy. These signs may be a variation of typical development, but could also mark underlying damage of the central nervous system and thus be an indicator of atypical development. The clinical significance of neurological signs is not always immediately clear. This thesis aims to shed a light on occurrence and pathophysiology of neurological signs in infancy and their relation with later developmental outcome in both low-risk and high-risk infants. Such information will contribute to a better understanding of underlying developmental processes of the central nervous system, and will facilitate early detection of children at risk of neurodevelopmental disorders such as cerebral palsy, with the ultimate goal to provide children and their families with optimal intervention tailored to their needs. Some central concepts that will be discussed in this thesis are illustrated in the case description below. Thereafter, I will elaborate on these concepts in more detail, followed by a description of the aim and outline of this thesis.

*Twins Anne and Bas were born at 30 weeks' gestation with a birth weight of 1100 and 1250 grams, respectively. Because of their preterm birth, they were admitted to the NICU. The cranial ultrasound of Anne did not show significant brain injury; it only indicated transient periventricular flaring. However, repeated cranial ultrasound of Bas' brain showed bilateral cystic periventricular leukomalacia, indicating cyst formation and damage of the white matter of the brain around the ventricles.*

*During their hospital stay, the paediatrician and physical therapist regularly assessed the twins' neurological condition. Anne did not show evident neurological dysfunction, but Bas presented with atypical muscle tone and reflexes. Parents asked the paediatrician about implications for Bas' development. The paediatrician explained that at such a young age, early prediction of developmental outcome is difficult. Yet, Bas' clinical history and neurological condition indicated an increased risk of a developmental disorder, and implicated that he should not only be supported with early intervention, but also closely monitored. After a hospital admission of 6 weeks, Anne was stable enough to go home and at term age, Bas was discharged as well. The family received early physiotherapy intervention at home to support the twins' motor development. Anne developed well, but Bas still presented atypically at neurological examinations during regular outpatient check-ups at his paediatrician. After referral of Bas to the paediatric rehabilitation centre, at 21 months, the diagnosis of bilateral spastic cerebral palsy (CP), GMFCS level 3, was made.*

*Now, the twins are 8 years old. Anne attends regular primary school, while Bas gets extra personal support at a school for special primary education. He uses a manual wheelchair for long distances outside the house, scores in the low typical range at cognitive tests, and experiences visual problems. He has regular check-ups at the rehabilitation centre where he is supported by a multidisciplinary team, including a physical, occupational and speech therapist, to improve his functioning in daily life. Mum quit her paid job and is full-time taking care of her son when he is not at school. This all places a heavy burden on the family. Yet, parents try their best to meet the needs of both of their children and they are proud of them both developing in their own unique way.*

## Early development of the nervous system

The development of the nervous system is a fascinating process that starts very early in life. One of the first milestones in development of the nervous system, is the formation of the neural tube in the fifth postmenstrual week.[1] This is also the moment that generation of most of the neurons starts. Shortly thereafter, at 7 weeks PMA, the first foetal movements are observable.[2] The neural tube gradually differentiates into the brain and the spinal cord. During this process, many developments take place. In early development, a key role is reserved for the subplate: a transient structure between the cortical plate and the future white matter.[3-4] The subplate emerges shortly after formation of the neural tube. The subplate is a hotspot for neuronal differentiation, formation of axons, dendrites and synapses, and migration of neurons from the germinal layers near the ventricles to the cortical plate. In the primary motor and sensory areas, the subplate gradually dissolves between early preterm age and 3 months post-term due to programmed cell death of its neurons. At the same time the cortex increases in volume. An important process during the second half of pregnancy is glial cell formation. A specific group of glial cells, the oligodendrocytes, are involved in myelination of axons. Myelination mostly takes place in the third trimester of pregnancy and during the first 6 months after birth, but continues until the age of 40 years.[5-8] Developmental organization of the nervous system thus does not only comprise generation of cells and structures, but also regressive processes in which redundant structures are eliminated. The process of retraction of axons and dendrites mainly takes place between the third trimester of pregnancy and the end of the second year of life, while elimination of synapses reaches its peak activity between the start of puberty and early adulthood.[9] The ongoing interplay between generative and eliminative processes illustrates that development of the nervous system is not limited to early childhood. In fact, the nervous system only reaches its adult configuration around the age of 40 years.[3,7]

## Neural plasticity

The high developmental activity in the young nervous system is accompanied by a high rate of neuroplasticity, indicating that neural networks are, to a certain extent, able to reorganise themselves in response to the environment and experience.[10] Such reorganization processes comprise formation of new connections as well as elimination of others.[11] The clinical implications of plasticity often become apparent after an adverse event.[11-12] In case of a unilateral lesion of the infant brain, neural reorganization does not only take place in the damaged hemisphere; also the contralateral hemisphere and spinal cord can take over certain functions of the affected hemisphere.[13-14] The unilateral lesion may be clinically expressed as a neurological dysfunction that gradually resolves. Also in children without an evident brain lesion, early neurological signs that are suggestive of a developmental disorder such as CP can disappear without any neurological sequelae. This phenomenon was illustrated in the Groningen Perinatal Project, a long-term, longitudinal follow-up study that evaluated associations between perinatal events and later neuromotor, cognitive and behavioural development. A considerable part of the infants with early neurological dysfunctions recovered during the first 18 months postnatally.[15] These infants grew out of their deficit. On the other hand, early brain lesions are not always clinically expressed early in life,[11] but they can start to do so when the child grows older and higher cortical

functions get into function.[15-16] Children then grow into a deficit. This also indicates that plastic activity not always results in full recovery of the damage. In fact, the rate of reorganization after an early lesion is dependent on an interplay of factors, including the extent and location of the lesion, the developmental phase of the central nervous system at the time of the insult, and environmental factors.[13-14,17-21] Due to the high rate of developmental changes, adverse factors causing injury during sensitive periods in development of the central nervous system might have other consequences than damage before or after such a time window.[7,22] Another important clinical implication of plasticity and sensitive windows in brain development, is that it offers an opportunity for early intervention for infants at high risk of neurodevelopmental disorders.[11-12, 23-24]

## Neuronal Group Selection Theory (NGST)

A well-known theory on motor development is the neuronal group selection theory (NGST). This theory states that variation is a hallmark of typical motor development.[25-28] The NGST describes the phases of primary and secondary variability.[25] The primary variability phase is characterized by the nervous system exploring all motor possibilities. Self-produced motor activity results in a repertoire with many variants. During this phase, motor behaviour is not, or only minimally adapted to the environment. Adaptation starts to develop during the phase of secondary variability, by integrating afferent information achieved in active trial-and-error experiences in self-produced motor behaviour. The child develops adaptability, implying that the infant learns to adapt its motor behaviour to its surroundings. Optimal conditions for secondary variability to develop occur especially in a surrounding where the infant is in interaction with others and has ample possibilities to engage in trial-and-error experiences. The first stages of the secondary variability of all basic motor functions, including reaching and grasping, and locomotion, are typically reached around 18 months of age.[29] If motor development is disturbed, for example due to an early brain lesion, both primary and secondary repertoires may be limited: children have to select a strategy from a limited variety of solutions, which interferes with the process of selection.[27,30] An additional factor that challenges selection of an appropriate strategy, is that children also have impairments in the processing of sensory information, such as proprioceptive, tactile or visual input.[29]

## Early brain lesions

Perinatal brain damage puts the infant at risk of neurodevelopmental disorders.[31-34] Clinical presentation and, to a greater extent, later developmental outcome after a brain lesion is often associated with the duration and severity of the insult, as well as the infant's gestational age at the time of the insult.[35-36] Preterm lesions often have different pathophysiological mechanisms than lesions that occur around term age.

Preterm birth interferes with neurodevelopmental events that typically take place in utero during the third trimester of pregnancy; a phase characterized by many processes including dendrite and axon formation and a high rate of myelination.[37-39] In the beginning of the third trimester, the periventricular area is vulnerable for lesions caused by inflammatory and hypoxic-

ischaemic events.[40-42] The most well-known brain lesion associated with preterm birth, is periventricular leukomalacia (PVL), nowadays increasingly referred to as periventricular white matter injury (WMI).[43] It has a high prevalence in infants born at a gestational age of less than 34 weeks[44-45] and in infants with low birth weight.[46] Other common risk factors are chronic placental insufficiency, intra-uterine and postnatal infection, and foetal cardiopulmonary instability, e.g. due to congenital heart disease of the infant.[47-49] PVL is the brain lesion most clearly associated with CP.[31,50-51] The term PVL covers the spectrum from transient periventricular echodensities to densities that extend into the deep white matter and evolve into cystic lesions, indicated by the term cystic PVL (cPVL).[52] The characteristic clinical picture of PVL, that develops over time, is bilateral spastic CP, in which the legs are often more affected than the arms, since fibres of the corticospinal tract of the lower limbs are closest to the ventricles.[37] Another brain lesion associated with preterm birth is posthaemorrhagic porencephaly: due to local parenchymal destruction by the haemorrhage, cysts and/or cavities are formed.[53-55] Clinical symptoms, such as hypertonia and seizures, depend on the location and size of the injury. They vary in severity and often become evident during the first year of life.



From the late third trimester onwards, the developmental focus is in the cortical areas, which makes the cortex vulnerable to injury.[56-57] MRI studies have shown that types of term brain lesions are heterogeneous. Around term-age, the basal ganglia and thalamus are extra vulnerable because of their high metabolic demand during this period.[58-59] Common later clinical manifestations are involuntary movements (dystonia, chorea and athetosis), and feeding difficulties, and in the more severely affected children cognitive impairment and epilepsy often occur.[60-62] Another example of a brain lesion that mostly occurs during the end of the third trimester or shortly after term birth is cortical infarction. An arterial or venous thrombosis or embolization leads to a local disruption of blood flow in the brain. Most often, this takes place in one or more branches of the median cerebral artery with the left hemisphere more often affected than the right.[63] At or shortly after birth there are usually no clear clinical manifestations, but seizures may appear during the first hours or days of life.[64-66] Motor impairment, often more pronounced on one side of the body, often develops later.[67]

## Cerebral palsy (CP)

One of the most common developmental motor disorders in children is cerebral palsy (CP), with an incidence of 2-3 per 1000 live births in Western countries.[68] The most common definition of CP is the one of Rosenbaum and colleagues in 2007: "*Cerebral palsy 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, perception, cognition, communication, behaviour, by epilepsy and by secondary musculoskeletal problems.*" [69] The term CP thus describes a heterogeneous group of children with a wide variety in aetiologies and clinical manifestations. Major risk factors for CP are a low birth weight and preterm birth.[70-72] Three major motor types of CP are distinguished by the Surveillance of Cerebral Palsy in Europe (SCPE): spastic (unilaterally or bilaterally distributed), dyskinetic, and ataxic.[70,73] Spastic

CP is the most common form, with a prevalence of 60-80% in children diagnosed with CP.[74] It is characterized by an increased muscle tone, pathological reflexes, accompanied by consistent impairments in posture and movement. Seventy percent of the children with spastic CP is bilaterally affected, and thirty percent unilaterally.[75] The second most common form, dyskinetic CP, is reported in about 15% of children with CP.[74] Its clinical picture consists of an abnormal pattern of posture and/or movement, along with involuntary, uncontrolled, recurring, or occasionally stereotyped movements.[70] The third major type, ataxic CP, is characterized by an abnormal pattern of posture and/or movement in combination with loss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy.[70] Ataxic CP occurs in less than 10% of the children diagnosed with CP.[74] Thus, CP is a diagnosis based on patterns of impaired neuromotor development, i.e., a combination of clinical signs. This underlines the clinical relevance of a neurological examination. Besides the clinical examination for making the diagnosis, classification systems are used to objectify the functioning of the child with CP. Such classification facilitates communication among health care professionals, and caregivers and the child, and could also help in measuring change over time.[76-77] The Gross Motor Function Classification System (GMFCS)[78,79], the Manual Ability Classification System (MACS)[80], and Communication Function Classification System (CFCS)[81] are well-known and widely-used examples.

## Minor neurological dysfunction (MND)

During the last decades, more clinical and scientific interest has emerged for children with neuromotor impairments who do not get diagnosed with CP, but have minor neurological dysfunction (MND).[15] The classification of MND serves as a description of the neurological profile of the child, who may have motor impairments associated with cognitive and behavioural difficulties which possibly affect daily activities.[82] The assessment of MND underlines that single signs of neurological dysfunction generally do not have clinical significance;[83-85] they only have significance in combination with other signs in functional domains.[15,83,86] Therefore, the MND examination describes the child's neurological condition in terms of the number or type of domains fulfilling the criteria of dysfunction. To assess MND, age-specific examinations are needed. In the current thesis two assessments were used: the Hempel assessment that has been designed for children aged 1.5-4 years,[87-88] and the MND-assessment, which is applicable in children from 4 years onwards.[89]

Two forms of MND are distinguished: simple MND (sMND) and complex MND (cMND).[15] The distinction between the two forms is dependent on the age and based on the number of dysfunctional domains. According to the Hempel assessment, a pre-school child (age 1.5-4 years) is classified as having sMND when 1, and cMND when 2 or more of the following domains fulfil the criteria for dysfunction: fine motor function, gross motor function, posture and muscle tone, reflexes, and visuomotor function. The MND-assessment (from 4 years onwards) provides information on the following neurological domains: posture and muscle tone, reflexes, associated movements, choreiform dyskinesia, fine manipulative ability, coordination, sensory deficits and cranial nerve function. From 4 years of age until the onset of puberty, a child is classified with

sMND when 1 or 2 of those domains fulfil the criteria for dysfunction, and with cMND in case of 3 or more dysfunctional domains. sMND has a prevalence of 15-20% in school-aged children.[15,83,86] The aetiology of sMND is either genetic or caused by early perinatal stress, that may affect for instance the monoaminergic system in the brain.[90-91] sMND can be regarded as typical, yet non-optimal brain function.[15] cMND occurs in about 5-10% of school-aged children.[15,86,89] This is considered as the clinically relevant form of MND, since it is strongly associated with perinatal adversities and developmental disorders, such as ADHD, autism spectrum disorders, DCD, and dyslexia, as well as poor handwriting, visuomotor integration and dyslexia.[15,86,92-95] The complex form of MND is thought to reflect impaired function of brain regions that are also involved in cognitive and behavioural functioning.



## Early detection methods for infants at high risk

The ultimate aim of early detection of infants at risk of neurodevelopmental disorders, is to provide them and their families with appropriate early intervention.[96] For early detection of high-risk infants, recent clinical guidelines recommend a combination of brain imaging, general movement assessment (GMA) and a traditional neurological examination.[11,96-97]

Newborn brain imaging, performed with cranial ultrasound (cUS) or magnetic resonance imaging (MRI), aims for better understanding of cerebral pathologies.[96,98-99] Major brain lesions detected with cUS, such as intraventricular haemorrhage grade III, venous and focal infarctions, and cystic PVL have a high specificity up to 95-99% and sensitivity up to 76-86% for CP in high-risk preterm infants.[98] Also abnormalities on MRI have a good predictive value for CP: more than 80% of the children with CP show abnormal findings.[100-103] The most predictive brain imaging patterns for CP are white matter injury, cortical and deep grey matter lesions, and brain maldevelopments.[31,96,103]

Assessment of the quality of general movements (GMs) assists early detection of high-risk infants.[104-106] GMs are varied and complex spontaneous movements of the infant in which all body parts are involved. They start in early foetal life, i.e., from 9-10 weeks PMA, and disappear when goal-oriented behaviour gradually takes over, i.e., between 3 and 5 months post-term.[107-109] GM's quality, including movement complexity (spatial variation) and variation (temporal variation), gives an indication about the integrity of the nervous system.[110] Typical GMs are characterized by complexity and variation, whereas atypical GMs lack variation and complexity.[104-105] Atypical GMs with a limited repertoire and fluency, whether or not in combination with the absence of fidgety movements, are associated with perinatal risk factors, such as preterm birth and brain lesions, and have a high predictive power for CP.[104-106,111]

A traditional neurological examination is relevant in early detection of infants at risk and diagnosis of neurodevelopmental disorders, such as CP. This is not only the case because brain imaging is not available for all infants at risk, but also because infants may present with neurological dysfunction suggestive for CP without having visible injury on brain imaging.[112] Abnormalities in the neurological examination may provide clues for a neurodevelopmental disorder.[15,86,89] Prerequisite is that the assessment is adapted to the child's age.[11] A broadly used

neurological examination in infancy is the Hammersmith Infant Neurological Examination (HINE)[113-115] The HINE has a good construct validity, and suboptimal scores have a high predictive validity for development of major neuromotor disorders, such as CP.[113,116-118] Despite its good predictive ability, the assessment does have some drawbacks. For instance, the HINE pays relatively little attention to the quality of spontaneous movements, whereas during the last decades it has become clear that evaluation of spontaneous movement quality is clinically relevant in assessment of the integrity of the young brain.[29,119-122] In addition, HINE's criteria for an increased risk of developmental disorders are age-dependent and not available for all infant age-months. The recently developed Standardized Infant NeuroDevelopmental Assessment (SINDA) is not hampered by these drawbacks.[123] The SINDA is described in more detail in one of the following sections.

In the neurological examination at young age, especially the number of symptoms is of clinical significance. Isolated symptoms do generally not have a high predictive value for neurodevelopmental disorders. Nevertheless, improved knowledge of the significance and contribution of single neurological signs is desirable. A systematic review on the prognostic significance of neurological signs in high-risk infants reported that specific findings in the neurological examination in early infancy may be associated with an adverse developmental outcome, such as a persistent Moro response and an abnormal pull-to-sit manoeuvre. [124] However, the predictive value of such reflexes and reactions depends on the infant's age, the criteria for an atypical finding, and the a priori risk of developmental disorders. The risk of persistent neurological disorders increases when the infant presents with more symptoms, and when symptoms persist throughout infancy.

The presence of brain lesions on imaging, atypical general movements and an atypical neurological examination are complementary in the prediction of an adverse neurodevelopmental outcome. In combination, the assessment tools, i.e., brain imaging, GM assessment and neurological examination, have a higher predictive power than the single tools separately.[106,115]

## STUDY GROUPS

In the current thesis, we studied early neurological signs in 2 groups of children: the IMP-SINDA cohort and the LEARN2MOVE 0-2 cohort.

### IMP-SINDA project

In the IMP-SINDA project normative data were collected for two novel infant neurodevelopmental assessments: the Infant Motor Profile (IMP)[125-129] and the Standardized Infant NeuroDevelopmental Assessment (SINDA).[123,130-131] Between 2017 and 2019, 1700 infants between the corrected age of 6 weeks and 18 months were assessed. Infants had been recruited in the three northern provinces of the Netherlands, i.e., Groningen, Friesland, Drenthe. Per age-month, 100 infants were included. The study group was representative of the general Dutch population in terms of socio-economic background, ethnicity and perinatal risk factors. The resulting normative data

have recently been published in the manuals of both assessments.[123,129] The IMP-SINDA project not only allowed for collection of normative data for the IMP and the SINDA; it also offered the opportunity to study the prevalence of early neurological signs and their associations with neurodevelopmental condition in a low-risk infant population. In this thesis, prevailing head position (PHP) and atypical muscle tone will be discussed.

## Infant Motor Profile (IMP)

The Infant Motor Profile (IMP) is a standardized and qualitative video-based assessment of spontaneous motor behaviour of infants between 3 and 18 months corrected age, or until the age at which the infant can walk independently for some months.[125,129] By evaluating motor behaviour in different positions (supine, prone, sitting, standing and walking), and during reaching, grasping and manipulation, the IMP can be used for monitoring motor development throughout infancy, and for detection of motor disorders and prediction of developmental disorders.[129] Motor behaviour is assessed with 80 items divided distributed over five domains: variation, adaptability, fluency, symmetry and performance. The total IMP score is calculated as the mean of the domain scores. The IMP finds its theoretical background in the NGST.[28-29,125] The IMP can be assessed in 15 minutes. It takes another 10 minutes to assess the video. Several studies have evaluated IMP's psychometric properties. It has a satisfactory reliability,[125,128,132-133] and a good concurrent validity with the Alberta Infant Motor Scale (AIMS),[128] SINDA's neurological scale,[123] and general movement assessment.[134] IMP scores are clearly associated with perinatal risk factors, which is a manifestation of a good construct validity.[126] The IMP scores show strong relations with later developmental outcome in low-risk populations, and have a high predictive validity for neurodevelopmental disorders - particularly CP - in high-risk populations, to which variation and performance domain scores contribute most.[127,134-136]

## Standardized Infant NeuroDevelopmental Assessment (SINDA)

SINDA is a novel neurodevelopmental assessment, designed for infants from 6 weeks to 12 months corrected age. SINDA's aims are the identification of infants at risk of neurodevelopmental disorders, i.e., infants that are in need of intervention, and it provides health care professionals with information on the current developmental status of the child.[123,130-131] The SINDA takes 15 to 25 minutes to assess. SINDA consists of three scales: a neurological, developmental and socio-emotional scale. Items on the 3 scales are classified as typical/pass (1) or atypical/fail (0), according to well-described criteria. The neurological scale comprises 28 items that can be applied in infants throughout SINDA's entire age range. It consists of five neurological domains evaluating spontaneous movements, cranial nerves, motor reactions to postural stimulation, muscle tone, and reflexes and responses. A higher score represents a better neurological condition. A score of 21 points or less, i.e., an at-risk score, has a high predictive power for atypical developmental outcome, such as CP.[130] SINDA's developmental scale comprises 15 age-specific items per month of age and covers the domains of cognition, communication, fine and gross motor skills. It has satisfactory predictive validity for intellectual disability at 24 months of age or older. The socio-emotional scale assesses four types of behaviour: interaction, emotionality, self-regulation and reactivity. The behaviours emotionality and self-regulation are able to predict a behavioural or

emotional disorder at 24 months or older with high specificity but low sensitivity. Both SINDA's developmental and socio-emotional scales have an excellent interrater reliability.[131]

## LEARN2MOVE 0-2 years project

The LEARN2MOVE 0-2 years project (L2M0-2) was coordinated and performed by the University Medical Center Groningen as part of the Dutch national LEARN2MOVE research program in which the effects and mechanisms of age-specific treatments for children and youth with CP are studied. The L2M 0-2-cohort is a very well-documented group of 43 term and preterm born children who were perinatally at very high risk of a neurodevelopmental disorder, such as cerebral palsy, due to an evident brain lesion and/or severe neurological dysfunction. The longitudinal study design of L2M 0-2 allowed to: 1) evaluate the effects of the family-centred infant physiotherapeutic programme COPing and CAring for infants with special needs (COPCA)[137-138] in comparison to traditional infant physical therapy (TIP)[139-141] by means of a randomised controlled trial (RCT), and 2) quantify specific components of the physiotherapeutic interventions by means of process evaluation. For detailed information about the interventions, see [140]. Infants were longitudinally assessed to evaluate neuromotor, cognitive, behavioural, functional and family outcome. We previously reported that at the last assessment at 21 months CA, neurodevelopmental, family and functional outcome in both intervention groups was similar.[142-143] However, specific COPCA-intervention elements, such as caregiver coaching, were associated with better family empowerment and higher quality of life.[143] Additional to L2M's original design described above, this group of children offered the opportunity to study associations between infant neurological signs, such as atypical muscle tone and atypical knee jerk responses, and between infant motor behaviour and neurodevelopmental outcome at school-age (LEARN2MOVE 0-2 follow-up study).

## AIM AND OUTLINE OF THE THESIS

In young children, the distinction between typical and atypical neurodevelopment is not always clear. Therefore, the aim of this thesis is to contribute to the growing area of research on early detection of children at risk of neurodevelopmental disorders, by studying early neurological signs and evaluating their associations with neurodevelopmental conditions, both in a group of infants representative of the general Dutch population, and in infants at very high-risk of neurodevelopmental disorders. The thesis therefore consists of 2 parts: the first part is on early neurological development in the general infant population, whereas the second part deals with neurological signs and later outcome in very high-risk children (Figure 1).

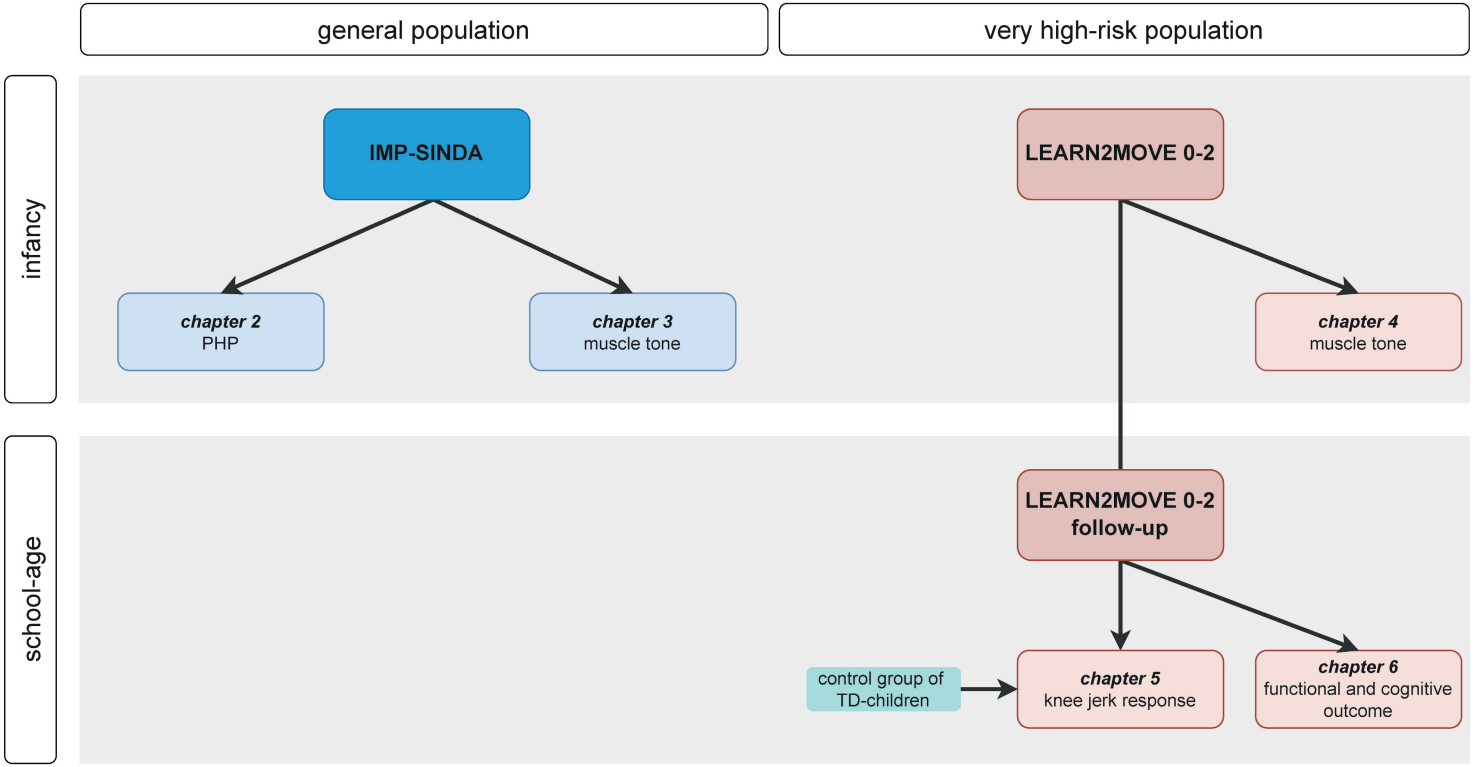


**FIGURE 1** OVERVIEW OF THE CHAPTERS AND STUDY GROUPS IN THIS THESIS

IMP: Infant Motor Profile. SINDA: Standardized Infant NeuroDevelopmental Assessment. PHP: prevailing head position. TD: typically developing.

## Part 1
### Early neurological development in the general infant population

Part 1 consists of two studies in the general infant population: the IMP-SINDA project. During the assessments we observed that a considerable part of the infants showed a prevailing head position. Data on its prevalence and associations with functional outcome in the general infant population are sparse. Therefore, we performed a cross-sectional study to assess its prevalence in the youngest infants of the IMP-SINDA project, and assessed whether it was associated with perinatal risk and neurodevelopmental disorders (**chapter 2**). In **chapter 3** we explored muscle tone impairments in the general infant population in terms of prevalence, the most common patterns of atypical muscle tone, and their associations with perinatal risk factors and neurodevelopment.

## Part 2
### Neurological signs and later outcome in children at very high risk of cerebral palsy

Knowledge about early development of muscle tone impairments and atypical reflex organization in high-risk infants is scarce, yet clinically relevant, as they are key symptoms in the diagnosis of CP. Therefore, in **chapter 4** we longitudinally assessed muscle tone impairments in the very high-risk children of the L2M0-2 years trial (hereafter referred to as VHR-children), by evaluating their prevalence and development throughout infancy. In addition, we looked at the relation between muscle tone impairments and diagnosis of CP and the presence of specific brain lesions. In **chapter 5** we studied the role of atypical knee jerk response in early detection of CP. We performed a follow-up study of the knee jerk responses in the VHR-children at school-age by means of surface electromyography. Additionally, we compared their knee jerk parameters with those of their typically developing peers. In **chapter 6** we studied in the VHR-children associations between early motor behaviour and functional and cognitive outcome at school-age.

**Chapter 7** provides a general discussion of the findings in this thesis, including clinical implications and future directions. Finally, the content of this thesis is summarized in **chapter 8**.

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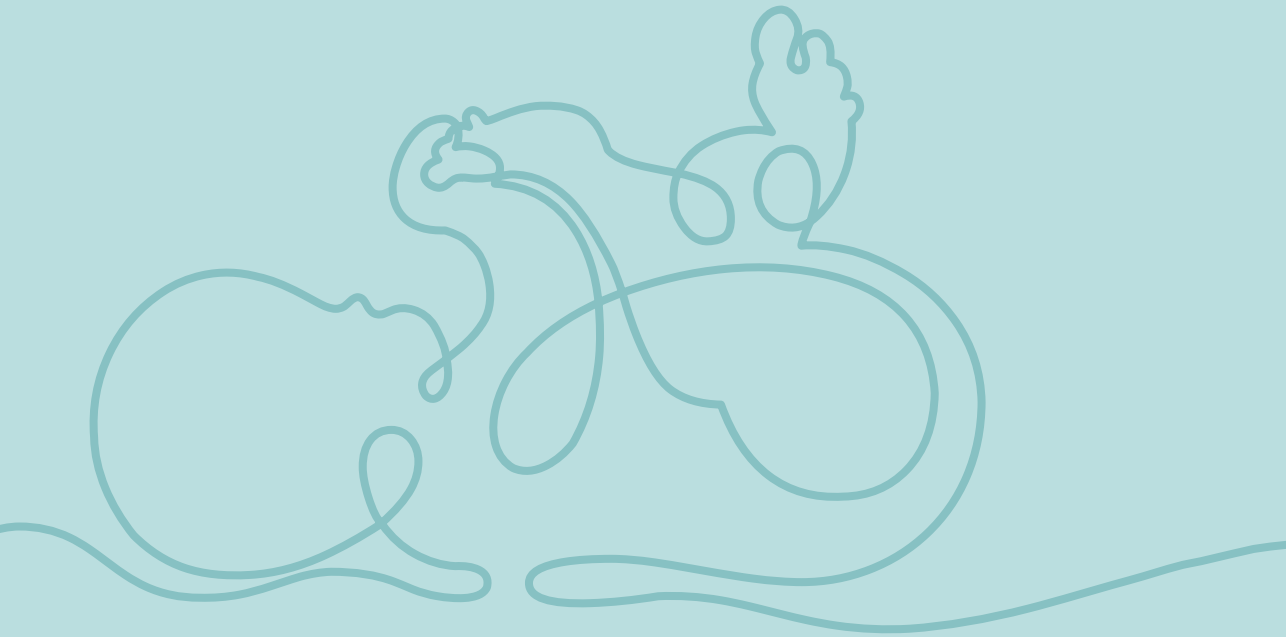
# Part 1

## Early neurological development in the general infant population



# 2

# Prevailing head position to one side in early infancy - a population-based study

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*Acta Paediatrica 2020; 109(7): 1423-1429*

*doi: 10.1111/apa.15112*

## ABSTRACT

**Aim**: To determine the prevalence of prevailing head position to one side (PHP) in young infants and to evaluate its associations with reaching performance, neurological condition and perinatal and socio-economic factors.

**Methods**: Observational study in 500 infants (273 boys) 2-6 months corrected age, representative of the Dutch population (median gestational age 39.7 weeks (27-42); birthweight 3438 g (1120-4950). Prevailing head position to one side and reaching performance were assessed with the Infant Motor Profile; neurological condition with the Standardized Infant NeuroDevelopmental Assessment. Socio-economic information and perinatal information were obtained by questionnaire and medical records. Associations were analysed with uni- and multivariable statistics.

**Results**: Prevailing head position to one side was observed in 100 infants (20%), and its prevalence decreased from 49% at 2 months to 0% at 6 months. Only in infants aged 4-5 months PHP was significantly associated with worse reaching and an at-risk neurological score. Prevailing head position to one side was weakly associated with prenatal substance exposure, post-natal admission to a paediatric ward and paternal native Dutch background.

**Conclusion**: Prevailing head position to one side at 2-3 months is a frequently occurring sign with limited clinical significance. Yet, PHP at 4-5 months is associated with a worse functional and neurological condition. Therefore, PHP at 4-5 months could serve as a red flag indicating possible challenges in later development.


### KEY NOTES

- In the general Dutch population, the prevalence of prevailing head position (PHP) steeply decreases from 49% at 2 months to 0% at 6 months.
- PHP at 2-3 months has limited clinical significance, but PHP at 4-5 months is associated with worse functional and neurological condition.
- PHP in the general population is only weakly associated with perinatal risk factors.


### KEYWORDS

infancy, motor development, neurological condition, perinatal risk, prevailing head position

# INTRODUCTION

Head control is one of the prerequisites for young infants to learn and explore their environment.[1] In early infancy, proper head control is not yet fully established, reflecting that development needs time. In the first month after birth, head movements may be considered as an element of non-object-oriented exploratory behaviour, that is head movements against gravity and towards the midline or to the contralateral side. This exploratory behaviour allows infants to learn to control their bodies.[2] This, in turn, is essential for the development of early behaviours in which vision and movements of trunk and arms are involved, such as reaching and grasping – behaviours that are largely dependent on adequate postural control.[3-5] Impaired head control is regarded as a manifestation of neurological non-optimality. Therefore, items evaluating head behaviour are included in all common infant neurological assessment methods.[6-8]



A frequently occurring clinical manifestation of non-optimal head control is a prevailing head position to one side (PHP).[9] The prevalence of PHP increased after the launch of the Back to Sleep campaign by the American Academy of Pediatrics in 1994, rising to 10%-11% in infants aged 2-4 months in the Netherlands in 2001.[10-11] PHP may lead to deformational plagiocephaly, a condition that has been associated with developmental delays in gross and fine motor function, problem-solving and personal social skills.[12-14] Although the studies reporting these associations have several limitations and only show tentative results, they do state that PHP could be a marker of conditions impeding typical development, such as neuromuscular conditions and environmental positioning limitations.[15] Professional awareness of these associations and caregivers' concerns about the asymmetric motor behaviour of the infant frequently results in referral to paediatric physiotherapy.[10]

Knowledge about the current prevalence of PHP in the general population is sparse. The data available are Dutch data of infants aged 2-6 months of the general population in 1995,[10] data of 4-month-olds in the general New Zealand population in 2004,[16] and data of 2-3 months old term born infants from the Netherlands and Italy, studied in 2005[17] and 2015,[18] respectively. In addition, no data are available on PHP's association with functional abilities, such as reaching, and with perinatal risk factors. The IMP-SINDA project offered an excellent opportunity to fill this knowledge gap. In the IMP-SINDA project, we collected norm data for two novel infant assessments: the Infant Motor Profile (IMP)[19] and the Standardized Infant NeuroDevelopmental Assessment (SINDA)[7] in a large sample representative of the Dutch population. The current study focussed on infants aged 2-6 months. In these infants, we addressed the following questions: (a) What is the prevalence of PHP?; (b) Is PHP associated with worse performance in reaching, grasping and manipulation?; (c) Is PHP associated with an impaired neurological condition in general, and - more specifically - with impaired postural control reflected by an atypical performance during the pull-to-sit manoeuvre?; and (d) Is PHP associated with perinatal and socio-economic risk factors?

# PATIENTS AND METHODS

## Study population

In this cross-sectional study, we evaluated motor behaviour of 500 infants (273 boys and 227 girls) aged 2-6 months corrected age (CA). The infants were the youngest infants of the IMP-SINDA project. Inclusion criteria of the IMP-SINDA project were as follows: age 2-18 months CA living in the northern part of the Netherlands (covering about a quarter of the surface area of the Netherlands) and having caregivers with sufficient comprehension of the Dutch language. Infants were only excluded if they were too ill to be assessed (e.g., severe congenital heart disease with insufficient oxygen saturation). We achieved the aim to recruit 100 infants per age month, whose socio-economic background is representative of the general Dutch population. Recruitment took place at well-baby clinics and by advertisements. Each infant was assessed once. The infant's age in a specific age month category ranged from 2 weeks prior to the exact age in months CA to 2 weeks after that exact age, for example the age of 3 months CA ranged from 2 months and 15 days to 3 months and 14 days. The Medical Ethical Committee of the University Medical Center Groningen (UMCG) approved the study design (approval number: METc 2016/294). All caregivers provided written informed consent.

## Procedures

Infants were assessed between January 2017 and March 2019 at the Institute of Developmental Neurology of the UMCG, at well-baby clinics or at the infant's home, depending on caregivers' preferences. A team of trained assessors examined the infants. The entire assessment was video-recorded. The videos served two goals: (a) enabling the assessors to perform the IMP-assessment, which is a video-based assessment; and (b) serving as a means for supervision of the SINDA. The assessors were supervised by two experts (MHA and KRH for the IMP; MHA for the SINDA), who were not aware of the socio-economic background and clinical history of the infant. The experts are reliable assessors of the IMP and SINDA; the good reliability of their performances was reported elsewhere.[7,19]

## Measurements

*Perinatal and socio-economic characteristics*

Caregivers filled out a standardised questionnaire on prenatal, perinatal and neonatal (in short: perinatal) and socio-economic history. If the questionnaire revealed complications, medical records were consulted. Based on these data, a perinatal risk score was calculated (Table 1).

*Infant Motor Profile*

Prevailing head position to one side was determined on the basis of the IMP, a valid and reliable video-based assessment of self-produced motor behaviour in different positions in infants aged 3-18 months. Its 80 items provide information on the domains variation, adaptability, symmetry, fluency and motor performance.[19] The IMP includes three items on PHP, that is items evaluate the presence of asymmetrical head position in supine, prone and (supported) sitting position. These IMP items are scored as no or mildly/moderately/strongly PHP. Prevailing head position

to one side was defined as the presence of a moderately or strongly prevailing head position in at least two of the three positions mentioned above. The infant's ability to reach, grasp and manipulate was based on the IMP performance item assessing this ability when the infant sits on the caregiver's lap (score range 1-7; a higher score denotes a better performance; Table 2).

*SINDA's neurological scale*

The SINDA is a novel neurodevelopmental screening instrument applicable for infants aged 6 weeks to 12 months. SINDA's neurological scale consists of 28 items, scored as typical or atypical. It results in a score ranging from 0 to 28, with 28 indicating best performance. A total score of ≤ 21 (the at-risk neurological score) was associated with an increased risk of a developmental disorder.[7] One of the items evaluates the infant's behaviour during the pull-to-sit manoeuvre. Atypical performance implies the presence of head lag, active head retroflection and/or insufficient hip flexion. The first study on SINDA's neurological scale indicated that it is a reliable and valid assessment tool.[7]



## Statistical analysis

To calculate the study's power a two-sample t-test for the reaching parameter was performed, assuming that the overall prevalence of PHP at 2-6 months was 6%.[10] Considering a 1-point difference in the reaching score as clinically relevant, the sample size of 500 results in a power of 80% ($\alpha$=0.05).

Associations between PHP on the one hand and reaching behaviour and SINDA's total neurological score on the other were evaluated with the Mann-Whitney U test; those between PHP and an at-risk neurological score and atypical pull-to-sit manoeuvre with the chi-square test, with Phi as the measure of the effect size. Associations between PHP and perinatal risk factors were assessed with the chi-square test and the Mann-Whitney U test. Next, we performed backward multivariable logistic regression analysis to determine which factors contributed most to PHP; only factors that reached $p < 0.15$ in the univariable analyses were entered into this analysis. Throughout the analyses, confidence intervals (CI) were set at 95%, and p-values <0.05 were considered statistically significant (two-tailed). In case of missing data on perinatal characteristics, cases were omitted from the association analyses. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 23 (SPSS IC., Chicago, IL).

# RESULTS

The background characteristics of the study group are shown in Table 1. They reflect the low-risk nature of the group with a median gestational age of 39.7 weeks (range 27-42) and a median birthweight of 3438 grams (range 1120-4950). The study group contained two infants with a known syndrome: one was diagnosed with trisomy 21 and one with Gorlin syndrome. The background characteristics resemble those of the general Dutch population, including the prevalence of preterm birth (6.2% in our study and 6.8% in the general population)[20] and the infants' socio-economic background (prevalence of highly educated mothers 40% in our study and 37% in the general population).[21]

**TABLE 1** SOCIO-ECONOMIC AND PERINATAL CHARACTERISTICS

| | |
|---|---|
| sex (boy/girl), *n* (%) | 273 (55)/227 (45) |
| maternal education level * [a]<br>**I** / II / III / IV, *n* (%) | <br>10 (2)/53 (11)/234 (47)/202 (40) |
| paternal education level * [a]<br>**I** / II / III / IV, *n* (%) | <br>18 (4)/42 (9)/228 (48)/189 (40) |
| maternal occupation level * [b]<br>**I** / II / III / IV, *n* (%) | <br>110 (22)/121 (24)/116 (23)/150 (30) |
| paternal occupation level * [b]<br>**I** / II / III / IV, *n* (%) | <br>63 (13)/190 (40)/92 (19)/130 (27) |
| maternal age<br>in years, mean +/-SD<br>< 20 / 20-34 / **≥ 35**, *n* (%) | <br>29.9 +/- 4.7<br>2 (0.4)/416 (83)/82 (16) |
| paternal age *<br>in years, mean +/- SD<br>< 20 / 20-39 / ≥ 40 | <br>32.9 +/- 6.3<br>0/427 (88)/57 (12) |
| maternal ethnicity [c]: native Dutch / **non-native Dutch**, *n* (%) | 447 (89)/53 (11) |
| paternal ethnicity * [c]: native Dutch / **non-native Dutch**, *n* (%) | 440 (90)/48 (10) |
| pre-pregnancy maternal BMI *<br>in kg/m$^2$, median (range)<br>< 25 / **25 – 29 / ≥ 30**, *n* (%) | <br>24.1 (17.2-48.4)<br>285 (57)/134 (27)/79 (16) |
| **assisted reproduction** *, *n* (%)<br>hormonal treatment, *n* (%)<br>intrauterine insemination, *n* (%)<br>IVF/ICSI, *n (%)* | 36 (7)<br>11 (2)<br>15 (3)<br>10 (2) |
| **maternal smoking** *, *n* (%) | 53 (11) |
| **prenatal substance exposure (alcohol a/o drugs)** *, *n* (%) | 5 (1) |

**TABLE 1** SOCIO-ECONOMIC AND PERINATAL CHARACTERISTICS (CONTINUED)

| | |
|---|---|
| **maternal medication** * [d], *n* (%) | 58 (12) |
| **diabetes** *, *n* (%)<br>without medication, *n* (%)<br>with medication, *n* (%) | 37 (7)<br>18 (4)<br>19 (4) |
| **hypertension** *, *n* (%)<br>without medication, *n* (%)<br>with medication, *n* (%) | 68 (14)<br>49 (10)<br>19 (4) |
| **thyroid disease** *, *n* (%)<br>without medication, *n* (%)<br>with medication, *n* (%) | 15 (3)<br>3 (0.6)<br>12 (2) |
| **instrumental delivery**, *n* (%)<br>caesarean section, *n* (%)<br>vacuum or forcipal extraction, *n* (%) | 123 (25)<br>85 (17)<br>38 (8) |
| gestational age<br>in weeks, median (range)<br>**preterm /** term, *n* (%) | <br>39.7 (27.3-42.1)<br>31 (6)/469 (94) |
| birth weight<br>in grams, median (range)<br>**SGA (<P10)** / AGA (P10-90) / LGA (≥P90), *n* (%) | <br>3438 (1120-4950)<br>60 (12)/384 (77)/56 (11) |
| **twin**, *n* (%) | 12 (2) |
| **meconium in amniotic fluid** *, *n* (%) | 73 (15) |
| **non-optimal start** * [e], *n* (%) | 43 (9) |
| **admission to neonatal ward**, *n* (%) | 101 (20) |
| **jaundice requiring phototherapy**, *n* (%) | 21 (4) |
| perinatal risk score *, median (range) | 2 (0-7) |

Bold: factors included in the perinatal risk score and their criteria; score range 0-23; a higher score denotes a higher risk; at the bottom of the table.

* Missing: maternal education level n=1; paternal education level n=23; maternal occupation level n=3; paternal occupation level n=25; paternal age n=16; paternal ethnicity n=12; maternal BMI n=2; assisted reproduction n=4; maternal smoking, prenatal substance exposure, maternal medication, diabetes, hypertension, thyroid disease n=1; meconium in amniotic fluid n=2; non-optimal start, admission to neonatal ward, jaundice requiring phototherapy n=1; perinatal risk score n=34.

[a] I = no or only primary education / II = primary or secondary vocational education and training / III = secondary vocational training, senior general secondary education and university preparatory education / IV = vocational college and university.

[b] Based on the International Standard Classification of Occupations, ISCO.28 I = ISCO1 and unemployed / II = ISCO2 / III = ISCO3 / IV = ISCO4.

[c] Native Dutch: location of birth is the Netherlands. Non-native Dutch: location of birth is not the Netherlands.

[d] Used one of the following: insulin; antihypertensive medication; thyroid stimulating medication; antidepressants/antipsychotics/benzodiazepines; anti-epileptic medication.

[e] The presence of delayed onset of crying, respiratory difficulties requiring monitoring on the neonatal ward and/or respiratory intervention, short-lasting floppiness or cyanosis.

## Prevalence of PHP

The prevalence of PHP in our total study group was 20%, with a steady and significant decrease from 49% at 2 months to 0% at 6 months (Table 2, Figure 1A).

**TABLE 2** NEUROMOTOR PERFORMANCE FROM 2 TO 6 MONTHS

| | age in months | | | | | |
|---|---|---|---|---|---|---|
| **neuromotor behaviour** | 2 (*n*=100) | 3 (*n*=100) | 4 (*n*=100) | 5 (*n*=100) | 6 (*n*=100) | total (*n*=500) |
| PHP [a], *n* (%) | 49 (49) | 32 (32) | 16 (16) | 3 (3) | 0 (0) | 100 (20) |
| reaching, grasping and manipulation [b], *n* (%) | | | | | | |
| no prereaching or reaching | 44 | 17 | 3 | 0 | 0 | 64 (13) |
| no reaching, but prereaching | 48 | 56 | 39 | 12 | 0 | 155 (31) |
| reaching, but no grasping | 7 | 22 | 15 | 7 | 1 | 52 (10) |
| reaching, grasping and holding but no manipulation | 1 | 4 | 7 | 5 | 0 | 17 (3) |
| reaching, holding and manipulation of 1 object | 0 | 1 | 27 | 40 | 19 | 87 (17) |
| reaching, holding and manipulation of 2 objects | 0 | 0 | 9 | 35 | 79 | 123 (25) |
| reaching, holding and manipulation of ≥ 3 objects | 0 | 0 | 0 | 1 | 1 | 2 (0.4) |
| SINDA | | | | | | |
| neurological score [c], median (25-75th percentile) | 24 (22-26) | 25 (23-26) | 25 (23-27) | 25 (24-26) | 25 (24-26) | 25 (23-26) |
| at-risk neurological score ≤21, *n* (%) | 20 (20) | 14 (14) | 9 (9) | 7 (7) | 5 (5) | 55 (11) |
| atypical pull-to-sit manoeuvre [d], *n* (%) | 71 (71) | 46 (46) | 26 (26) | 17 (17) | 12 (12) | 172 (34) |

[a] Prevalence decreased with increasing age: H(4)=105, r=-0.45, p<0.001

[b] Score increased with increasing age: $r_s$=0.818, p<0.001

[c] Score increased with increasing age: $r_s$=0.212, p<0.001

[d] Prevalence decreased with increasing age: H(4)=103.9, r=-0.437, p<0.001

Associations between PHP and a) reaching, grasping and manipulation: U=7750.5, p<0.001; b) SINDA neurological score: U=13013.5, p<0.001; c) SINDA at-risk neurological score: $\chi^2$(1)=21.478, Phi=0.207, p<0.001; d) atypical pull-to-sit manoeuvre: $\chi$2(1)=33.318, Phi=0.258, p<0.001.

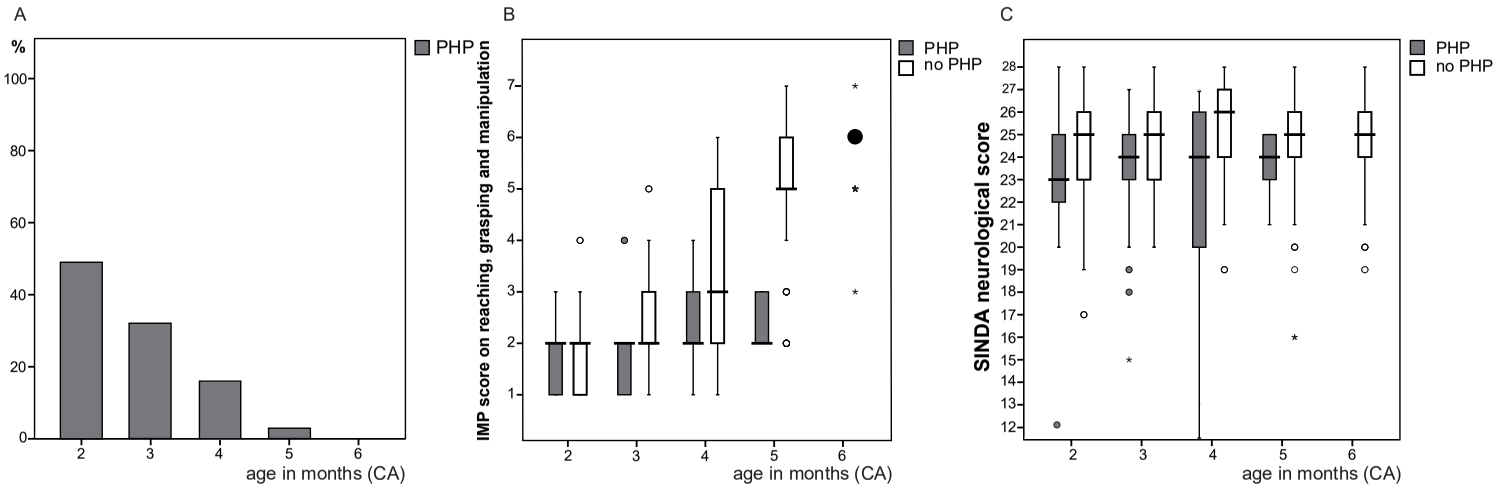


**FIGURE 1** PREVALENCE OF PHP, SCORES ON REACHING PERFORMANCE AND SINDA'S NEUROLOGICAL SCALE

A) Prevalence of PHP at various ages. Panels B and C: Bold horizontal lines indicate median values, boxes present 25th and 75th centiles, vertical lines indicate ranges, outliers are represented by dots or asterisks. B) Boxplot of IMP-scores on reaching, grasping and manipulation in infants with and without PHP at the various ages. The large black dot at 6 months indicates that the vast majority of infants obtained score 6, implying that they could hold and manipulate two objects (infants 2-3 months: difference between infants with and without PHP: Mann-Whitney, $p=0.107$; infants 4-5 months: difference between infants with and without PHP: Mann-Whitney, $p<0.001$). C) SINDA's neurological scale scores in infants with and without PHP at the various ages (difference between infants with and without PHP: Mann-Whitney, $p<0.001$.

## PHP and performance on reaching, grasping and manipulation

Prevailing head position to one side was significantly associated with worse reaching, grasping and manipulation (in short: reaching; $p<0.001$; Table 2). This association was age dependent (Figure 1B): only infants aged 4-5 months with PHP scored significantly lower on reaching than their peers without PHP ($p<0.001$).

## SINDA's neurological scale scores and PHP

SINDA's neurological scores ranged from 11 to 28 points, with a median value of 25. This reflects the low-risk nature of the study group. Prevailing head position to one side was associated with a significantly lower SINDA neurological score; this held true for all ages (Figure 1C). Fifty-five infants of the total group (11%) had an at-risk neurological score. Also, the at-risk score was associated with PHP ($p<0.001$). The association was age dependent. In the infants aged 2-3 months, the at-risk score was not associated with PHP (at-risk score in infants with PHP: 18/81 (22%); in infants without PHP 16/119 (13%)) ($\chi^2(1)=2.631$, Phi=0.115, $p=0.105$). However, in infants aged 4-5 months the at-risk score was associated with PHP (at-risk score in infants with PHP: 6/19 (32%); in infants without PHP: 10/181 (6%); $\chi^2(1)=15.859$, Phi=0.282, $p<0.001$). An atypical performance on the pull-to-sit manoeuvre was present in 172 infants (34%). It was clearly associated with PHP ($\chi^2(1)=33.318$, Phi=0.258, $p<0.001$). This association was not age dependent.

## Perinatal risk factors and PHP

Univariable analyses revealed that PHP was significantly associated with prenatal substance exposure ($\chi^2(1)=5.015$, Phi=0.100, $p=0.025$), post-natal admission to the neonatal ward ($\chi^2(1)=4.611$, Phi=0.096, $p=0.032$), jaundice requiring phototherapy ($\chi^2(1)=7.087$, Phi=0.119, $p=0.008$), a lower paternal occupation level ($U=15569$, $p=0.022$), and paternal native Dutch background ($\chi^2(1)=6.098$, Phi=0.112, $p=0.014$). The perinatal risk score was not associated with PHP ($p=0.748$). Multivariable logistic regression analysis indicated that prenatal substance exposure (OR 10.08, 95% CI 1.02-99.77), post-natal admission to neonatal ward (OR 1.72, 95% CI 1.02-2.91) and paternal native Dutch background (OR 3.89, 95% CI 1.18-12.86), explained PHP best. Note that these variables together only explained 5.3% of the variance. The infant's age did not play a role.

## DISCUSSION

In our low-risk study group, 20% of infants showed PHP, with a prevalence that decreased from 49% at 2 months to 0% at 6 months. Prevailing head position to one side in infants aged 2-3 months was not related to reaching nor to an at-risk neurological score. However, in infants aged 4-5 months PHP was associated with less optimal reaching and an at-risk neurological condition. Perinatal factors were only weakly associated with PHP.

The prevalence of PHP at 4 months in our study (16%) is somewhat higher than the 11% previously reported in a large study group of infants younger than 6 months assessed in 1995 that was relatively representative of the Dutch population.[10] The different figures could imply that the prevalence of PHP in young infancy has increased during the last two decades. However, Hutchison and colleagues who studied PHP in a cohort of 200 infants - being qualified by the presence of plagiocephaly and brachycephaly - in New Zealand in 2004, reported a PHP prevalence at 4 months of 19.7%.[16] This would argue against an evident increase over the years. Most likely, the different prevalence percentages reported in the studies may be attributed to the differences in criteria for PHP and cultural differences in infant handling and positioning. The data do not allow for a conclusion on the effect of culture on PHP over time.

Our data indicated that PHP in infants aged 2-3 months was not associated with reaching performance and neurological condition, whereas in infants aged 4-5 months it was. It is conceivable that this age-related difference is brought about by the major transition in the brain occurring at this time. Around 3 months of age the primary sensory and motor cortices no longer involve the temporary structure of the subplate; from that age onwards, they only rely on the permanent circuitries of the cortical plate.[22] This developmental change is accompanied by a transition in the infant's behaviour: the general movements are in their final phase and are getting replaced by goal-directed behaviour.[23-24] Simultaneously the infant has achieved the ability to balance the head.[25] Proper head balance is one of the prerequisites for goal-directed reaching.[3-5]

Interestingly, having a non-native Dutch father was associated with a lower risk of PHP, which supports the suggestion that ethnic background and cultural habits may play a role in the genesis of PHP.[18,26] PHP was only associated with two perinatal risk factors: prenatal substance exposure and post-natal admission to the neonatal ward. The latter suggests that PHP is associated with an impaired capacity to cope with the transition from intra- to extrauterine life, which in turn corresponds to the less optimal neurological condition of infants with PHP (Figure 1). In contrast to other reports,[10,17] we did not find an association between PHP and preterm birth and male sex. The reason that we did not find an association with preterm birth could be that in our sample, that was representative of the Dutch population, only a few children had been born very preterm. Especially infants who have been born very preterm have an increased risk of PHP. For instance, Nuysink et al reported that the prevalence of PHP at 3 months CA in infants

born before 30 weeks gestational age was 37% and that of deformational plagiocephaly 50%.[27] Similar to PHP in term infants, PHP in very preterm infants mostly has a favourable prognosis.

A major strength of our study is the relatively large group of well-documented infants that - despite being recruited in the northern parts of the Netherlands - is representative of the general Dutch population in terms of perinatal and demographic characteristics. This supports the generalisability of the study's findings to the general population of Dutch infants aged 2-6 months. An additional strength is the use of two standardised assessments - the IMP and SINDA – to evaluate PHP, reaching and neurological condition. It may be considered a limitation that we performed the IMP in infants aged 2 months, whereas the IMP has been designed for infants aged 3-18 months. Two-month-olds were included to facilitate the calculation of norm curves. It turned out that the IMP could be well assessed in all 1.5- to 2.5-month-old infants. Another limitation is the absence of information on daily life activities, such as positioning during sleeping, feeding and playing, as these activities may have acted as effect mediators.[17]

## CONCLUSION

We found a 20% overall prevalence of PHP in young infants. Our study confirms that PHP in young infants is largely age dependent. In our representative Dutch sample, it had a high prevalence at 2 months and it had disappeared at 6 months, suggesting that it is a transient form of neurological non-optimality. Prevailing head position to one side was only weakly associated with perinatal risk factors. Prevailing head position to one side at 2-3 months had a high prevalence and was not associated with reaching and an at-risk neurological condition. This indicates that PHP at 2-3 months has limited clinical significance. Yet, PHP at 4-5 months was associated with worse reaching skills and with an at-risk neurological condition. The latter may imply PHP in infants aged 4-5 months may serve as a red flag indicating possible challenges for later development. We therefore suggest the following: (a) when the infant does not show clear neurological dysfunction accompanying PHP, caregivers may be reassured by receiving information on the transient nature of PHP; yet, caregivers also need to be informed that when PHP persists until 4-5 months, physiotherapeutic intervention is warranted; (b) that health professionals provide caregivers of all young infants with PHP with information on how they can promote the infant's ability to achieve symmetric head positioning and symmetric and varied head movements in all directions, how they can promote the infant's head balancing abilities and how they can encourage the infant's reaching and grasping activities; and (c) that 4- to 5-month-old infants with PHP receive physiotherapeutic intervention.

## CONFLICTS OF INTERESTS

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

## ACKNOWLEDGEMENTS

We thank all infants and parents who participated in the IMP-SINDA project. We acknowledge the assistance of the medical students and the research assistants of the Kinderacademie Groningen in data collection. We also gratefully acknowledge the technical assistance of Anneke Kracht-Tilman.

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# 3

# Patterns of atypical muscle tone in the general infant population – prevalence and associations with perinatal risk and neurodevelopmental status

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*Early Human Development 2021; 152: 105276*

*doi: 10.1016/j.earlhumdev.2020.105276*

## ABSTRACT

**Background**: Muscle tone is an indispensable element in motor development. Its assessment forms an integral part of the infant neurological examination. Knowledge on the prevalence of atypical tone in infancy is lacking.

**Aim**: To assess the prevalence of atypical muscle tone in infancy and of the most common atypical muscle tone patterns, and associations between atypical tone and perinatal risk and neurodevelopmental status.

**Study design**: Cross-sectional study.

**Outcome measures:** Muscle tone and neurodevelopmental status were assessed with the Standardized Infant NeuroDevelopmental Assessment (SINDA). Perinatal information was obtained by questionnaire and medical records. Univariable and multivariable statistics were applied.

**Results**: Ninety-two infants (8%) had atypical muscle tone in 3–4 body parts (impaired pattern), while atypical muscle tone in 1–2 body parts was observed in 50%. Isolated leg hypotonia and isolated arm hypertonia were most common. Isolated arm hypertonia and the impaired pattern were most clearly but only moderately associated with perinatal risk. These patterns were also most clearly associated with lower neurological scores. Only the impaired pattern was associated with lower developmental scores.

**Conclusion**: Atypical muscle tone in one or two body parts is common in infancy and has in general little clinical significance. This finding corresponds to the well-known high prevalence of a typical but non-optimal neurological condition. Eight percent of infants show atypical muscle tone in 3–4 body parts. This clinically relevant pattern is associated with perinatal risk and less favourable neurodevelopmental status.


### HIGHLIGHTS

- Atypical muscle tone in 1-2 body parts is common in infancy.
- Arm hypertonia is associated with perinatal risk and non-optimal neurodevelopment.
- Atypical muscle tone in 3-4 body parts occurs in 8% of infants.
- Atypical muscle tone in 3-4 body parts is associated with perinatal risk.
- Atypical muscle tone in 3-4 body parts is associated with non-optimal neurodevelopment.


### KEYWORDS

hypertonia, hypotonia, infancy, motor development, muscle tone, perinatal risk

# INTRODUCTION

Motor development in infancy is a complex process in which many elements are involved. Muscle tone is one of them. Most muscles are always more or less active, i.e., in some degree of contraction. Muscle tone is therefore defined as the continuous and passive partial contraction of the muscles, or as the resistance of a muscle to passive stretch during resting state.[1] Muscle tone plays a pivotal role in postural control and performance of movements.[2] It is continuously affected by a feedback loop between the brain and the peripheral nervous system.[3] Any disturbance in this feedback cycle may result in atypical muscle tone: hypotonia, hypertonia or changing muscle tone. Hypotonia is too low muscle tone, implying an abnormally low resistance during passive movements. Hypotonia frequently occurs in infants below the age of 6 months and is of little clinical significance in the absence of other neurological signs.[4-5]



Hypotonia is considered atypical when associated with motor developmental delay,[3] is very pronounced ('floppy infant'),[6] or if it occurs in combination with other neurological signs, such as abnormal reflexes or lack of muscle strength.[7-8] Known risk factors for hypotonia are preterm birth,[9] prenatal drug exposure,[10] and acute infectious diseases.[11] Neurological disorders that often present with hypotonia are for instance congenital myotonic dystrophy, myasthenia gravis, and cerebral palsy (CP).[6-7]

Hypertonia is defined as an abnormally high resistance during passive movements.[12] Hypertonia starting from birth is relatively rare and is often associated with serious neurological pathology,[4,13] such as a brain lesion or a metabolic disorder.[13] Infants who later are diagnosed with spastic CP often do not present with hypertonia in early life.[8,13-14]

Muscle tone assessment is an integral part of the infant neurological examination. It is well-known that many infants show one or two signs of atypical neurological function and that generally only a combination of multiple signs of atypical neurological function is associated with increased risk of neurodevelopmental disorders.[15] Yet, specific data on atypical muscle tone in infancy are lacking. The IMP-SINDA project offers an excellent opportunity to fill this knowledge gap. In the IMP-SINDA project we collected norm data for the Infant Motor Profile (IMP)16 and the Standardized Infant NeuroDevelopmental Assessment (SINDA)[17]. SINDA is a recently developed reliable and valid neurodevelopmental assessment that has been designed for infants aged 6 weeks to 12 months.[17-18] Therefore, we focussed on the infants in this age range. SINDA's neurological scale includes the assessment of muscle tone.[17] We addressed the following questions: (1) What is the prevalence of atypical muscle tone in infancy; (2) What are the most common patterns of atypical muscle tone distribution across the body in the general infant population; (3) Are particular atypical muscle tone patterns associated with a) the infant's age; b) perinatal risk; and c) lower scores in other neurological domains and on the developmental scale? We hypothesized that in the general population (a) the prevalence of atypical muscle tone is not associated with the infant's age, as infants may grow into and out

of neurological impairment, (b) atypical muscle tone is associated with perinatal risk, and (c) with lower scores on SINDA's neurological domains and developmental scale.

# METHODS

## Participants

The participants were the 1100 infants of the IMP-SINDA project aged 6 weeks to 12.5 months. Inclusion criteria for the IMP-SINDA project were: (corrected) age between 6 weeks and 18.5 months (corrected age (CA) in infants born before 37 weeks of gestation), living in one of the three northern provinces of the Netherlands and having caregivers with sufficient comprehension of the Dutch or English language to give informed consent. Infants were excluded in case they were too ill to be assessed (due to e.g., severe congenital heart disease with insufficient oxygen saturation). Infants were recruited at well-baby clinics and by advertisements. The IMP-SINDA project included 100 infants per age month.19-20 The infant's age in a specific age month category ranged from 2 weeks prior to CA in months to 2 weeks after that age; for example, 3 months CA ranged from 2 months and 15 days to 3 months and 14 days. All ages mentioned in the text are corrected ages.

## Procedures

Assessments took place between January 2017 and March 2019 at the Institute of Developmental Neurology, University Medical Center Groningen, at well-baby clinics, or at the infants' homes, depending on caregivers' preferences. Each infant was assessed once. All infants had a SINDA performed by a trained member of the IMP-SINDA project team. Assessments were video-taped and supervised by an expert (MHA or KRH). The assessors were not aware of the clinical history of the infants. The Medical Ethical Committee of the University Medical Center Groningen (UMCG) approved the study design (approval number: METc 2016/294). All caregivers provided written informed consent.

## Assessments

All caregivers filled out a questionnaire on socio-economic background and perinatal events. In case of perinatal complications, medical records were consulted. On the basis of the perinatal information a composite perinatal risk score (range 0–23; labelled perinatal risk score) was computed, with higher scores indicating higher perinatal risk (for details see legends of Table 1).

The SINDA is a neurodevelopmental assessment for infants aged 6 weeks to 12 months. It consists of a neurological, developmental, and socio-emotional scale. SINDA can be performed in virtually any environment, provided that there is not too much distraction. The three scales can be assessed in isolation and in combination.[17,18] In the present study only the neurological and developmental scales of the SINDA were used to characterize the infant's current neurodevelopmental status. The neurological scale contains 28 items which constitute five domains: (A) spontaneous movements (eight items), (B) cranial nerve function (seven items), (C) motor reactions to postural stimulation (five items), (D) muscle tone (four items; labelled

muscle tone domain), and (E) reflexes (four items). Each item is scored as pass (typical =1) or fail (atypical = 0). A total neurological score and five domain scores can be calculated by adding the items scored as passed. Maximum total score is 28 and a score of ≤21 indicates an increased risk of developmental disorders.[17-18] A prerequisite for the performance of a neurodevelopmental test is that the infant is in an adequate behavioural state, i.e., awake and not crying.

Muscle tone in SINDA is assessed with four items; one item for each of the following body parts: neck and trunk, arms (shoulders, elbows, wrists), legs (hips and knees), and ankles. Muscle tone is assessed by evaluating the resistance during passive movements. In the youngest infants, i.e., infants who can be easily assessed in supine, the evaluation of muscle tone of the limbs also includes arm and leg traction. Like the other SINDA items, each tone item is scored as typical (moderate and symmetric resistance against passive movements) or atypical. Atypical tone implied a muscle tone other than normal tone, i.e., one of the following: hypotonia, hypertonia, changing tone (the presence of sudden changes in muscle tone), or the presence of asymmetry. In case of asymmetry, tone of the worst side was assigned in the analyses. We opted for the term 'atypical' according to the Oxford English Dictionary: not typical; not conformable to the ordinary type. It means that the sign or behaviour is absent in the majority of infants, without directly referring to impairment status. The maximum muscle tone domain score is 4, denoting typical muscle tone in all body parts.



The developmental scale has 15 standardized items for each month of age, covering the domains of cognition, communication, and fine and gross motor development. Items are scored as pass (1) or fail (0). The maximum score is 15. A score ≤ 7 is atypical and associated with an increased risk of learning disabilities.18 SINDA's reliability is good. In addition, it has been demonstrated that SINDA has a good ability to predict atypical neurodevelopmental outcome at 24 months or older (i.e., CP, intellectual disability) in a non-academic out-patient clinic setting.[17-18] Performing and scoring of SINDA takes relatively little time: the neurological scale takes about 10 min and the developmental scale depending on infant's age between 5 and 15 min. SINDA assessment forms are available online (see supporting material of[17] for neurological scale and[18] for developmental scale).

## Statistical analysis

Based on the reported prevalence of atypical muscle tone in older children of 5–8%,[25] sample size calculation revealed that for the current study a sample size of 114 infants would be large enough to investigate the prevalence of atypical tone in infancy (95%CI, level of accuracy 5%). Descriptive statistics were used to report prevalence numbers of atypical muscle tone. Non-parametric statistics were used since variables had a non-normal distribution. Relations between atypical muscle tone patterns and age were assessed with Spearman's rho correlation coefficient (ρ). Associations between atypical muscle tone and the perinatal risk score were assessed with the Mann-Whitney test. In order to determine which single perinatal risk factors contributed most to the prevalence of a particular muscle tone pattern, univariable and multivariable regression analyses were performed. Results are presented as

odds ratios (ORs) and their 95% confidence intervals (95%CI). Mann-Whitney tests were used to evaluate associations between atypical muscle tone patterns and SINDA neurological and developmental scores. Throughout the analyses, p-values <0.05 were considered statistically significant (two-tailed) and CIs were set at 95%. We performed statistical analysis using Statistical Package for the Social Sciences (SPSS), version 23 (SPSS IC., Chicago, IL).

## RESULTS

Table 1 shows the background characteristics of the 1100 infants of the study group. Mean birth weight was 3431 g (SD 585) and mean gestational age was 39.4 weeks (range 27.3-42.4 weeks). The study group was representative of the general Dutch population in terms of prevalence of preterm birth and socio-economic background, including maternal education and ethnicity. The study group had a median SINDA neurological score of 25 (range 11-28); 76 infants (7%) had an at-risk neurological score (score ≤21). The mean SINDA developmental scale score was 10 (SD 2.3), with 165 infants (15%) having an at-risk score of ≤7.

**TABLE 1** SOCIO-ECONOMIC AND PERINATAL CHARACTERISTICS OF THE STUDY GROUP

| | |
|---|---|
| (boy/girl), *n* (%) | 585 (53)/515 (47) |
| maternal educational level [a]<br>**I** / II / III / IV, *n* (%) | 23 (2)/100 (9)/492 (45)/483 (44) |
| paternal educational level [a]<br>**I** / II / III / IV, *n* (%) | 39 (4)/93 (9)/495 (45)/432 (39) |
| maternal occupational level [b]<br>**I** / II / III / IV, *n* (%) | 217 (20)/253 (23)/261 (24)/359 (33) |
| paternal occupational level [b]<br>**I** / II / III / IV, *n* (%) | 129 (12)/408 (37)/215 (20)/301 (27) |
| maternal age<br>- in years, mean (SD)<br>- < 20 / 20-34 / ≥ **35**, *n* (%) | <br>30.2 (4.6)<br>12 (1)/898 (82)/188 (17) |
| paternal age<br>- in years, mean (SD)<br>- < 20 / 20-39 / ≥ 40, *n* (%) | <br>32.9 (5.9)<br>5 (1)/937 (85)/128 (12) |
| maternal ethnicity: native Dutch / **non-native Dutch** [c], *n* (%) | 992 (90)/108 (10) |
| paternal ethnicity: native Dutch / **non-native Dutch** [c], *n* (%) | 964 (88)/114 (11) |
| pre-pregnancy maternal BMI<br>- in kg/m$^2$, median (min-max)<br>- < 25 / **25 – 29 / ≥ 30**, *n* (%) | <br>24 (16-48)<br>648 (59)/297 (27)/152 (14) |
| **assisted reproduction** [d], *n* (%) | 79 (5) |
| **maternal smoking**, *n* (%) | 111 (10) |
| **prenatal substance exposure (alcohol a/o drugs)**, *n* (%) | 11 (1) |
| **maternal medication**, *n* (%) | 110 (10) |

**TABLE 1** SOCIO-ECONOMIC AND PERINATAL CHARACTERISTICS OF THE STUDY GROUP (CONTINUED)

| | |
|---|---|
| **maternal diabetes during pregnancy**, *n* (%) | 79 (7) |
| **maternal hypertension during pregnancy**, *n* (%) | 132 (12) |
| **maternal thyroid disease during pregnancy**, *n* (%) | 26 (2) |
| **instrumental delivery** [e], *n* (%) | 288 (26) |
| gestational age<br>in weeks, mean (SD)<br>**preterm (< 37 wks)** / term, *n* (%)<br>very preterm (28-32 wks) | <br>39.4 (1.8)<br>75 (7)/1024 (93)<br>7 (0.6) |
| birth weight<br>in grams, mean (SD)<br>**SGA (<p10)** / AGA (p10-90) / LGA (≥p90), *n* (%) | <br>3431 (585)<br>123 (11)/840 (76)/134 (12) |
| **meconium-stained amniotic fluid**, *n* (%) | 153 (14) |
| **twin**, *n* (%) | 38 (4) |
| **non-optimal start** [f], *n* (%) | 94 (9) |
| **admission to neonatal ward**, *n* (%) | 241 (22) |
| **hyperbilirubinemia requiring phototherapy**, *n* (%) | 39 (4) |
| perinatal risk score, median (min-max) | 2 (0-11) |

Bold denotes the risk factors and their criteria included in the perinatal risk score (range 0-23, a higher score denotes a higher risk), presented at the bottom of the table.

Missing data: maternal educational level n=2; paternal educational level n=41; maternal occupational level n=10; paternal occupational level n=47; paternal ethnicity n=22; maternal age n=2; paternal age n=30; maternal BMI n=3; maternal smoking, prenatal substance exposure, maternal medication, diabetes, hypertension, thyroid disease, instrumental delivery, gestational age, admission neonatal ward, hyperbilirubinemia requiring phototherapy n=1; birth weight (SGA/AGA/LGA) n=3; meconium-stained amniotic fluid n=3; non-optimal start n=2. Note: in case of missing information of a risk factor, a score 0 (no risk) was assigned in the computation of the perinatal risk score.

[a] I = no or only primary education / II = primary or secondary vocational education and training / III = secondary vocational training, senior general secondary education and university preparatory education / IV = vocational college and university.

[b] Based on the International Standard Classification of Occupations, ISCO. I = ISCO1 and unemployed / II = ISCO2 / III = ISCO3 / IV = ISCO 4.

[c] Native Dutch: location of birth is the Netherlands. Non-native Dutch: location of birth is other than the Netherlands. Non-native Dutch is considered a risk factor since non-native Dutch women experience culture and language barriers in their access to the Dutch obstetric system, reflected in an increased perinatal mortality of infants born in non-native Dutch families compared to native Dutch families.[33,34]

[d] One of the following: hormonal treatment n=23, intrauterine insemination n=19, IVF/ICSI n=30, other n=7.

[e] Caesarean section n=193, vacuum or forcipal delivery n=95.

[f] The presence of delayed onset of crying, respiratory difficulties requiring monitoring on the neonatal ward and/or respiratory intervention, short-lasting floppiness or cyanosis.

**TABLE 2** CLINICAL CHARACTERISTICS OF INFANTS WITH ATYPICAL MUSCLE TONE IN FOUR BODY PARTS OR ASYMMETRICAL MUSCLE TONE IN TWO BODY PARTS

| *infant no.* | *gender* | *muscle tone pattern** | *corrected age (months)* | *GA (weeks)* | *birth weight (grams)* | *SGA/ AGA/ LGA* | *twin* | *maternal history* | *perinatal and neonatal events* | *medical diagnosis* |
|---|---|---|---|---|---|---|---|---|---|---|
| **infants with atypical muscle tone in four body parts (*n*=15)** | | | | | | | | | | |
| **1** | F | 2222 | 2 | 39.9 | 3098 | AGA | n | n | HB, no PhT | sickle cell anaemia |
| **2** | F | 2222 | 2 | 38.7 | 3660 | AGA | n | depression for which antidepressant drugs; IUI | NICU admission due to respiratory distress; HB, no PhT | general developmental delay and dysmorphic features (no established genetic diagnosis) |
| **3** | F | 2222 | 2 | 34.6 | 2700 | AGA | n | 7 miscarriages | placenta praevia; maternal blood loss; emergency CS | n |
| **4** | M | 2222 | 7 | 36.7 | 3712 | LGA | n | n | HB, no PhT | n |
| **5** | F | 2222 | 9 | 39.9 | 3300 | AGA | n | n | HB, no PhT | n |
| **6** | F | 2222 | 8 | 41.4 | 4180 | AGA | n | hypertension | HB, no PhT | n |
| **7** | M | 2222 | 10 | 36.7 | 1900 | SGA | y | hypertension, pre-eclampsia | ward admission due to prematurity | n |
| **8** | F | 2222 | 12 | 40.6 | 3910 | AGA | n | n | HB, no PhT | n |
| **9** | M | 2222 | 11 | 38.9 | 4032 | LGA | n | n | HB, no PhT | n |
| **10** | M | 2224 | 9 | 39.6 | 3630 | AGA | n | n | HB, no PhT | n |
| **11** | F | 2343 | 5 | 40.3 | 3680 | AGA | n | n | neonatal hypotonia | trisomy 21 |
| **12** | F | 2444 | 11 | 39.3 | 3500 | AGA | n | gestational diabetes | emergency CS after non-successful VE due to non-progressive labour; non-optimal start; pneumothorax | n |
| **13** | F | 3444 | 7 | 37.4 | 3966 | LGA | n | gestational diabetes treated with metformin and insulin | neonatal hypoglycaemia | n |

**TABLE 2** CLINICAL CHARACTERISTICS OF INFANTS WITH ATYPICAL MUSCLE TONE IN FOUR BODY PARTS OR ASYMMETRICAL MUSCLE TONE IN TWO BODY PARTS (CONTINUED)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **14** | M | 4444 | 3 | 31.0 | 1500 | AGA | y | depression treated with antidepressant drugs | PROM; HB requiring PhT, NICU admission; neonatal infection; IVH grade 1 | n |
| **15** | M | 4444 | 5 | 40.9 | 3115 | SGA | n | gestational diabetes | n | n |
| **infants with asymmetrical muscle tone in two body parts (*n*=2)** | | | | | | | | | | |
| **16** | M | 1331 | 5 | 38.3 | 3490 | AGA | n | n | HB, no PhT | n |
| **17** | M | 1144 | 6 | 40.7 | 3900 | AGA | n | n | forceps delivery; respiratory problems requiring CPAP | n |

F: female. M: male. S/A/LGA: small/appropriate/large for gestational age. n: no/none. y: yes. IUI: intrauterine insemination. HB: hyperbilirubinemia. PhT: phototherapy. CS: caesarean section. VE: vacuum extraction. PROM: premature rupture of membranes. IVH: intraventricular haemorrhage.

* 2222: overall hypotonic. 2224: hypotonic trunk, arms and legs, changing tone ankles. 2343: hypotonic trunk, hypertonic arms and ankles, changing tone legs. 2444: hypotonic trunk; changing tone arms, legs and ankles. 3444: hypertonic trunk, changing tone arms, legs and ankles. 4444: overall changing tone. 1331: typical tone trunk, hypertonic arms and legs (right side), typical tone ankles. 1144: typical tone trunk and arms, changing tone legs and ankles (left side).

## Prevalence of atypical muscle tone and muscle tone patterns

A total of 464 infants (42%) had typical muscle tone in all body parts ('optimal pattern'; muscle tone domain score 4). Atypical muscle tone in one body part was present in 360 infants (33%), atypical tone in two body parts in 184 (17%). Atypical muscle tone in three or four body parts was present in 92 infants (8.4%; 'impaired pattern'). Fifteen of the latter infants (1.4% of the total group) had atypical muscle tone in all body parts (muscle tone domain score 0): nine showed hypotonia in all body parts, two infants had changing muscle tone in all body parts, and four infants had combinations of hypotonia, hypertonia and changing muscle tone. The clinical data of these 15 infants are shown in Table 2.

Asymmetry in muscle tone had a low prevalence: nine infants (0.8%) showed asymmetry in muscle tone in the arms, eight (0.7%) in the legs, and 34 (3.1%) in the ankles. Two infants had a consistent asymmetry in two body parts (arms and legs; legs and ankles). These two infants had generalized muscle tone impairment; they are included in Table 2.

The five most prevalent atypical patterns are depicted in Figure 1. These patterns cover 284 out of 636 (45%) of the infants with atypical tone: (1) isolated hypotonia in the legs, i.e., hypotonic legs combined with typical tone in the rest of the body (*n*=91, 8%); (2) isolated hypertonia in the arms (*n*=78, 7%); (3) isolated hypertonia in the ankles (*n*=57, 5%); (4) hypotonic legs and hypotonic ankles combined with typical tone in neck, trunk and arms (*n*=33, 3%); (5) isolated changing muscle tone in the legs (*n*=25, 2%).

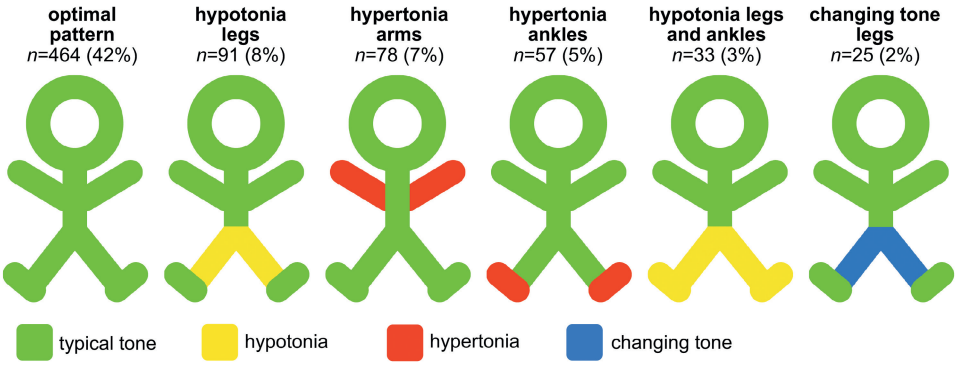


**FIGURE 1** MOST PREVALENT MUSCLE TONE PATTERNS

Note that not all infants are included in the figure: only the prevalence numbers are reported of the infants presenting either with an 'optimal pattern' or one of the 5 most prevalent muscle tone patterns. SINDA neurological scores in the various groups (median and interquartile range): optimal pattern: 27 (26-27); hypotonic legs: 26 (25-27); hypertonic arms: 25 (24-26); hypertonic ankles: 25 (24-26); hypotonic legs and ankles: 24 (23-26); changing tone in legs: 25 (25-26).

## Associations between muscle tone and age

The prevalence of the two most common patterns with hypotonia in the lower extremities was age-dependent: the presence of isolated hypotonia in the legs, and hypotonia in both legs and ankles increased with age (ρ=0.648; p=0.031 and ρ=0.896; p<0.001, respectively). The prevalence of both patterns especially rose after the age of 5 months: the prevalence of isolated hypotonia in the legs was 3% at 2-5 months and 11% at 6-12 months, that of hypotonia in both legs and ankles 0% at 2–5 months and 5% at 6-12 months. None of the other muscle tone patterns, including the optimal and the impaired pattern, were associated with age (range ρ=0.584-0.568; p=0.059-0.719). Also, the muscle tone domain score was not associated with age (ρ=0.037, p=0.226).

## Associations between muscle tone and perinatal risk score

The median perinatal risk score of the study group was 2 (range 0-11; Table 1), reflecting the group's low perinatal risk. Lower, i.e., worse muscle tone domain scores were weakly associated with a higher perinatal risk score (ρ=-0.069; p=0.023). The majority of the muscle tone patterns described above were not associated with the perinatal risk score (Mann-Whitney, p=0.302–0.840). The only exception was the pattern consisting of isolated hypertonia in the arms: infants with this type of atypical muscle tone had a significantly higher perinatal risk score than infants with optimal muscle tone (median scores 3 versus 2; Mann-Whitney, p=0.013). Multivariable analysis revealed that the single factors that contributed most to this pattern were low maternal occupational level (OR 2.20 [1.26-3.84]) and admission to the neonatal ward (OR 1.80 [1.03-3.12]). Three of the atypical patterns were associated with a single perinatal risk factor: hypotonic legs were associated with low maternal occupational level (OR 1.94 [1.14-3.29]), hypertonic ankles with maternal medication during pregnancy (OR 2.61 [1.21-5.60]), and hypotonic legs and ankles with preterm birth (OR 3.27 [1.16-9.23]).

The impaired pattern (atypical muscle tone in three or four body parts, n=92) was not associated with the perinatal risk score (Mann-Whitney, p=0.186). However, multivariable analysis of the single perinatal risk factors indicated an association between the presence of the impaired pattern and preterm birth (OR 1.94 [1.23-3.05]) and having a birthweight that was either small or large for gestational age (birthweight <10th and >90th percentile, respectively; OR 2.52 [1.34-4.75]).

## Relation between muscle tone and SINDA scores

Infants with isolated hypertonia in the arms, those with isolated hypertonia in the ankles, and those with atypical muscle tone in three or four body parts (i.e., the impaired pattern) had lower scores on the domain of spontaneous movements than infants with optimal muscle tone (Mann-Whitney, p=0.022, p=0.027, p<0.001, respectively). Infants with isolated hypertonia in the arms and those with the impaired pattern had lower scores on the domain of motor reaction to postural stimulation than infants with optimal tone (Mann-Whitney, p=0.001 and p<0.001). Finally, infants with hypotonia in legs and ankles, and infants with the impaired pattern had lower scores on the domain of reflexes than infants with optimal tone (Mann-Whitney, p=0.015 and p=0.017, respectively). Infants with the impaired pattern (i.e., atypical muscle tone in 3-4 body parts) had significantly lower developmental scores than the rest of the study group

(medians 9 versus 10; Mann-Whitney, p<0.001). The five most prevalent atypical muscle tone patterns were not associated with the developmental score.

## DISCUSSION

This cross-sectional study demonstrated that about 8% of the infants of the general Dutch population have an impaired muscle tone pattern, that is, atypical muscle tone in three of four body parts. The prevalence of atypical muscle tone in one or two body parts was relatively high (50%). The most prevalent atypical patterns were isolated hypotonia in the legs (8%) and isolated hypertonia in the arms (7%). Asymmetries in muscle tone had a relatively low prevalence (4.5%) and were usually restricted to one body part. Asymmetries in two or more body parts weakly associated with the infant's age. Most atypical muscle tone patterns showed a minor association with perinatal risk, whereas isolated hypertonia in the arms and atypical muscle tone in three or four body parts (the impaired pattern) were moderately associated with perinatal risk. Only the impaired pattern was associated with lower developmental scores.

The high prevalence of 1-2 signs of atypical muscle tone corresponds well to other reports that children with a typical neurological condition often show some signs of non-optimality. This is true for children at any age.[21-24]

The prevalence of about 8% of atypical muscle tone in three or four body parts is in line with the prevalence of muscle tone abnormalities of 10% reported in older children, including children with evident neuropathology and children with minor neurological dysfunction.[4,25] Atypical muscle tone was generally not associated with infant age. The exception to this rule was the higher prevalence of hypotonia of the lower extremities in the second half of the first year compared to that in the first half year. The second half of the first year of life is the period of 'physiologic astasia and abasia' - denoting the phase shown by most infants in which they do not bear weight on their legs and therefore cannot stand or walk, respectively,[26] i.e., the phase during which the infants do not bear weight on their legs when put in standing position. It signals the neural reorganization in anticipation of the major motor milestones of standing and walking independently.[27] It is conceivable that this reorganization results in hypotonia in the legs in part of the infants.

Two of the six atypical muscle tone patterns that we identified are of particular interest: isolated hypertonia in the arms and atypical tone in three or four parts of the body, i.e., the impaired pattern. Isolated hypertonia in the arms was among the patterns of isolated atypical tone the one that was most clearly associated with perinatal risk - low maternal occupational level and admission to the neonatal ward - and with accompanying neurological signs. It is known that the finding of atypical tone is especially relevant when it is accompanied by other neurological signs.[7,8,13] It is conceivable that the association between perinatal risk and hypertonic arms in combination with additional neurological signs is due to dysfunction in the motor cortex

representing the arms.[13,28] This part of the brain is a so-called watershed area, which is relatively easily prone to injury.[29]

The pattern that is clinically most relevant is the impaired pattern, i.e., atypical tone in three or four parts of the body. This group also comprised the infants with an asymmetrical muscle tone in more than one body part. Atypical tone in three or four parts of the body was associated with preterm birth and a birthweight not appropriate for gestational age. Generally, these risk factors signal an unfavourable prenatal and perinatal condition that is associated with increased vulnerability of the nervous system.[30] Also, others observed that infants born preterm or with a low birthweight are at risk of muscle tone regulation problems.[31] The clinical significance of the impaired tone pattern is underlined by its association with lower neurological and developmental SINDA scores. Lower SINDA scores are associated with a higher risk of developmental disorders.[17,18]



A strength of the current study is the large study group of 1100 infants representative of the Dutch population. To our knowledge, this is the first study describing atypical muscle tone patterns in infancy and therewith exploring which muscle tone patterns may be clinically relevant. Another strength is the use of a standardized assessment to evaluate muscle tone: the SINDA.[17-18] A limitation of the study is its cross-sectional character - which was inherent to its primary aim of reporting prevalence numbers - and lack of follow-up data. It is known that muscle tone abnormalities in infancy may be transient and have no clinical significance, while other tone deviancies may emerge with age.[32] This means that long term follow-up is warranted. The follow-up of our participants at the age of 4-5 years is currently planned.

In conclusion, during the first year a high proportion of infants presents with atypical muscle tone in one or more body parts. In general, the atypical tone has little clinical significance. However, the pattern of isolated hypertonia in the arms was associated with perinatal risk. Its long-term significance deserves further study. Eight percent of infants presented with atypical muscle tone in three or four body parts. This pattern is clinically relevant: it is associated with an increased risk of developmental disorders. For these infants, further medical diagnostics are recommended.

## DECLARATION OF COMPETING INTEREST

none

## ACKNOWLEDGEMENTS

We thank all infants and parents who participated in the IMP-SINDA project. We acknowledge the assistance of the medical students and research assistants of the Kinderacademie Groningen in data collection. We also gratefully acknowledge the technical assistance of Anneke Kracht-Tilman.

## FUNDING

The study was supported by the CorneliaStichting and the Stichting Ontwikkelings-neurofysiologie Groningen.

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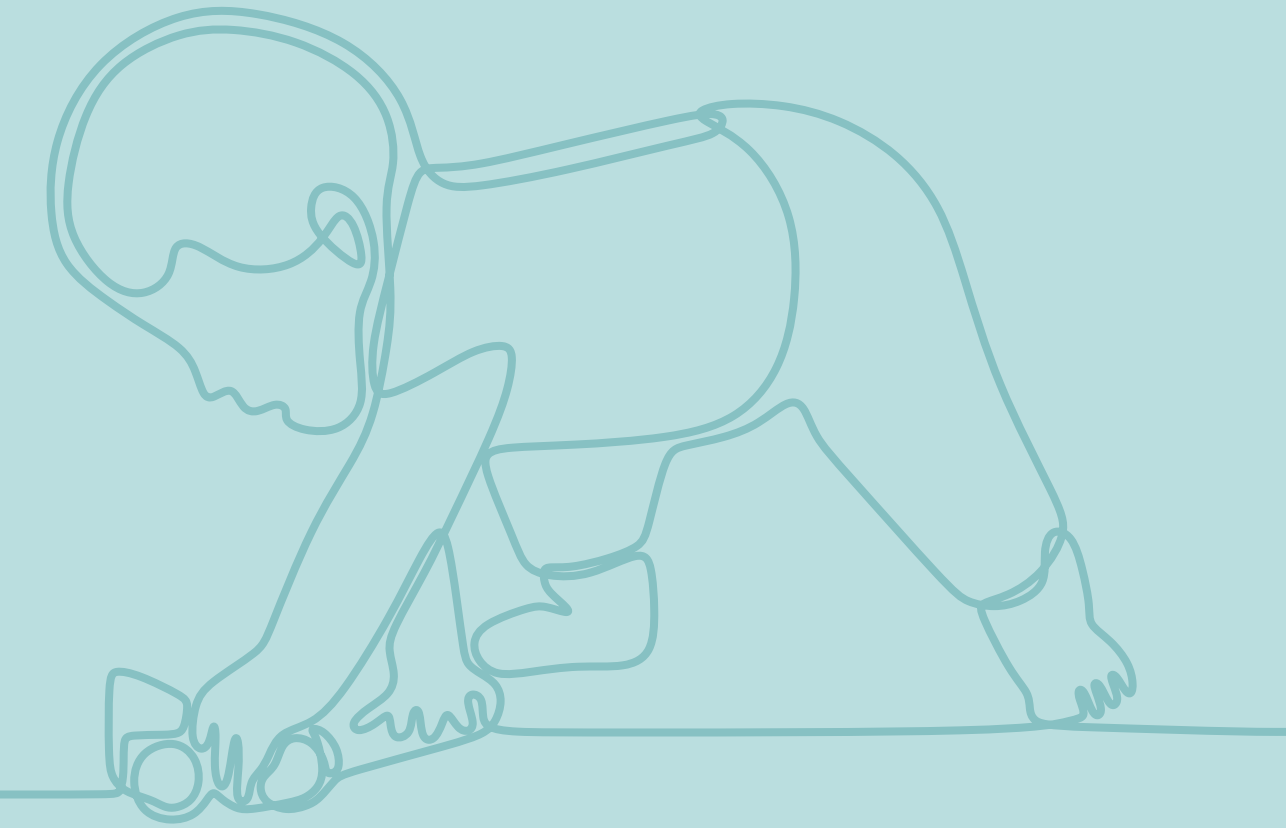
# Part 2

## Neurological signs and later outcome in children at very high risk of cerebral palsy



# 4

# Development of muscle tone impairments in high-risk infants: associations with cerebral palsy and cystic periventricular leukomalacia

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*European Journal of Paediatric Neurology 2022; 37: 12-18*

*doi: 10.1016/j.ejpn.2021.12.015*

## ABSTRACT

**Aim**: To assess the prevalence and development of muscle tone impairments in infants at high risk of developmental disorders, and their associations with cerebral palsy (CP) and cystic periventricular leukomalacia (cPVL).

**Method**: Longitudinal exploration of muscle tone in 39 infants at high risk of CP (LEARN2MOVE 0-2 project) mostly due to an early lesion of the brain. Muscle tone was assessed ≥4 times between 0-21 months corrected age (CA) with the Touwen Infant Neurological Examination. Diagnosis of CP was determined at 21 months CA. Neonatal neuro-imaging was available. Developmental trajectories were calculated using generalized linear mixed effect models.

**Results**: Infants showed atypical muscle tone in three or four body parts in 93% (172/185) of the assessments. The most prevalent muscle tone pattern was hypotonia of neck and trunk with hypertonia of the limbs (28%). From 7 months CA onwards hypertonia of the arms was associated with CP. Asymmetric arm tone during infancy was associated with unilateral CP. At 18-21 months CA ankle hypertonia was associated with CP at 21 months; leg hypertonia in infancy was not associated with CP. Leg hypertonia was associated with cPVL, regardless of age.

**Interpretation**: High-risk infants due to an early lesion of the brain often present with muscle tone impairment. In these infants, hypertonia and asymmetric muscle tone of the arms were from 7 months onwards associated with the diagnosis of CP at 21 months; hypertonia of the legs was not.


### HIGHLIGHTS

- High-risk infants have a high prevalence of muscle tone impairments (>90%)
- Axial hypotonia with limb hypertonia is most common pattern in high-risk infants
- From 7 months onwards arm hypertonia was associated with CP
- Asymmetrical muscle tone of the arms was associated with unilateral CP
- Hypertonia of the legs was associated with cPVL


### KEYWORDS

infancy, cerebral palsy, hypertonia, hypotonia, muscle tone

# INTRODUCTION

Muscle tone regulation is one of the building blocks of motor control and therefore atypical muscle tone affects motor development.[1] Muscle tone is brought about by a constant feedback loop between the peripheral and central nervous system. When the feedback loop is interrupted, for example due to an early lesion of the brain, atypical muscle tone may occur.[2]

Atypical muscle tone is a key symptom in the diagnosis of cerebral palsy (CP).[3] However, it takes developmental time before the clinical picture of CP, including its atypical muscle tone, is established. The median age of diagnosis is 11 months and varies between 6 months and 5 years or later.[4] Infants at high risk of CP or other neurodevelopmental disorders may show atypical muscle tone that varies in type, severity and occurrence over time.[5-6] Recent guidelines recommend a combination of clinical tools for the early detection of CP, including neonatal magnetic resonance imaging (MRI), general movement assessment and a standardized infant neurological examination.[7] The latter is relevant since the diagnosis of CP is a clinical one, i.e., based on the clinical and neurological signs. In addition, it is important to realize that in the majority of infants at risk of neurodevelopmental disorders neonatal MRIs are lacking.[8]



Hypotonia in a single part of the body is rather prevalent in the general infant population.[9-10] Without other accompanying neurological signs, it has little clinical significance.[11] However, hypotonia present from birth onwards, and persisting hypotonia during infancy warrant clinical attention. Infants later diagnosed with CP, for example due to periventricular leukomalacia (PVL), may present with generalized neonatal hypotonia that gradually changes into hypertonia during the first year of life, mainly in the extremities.[10] In these infants, hypotonia in neck and trunk often persists throughout infancy.[12]

Hypertonia in infancy is less common. It raises clinical attention when present from birth onwards, as it may be an indicator of severe neurological pathology.[13] Probable causes are brain lesions, for example lesions of the cerebral cortex or white matter; lesions that are also risk factors for the development of CP.[13] However, infants who later get diagnosed with spastic CP often do not present with hypertonia in early life.[10, 13-14] Hypertonia often emerges with increasing age.[12,15] In a Swedish registry population of children with CP, the prevalence of spasticity of the gastrocnemius muscle rose from 25% at 1 to 38% at 5 years of age.[16] In infants later diagnosed with unilateral CP hypertonia in the extremities on one side of the body generally emerges with increasing age.[12]

Knowledge on the early development of muscle tone impairments is scarce. Yet, such knowledge is needed to understand the development of spasticity, a core symptom of most children with CP. In addition, such knowledge is important information for family counselling.[8,17] To the best of our knowledge no studies exist that longitudinally assessed muscle tone impairments in infants with an early brain lesion. The LEARN2MOVE 0-2 years project (in short: L2M0-2) offered an opportunity to evaluate which developmental trajectories of atypical muscle tone are associated with CP at

21 months corrected age (CA). In L2M0-2, infants were assessed longitudinally with standardized neurological examinations during their first 21 months after term age. In these very high-risk infants we addressed the following questions: (1) What is the prevalence of specific types of atypical muscle tone, e.g., hypotonia of neck and trunk, hypertonia in the legs, or asymmetric muscle tone?; (2) Are specific types of atypical muscle tone associated with an increased risk of CP and if so, from which age onwards?; (3) Are specific types of atypical muscle tone associated with specific brain lesions, in particular cystic periventricular leukomalacia (cPVL), i.e., the brain lesion most strongly associated with CP,[18] and if so, is the association related to the infants' age at the neurological assessment?

# MATERIALS AND METHODS

## Study design and participants

This exploratory study is part of L2M0-2, a randomized controlled trial to evaluate the effect of two different forms of early intervention in infants at high risk of CP. Neurological outcome in both groups was similar.19 Inclusion criteria of L2M0-2 were age at enrolment between 0-9 months CA and the presence of at least one of the following conditions: 1) cystic periventricular leukomalacia (cPVL); 2) parenchymal lesion of the brain; 3) neonatal hypoxic-ischaemic encephalopathy with brain lesions on MRI; and 4) neurological dysfunctions suggestive of development of CP. Infants with severe congenital disorders or having caregivers with insufficient comprehension of the Dutch language were excluded. Forty-three infants were included between 2008 and 2013.[19] L2M0-2's study design was approved by the Medical Ethical Committee of the University Medical Center Groningen (METc 2008.176) and registered in the Dutch trial register (NTR1428). Parents gave informed consent.

## Brain imaging

All infants underwent neonatal brain imaging (mostly MRI) as part of standard clinical care (see Table 1). An experienced paediatric neurologist blinded to clinical data classified brain imaging data based on the predominant pattern: a) periventricular leukomalacia (PVL; cystic and non-cystic), b) cortical infarction (full-term border-zone infarction or middle cerebral artery infarction), c) posthaemorrhagic porencephaly, d) basal ganglia or thalamic lesions, and e) non-specific lesions (e.g., ventriculomegaly) or no lesions.[20]

## Neurological assessment

Infants were assessed five times: at inclusion (T0), after 3 (T1), 6 (T2), and 12 (T3) months, and at 21 months CA (T4). For some infants, T3 and T4 coincided. Infants with four or five neurological assessments during the study period were included in the current study (n=39). For descriptive purposes, the assessment moments were reclassified into the following (corrected) age categories: i) 0-3 months (n=29); ii) 4-6 months (n=36); iii) 7-9 months (n=35); iv) 10-12 months (n=19); v) 13-17 months (n=28); and vi) 18-22 months (n=38), resulting in a total of 185 neurological assessments. If infants had two assessments within one age category (n=4), only the assessment performed at the oldest age was included into the descriptive analyses.

At each time point, infants were neurologically assessed with the Touwen Infant Neurological Examination (TINE). TINE is one of the standardized infant neurological assessments with good psychometric properties, including a good reliability (inter-assessor agreement κ=0.83, 95% CI 0.68–0.99). Its validity has been established in term and preterm infants, which makes it suitable for the neurological evaluation of infants at risk of neurological disorders with different aetiologies.[21] According to TINE, muscle tone was assessed by evaluating resistance to passive movements in each of the following body parts separately: neck/trunk, arms, legs, and ankles. Muscle tone was reported as i) typical, or atypical: ii) hypotonia; iii) hypertonia; or iv) changing tone, the latter indicating a varying muscle tone. In case of asymmetry between left and right extremity, its presence was recorded and muscle tone of the worst side was assigned in the analyses. At the final assessment (18-22 months CA) the diagnosis of CP was made based on the TINE. In infants diagnosed with CP, motor function was classified using the Gross Motor Function Classification System (GMFCS).[22] In infants without CP neurological condition was assessed with the Hempel examination.[23] This standardized assessment focuses on the presence of minor neurological dysfunction (MND), i.e., neurological dysfunction without evident neurological pathology, such as CP. The Hempel examination evaluates signs in five domains of function: fine motor function, gross motor function, posture and muscle tone, reflexes and visuomotor function. When domain specific criteria are met, a domain is classified as atypical. Children are classified as neurologically normal when none of the domains is atypical, as simple MND (sMND) when one domain is atypical and complex MND (cMND) when more than one domain is atypical.[24] sMND represents a non-optimal but normal brain function, whereas cMND is considered the clinically relevant form of MND, since it is clearly associated with perinatal adversities, and learning and behavioural problems.[25]



## Statistical analyses

Muscle tone was dichotomized into hypertonia and other muscle tone (see results section). Type of brain lesion was dichotomized into present or absent cystic PVL (cPVL). Descriptive statistics were performed with SPSS, version 26. Generalized linear mixed effects model analyses, including all assessments at their exact CA's, were performed to evaluate associations between the developmental trajectories of those muscle tone patterns that showed most clear associations with CP in the univariable analyses, and CP and cPVL, using R version 3.6.3.[26] Random subject effects were incorporated to account for repeated assessments within an infant. Fixed effects were included for time (age), group (CP versus no CP, and cPVL versus non-cPVL) and interaction between age and group. From these subject specific models, time profiles were created describing the average developmental trajectory of the muscle tone impairment per group. Using these profiles, the earliest age was calculated at which the difference between the groups became statistically significant. P-values <0.05 were considered statistically significant.

# RESULTS

## Background characteristics

Background characteristics of the study group are shown in Table 1. The high-risk nature of the group is reflected by a median gestational age of 30.9 weeks, with almost 75% infants born preterm (< 37 weeks). The most prevalent brain lesions were posthaemorrhagic (n=10) porencephaly and cystic PVL (n=9; Table 1). At 21 months CA, 20 infants (51%) were diagnosed with CP; 19 (49%) were not. The 20 infants with CP had spastic CP; 5 of them had unilateral CP, 15 had bilateral CP. The majority of children without CP (11/19) were diagnosed with cMND.

**TABLE 1** BACKGROUND CHARACTERISTICS

| | total (n=39) |
|---|---|
| sex (girls/boys), n | 15 / 24 |
| gestational age, weeks (median + range) | 30.9 (25.9 - 41.4) |
| preterm birth (GA < 37 weeks), n (%) | 28 (72) |
| birth weight, grams (median + range) | 1788 (720 - 5400) |
| neonatal brain imaging, n | |
| MRI / cranial ultrasound | 33 / 6 |
| type of brain lesion, n (%) | |
| periventricular leukomalacia | 13 (33) |
| cystic | 9 (23) |
| non-cystic | 4 (10) |
| cortical infarction | 3 (8) |
| posthaemorrhagic porencephaly | 10 (26) |
| basal ganglia / thalamic lesion | 6 (15) |
| no / nonspecific lesion | 7 (18) |
| neurological outcome at 21 months CA, n (%) | |
| no CP | 19 (49) |
| typical | 1 (3) |
| sMND | 5 (13) |
| cMND | 11 (28) |
| no Hempel assessment | 2 (5) |
| CP | 20 (51) |
| unilateral / bilateral | 5 / 15 |
| GMFCS I / II / III / IV / V | 3 / 7 / 4 / 3 / 3 |

## Prevalence of atypical muscle tone in the various body parts

The neurological vulnerability of the study group was reflected by the high prevalence of atypical muscle tone: in 172 out of the 185 assessments (93%), infants had an atypical muscle tone in three or four body parts (Figure 1). We observed a high heterogeneity in muscle tone patterns throughout infancy (45 different patterns; Supplementary Material S1).

In the neck and trunk, hypotonia was the most frequently observed muscle tone impairment. Its prevalence varied between 93% at 0-3 months (27/29) and 68% at 10-12 months (13/19). In the arms, hypertonia was the most frequently observed deviation in muscle tone. Its prevalence decreased with increasing age from 76% at 0-3 months (22/29) to 35% at 18-22 months (13/38). In the legs, hypertonia was the most frequently observed muscle tone impairment up to and including 17 months. Its prevalence decreased from 86% at 0-3 months (25/29) to 39% at 13-17 months (11/28). At 18-22 months, hypotonia was the most frequently observed muscle tone impairment in the legs with a prevalence of 47% (18/38). In the ankles, hypertonia was the most frequently observed impairment in muscle tone, fluctuating between 91% at 7-9 months (32/35) and 63% at 18-22 months (24/38).



The most frequently observed muscle tone pattern in the total of 185 assessments was hypotonia of the neck and trunk in combination with hypertonia of arms, legs and ankles (28%). Its prevalence decreased with increasing age: from 62% at 0-3 months CA (18/29) to 8% at 18-22 months CA (3/38).

Inspection of the raw data presented in Figure 1 indicates that hypotonia in neck and trunk, whether or not in combination with hypertonia of the extremities, continued to be highly prevalent in all infants, therewith not differentiating between children later diagnosed with CP or not. The figure also indicates that hypertonia was the most prevalent muscle tone classification in the extremities and that this might be associated with the diagnosis of CP. We therefore analysed the developmental changes in the prevalence of hypertonia in the extremities in more detail, including their associations with CP and brain lesion.

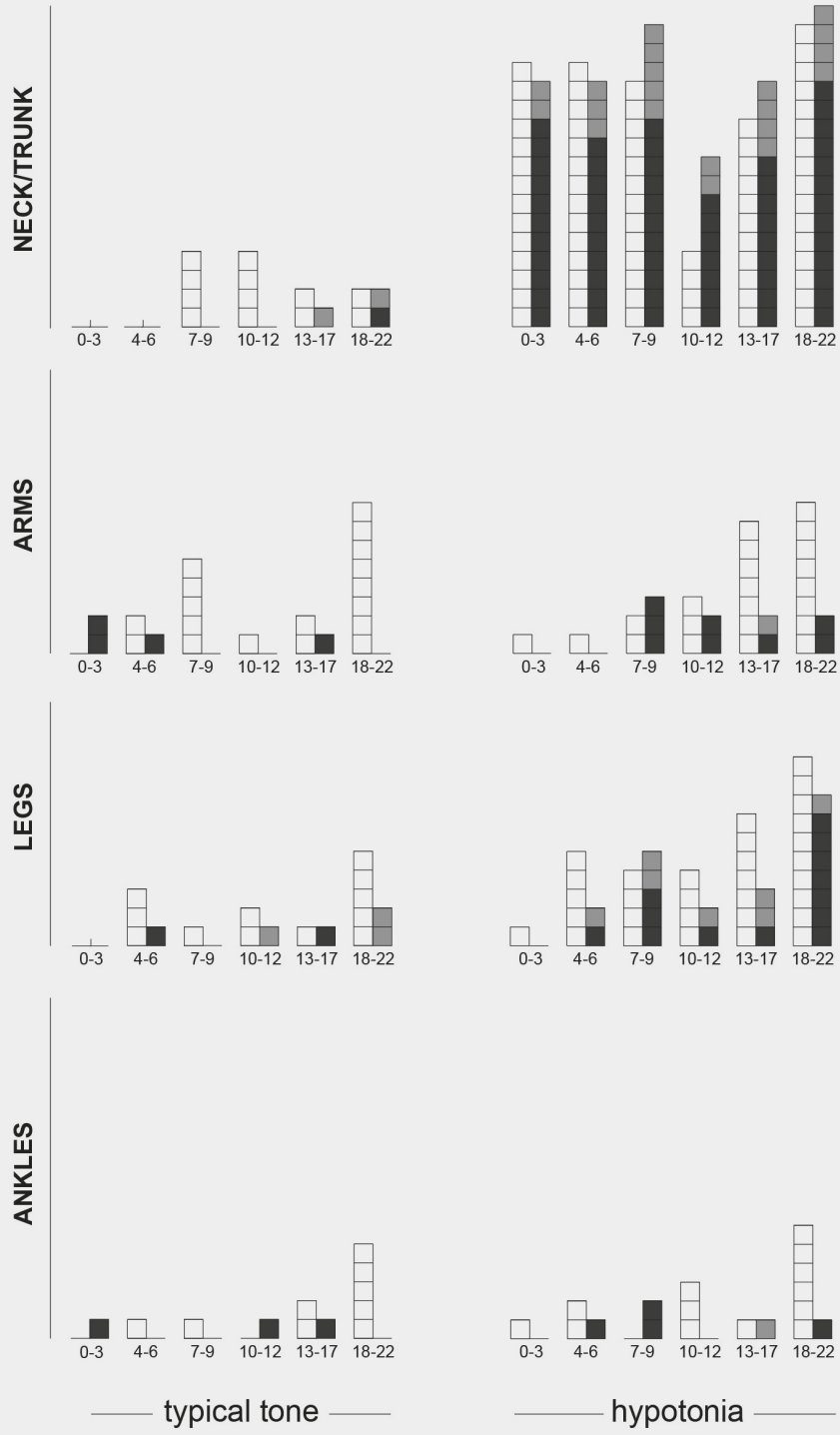
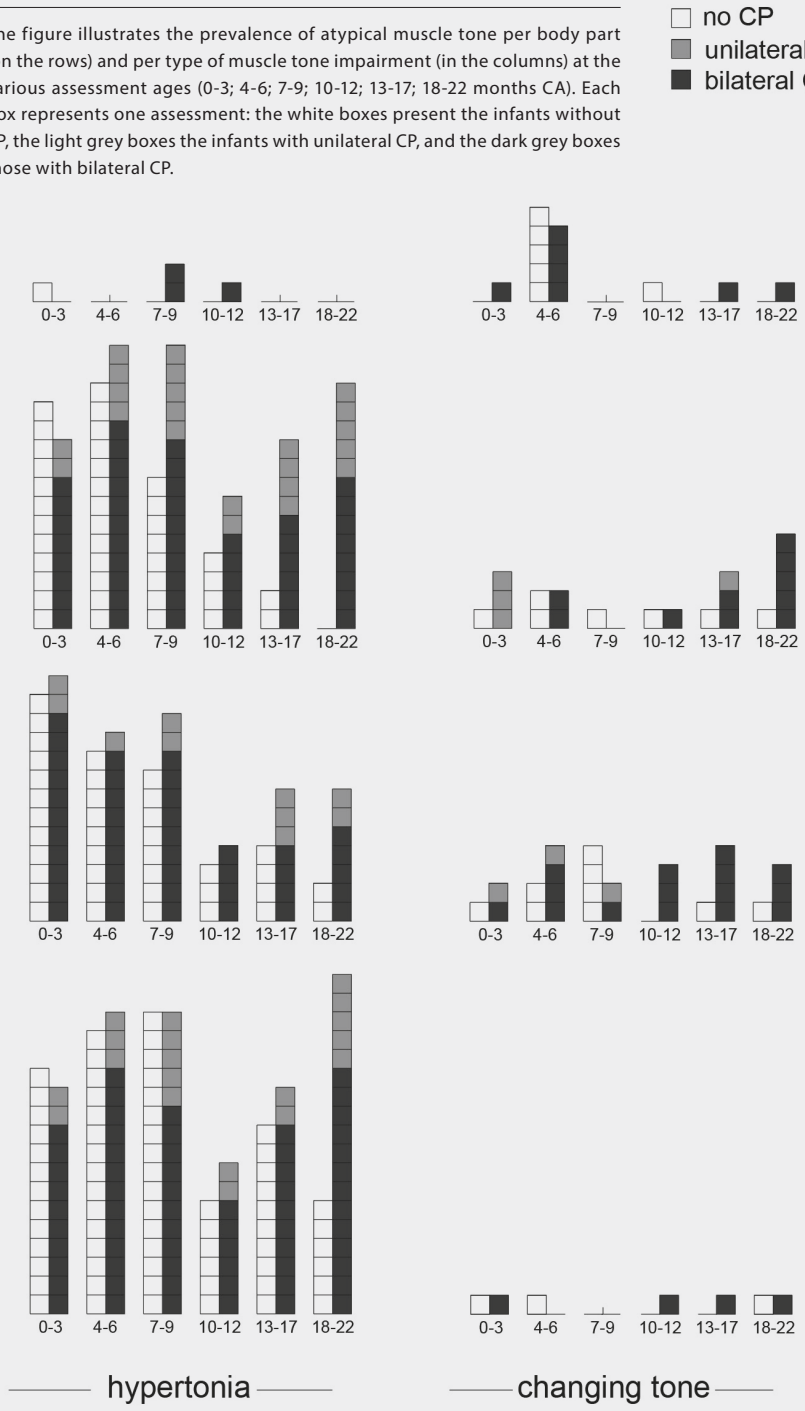

NECK/TRUNK
ARMS
LEGS
ANKLES
0-3
4-6
7-9
10-12
13-17
18-22
typical tone
hypotonia

**FIGURE 1** PREVALENCE OF ATYPICAL MUSCLE TONE IN VARIOUS BODY PARTS ACROSS INFANT AGE IN RELATION TO DIAGNOSIS OF CP

The figure illustrates the prevalence of atypical muscle tone per body part (on the rows) and per type of muscle tone impairment (in the columns) at the various assessment ages (0-3; 4-6; 7-9; 10-12; 13-17; 18-22 months CA). Each box represents one assessment: the white boxes present the infants without CP, the light grey boxes the infants with unilateral CP, and the dark grey boxes those with bilateral CP.



## Hypertonia in the extremities and CP

*Upper extremities*

Univariable analysis showed that the presence of arm hypertonia at 0-3 months CA was not associated with development of CP at 21 months CA: ten out of the 22 infants (45%) with hypertonia of the arms developed CP, while 57% (4/7) of the infants without hypertonia did develop CP (Figure 1; p=0.458). At 18-22 months, hypertonia of the arms was associated with CP: infants with hypertonic arms had a significantly higher prevalence of CP than the infants without hypertonia (100% vs 29%, p<0.001). The mixed effects models indicated that the developmental trajectories of infants who were and were not diagnosed with CP, started to differ at 7 months CA (OR 1.23, 95%CI 1.08-1.42; Supplementary Material S2). This means that from 7 months CA onwards, infants later diagnosed with CP had a significantly higher prevalence of hypertonia in the arms than infants without CP (Figure 2A). We paid special attention to asymmetries in arm muscle tone. Their prevalence varied between 10% (3/29) at 0-3 months to 34% (12/35) at 7-9 months. Further inspection of the data indicated that at 4-6, 7-9, 13-17, and - not surprisingly - at 18-22 months, unilateral arm hypertonia was associated with the diagnosis of unilateral CP (Table 2).

**TABLE 2** ASSOCIATIONS BETWEEN ASYMMETRICAL MUSCLE TONE AND UNILATERAL CP

| | | ARMS | | | LEGS | | | ANKLES | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | uni | no CP | p-value | uni | no CP | p-value | uni | no CP | p-value |
| 0-3 mo | asym | 0 | 1 | 1.000 | 0 | 8 | 0.471 | 1 | 8 | 1.000 |
| | no asym | 2 | 14 | | 2 | 7 | | 1 | 7 | |
| 4-6 mo | asym | 3 | 5 | **0.036*** | 0 | 6 | 0.526 | 2 | 11 | 1.000 |
| | no asym | 0 | 14 | | 3 | 12 | | 1 | 8 | |
| 7-9 mo | asym | 4 | 4 | **0.039*** | 3 | 4 | 0.274 | 5 | 11 | 0.266 |
| | no asym | 1 | 13 | | 2 | 13 | | 0 | 6 | |
| 10-12 mo | asym | 2 | 1 | 0.055 | 0 | 2 | 1.000 | 0 | 2 | 0.109 |
| | no asym | 0 | 8 | | 2 | 7 | | 2 | 7 | |
| 13-17 mo | asym | 3 | 1 | **0.044*** | 3 | 4 | 0.326 | 4 | 8 | 0.615 |
| | no asym | 2 | 12 | | 2 | 9 | | 1 | 5 | |
| 18-22 mo | asym | 3 | 1 | **0.012*** | 2 | 2 | 0.135 | 4 | 6 | **0.029*** |
| | no asym | 1 | 16 | | 2 | 16 | | 0 | 12 | |

This table is a compilation of small cross-tables (3rd / 5th / 7th column) that provide the raw numbers of infants with asymmetrical muscle tone in the various parts of the body and various ages. The crosstabs show the numbers of infants with and without asymmetrical muscle tone (presented in the rows) and the later diagnosis of unilateral CP or no CP (presented in the columns). Note that the table only includes the children with unilateral CP or no CP.
P-values are based on the Fisher's exact test. Significant associations in bold: * p<0.05. Asym: asymmetry. No asym: no asymmetry. Uni: unilateral CP.

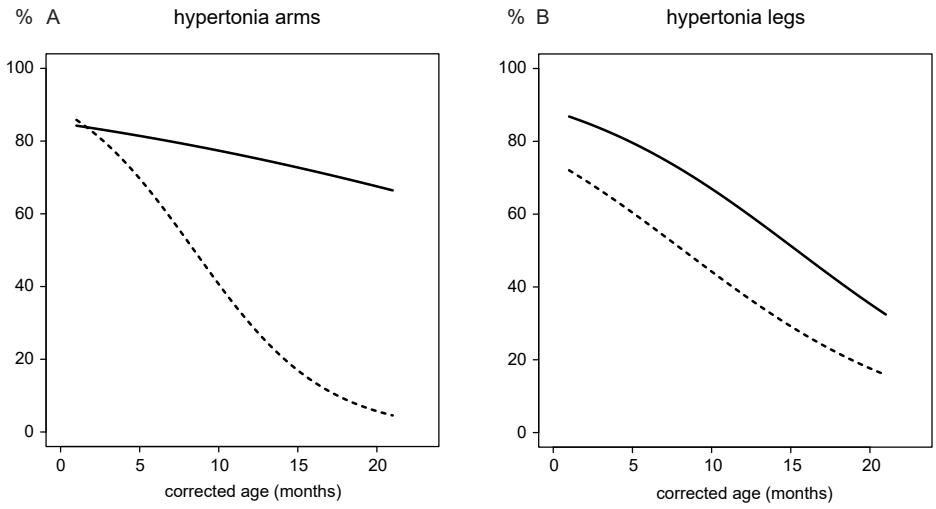





**FIGURE 2** DEVELOPMENT OF HYPERTONIA IN ARMS AND LEGS OF INFANTS WITH AND WITHOUT CP OR CPVL

Average developmental trajectories of A) of infants with hypertonia in arms in relation to the diagnosis of CP, and B) of infants with hypertonia in the legs in relation to the presence of cPVL. The x-axes present (corrected) age in months; the y-axes the percentage of infants showing hypertonia in either arms or legs. The continuous lines present trajectories of infants diagnosed with CP or cPVL, respectively. The dotted lines show trajectories of infants without CP or without cPVL, respectively.

*Lower extremities*

Univariable analysis showed that 13 infants (52%) of the 25 presenting with hypertonic legs at 0-3 months CA were later diagnosed with CP, while 1 of the 4 infants without hypertonia developed CP. In the infants with hypertonic legs at the age of 18-22 months, 78% (7/9) had CP, while 45% (13/29) of the infants without hypertonic legs was diagnosed with CP. At both time points, the presence of hypertonia was not significantly associated with CP (p=0.598 and 0.130, respectively). The mixed effects models also showed that there was no significant difference in probability of hypertonic legs between infants who were and were not diagnosed with CP (OR 2.16, 95%CI 0.99-5.08; Supplementary Material S2). The prevalence of an asymmetry in leg muscle tone decreased from 48% at 0-3 months (14/29) to 18% at 18-22 months (7/38). The asymmetries were not associated with a later diagnosis of unilateral CP (Table 2).

Figure 1 shows that 48% (12/25) of the infants with hypertonic ankles at 0-3 months CA developed CP, whereas 50% (2/4) of the infants without hypertonia did (p=1.000). Seventy-five percent (18/24) of the infants with hypertonic ankles at 18-22 months CA were diagnosed with CP, whereas 14% (2/14) of the infants without hypertonic ankles were. This difference was statistically significant (p=0.001). Yet - as Figure 1 illustrates - at none of the younger ages was

hypertonia in the ankles associated with CP. The prevalence of an asymmetry in ankle muscle tone fluctuated between 42% at 10-12 months (8/19) and 18-22 months (16/38), and 63% at 7-9 months (22/36). Only at the age of the diagnosis of CP, unilateral CP was associated with a unilateral ankle hypertonia (Table 2).

### Hypertonia in the extremities and cPVL

The mixed effects models indicated that the prevalence of hypertonic arms in infants with cPVL resembled that of infants without cPVL (OR 1.58, 95%CI 0.41-6.28; Supplementary Material S2). The mixed effects models indicated that from the earliest assessment age onwards hypertonia in the legs was more frequently found in infants with cPVL than in infants without cPVL (OR 2.61, 95%CI 1.03-7.16; Supplementary Material S2). This difference did not change with increasing age, also shown by the more or less parallel lines in panel B of Figure 2. Univariable analysis indicated that at none of the assessment ages cPVL was associated with ankle hypertonia. For instance, at 0-3 months, seven out of eight infants (88%) with cPVL had hypertonia in the ankles and 18 out of 21 infants (86%) without cPVL (p=1.000). At 18-22 months, 89% (8/9) of the infants with cPVL had hypertonia in the ankles, versus 55% (16/29) of the infants without cPVL (p=0.115).

## DISCUSSION

The current study showed that infants at very high risk of a neurodevelopmental disorder - mostly due to a lesion of the brain – had a high prevalence and wide diversity of muscle tone impairments throughout infancy. The most prevalent muscle tone pattern was the combination of hypotonia of neck and trunk and hypertonia in the extremities occurring both in children with and without CP. During the first half year of life prevalence of specific types of muscle tone impairment did not differ between infants who were and who were not diagnosed with CP. From 7 months onwards, hypertonia in the arms was associated with CP. Asymmetrical arm muscle tone was associated with unilateral CP. Additionally, infants with cPVL had throughout infancy a higher prevalence of hypertonia in the legs than infants without cPVL.

Our data illustrate that some infants outgrow their initial muscle tone impairment, which is in line with the study of Chaudhari and co-workers, who reported a decreasing prevalence of muscle tone impairment during the first year in a mixed group of infants at risk.[27] The normalization of muscle tone could be a sign of full functional recovery of the nervous system or a transient phase in the development of other neurodevelopmental impairments, such as learning or behavioural disorders.[28] Nonetheless, in many children with an early brain lesion the muscle tone impairments persisted; around 21 months the large majority of children were diagnosed with CP or cMND, which included the presence of impaired muscle tone.

In our high-risk infants, muscle tone impairments during the first half year post-term had a high prevalence but did not predict CP. This may explain why a traditional neurological examination that pays relatively much attention to muscle tone, such as the Hammersmith Infant Neurological Examination[29] or the Amiel-Tison examination,[30] does predict CP in early infancy less well than general movement assessment.[31] It is well-known that early prediction of CP is best on the basis of an MRI at term age and a general movement assessment around 3 months CA.7,8 In older infants a standardized neurological assessment, such as HINE, is recommended.[7,8] This does not mean that we should not evaluate muscle tone at early age: muscle tone assessment remains an integral and important part of the neurological examination. Our results, however, do underline that it takes developmental time before neurological signs become specific.[8]

In our study, hypertonia in the arms was from 7 months onwards associated with CP and asymmetric arm muscle tone with unilateral CP. It is well known that in unilateral CP, increased muscle tone manifests especially in the arm.[15] The infants with asymmetric arm muscle tone had shown unilateral hypertonia as a precursor of unilateral CP. This means that part of the infants with unilateral CP contributed to the association between hypertonia in the arms and CP. Nonetheless, they were not entirely responsible for the association (Figure 1). Our results are in line with those of Ryll and colleagues, who recently reported that prediction of unilateral CP in infants with a specific high risk for unilateral CP on the basis of arm-hand activities can be reliably done from 3.5-4.5 months CA onwards, and that its diagnostic accuracy increases with increasing age.[32]

Muscle tone impairment in the lower extremities during infancy did not predict CP; only at the age of the diagnosis of CP hypertonia in the ankles was significantly associated with CP. Figure 1 shows that both infants with unilateral and bilateral CP contributed to this association. Muscle tone in the legs was not associated with CP. Our findings may be explained by the size of the cortical motor areas contributing to motor control of each of the three body parts: the area involved and its descending corticospinal projections in the control of arm movements is larger than that involved in control of the ankle and foot, which in turn is larger than that in charge of the leg.[33]

Our results also indicated that infants with cPVL had a higher prevalence of hypertonic legs than infants without this brain lesion, regardless of age. cPVL is a white matter lesion of the preterm brain that interferes with functioning of the corticospinal tract.[34] Damage of the white matter near the posterior parts of the lateral ventricles typically affects the motor fibres to the lower extremities.[15] This may explain why we did not find an association between cPVL and hypertonia in the arms. Despite the association between cPVL and hypertonia in the legs, hypertonic legs did not predict CP.

To the best of our knowledge, this is the first study describing the development of muscle tone in different body parts in infants at high risk of neurodevelopmental disorders and its association with CP. The study's major strength is the longitudinal data collection using a reliable infant neurological assessment: all infants were assessed at least four times throughout infancy. Additionally, information was available on neonatal brain imaging which enabled us to investigate possible relations between atypical muscle tone and cPVL. A limitation of the current study is the small size of the study group, implying that the results cannot be generalized. The brain imaging data were obtained as part of clinical practice, which in the Netherlands includes for infants at very high risk an MRI-scan. Worldwide MRI-scans are not always available for infants; in these situations, repeated neonatal cranial ultrasound scans form an adequate alternative to detect the infants' brain lesions.[35] In our study, the large heterogeneity in brain lesions and muscle tone patterns hampered subgroup analyses, for example exploration of muscle tone development in children with other brain lesions than cPVL (see Supplementary Material S1). The study's small sample size also implies that the findings of the study cannot be generalized.

## CONCLUSION

Our study underlines the importance of documenting development of atypical muscle tone as part of a standardized neurologic assessment, since it assists the prediction of CP. The study indicated that hypertonia in the arms is in high-risk infants from 7 months onwards associated with an increased risk of CP, and that asymmetric arm muscle tone is an early marker of unilateral CP. Hypertonia in the arms, either unilateral or bilateral, thus may serve early detection of CP and providing infants and families with proper early intervention.

### DECLARATION OF INTEREST

none

### ACKNOWLEDGEMENTS

We thank all the infants and their caregivers for participation in L2M0-2, that was part of the Dutch national LEARN2MOVE research program. We also gratefully acknowledge the technical assistance of Anneke Kracht-Tilman.

### FUNDING

L2M0-2 was part of the Dutch national LEARN2MOVE research programme and was supported financially by ZonMW (89000002), Johanna Kinderfonds, Stichting Rotterdams Kinderrevalidatie Fonds Adriaanstichting, Revalidatiefonds, Phelps Stichting, Revalidatie Nederland, and the Nederlandse Vereniging van Revalidiatieartsen. None of the funders were involved in study design, data collection, data analysis, manuscript preparation and/or publication decisions.

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**SUPPLEMENTARY MATERIAL S1** MUSCLE TONE FINDINGS PER INFANT AND BRAIN LESION

| | | | *muscle tone pattern per assessment* | | | | |
|---|---|---|---|---|---|---|---|
| **infant ID** | **brain lesion** | **neurological outcome** | 1 | 2 | 3 | 4 | 5 |
| 1 | cPVL | bi CP | 4333 | 2333 | 2333 | 4333 | 4444 |
| 2 | cPVL | bi CP | 2333 | 2443 | 2233 | 2443 | 2423 |
| 3 | cPVL | bi CP | 2333 | 4333 | 3333 | 2444 | 2433 |
| 4 | cPVL | bi CP | 2333 | 2343 | 2333 | 2333 | 2443 |
| 5 | cPVL | bi CP | 2433 | 2443 | 2222 | 2343 | 2223 |
| 6 | cPVL | bi CP | 2333 | 2333 | 2443 | 2333 | - |
| 7 | cPVL | bi CP | 2333 | 2333 | 2343 | 3333 | 2333 |
| 8 | cPVL | bi CP | 2444 | 2333 | 2333 | 2333 | 1333 |
| 9 | cPVL | bi CP | 2133 | 2333 | 2333 | 2313 | 2323 |
| 10 | CI | uni CP | 2333 | 2323 | 2323 | 2313 | - |
| 11 | CI | uni CP | 2333 | 2323 | 2333 | 2333 | 2313 |
| 12 | CI | bi CP | 2313 | 2223 | 2221 | 2241 | 2223 |
| 13 | PP | bi CP | 2333 | 2333 | 3333 | 2333 | 2333 |
| 14 | PP | uni CP | 2333 | 2343 | 2323 | 2222 | 2333 |
| 15 | PP | uni CP | 2333 | 2313 | 1333 | 2333 | - |
| 16 | PP | uni CP | 2343 | 2323 | 2433 | 1323 | - |
| 17 | PP | bi CP | 2333 | 4333 | 2344 | 2343 | - |
| 18 | PP | cMND | 2333 | 1333 | 1222 | 2433 | 2113 |
| 19 | PP | cMND | 2333 | 2333 | 2113 | 2221 | 2123 |
| 20 | PP | cMND | 1122 | 2333 | 2222 | 2141 | - |
| 21 | PP | cMND | 2233 | 2333 | 1333 | 1333 | 2122 |
| 22 | PP | missing | 2442 | 2313 | 2443 | 1333 | - |
| 23 | BG/T | bi CP | 2333 | 2333 | 2323 | 2323 | - |
| 24 | BG/T | bi CP | 4131 | 2122 | 2322 | 2133 | 2322 |
| 25 | BG/T | cMND | 2333 | 2343 | 2323 | 2323 | 2x22 |
| 26 | BG/T | cMND | 2333 | 2243 | 4222 | 2221 | 2222 |
| 27 | BG/T | cMND | 2343 | 2323 | 2333 | 2223 | 1113 |
| 28 | BG/T | sMND | 2333 | 4322 | 2143 | 2243 | 2222 |
| 29 | n-cPVL | bi CP | 2333 | 4333 | 2333 | 2243 | 2423 |

**SUPPLEMENTARY MATERIAL S1** MUSCLE TONE FINDINGS PER INFANT AND BRAIN LESION (CONTINUED)

| | | | *muscle tone pattern per assessment* | | | | |
|---|---|---|---|---|---|---|---|
| **infant ID** | **brain lesion** | **neurological outcome** | **1** | **2** | **3** | **4** | **5** |
| 30 | n-cPVL | cMND | 2333 | 2323 | 2143 | 2223 | 2223 |
| 31 | n-cPVL | cMND | 2333 | 4333 | 2133 | 2433 | 2222 |
| 32 | n-cPVL | cMND | 2433 | 2122 | 2133 | 2121 | – |
| 33 | n/n.s. | cMND | 2433 | 2221 | 2223 | 1333 | 2223 |
| 34 | n/n.s. | cMND | 2333 | 2113 | 1133 | 2222 | 2211 |
| 35 | n/n.s. | sMND | 4343 | 2321 | 2323 | 2222 | – |
| 36 | n/n.s. | sMND | 3333 | 4333 | 1323 | 2123 | 2234 |
| 37 | n/n.s. | sMND | 2433 | 2333 | 1313 | 2233 | 2433 |
| 38 | n/n.s. | sMND | 2333 | 2431 | 2433 | 1313 | 2111 |
| 39 | n/n.s. | typical | 2333 | 4333 | 2333 | 2113 | 1111 |

The colored number codes represent the muscle tone patterns per assessment. The first number in the code represents the muscle tone classification in neck/trunk, the second in arms, the third in legs, and the fourth in ankles. The green 1's represent typical tone, the red 2's hypotonia, the red 3's hypertonia and the blue 4's changing tone. For example: 2343 represents the pattern with hypotonia in neck/trunk, hypertonia in arms, changing tone in legs, and hypertonia in ankles. cPVL: cystic periventricular leukomalacia. CI: cortical infarction. PP: posthemorrhagic porencephaly. BG/T: basal ganglia / thalamus lesion. n-cPVL: non-cystic periventricular leukomalacia. n/n.s.: no / non-specific lesion. uni: unilateral. bi:bilateral.

**SUPPLEMENTARY MATERIAL S2** GENERALIZED MIXED EFFECT MODEL ANALYSES: ASSOCIATIONS BETWEEN HYPERTONIA AND CP AND CPVL

| | variables in model | fixed effects (β) | OR (exp(β)) (95% CI) | | age difference (months) |
|---|---|---|---|---|---|
| **hypertonia arms** | intercept | **2.170*** ** | 8.76 | (2.891 – 32.76) | ≥ 7.0 |
| | age | **-0.257*** ** | 0.773 | (0.681 – 0.856) | |
| | CP | -0.344 | 0.709 | (0.140-3.560) | |
| | CP*age | **0.205** ** | 1.23 | (1.082-1.42) | |
| | intercept | **1.85*** ** | 6.34 | (2.67 – 18.0) | none |
| | age | **-0.133*** ** | 0.875 | (0.820 – 0.927) | |
| | cPVL [a] | 0.459 | 1.58 | (0.409 – 6.28) | |
| **hypertonia legs** | intercept | **0.959*** | 2.61 | (1.00 – 3.61) | |
| | age | **-0.137*** ** | 0.872 | (0.822 – 0.919) | *none* |
| | CP [a] | 0.772 | 2.16 | (0.998 – 5.08) | |
| | intercept | **1.10** ** | 3.01 | (2.67 – 18.0) | ≥ 0 [b] |
| | age | **-0.134*** ** | 0.875 | (0.824 – 0.922) | |
| | cPVL [a] | **0.958*** | 2.61 | (1.03 – 7.16) | |

Summary of the variables that were and were not associated with hypertonia in the arms and legs in the generalized mixed effect model analyses. The intercept indicates the mean value of the chance of hypertonia when the other variables are 0. CP*age denotes the statistical interaction between CP and age. Significant effects of variable in bold: * p<0.05, ** p<0.01, *** p<0.001. Exp (β) is presented here as odds ratio (OR): it represents the growth factor of the developmental trajectory. For age it reflects the growth factor per month. The most right column presents the age at which the estimated mean starts to differ between the groups (CP vs no CP, cPVL vs non-cPVL).

[a] The interaction term was not statistically significant in this model and therefore not presented in the table.

[b] There is a constant, age-independent significant difference in the proportion of infants with hypertonic legs between the group with cPVL and the group without.

CP: cerebral palsy. cPVL: cystic periventricular leukomalacia. OR: odds ratio.

# 5

# Atypical knee jerk responses in high-risk children: a longitudinal EMG-study

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*European Journal of Paediatric Neurology 2022; 40: 11-17*

*doi: 10.1016/j.ejpn.2022.07.003*

## ABSTRACT

**Introduction**: We previously found that atypical responses to the knee jerk reflex, i.e., tonic responses (TRs), clonus and contralateral responses in very high-risk (VHR) infants were associated with cerebral palsy (CP) at 21 months. The current study aimed for a better understanding of pathophysiology of atypical knee jerk responses by evaluating whether infant atypical knee jerk responses are associated with CP and atypical knee jerk responses at school-age.

**Methods**: 31 VHR-children, who had also been assessed longitudinally during infancy, and 24 typically developing children, were assessed at 7-10 years (school-age). We continuously recorded surface EMG of thigh muscles during knee jerk responses longitudinally during infancy and once at school-age. Neurological condition was assessed with age-appropriate neurological examinations. It included the diagnosis of CP at 21 months corrected age and school-age. CP's type and severity (Gross Motor Function Classification System (GMFCS)) were reported.

**Results**: Persistent TRs in infancy were associated with CP at school-age. TR prevalence decreased from infancy to childhood. At school-age it was no longer associated with CP. Clonus prevalence in VHR-children did not change with increasing age; it was significantly higher in children without than those with CP. Reflex irradiation was common in all school-age children, and its prevalence in contralateral muscles in VHR-children decreased between infancy and childhood.

**Conclusions**: In infancy, TRs indicated an increased risk of CP, but at school-age TRs were not associated with CP. In general, spinal hyperexcitability, expressed as reflex irradiation and TRs, decreased between infancy and school-age.


## HIGHLIGHTS

- Infant tonic knee jerk responses were associated with CP at school-age
- Prevalence of tonic knee jerk response in VHR-infants decreased with increasing age
- Tonic knee jerk responses at school-age were not associated with CP
- In our study group, clonus at school-age occurred mainly in VHR-children without CP
- At school-age, reflex irradiation occurred in VHR- and typically developing children


## KEYWORDS

brain injury, cerebral palsy, electromyography, knee jerk response, neurodevelopment, paediatrics

# INTRODUCTION

Assessment of the knee jerk response is an integral part of the neurological examination. An absent knee jerk response indicates an abnormality in the reflex arc, an asymmetry points to peripheral or central dysfunction, and hyperreflexia reflects neural dysfunction above the level of the reflex arc, i.e., a lesion of the corticospinal tract.[1-3] Damage to the corticospinal tract, for example due to an early brain lesion, may result in loss of inhibitory activity from descending motor pathways, causing hyperexcitability of the motoneuronal spinal system as often seen in children with cerebral palsy (CP). CP is the most common neuromotor disability in childhood with a prevalence in most high-income countries of 1 in 500 live births.[4] Key symptoms of CP are - regardless of subtype - hyperreflexia, atypical muscle tone and motor and/or postural control impairments.[5] Most children diagnosed with CP have the spastic form (60-80%).[5,6]

In infants later diagnosed with CP it usually takes time before the specific signs of CP emerge.[7] For example, hypertonia and spasticity are seldomly present in early infancy in children who are later diagnosed with CP, and will become more evident during childhood.[8] Due to the complex development of the nervous system during infancy, early diagnosis of CP is challenging. At the same time, early detection of infants at risk is highly recommended since the plasticity of the nervous system during this phase of life offers the possibility of early intervention.[7,9]



The present paper focuses on associations between atypical knee jerk responses and the later diagnosis of CP. We were especially interested in the tonic response, as we previously had found that the presence of a tonic response, i.e., a long-lasting contraction as a response to the knee jerk, was associated with the diagnosis of CP at 21 months.[10,11] It was hypothesized that tonic responses may be one of the preliminary expressions of hypertonia. High-risk infants who later got diagnosed with CP also showed more often clonus and contralateral responses than their peers who did not develop CP.

The aim of the current study was threefold. Our primary aim was to evaluate whether tonic responses to the knee jerk during infancy in very high-risk (VHR) children were associated with the presence and severity of CP at school-age. Secondly, we assessed whether in VHR-children the prevalence of specific knee jerk responses, such as tonic and contralateral responses, changes between infancy and school-age. The tertiary aim was to assess whether and how reflex organization at school-age, in terms of tonic response, clonus and contralateral phasic responses differs between VHR-children and their typically developing (TD) peers. Previous studies indicated that in TD-children the occurrence of phasic responses in antagonist and contralateral muscles decreases between infancy and adulthood.[12-14] Yet, we do not know to what extent a developmental decrease in excitability occurs in VHR-children. The information resulting from our study may contribute to a better understanding of reflex pathways in high-risk infants, in particular in terms of motoneuronal hyperexcitability, and its clinical expressions in children with CP.

# MATERIALS AND METHODS

## Participants

We assessed knee jerk responses in two groups of school-aged children: a group of VHR-children and a group of TD-children. The VHR-children were participants of the LEARN2MOVE 0-2 years trial (L2M0-2). L2M0-2 was a randomized controlled trial that evaluated the effect of two forms of early intervention in VHR-infants (for details see [15-17]). Most infants had an evident brain lesion on neuroimaging, that was performed as part of standard clinical care (mostly MRI, see Table 1). Infants were assessed at baseline (between 0-9 months corrected age (CA)), at 6 and 12 months after baseline and at 21 months CA. This resulted in a maximum of four EMG-assessments during infancy for each child. All L2M-0-2 participants were approached to participate in the current follow-up study when they were 7-10 years. There were no additional inclusion or exclusion criteria.

The TD-group consisted of healthy school-aged children. Recruitment took place via staff's acquaintances and social media. Inclusion criteria were: age between 7 and 10 years, attending mainstream primary education, and having caregivers with sufficient understanding of the Dutch language. Children were excluded from participation in the TD-group in case of a complicated perinatal history (for example preterm birth (gestational age <37 weeks), or admission to the neonatal ward), and atypical neurological function, such as CP or the complex form of minor neurological dysfunction.

The work described has been carried out in accordance with the Declaration of Helsinki. For all participating children informed consent was obtained. The Medical Ethics Committee of the University Medical Center Groningen (UMCG) approved the follow-up study protocol under registration number METC 2017.321.

## Procedures

The children were assessed once between November 2017 and March 2021, either in the child's home or at the research lab of the Institute of Developmental Neurology of the UMCG, depending on families' preferences. The assessments were carried out by trained assessors and were video-recorded to facilitate supervision, which was performed by a neurodevelopmental expert (MHA). Within the groups of VHR- and TD-children, both assessors and supervisor were not aware of clinical background of the children.

*Neurological assessment*

At school-age, children were assessed with the age-specific and standardized MND assessment.[18] The examination is organized into eight functional domains: posture and muscle tone, reflexes, dyskinesia, coordination, fine manipulative ability, associated movements, sensory functioning and cranial nerve functioning. The examination results in a clinical classification in four categories: normal, simple MND (sMND), complex MND (cMND), and abnormal, for example the presence of cerebral palsy (CP). sMND implies the presence of one or two dysfunctional

domains; it is considered a typical, but non-optimal form of typical brain function that is present in about 25% of children.[18] cMND denotes the presence of more than two dysfunctional domains; it is considered a clinically relevant form of brain dysfunction.18 We classified the children with a normal neurological condition and with sMND as having a typical neurological condition. Children with cMND were excluded from the TD-group. In VHR-children with CP, a further classification was made based on type and distribution of CP (for example: unilateral spastic CP) 5, and gross motor function assessed with GMFCS.[19]

*Perinatal risk*

Perinatal risk factors of the VHR-children were obtained from clinical records during L2M0-2. Caregivers of the TD-children filled out a short questionnaire on perinatal, childhood medical and social characteristics.

*Knee jerk assessment and EMG data analysis*

Our methodological set-up at school-age was comparable to that of the infant study of Hamer et al.[11] We continuously recorded surface EMG of the right and left quadriceps and hamstrings during the knee jerk response with bipolar electrodes placed over the muscles' bellies. An electro-physiological front-end amplifier (Twente Medical Systems International, Enschede, the Netherlands) recorded surface EMG signals with a sampling rate of 2000 Hz, as well as accelerations of the connected reflex hammer. The knee jerk reflex was elicited at least 10 times on each leg by tapping the patellar tendon with the reflex hammer. As described above, the EMG assessment was video-recorded.



Integrated analysis of signals of surface EMG and reflex hammer, and video recordings was performed with the software package PedEMG (Developmental Neurology, University Medical Center Groningen, the Netherlands).[20] We started with video analysis to indicate when a tap was applied and whether it was applied to the left or right patellar tendon. Next, the EMGs of all four muscles (ipsilateral and contralateral quadriceps and hamstrings) were analysed without video in random order, implying that the assessor was masked for all child information. The hammer tap signal was used to define T0, i.e., the starting point of the calculation of onset latencies.

We defined a phasic response (PR) based on the following criteria: 1) occurrence within 30 milliseconds (ms) after T0 in ipsilateral quadriceps, and within 35 ms in ipsilateral hamstrings and contralateral quadriceps and hamstrings, 2) duration between 10 and 35 ms, and 3) bi-, tri-, or pentaphasic form (Figure 1, panel A). A response was considered tonic (tonic response; TR) when it 1) occurred within 150 ms after a phasic response, 2) had a minimal duration of 200 ms, and 3) had a prolonged activity of similar intensity throughout the response (Figure 1, panel B). The presence of clonus (repetitive phasic responses) was reported (Figure 1, panel C), as well as reflex irradiation to non-homonymous muscles, i.e., the presence of PRs in muscles other than the ipsilateral quadriceps.

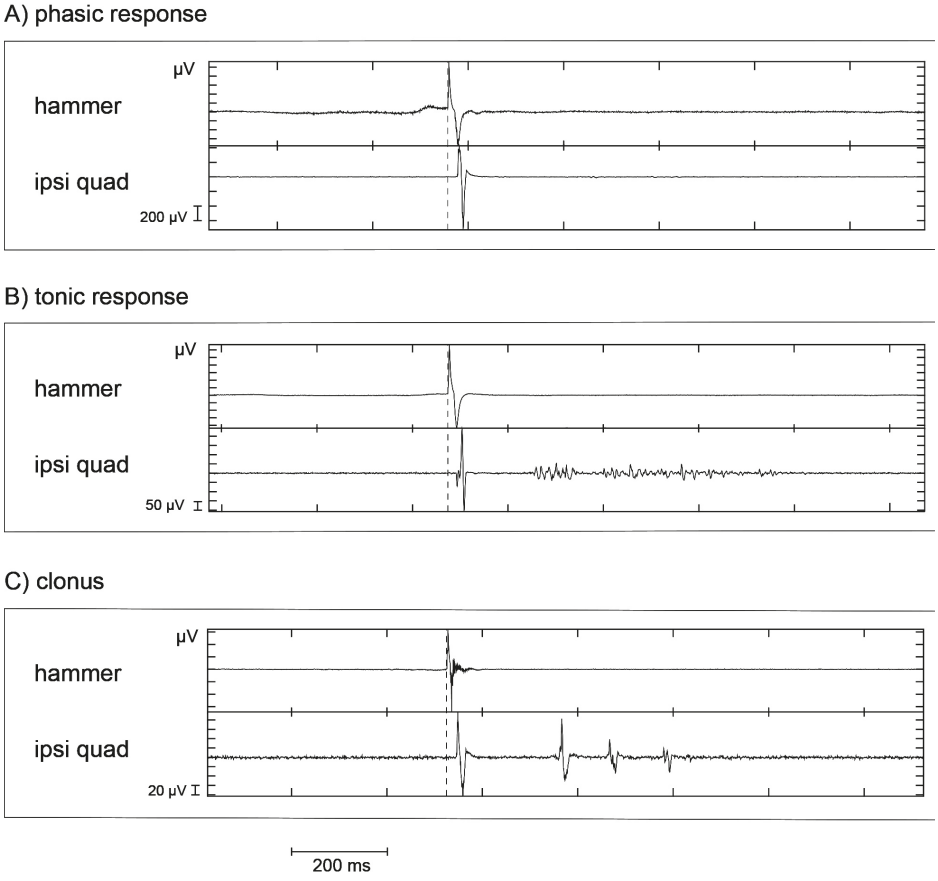


**FIGURE 1** TYPICAL EXAMPLES OF PHASIC AND TONIC RESPONSE AND CLONUS

A) phasic response, B) phasic response followed by a tonic response, C) clonus, i.e., phasic response followed by 3 clonic beats. In each panel the upper signal indicates the hammer tap, whilst the lower signal shows the EMG of the ipsilateral quadriceps (ipsi quad). EMG amplitude units represent 200, 50 and 20 μv in panel A, B and C, respectively. T0 is indicated by the vertical dashed line.

In the VHR-group a persistent TR in infancy was defined as having had at least one TR during the last EMG assessment - for most children at 21 months CA - in combination with at least one TR during a previous EMG assessment at earlier ages (see [11]). Data of the last infant assessment were used for the comparison of the prevalence of clonus and reflex irradiation between infancy and school-age.

### Statistical analyses

Statistical analyses were carried out using the software Statistical Package for Social Sciences (SPSS), version 26. In previous studies, no significant differences in developmental outcome of the VHR-infants between the two intervention groups at RCT-level were found.[16,17] This allowed for pooling of the two groups to study associations between the knee jerk response and neurological outcome. We calculated for the ipsilateral quadriceps the mean onset latency and duration of the phasic response. Differences in onset latency and duration were analysed with independent t-tests and one-way ANOVA. We also calculated the prevalence of a specific response (PR, TR or clonus) for each assessment as a percentage of the total amount of appropriate trials per child. We presented the median percentages and their range. Associations between dichotomic variables (for example between TR and CP) were analysed with Chi-square tests or Fisher's exact test. Odds ratios are presented with the 95% confidence interval (CI) between brackets. Mann-Whitney tests and Kruskal-Wallis tests were used for analysis of differences in prevalence of specific responses between subgroups (for example, children with and without CP). In case of a significant difference between the subgroups, post-hoc tests were applied. Throughout the analyses, differences and correlations with a p-value < 0.05 or 95%CI were considered statistically significant (two-tailed testing).



## RESULTS

### Study groups

Thirty-one of the 43 VHR-children included in L2M0-2 participated in the current knee jerk follow-up study. From the 12 children who did not participate, nine had insufficient infant EMG-assessments and three others were lost to follow-up (see flowchart in Figure 2). The neurological risk profile (gestational age, birthweight, type of brain lesion) of the 12 children who did not participate at school-age was similar to that of the re-assessed children (data not shown). Also the prevalence of CP at 21 months was similar in participants and non-participants (known in 10 non-participants: 5 had CP). All 31 children had a neurological assessment at school-age, but in six we could not obtain an EMG-assessment due to technical or logistical reasons associated with the COVID-19 pandemic. Seventeen of the 31 children participating in the follow-up were diagnosed with CP at 21 months. In all the diagnosis of CP was confirmed at school-age. Their GMFCS level varied from I to V (Table 1). None of the children without CP at 21 months were diagnosed with CP at school-age. Eleven of the VHR-children without CP (n=14) had cMND. All 24 TD-children had a typical neurological condition. Their age at assessment was not different from that of the VHR-children (Table 1).

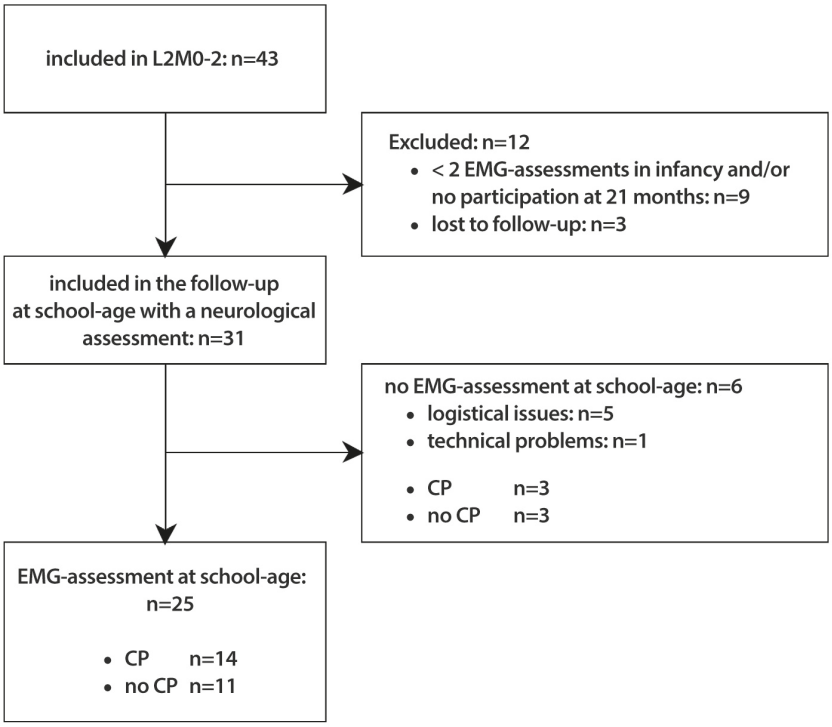


**FIGURE 2** PARTICIPATION FLOW DIAGRAM OF VHR-INFANTS

**TABLE 1** CHARACTERISTICS OF VHR-CHILDREN AND TD-CHILDREN

| | VHR-children | TD-children | |
|---|---|---|---|
| | *n*=31 | *n*=24 | *p*-value |
| age at assessment in years, median (min-max) | 8.4 (7-10.5) | 8.0 (7.0-10.8) | 0.734 |
| sex (boys / girls), n | 18 / 13 | 11 / 13 | |
| gestational age in weeks + days, median (min-max) | 30+6 (25+6–41+2) | 40+3 (38+1–41+6) | **<0.001** |
| preterm birth (GA <37 weeks), n (%) | 24 (77) | 0 | |
| birth weight in grams, median (min-max) | 1550 (720-4410) | 3525 (2488-4500) | **<0.001** |
| neonatal brain imaging, n (%) | | | |
| MRI / cranial ultrasound | 25 / 6 | | |
| type of brain lesion | | | |
| periventricular leukomalacia | 13 (42) | | |
| cystic | 10 | | |
| non-cystic | 3 | | |
| cortical infarction | 2 (6) | | |
| posthaemorrhagic porencephaly | 7 (23) | | |
| basal ganglia / thalamic lesion | 3 (10) | | |
| no / non-specific lesion | 6 (19) | | |
| neurological outcome at school-age[a], n (%) | | | |
| typical | 2 (6) | 24 (100) | |
| complex MND | 11 (35) | | |
| CP | 17 (55) | | |
| unilateral / bilateral | 3 / 14 | | |
| GMFCS I / II / III / IV / V | 3 / 5 / 0 / 7 / 2 | | |
| spastic / ataxic | 16 / 1 | | |

VHR: very high risk of cerebral palsy. TD: typically developing. MND: minor neurological dysfunction.

a n=1: no CP but type of MND unknown.

Note that Hamer et al included the 34 infants who had undergone at least one proper knee jerk EMG during L2M0-2 and participated in the last assessment of L2M0-2 around 21 months CA.11 For the current study, additional EMG data of 5 infants at 21 months were analysed.

## EMG assessments

The 49 EMG assessments at school-age (VHR n=25, TD n=24) resulted in 1021 appropriate trials (median number per child 21, range 4-35). Preliminary analysis revealed differences in reflex activity between VHR-children with and without CP, and between children with CP with low and high GMFCS-levels. Therefore, we split the total group of children with an EMG assessment at school-age into four subgroups: a) TD-children (n=24), b) VHR-children without CP (n=11), c) VHR with CP functioning at GMFCS-levels I-II (n=6), and d) VHR with CP functioning at GMFCS-levels IV-V (n=8). The EMG knee jerk parameters are presented in Table 2 and will be discussed below in more detail.

*Persistent tonic response in infancy and CP at school-age in VHR-children*
Fifteen of the 31 VHR-children (48%) had shown a persistent TR in infancy; thirteen of them (87%) had developed CP. A persistent TR in infancy was associated with CP at school-age: OR 19.5 (95% CI 3.0-126.5). Also, the presence of TRs during the last assessment in infancy, i.e., independent of previous assessments, was associated with CP at school-age: OR 11.9 (95% CI 2.2-65.1; Supplementary Material S1). A persistent TR in infancy was not associated with GMFCS-level at school-age (Fisher's exact test; p=1.000) (Supplementary Material S1).

*Tonic responses at school-age*
In the VHR-children, TR prevalence decreased significantly between infancy and school-age: at the last assessment in infancy 7 out of 31 (23%) infants had a TR prevalence of at least 30% of trials, whereas its prevalence at school-age was consistently below 30% (OR 0.490 [95% CI 0.368-0.652]). The presence of at least one TR at school-age in VHR-children was not associated with CP (CP: 5/14; no CP: 4/11; OR 0.972 [95% CI 0.2-5.0]) nor with GMFCS level (Fisher's exact test; p=0.880; Supplementary Material S1).

Fourteen of the 49 VHR- and TD-children (29%) showed at least one TR during the school-age assessment. The prevalence of at least one TR was highest in the children with CP GMFCS-levels I or II (3 out of 6 children; 50%), followed by VHR-children without CP (4 out of 11; 36%) and VHR-children with CP GMFCS-levels IV or V (2 out of 8; 25%). The TD-children had the lowest prevalence of TR (5 out of 24; 21%); the neurological condition of the 5 children who showed an occasional TR was classified as sMND. The differences between the subgroups were not statistically significant (ANOVA; p=0.510).

*Clonus*
In the VHR-group, the prevalence of clonus did not differ between infancy and school-age (median percentages per assessment 0% in infancy versus 5.6% at school-age; p=0.104). Twenty-seven of all 49 assessed children (55%) had at least once a clonus in the ipsilateral quadriceps at school-age. VHR-children without CP most often showed this phenomenon (9 out of 11; 82%), followed by TD-children (14 out of 24; 58%), children with CP functioning at GMFCS levels I-II (3 out of 6; 50%) and children with CP functioning at GMFCS levels IV-V (1 out of 8; 13%). The prevalence of clonus in VHR-children without CP was significantly higher than in VHR-children with CP (p=0.009), and in particular higher than in the children with CP functioning at GMFCS level IV-V (p=0.004; Table 2).

**TABLE 2** EMG KNEE JERK PARAMETERS

| | TD *n*=24 | | VHR *n*=25 | | | | | | p-value[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | no cerebral palsy n=11 | | cerebral palsy: GMFCS I-II n=6 | | cerebral palsy: GMFCS IV-V n=8 | | |
| | mean (SD) or median (range) | *n* (%) | mean (SD) or median (range) | *n* (%) | mean (SD) or median (range) | *n* (%) | mean (SD) or median (range) | *n* (%) | |
| ipsi quadriceps | | | | | | | | | |
| onset latency PR, ms | 18 (2) | 24 (100) | 18 (2) | 11 (100) | 19 (5) | 6 (100) | 18 (2) | 8 (100) | 0.833 |
| clonus, % | 5 (0-53) | 14 (58) | 12 (0-40) | 9 (82) | 5 (0-23) | 3 (50) | 0 (0-8) | 1 (13) | **0.031** |
| TR, % | 0 (0-13) | 5 (21) | 0 (0-26) | 4 (36) | 2 (0-21) | 3 (50) | 0 (0-5) | 2 (25) | 0.418 |
| irradiation - prevalence | | | | | | | | | |
| ipsi hamstrings: PR, % | 86 (47-100) | 24 (100) | 91 (47-100) | 11 (100) | 76 (0-100) | 5 (83) | 93 (75-100) | 8 (100) | 0.152 |
| contra quadriceps: PR, % | 0 (0-69) | 6 (25) | 0 (0-5) | 1 (9) | 0 (0-0) | 0 | 0 (0-26) | 1 (13) | 0.411 |
| contra hamstrings: PR, % | 0 (0-46) | 10 (42) | 0 (0-5) | 3 (27) | 2 (0-15) | 3 (50) | 0 (0-6) | 2 (25) | 0.470 |
| irradiation - onset latency | | | | | | | | | |
| ipsi hamstrings: ms | 23 (5-30) | | 24 (16-29) | | 21 (5-27) | | 22 (19-24) | | 0.489 |
| contra quadriceps: ms | 24 (15-31) | | 25 (-) | | - | | 26 (-) | | 0.687 |
| contra hamstrings: ms | 22 (12-29) | | 25 (14-32) | | 25 (24-31) | | 22 (20-24) | | 0.829 |

TD: typically developing. VHR: very high risk of cerebral palsy. SD: standard deviation. PR: phasic response. TR: tonic response. Ipsi: ipsilateral. Contra: contralateral. *n* presents the number of children with at least 1 specific response (PR, TR or clonus). Note that the medians and ranges of the prevalence have been calculated in all children in the subgroup, while the medians and ranges of the onset latency were calculated only in the children that showed the relevant response. [a] Kruskal-Wallis or one-way ANOVA.

In the tree children with a unilateral CP, we did not find significant differences in knee jerk parameters between the most and least affected side. Therefore, we pooled the trials of the leg and right leg of all children in the analyses.

*Phasic responses in ipsilateral and contralateral muscles (reflex irradiation)*
The prevalence of PRs in the ipsilateral hamstrings of VHR-children did not differ between infancy and school-age (96.3 and 83.3%, respectively; p=0.134). However, PRs in contralateral muscles occurred significantly less often at school-age than in infancy (quadriceps: 16.8% in infancy and 0% at school-age; p<0.001, and hamstrings: 37.5% in infancy and 0% at school-age; p<0.001).

At school-age, most assessed children (48/49) showed PRs in the ipsilateral hamstrings. In the 48 children, the prevalence varied between 19% and 100% (median value 85%; Table 2). Eight children (16%) showed PRs in the contralateral quadriceps and eighteen children (37%) in the contralateral hamstrings. The prevalence of reflex irradiation and the latencies to the PRs in the four recorded muscles did not differ between the four groups at school-age (Table 2).

# DISCUSSION

The present study indicates that a persistent tonic response to the knee jerk in infancy is associated with the diagnosis of CP at school-age, but not to its severity in terms of GMFCS-level. At school-age, TRs occurred significantly less often than in infancy, their presence was no longer associated with the diagnosis of CP, and their prevalence was now similar in VHR- and TD-children. At school-age, clonus was more often observed in VHR-children who had not developed CP than in VHR-children who had developed CP. In VHR-children the prevalence of reflex irradiation to the contralateral muscles decreased between infancy and school-age, reaching the low rates observed in TD-children. Reflex irradiation to the ipsilateral hamstrings was a common finding in both groups, and in VHR-children at both ages.

## Clinical and pathophysiological considerations

The association between a persistent TR during infancy and CP at school-age confirmed earlier findings of Hamer and colleagues. Hamer et al. had diagnosed CP at 21 months CA.[10,11] The latter age is relatively early as it may take up until the age of 5 years before the diagnosis of CP can be made.[21] The current study indicates that our children with an early evident lesion of the brain did not grow into or out of their diagnosis of CP after the age of 21 months CA. The assessment at school-age did not only allow for the confirmation of the diagnosis of CP, but also for a better determination of the subtype and severity of CP than at 21 months. At school-age most children with CP were diagnosed with spastic CP (16/17; 94%). Our findings therefore support the hypothesis that tonic responses in infancy and CP's spasticity may share the pathophysiological mechanism of reduced supraspinal inhibition[13], resulting in increased motoneuron excitability.[22,23]

The decrease in prevalence of both TR and reflex irradiation to contralateral muscles between infancy and school-age in VHR-children may be attributed to the general decrease in excitability of the spinal circuitries from infancy to school-age.[24] The latter is in line with findings of O'Sullivan and colleagues, who studied spread of reflex activity in healthy individuals

from early infancy into adulthood.[14] They found that in typical development redundancy of excitatory projections to motoneurons of non-homonymous muscles gradually reduces with increasing age. Our study illustrates that a similar decrease is also present in children who were perinatally at very high risk of CP. Our observation that the prevalence of reflex irradiation did not differ between the four subgroups at school-age extends to our previous hypothesis that contralateral responses are part of typical early ontogeny[10], thus that their presence does not necessarily indicate atypical development.

Both TRs and clonus are signs of increased neuronal excitability. Nevertheless, the pathophysiology of both signs is not identical. In TRs an additional mechanism is activated: the spinal hyperexcitability - and in particular a monoaminergic drive - induces activation of persistent inward currents (PICs) in the motoneurons.[25] The latter results in sustained activity in the motoneurons. Indeed, our results illustrate that the two signs are not identical. First, TRs were found with the highest prevalence in VHR-children with CP GMFCS levels I-III, whereas clonus occurred in particular in the VHR-children without CP. Second, TRs in VHR-children decreased with increasing age, but clonus did not. Yet, it should be realized that in our small subgroups, TR prevalence at school-age did not differ between the four subgroups, presumably also due to its general low prevalence at school-age. The VHR-children with CP in the highest GMFCS-levels had a lower prevalence of clonus than the VHR-children without CP. Also the prevalence of TRs was relatively low in the VHR-children with the highest GMFCS-levels. It is conceivable that two mechanisms prevented the expression of both TR and clonus in the children with the highest GMFCS levels. First, it is known that in these children the serious loss of supraspinal control results in long-lasting hypertonia.[26] In this hypertonia, PICs of the motoneurons may play a role, as PICs – activated by the long-term loss of supraspinal control – may result in prolonged high self-sustained firing activity of the motoneurons.[27] This relative overactivity of the motoneurons may have masked the expression of TR and clonus. Second, it is possible that the children's persisting hypertonia had induced long-term transformation of the muscles' morphology [28,29], leading to less compliant muscles. The latter does not only give rise to contractures leading to a decreased range of motion of the knee joint, but also may result in less compliant muscle fibres, therewith reducing the effective transmission of the stretch to the muscle spindle, resulting in a low prevalence of both TRs and clonus in the group of children with the highest GMFCS levels.[30]

## Methodological considerations

A unique property of the study is that it documented EMG activity of the knee jerk response in infancy and at school-age in a well-documented group of VHR-children.[10,11] Another strength of the study is the inclusion of a group of age-matched typically developing school-aged children. This allowed us to compare reflex activity between VHR- and TD-children. The study's main limitation is the small size of the study groups and subgroups. Additionally, the group of VHR-children was heterogeneous in terms of GMFCS-level and brain lesion. However, this heterogeneity is typical for CP, which is an umbrella diagnosis covering a wide variety of aetiologies, types, and severity of motor impairments and accompanying problems.[5]

## Concluding remarks

In conclusion, our findings indicate that a tonic response (TR) to the knee jerk in infancy is associated with the diagnosis of CP, but not with its severity in terms of GMFCS. The study also indicates that the presence of a TR at school-age is part of typical development. We did not find that the presence of TR or clonus at school-age in children with CP was associated with higher GMFCS-levels. We hypothesized that the lack of associations may have been caused by the long-lasting hypertonia in the children with higher GMFCS-level, resulting in (a) masking of TR and clonus, and (b) changed muscle morphology. Finally, our study indicated that in very-high risk children reflex irradiation to contralateral muscles decreases between infancy and childhood – just as is known for typically developing children.

## DECLARATION OF INTEREST

None

## ACKNOWLEDGEMENTS

We thank all the children and their caregivers for participation in the current follow-up study of L2M0-2, that was part of the Dutch national LEARN2MOVE research program. We gratefully acknowledge the accurate collection of the infant data by the members of the L2M0-2 years team, and the technical assistance of Linze Jaap Dijkstra and Anneke Kracht-Tilman.

## FUNDING

L2M0-2 was part of the Dutch national LEARN2MOVE research programme and was financially supported by ZonMW (89000002); Johanna Kinderfonds; Stichting Rotterdams Kinderrevalidatie Fonds Adriaanstichting; Revalidatiefonds; Phelps Stichting; Revalidatie Nederland; and the Nederlandse Vereniging van Revalidatieartsen. EJMS was financially supported by the Junior Scientific Masterclass Groningen. None of the funders were involved in study design, data collection, data analysis, manuscript preparation and/or publication decisions.

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**SUPPLEMENTARY MATERIAL S1** TONIC RESPONSES AND CP

## TR in infancy and CP at school-age

| | | *CP at school-age* | | |
|---|---|---|---|---|
| | | **no** | **yes** | |
| **Persistent TR in infancy** | **no** | 12 | 4 | 16 |
| | **yes** | 2 | 13 | 15 |
| | | 14 | 17 | 31 |

| | | *CP at school-age* | | |
|---|---|---|---|---|
| | | **no** | **yes** | |
| **TR at last assessment in infancy** | **no** | 11 | 4 | 15 |
| | **yes** | 3 | 13 | 16 |
| | | 14 | 17 | 31 |

| | | *GMFCS-level at school-age* | | | | | |
|---|---|---|---|---|---|---|---|
| | | **I** | **II** | **III** | **IV** | **V** | |
| **Persistent TR in infancy** | **no** | 1 | 1 | 0 | 2 | 0 | 4 |
| | **yes** | 2 | 4 | 0 | 5 | 2 | 13 |
| | | 3 | 5 | 0 | 7 | 2 | 17 |

## TR at school-age and CP at school-age

| | | *CP at school-age* | | |
|---|---|---|---|---|
| | | **no** | **yes** | |
| **TR at school-age** | **no** | 7 | 9 | 16 |
| | **yes** | 4 | 5 | 9 |
| | | 11 | 14 | 25 |

| | | *GMFCS-level at school-age* | | | | | |
|---|---|---|---|---|---|---|---|
| | | **I** | **II** | **III** | **IV** | **V** | |
| **TR at school-age** | **no** | 1 | 2 | 0 | 4 | 2 | 9 |
| | **yes** | 1 | 2 | 0 | 2 | 0 | 5 |
| | | 2 | 4 | 0 | 6 | 2 | 14 |

# 6

# Infant motor behaviour and functional and cognitive outcome at school-age: a follow-up study in very high-risk children

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*Early Human Development 2022; 170: 105597*
*doi: 10.1016/j.earlhumdev.2022.105597*

## ABSTRACT

**Background***:* The Infant Motor Profile (IMP) is an appropriate tool to assess and monitor infant motor behaviour over time. Infants at very high risk (VHR) due to a lesion of the brain generally show impaired motor development. They may grow into or out of their neurodevelopmental deficit.

**Aims***:* Evaluate associations between IMP-trajectories, summarised by IMP-scores in early infancy and rates of change, and functional and cognitive outcome at school-age in VHR-children.

**Study design***:* Longitudinal study.

**Subjects***:* 31 VHR-children, mainly due to a brain lesion, who had multiple IMP-assessments during infancy, were re-assessed at 7-10 years (school-age).

**Outcome measures***:* Functional outcome was assessed with the Vineland-II, cognition with RAKIT 2. Associations between IMP-trajectories and outcome were tested by multivariable linear regression analyses.

**Results***:* When corrected for sex, maternal education and follow-up age, initial scores of total IMP, variation and performance domains, as well as their rates of change were associated with better functional outcome (unstandardized coefficients [95% CI]): 36.44 [19.60-53.28], 33.46 [17.43-49.49], 16.52 [7.58-25.46], and 513.15 [262.51-763.79], 356.70 [148.24-565.15], and 269 [130.57-407.43], respectively. Positive rates of change in variation scores were associated with better cognition at school-age: 34.81 [16.58-53.03].

**Conclusion***:* Our study indicated that in VHR-children IMP-trajectories were associated with functional outcome at school-age, and to a minor extent also with cognition. Initial IMP-scores presumably reflect the effect of an early brain lesion on brain functioning, whereas IMP rate of change reflects whether infants are able to grow into or out of their initial neurodevelopmental deficit.


## HIGHLIGHTS

- IMP-scores in very high-risk infants are associated with outcome at school-age
- Initial IMP-scores and rates of change were associated with functional outcome
- In particular IMP variation and performance trajectories were associated with outcome
- The IMP is an adequate tool to monitor neurodevelopment in very high-risk infants


## KEYWORDS

brain injury, cognition, infant, functional outcome, motor development, school-age

# INTRODUCTION

Motor behaviour undergoes impressive developmental changes during infancy.[1] Its assessment always has been an essential part in the evaluation of infant development. Traditionally, much emphasis was on quantitative aspects of motor behaviour, i.e., attainment of motor milestones. Gradually, it has become clear that assessment of qualitative aspects is also an important tool in the prediction of neurodevelopmental outcomes, such as cerebral palsy (CP) and intellectual disability.[2] The Infant Motor Profile (IMP), a video-based assessment of motor behaviour that finds its theoretical background in the Neuronal Group Selection Theory (NGST), covers both quantitative and qualitative aspects.[3] The IMP evaluates motor behaviour in five domains: variation, adaptability, performance, symmetry and fluency. The IMP is an excellent tool to monitor the infant's motor developmental progress, i.e., it allows for longitudinal assessment of early motor behaviour and is responsive to change.[3] Longitudinal studies evaluating motor development in infancy are important to disentangle relationships between early motor development and later functional and cognitive skills, and to improve early identification and therewith possibilities for intervention in children at high risk of neurodevelopmental disorders.[4,5] Previous studies revealed that low total IMP-scores predict CP in infants at increased risk of neurodevelopmental disorders.[6,7] The domains that contributed most were variation and performance. Other studies in infants at low risk of developmental disorders showed that lower total IMP-scores are associated with lower IQ scores at school-age.[8,9] The domains variation, adaptability and performance contributed most to these associations. The aim of the current study was to evaluate whether IMP-trajectories, summarised by initial IMP-scores and IMP rate of change in children at very high risk of neurodevelopmental disorders, mainly due to an early lesion of the brain, are associated with functional outcome and cognition at school-age. In other words, our study addressed the question whether largely improving IMP-scores are associated with better outcomes at school-age and reflect growing out of a deficit, and whether deteriorating IMP-scores or IMP-scores that show a slower than typical increase in score are associated with worse outcomes as they reflect growing into a deficit.



# METHODS

## Participants

Participants of the current study were children who participated in the LEARN2MOVE 0–2 years trial in infancy (L2M0-2). In L2M0-2, two forms of early intervention were evaluated in infants at very high risk of (CP)[10,11]: the family-centred program COPing with and CAring for infants with special needs (COPCA)[12] and typical infant physiotherapy. Inclusion criteria for L2M0-2 were 0 to 9 months corrected age and being at very high risk of CP based on the presence of an evident brain lesion on neuroimaging, and/or clinical neurological dysfunction suspect for a developing CP. Children were assessed longitudinally throughout infancy with the final assessment around 21 months CA. Detailed descriptions of recruitment and content of the interventions of L2M0-2, and infants' outcome at 21 months have been published previously.[10,11] Caregivers of all 43

children who participated in L2M0- 2 were approached to participate in the current study when their children were between 7 and 10 years of age. The study protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen (UMCG) under registration number 2017.321. All caregivers gave written informed consent.

## Procedures

Assessments were carried out by trained assessors and took place at the children's home or at the Institute of Developmental Neurology in the UMCG, depending on caregivers' preferences. All assessments were video-recorded and scored under supervision of a neurodevelopmental expert (MHA). Both at infancy and school-age, neither assessors nor supervisor were aware of details of the clinical background and the type of intervention the children had received in infancy.

*Brain imaging*

All children underwent brain imaging during the neonatal period as part of standard care (mostly MRI, see Table 1). Brain imaging data were classified by an experienced paediatric neurologist, who was blinded to clinical data, based on the predominant pattern: a) periventricular leukomalacia (PVL; cystic and non-cystic), b) cortical infarction (full-term border-zone infarction or middle cerebral artery infarction), c) posthaemorrhagic porencephaly, d) basal ganglia or thalamic lesions, and e) non-specific lesions (e.g., ventriculomegaly) or no lesion.[13]

*Infant Motor Profile*

Motor development in infancy was assessed by means of the Infant Motor Profile (IMP).[3] The IMP is a video-based assessment that evaluates motor behaviour of infants between 3 and 18 months corrected age, or until the age at which the infant has mastered the ability to walk independently for a couple of months. Motor behaviour is assessed in supine, prone, sitting and standing and walking position. In addition, reaching, grasping and manipulation are assessed. The IMP comprises 80 items and consists of five domains: variation, adaptability, fluency, symmetry and performance. The first two domains are based on the NGST on motor development.[1] IMP domain scores are calculated as percentages of the maximum score per domain. The total IMP score is the mean of the five domain scores, however in infants aged 6 months or younger the adaptability domain is not taken into account when calculating the total score, as for most motor functions adaptability only starts to develop after the first half year of life. According to norm data from the general Dutch infant population, raw total and domain scores may be converted to percentile scores. A score below the 15th percentile (<P15) is regarded atypical. The IMP has a good construct validity, a good inter-rater and intra-rater reliability and a high predictive ability for neurodevelopmental outcome in both low-risk and high-risk populations.[3,7,9] Lastly, the IMP has a good responsiveness to change.[14,15] Although the IMP has originally been designed for infants aged 3–18 months, we also included assessments of the infants aged 2 months, since in earlier studies it turned out that the IMP could be well applied at this age.[16]

*Neurological condition at school-age*

In order to describe the children's clinical outcome at school-age, neurological condition was evaluated with the assessment of minor neurological dysfunction (MND).[17] The MND-assessment evaluates eight neurological domains: posture and muscle tone, reflexes, involuntary movements, coordination, fine manipulative ability, associated movements, sensory deficits and cranial nerve dysfunctions. The resulting neurological outcome is classified in four categories: typical, simple MND (sMND), complex MND (cMND), and abnormal, denoting the presence of a clear neurological syndrome, such as CP. sMND represents a non-optimal yet typical function of the nervous system, whereas cMND is considered the clinically relevant form of MND. The MND-assessment has good psychometric properties.[17] In children diagnosed with CP, the subtype, and gross motor function in terms of GMFCS level (Gross Motor Functioning Classification System) were also reported.[18,19]

*Functional outcome at school-age*

Our primary outcome was children's functional performance in daily life in terms of adaptive behaviour at school-age and was assessed with the Dutch translation of the Vineland Adaptive Behavior Scales, second edition (Vineland-II) expanded version.[20,21] We used daily functioning as our primary outcome since it addresses what matters most: how the child functions in daily life. In addition, it reflects multiple aspects of neurodevelopment and is therefore a common outcome measure in populations at high risk of neurodevelopmental disorders.[22] The Vineland-II is a structured parental interview that evaluates children's functional and adaptive behaviour in four domains: communication, daily competences, socialization and motor skills.[20] Each item is scored from 0 (never) to 4 (almost always). Vineland's total score is calculated by adding up the scores of the four domains and has a maximum of 2376. A higher score indicates a better performance. Most of the Vineland interviews were performed face-to-face, but occasionally, due to COVID-induced limitations, by means of telephone interview.

*Cognitive outcome at school-age*

Cognitive outcome was assessed with the Revisie Amsterdamse Kinder Intelligentietest 2 (RAKIT-2). The RAKIT-2 is a reliable, valid and norm-referenced assessment of cognitive function in children aged 4 to 12.5 years.[22] We used the short version, which is suitable for children with limited attention abilities and motor impairments. It consists of six subtests covering domains of perceptual reasoning, verbal learning, visual orientation, and verbal fluency. Raw total scores were converted to standardised scores with a mean of 100 and standard deviation of 15. We used the total standard score, i.e., the short RAKIT intelligence quotient (IQ) that provides an indication of the child's cognitive development. A total IQ ≥ 85 represents a typical cognitive outcome, a total IQ between 70 and 84 a mild cognitive delay, and a total IQ < 70 a definitive delay.

### Statistical analyses

At 21 months CA, there was no significant difference in developmental outcome between infants who received the COPCA intervention and infants who were treated with traditional infant physiotherapy.[10,11] Therefore, in the current study the groups were pooled to evaluate associations between motor behaviour in infancy (assessed with the IMP) and developmental outcome at school-age (assessed with Vineland and RAKIT). Sample size estimation was based on the follow-up study of another group of high-risk infants that also used the Vineland as outcome measure.[24] It revealed that a minimum of 36 (2 × 18) children would allow for the detection of a statistically significant difference in Vineland scores between children with an initial IMP-score <P5 and those with a higher initial IMP-score with a power of 80 % (α=0.05, SD=15). We performed multivariable linear regression analyses, with IMP-trajectories summarised by initial IMP-scores and IMP rate of change (difference between final and initial IMP-score divided by the time interval between final and initial assessment) of total IMP-scores and IMP domain scores of variation, adaptability, and performance, as the independent variables. We a priori adjusted for sex, maternal education level, and age at follow-up. Results are presented as unstandardised coefficients B and their 95% confidence intervals (95% CI). Analyses were performed with SPSS Statistics, version 28 (Armonk, NY: IBM Corp).

## RESULTS

### Study group

Thirty-one children with a median age at follow-up assessment of 8.4 years (range 7.0–10.5) participated in the follow-up assessments. Background characteristics of the children are shown in Table 1. Twelve (28%) of the forty-three children of the original L2M0-2 cohort did not participate in the follow-up. Their background characteristics did not significantly differ from the children that participated in the follow-up (data not shown). Reasons for not participating were high care burden, COVID-pandemic induced restrictions, and time constraints of the caregivers. From the participating children, seventeen (55%) were diagnosed with CP; thirteen of them were bilaterally and four were unilaterally affected. From the children without CP, the major part (11 out of 14; 79%) had the complex form of MND (Table 1).

**TABLE 1** BACKGROUND CHARACTERISTICS

| | n=31 |
|---|---|
| boys / girls | 18 / 13 |
| gestational age in weeks, median (min-max) | 30.3 (25.9-41.3) |
| birth weight in grams, median (min-max) | 1550 (720-4410) |
| maternal education [a]: low / middle / high, n (%) | 5 (16) / 15 (48) / 11 (35) |
| neonatal brain imaging, n (%) | |
| MRI / cranial ultrasound | 25 / 6 |
| type of brain lesion | |
| posthaemorrhagic porencephaly | 7 (23) |
| PVL: cystic / non-cystic | 9 (29) / 4 (13) |
| basal ganglia/thalamus | 3 (10) |
| cortical infarction | 2 (6) |
| no/non-specific lesion | 6 (19) |
| IMP-scores <P5, n (%) | |
| initial | |
| total | 15 (48) |
| variation | 30 (97) |
| adaptability [b] | 7 (23) |
| performance | 5 (16) |
| final | |
| total | 28 (90) |
| variation | 26 (84) |
| adaptability [b] | 22 (71) |
| performance | 17 (55) |
| intervention during infancy: TIP / COPCA | 12 / 19 |
| age at follow-up assessment in years, median (min-max) | 8.4 (7-10.5) |
| neurological condition at school-age, n (%) | |
| typical | 0 |
| simple MND | 2 (6) |
| complex MND | 11 (35) |
| no CP but MND unknown | 1 (3) |
| CP | 17 (55) |
| GMFCS I / II / III / IV / V / unknown | 3 / 4 / 0 / 6 / 2 / 2 |
| uni spastic / bi spastic / bi atactic | 4 / 12 / 1 |

[a] Level of highest completed education. Low: no or only primary education, primary or lower forms of secondary vocational education and training. Middle: higher forms of secondary vocational training, senior general secondary education and university preparatory education. High: vocational college and university.

[b] For the adaptability domain we used P15 for this domain conform the IMP-manual.[3]

Uni: unilaterally, bi: bilaterally, TIP: typical infant physiotherapy.

## Infant motor behaviour: IMP-scores

Most children had four (n=15) or five (n=15) IMP-assessments during infancy and one child had three assessments, resulting in a total of 138 IMP-assessments. There was a high prevalence of atypical total IMP-scores: 127 assessments (92%) were below the 15th percentile, of which 106 (76.8%) below the 5th percentile. At the initial and the final assessment these proportions were 81% (<P15) and 48% (<P5), and 94% (<P15) and 90% (<P5), respectively (Table 1). In Fig. 1, the individual trajectories of IMP-scores are shown. On average, all infants showed an increase of total IMP-scores and IMP performance scores with increasing age. In the domains variation and adaptability, the scores of most infants improved with increasing age, but in some infants scores decreased. The median rates of change for total IMP-score and the three domains (variation, adaptability, and performance) were 0.63 (total), 0.11 (variation), 0.91 (adaptability) and 2.23 (performance).

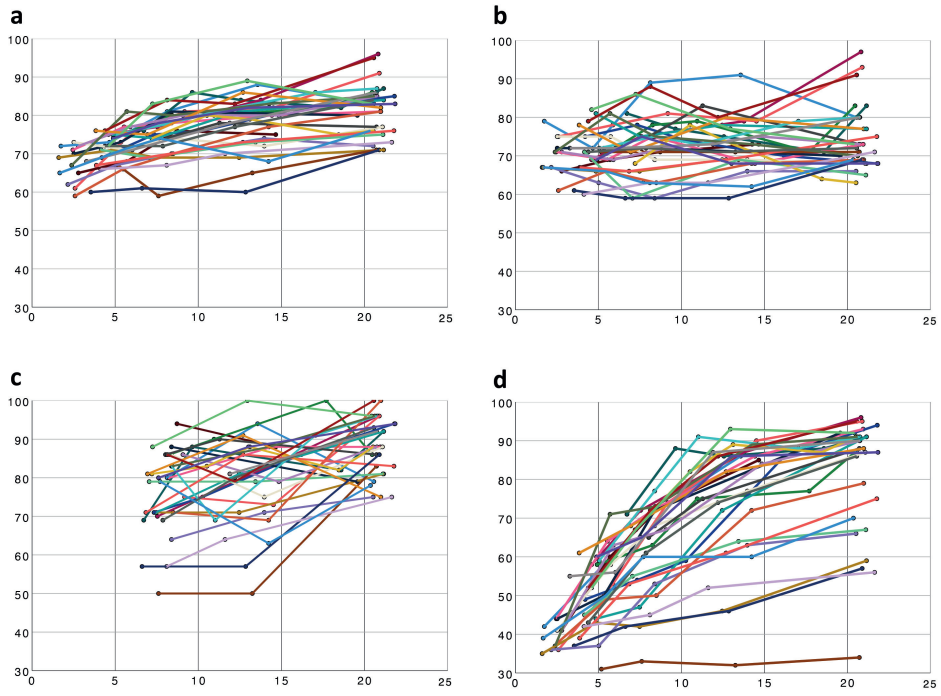


**FIGURE 1** INDIVIDUAL TRAJECTORIES OF IMP-SCORES BETWEEN INITIAL AND FINAL ASSESSMENT IN INFANCY

Individual trajectories of Infant Motor Profile (IMP) scores: (a) total IMP, (b) variation, (c) adaptability, (d) performance. The horizontal axes indicate the corrected age (CA) in months; the vertical axes the IMP-scores. Individual lines represent developmental changes in individual infants.

## IMP-scores and functional outcome at school-age

The Vineland-II was completed in 30 of the 31 children. Median total score was 1632 (range 242–2014) out of a maximum of 2376. Two children had severely outlying Vineland scores (scores 242 and 288) and were excluded from subsequent analyses. Higher initial scores and higher rates of change of total IMP-scores and the IMP domain scores of variation and performance were significantly associated with better Vineland scores when corrected for covariates (Table 2). No effect of adaptability trajectories on the Vineland at school-age was found.

## IMP-scores and cognitive outcome at school-age

The RAKIT was completed in 25 of the 31 children. Median RAKIT score was 79 (range 44–121). A typical cognitive outcome was seen in 10 children (40%), 8 (32%) had mild cognitive delay, and 7 (28%) definitive delay. No effect of trajectories of total IMP-scores on RAKIT scores was found. The same held true for the models on the associations between the IMP domains adaptability and performance and RAKIT scores. However, when corrected for initial IMP variation scores, a higher rate of change of the IMP variation score was significantly associated with better RAKIT scores (coefficient B=34.81, 95% CI=16.58-53.03; Table 3).

**TABLE 2** MULTIVARIABLE LINEAR REGRESSION ANALYSES OF THE EFFECT OF RATE OF CHANGE IN IMP-SCORES ON VINELAND SCORES AT SCHOOL-AGE

| | unstandardised coefficient B (95% CI) | | |
|---|---|---|---|
| | total IMP-score | IMP variation | IMP performance |
| constant | -1737.70 (-3202.73 to -272.66) | -1072.83 (-2413.54 - 267.88) | 5.38 (-1054.47- 1065.23) |
| **initial IMP-score** | 36.44 (19.60 - 53.28) | 33.46 (17.43 - 49.49) | 16.52 (7.58 - 25.46) |
| **IMP rate of change** | 513.15 (262.51 - 763.79) | 356.70 (148.24 - 565.15) | 269.00 (130.57 - 407.43) |
| sex | -158.34 (-330.21 - 13.54) | -183.57 (-400.26 - 33.11) | -67.27 (-251.48 - 116.94) |
| maternal education | | | |
| middle | -21.21 (-246.26 - 203.84) | -106.71 (-343.92 - 130.51) | -45.69 (-288.57 - 197.19) |
| high | 76.19 (-168.41 - 320.78) | 5.38 (-268.10 - 278.85) | 61.68 (-192.56 - 315.92) |
| age at follow-up | 5.96 (-2.52 - 14.44) | 4.79 (-4.33 - 13.90) | 2.77 (-6.00 - 11.54) |

Sex: male=1, female=2. Low maternal education was taken as the reference group in the regression analyses. IMP Rate of change: difference between final and initial IMP-score divided by the time interval between final and initial assessment. 95% CI: 95% confidence interval. IMP: Infant Motor Profile. The variables indicated in bold are the IMP-variables of interest.

**TABLE 3** MULTIVARIABLE LINEAR REGRESSION ANALYSES OF THE EFFECT OF RATE OF CHANGE IN IMP-SCORES ON RAKIT SCORES AT SCHOOL-AGE

| | unstandardised coefficient B (95% CI) |
|---|---|
| | IMP variation |
| constant | -25.84 (-140.64 - 88.95) |
| **initial IMP-score** | 1.67 (0.06 - 3.27) |
| **IMP rate of change** | 34.81 (16.58 - 53.03) |
| sex | -7.41 (-25.48 - 10.67) |
| maternal education | |
| middle | -11.32 (-31.34 - 8.70) |
| high | 11.38 (-13.00 - 35.76) |
| age at follow-up | -0.07 (-1.03 - 0.88) |

Sex: male=1, female=2. Low maternal education was taken as the reference group in the regression analyses. IMP Rate of change: difference between final and initial IMP-score divided by the time interval between final and initial assessment. 95% CI: 95% confidence interval. IMP: Infant Motor Profile. The variables in bold are the IMP-variables of interest.

## DISCUSSION

In our study group of children at high risk of neurodevelopmental disorders, we found that better motor development in infancy, summarised by higher initial scores and higher rates of change in scores of the total IMP and the domains of variation and performance, was associated with better functional outcome at school-age. IMP-trajectories were hardly associated with cognitive outcome: only positive rates of change in IMP variation scores were associated with better cognition at school-age. The high-risk nature of our group was not only reflected by the finding that at the final IMP assessment the large majority of infants (90%) had total IMP-scores <P5, but also by the high prevalence of CP (55%) and complex MND (35%) at school-age. Trajectories of total IMP-scores were clearly associated with Vineland scores as measure of functional outcome, but not with cognition at school-age. Total IMP-scores are based on the domain scores. In particular the trajectories of the IMP variation and performance domains were associated with better functional outcome. IMP's variation domain scores reflect the integrity of the nervous system, and specifically the connectivity in cortical-subcortical neural networks,[25,26] whereas performance domain scores reflect the net result of what the brain networks are able to accomplish in terms of motor skills. Especially these domains are related to neurodevelopmental outcome in high-risk infants.[6,7] The current results indicate that better initial scores, which conceivably reflect a lesser impact of the brain lesion on brain function, are associated with better functional outcomes. The associations between higher rates of change and better functional outcome suggest that the children's capacity to grow out of a deficit is associated with better outcome. In addition, it reflects that some children grow into a deficit; low positive rates of change, lower than typical for age, and - in particular in the variation domain - negative rates of change contributed to the association between rate of change and functional outcome. IMP-trajectories showed only a minor association with cognition at school-age. In fact, our study was not powered for finding associations between IMP-scores and cognition. We did not find associations between IMP adaptability trajectories and outcome at school-age. In low-risk infants adaptability scores are associated with cognition at school-age.[9] It is conceivable that the combination of the small group size and the very high-risk nature of our group precluded the finding of associations between adaptability and outcome. It is well known that children with an early lesion of the brain have major problems in the adaptability domain. Therefore, they need more trial-and-error experience to master adaptive behaviour.[27–29]

### Strengths and limitations

The major strength of our study is the longitudinal assessment of specific domains of motor behaviour in infancy and functional and cognitive outcome at school-age in a clinically very well-documented group of children at very high risk of neurodevelopmental disorders. The study's main limitation is the small size of the study group, which was aggravated by RAKIT data lacking for some children due to COVID-induced limitations hampering on-site assessment. For the Vineland, we could replace a face-to-face conversation by a telephone interview, therewith preventing further loss of data. The small study group also precluded the use of latent growth

modelling, as we did in previous studies on associations between early motor behaviour and later outcome in low-risk children.[8,9]

## Concluding remarks

Our study indicated that in children at very high risk of neurodevelopmental disorders developmental trajectories of variation and performance in motor behaviour during infancy are associated with functional outcome at school-age. Developmental changes in variation in motor behaviour were associated with cognition at school-age. Variation and performance are motor domains assessed with the IMP. This means that the IMP is not only an excellent instrument to evaluate the effect of early intervention,[15,30,31] but also an adequate tool to monitor developmental progress and to predict neurodevelopmental outcome in high-risk infants.

## DECLARATION OF COMPETING INTEREST

None

## ACKNOWLEDGEMENTS

We thank all the families for their enthusiastic participation in the current follow-up study of L2M0-2. L2M0-2 was part of the Dutch national LEARN2MOVE research program. We gratefully acknowledge the accurate collection of the infant data by the members of the L2M0-2 years team, the assistance of Anneke Kracht-Tilman in data collection in the current follow-up study, and the Kinderacademie for calculation of the RAKIT scores.

## STATEMENT OF FINANCIAL SUPPORT

L2M0-2 was part of the Dutch LEARN2MOVE research program and was financially supported by ZonMW (89000002), JKF Kinderfonds, Stichting Rotterdams Kinderrevalidatie Fonds Adriaanstichting, Revalidatiefonds, Phelps Stichting, Revalidatie Nederland, and the Nederlandse Vereniging van Revalidatieartsen. EJMS was financially supported by the Junior Scientific Masterclass Groningen. None of the funders were involved in study design, data collection, data analysis, manuscript preparation and/or publication decisions.

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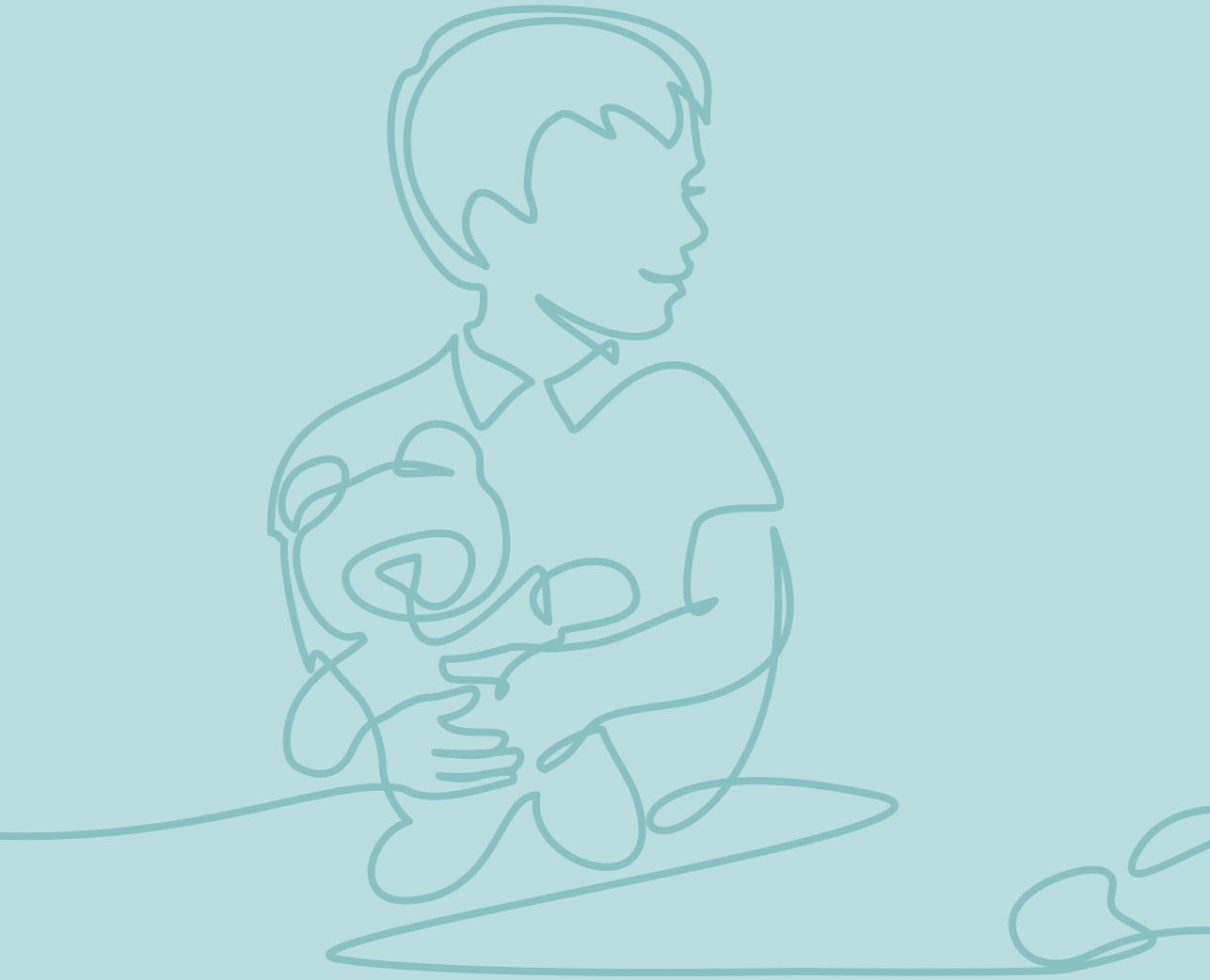

# 7

# General discussion

The aim of this thesis was to evaluate neurological signs in infancy in terms of their prevalence, associations with neurodevelopmental condition and long-term outcome. By evaluating specific neurological phenomena, we intended to get a better understanding of their underlying pathophysiological mechanisms and clinical significance, and to enhance early identification of children at risk of neurodevelopmental disorders, in particular cerebral palsy (CP). To this end we studied children who participated in either the IMP-SINDA project or the LEARN2MOVE 0-2 years study (L2M0-2). The IMP-SINDA project was originally designed to collect normative data of two novel neurodevelopmental assessments in the general infant population: the Infant Motor Profile (IMP) and the Standardized Infant NeuroDevelopmental Assessment (SINDA). The L2M0-2 study was initially set up to evaluate the effect of two physiotherapeutic interventions in a group of infants with a very high risk of neurodevelopmental disorders. Additional to their original aims, these projects offered a great opportunity to study early neurological development. Here, in the general discussion of the thesis, I start with a reflection on the main findings and discussion of their clinical implications per chapter. Thereafter, I review the methodological considerations and discuss suggestions for future research per part. I finish with concluding remarks.

## Part 1
## Early neurological development in the general infant population

### Reflection on main findings and clinical implications

In **chapter 2** we assessed in the general infant population the clinical meaning of a prevailing head position to one side. A prevailing head position occurred in 20% of the infants during the first half year of life, with its prevalence steadily decreasing from 49% at the age of 2 months to 0% at 6 months. In this low-risk population, it was only weakly associated with perinatal risk factors. Yet, a prevailing head position to one side was in infants aged 4-5 months associated with less optimal reaching and grasping behaviour.

The research group of Boere-Boonekamp studied positional preference in the general population two decades ago.[1] They also reported a decrease in prevalence with increasing age: from 10% in infants younger than 8 weeks to 3% in infants between 16 and 26 weeks. Both their and our results underline that proper head control needs time to develop: the phase in which the typically developing infant learns to adapt head movements to the specifics of the situation is entered from 3 to 4 months onwards.[2,3] Our results are thus in line with previous observations that a prevailing head position in young typically developing infants is often a transient phenomenon without serious clinical implications.[4,5,6] Our higher prevalence numbers may be explained by the fact that we applied a broader definition of a prevailing head position than Boere-Boonekamp and colleagues did: we assessed head position of infants in supine, sitting and prone, while they took only supine position into account. Thus, in our study, more infants fulfilled the criteria of a prevailing head position. The add-on of our study

is that we evaluated the effect of age on the association between a prevailing head position and functional performance, i.e., reaching and grasping behaviour: only in the infants aged 4 to 5 months, a prevailing head position was associated with less optimal functional behaviour.

The focus of our study was on spontaneous active movements of the head. Many other studies focussed on the clinical meaning of a cranial deformation, mainly plagiocephaly, which means that they took into account the shape of the head rather than its movements.[7-10] Outcomes of those studies also suggest that a persisting head preference during infancy, or a head preference co-occurring with plagiocephaly, is associated with an increased risk of developmental delay. A cranial deformation is increasingly considered as a marker for developmental delays, instead of causing them.[7-9] To assess the severity of the prevailing head position and association with other neurodevelopmental domains, clinical assessment is required. A persisting asymmetry in the shape and/or movements of the head could be an expression of pathology of the nervous system.[11] It also directly interferes with optimal motor development since it hinders the infant in exploring its own body and environment.[12]

*Conclusion and clinical implications*

In Western Europe, a prevailing head position is one of the most common reasons for referral to paediatric physiotherapy,[13-15] as it can cause concerns in caregivers about the cosmetic appearance of their infant's head and face and may have consequences for later physical and psychosocial development.[7,15,16] Therefore, our results are particularly relevant for health professionals who work with infants and toddlers in primary health care. In the Netherlands, routine check-ups of young children are organized in well-baby clinics. Well-baby clinics have an important role in monitoring and surveillance of development, as well as in caregiver counselling on motor development. The latter includes head control in the youngest infants.[15] Increased awareness among clinicians that a prevailing head position in otherwise healthy infants often belongs to typical development may help to reassure caregivers. The findings of our study contribute to such awareness and therewith provide clinical guidance. For infants with a prevailing head position who are younger than 4 months, we recommend caregiver advices on how to promote symmetrical head position, e.g., by applying variation in positioning and carrying the infant. In infants aged 4 months and older who have a prevailing head position, we recommend a) screening for additional neurodevelopmental signs, for example the presence of an evident asymmetry in neuromotor behaviour in general, or a clear delay in motor milestone attainment, and depending on the outcomes b) referral to paediatric physiotherapy for more extensive caregiver counselling.[4,17,18]

In **chapter 3**, we found that atypical muscle tone in one or two body parts is common in the first year of life in the general population: we observed this phenomenon in 50% of the infants. The prevalence of muscle tone impairments did not decrease with increasing age. Eight percent of the infants showed an atypical muscle tone in three or four parts of the body. This so-called impaired pattern was associated with a less optimal neurodevelopmental condition.

The high prevalence of an atypical muscle tone in one or two body parts together with its lack of associations with perinatal risk or problems in other neurological domains indicates that atypical muscle tone in one or two body parts represents typical but non-optimal neurological development. Our prevalence numbers are comparable with those of Romeo and colleagues, who assessed low-risk late preterm and full-term infants shortly after birth. They found a prevalence of an atypical muscle tone in various parts of the bodies of 25-50%.[19,20] It should be noted that Romeo and colleagues assessed preterm infants, who generally show more often impairments in muscle tone regulation than term-born infants.[21] Another study in older children reported a lower prevalence of atypical muscle tone: Goo and colleagues performed a review in which they evaluated psychometric properties of muscle tone assessments in children from the general population aged 0 to 12 years. They found a prevalence of evident atypical tone of 5-8%, which is comparable with the prevalence of the pattern that we consider clinically relevant, namely the pattern with an atypical muscle tone in three or four parts of the body. This was the pattern that in our study was associated with a less favourable neurodevelopmental condition. In addition, we found that an atypical tone in three or four parts of the body was associated with well-known risk factors for neurodevelopmental disorders, namely preterm birth and being small or large for gestational age.[22-24]

*Conclusion and clinical implications*

Just like our results of **chapter 2** on a prevailing head position, our findings of **chapter 3** are particularly interesting for professionals in primary health care. It is important that they are aware that atypical muscle tone in one or two parts of the body in low-risk infants is a common finding without clinical significance. Our study also indicates that atypical muscle tone in three or four body parts is clinically relevant, and only present in a small percentage of children in the general population. This finding underscores the general notion that neurological signs get clinical significance only when they occur in combination with other neurological impairments.[25,26] An accumulation of neurological signs in multiple body parts and across neurological domains, requires the need for further investigation, including medical history taking and neuroimaging. Depending on these findings the need of early intervention for infant and family is considered.[27]

## Methodological considerations

Major strengths of the first two studies of this thesis are the large size of the study groups and the representativeness of the Dutch population in terms of parental education level, ethnical background and perinatal characteristics.[27-29] The first two studies contribute to a better comprehension of neurological signs in the general population. Research on neurological signs in the general population is scarce because it requires large groups of children. Yet, it is the only way to determine the prevalence of neurological signs in the general infant population and to explore associations between those signs and the infant's neurodevelopmental condition. A particular strength of **chapter 3** is that we assessed and described muscle tone in four different body parts. This offered the opportunity to explore which specific muscle tone patterns have clinical relevance.

A limitation of the studies inherent to their cross-sectional design, is that infants were only assessed once which means that information on further neurodevelopment throughout infancy was not collected. Yet, a single SINDA assessment gives a good impression of the infant's neurodevelopment. Especially, an at-risk score on SINDA's neurological scale, which is independent of infant age, is a reliable predictor for atypical developmental outcome, such as CP and intellectual disability.[27,30] It can be regarded another limitation that we did not systematically collect information on early intervention including physiotherapy: we do not know whether and to what extent physiotherapy intervention influenced the infant's neuromotor condition. On the other hand, with the current knowledge we do know that the contribution of paediatric physiotherapy to the reduction of a prevailing head position in otherwise healthy infants is minor at best.[10,15,31]

## Suggestions for future research

In order to better appreciate the clinical value of a prevailing head position and muscle tone impairments in infancy, and to evaluate the natural course of those neurological signs as well as their associations with later neurological, functional and cognitive outcome, it would be interesting to extent our studies in the well-documented IMP-SINDA group with a follow-up assessment at school-age. Follow-up data could not only be helpful in tailoring early caregiver counselling and eventual physiotherapeutic intervention in infants with neurodevelopmental signs; it will also provide information on predictive abilities of the IMP and SINDA for developmental outcomes later in childhood in the general population, as until now, studies evaluating their psychometric properties and responsiveness to change were mainly performed in high-risk populations or limited by a small sample size.[27,29,32] Currently the follow-up of the IMP-SINDA project is running – Biomarkers in Infants at risk of Developmental disorders (BIRD) – in which the children are reassessed with neurological, motor and cognitive assessments at the age of 4-6 years, which offers the opportunity to address the above-mentioned questions.

## Part 2
## Early neurological development in the general infant population

### Reflection on main findings and clinical implications

Part 2 of the thesis describes development of muscle tone, reflex organisation and early motor behaviour in a group of children at very high risk of neurodevelopmental disorders who had participated in L2M (hereafter referred to as VHR-children). The high risk was mainly due to the presence of an evident early brain lesion and/or clear neurological dysfunction. Evaluation of these aspects of neuromotor development is relevant in children at high risk, because such knowledge may contribute to a better understanding of atypical child development and may provide clues for early detection of CP and early intervention of children at very high risk.

In **chapter 4** we found that the prevalence of an atypical muscle tone in three or four parts of the body in infants at very high risk of CP is high: it occurred in more than 90% of the assessments in the VHR-children that participated in L2M. Especially during the first half year of life, presentation of muscle tone impairments varied largely. At early age the various patterns were not associated with CP, but from 7 months corrected age onwards hypertonia in the arms was significantly more prevalent in infants who were later diagnosed with CP than in infants who were not. Hypertonia of the legs was continuously associated with the presence of cystic PVL (cPVL) but not with CP.

Hypertonia in the extremities was the most prevalent muscle tone impairment throughout infancy in our high-risk study group. Also in children with CP hypertonia is the most prevalent form of muscle tone impairment.[33,34] The neural substrate of hypertonia in CP presumably relies on disruption of the muscle tone feedback cycle due to central damage, resulting in increased excitatory, and/or decreased inhibitory synaptic output.[35] Yet, the early clinical presentation of our VHR-children who were later diagnosed with CP was not so uniform, since we found a high variety in patterns of muscle tone impairments during the first 6 months of life. Our data also indicated that with increasing age a decrease in prevalence of hypotonia in the extremities occurred in parallel with an increase of hypertonia prevalence. None of the patterns of muscle tone abnormalities in the first six months of life distinguished high-risk children who got later diagnosed with CP from those who were not. However, from the second half of the first year onwards, hypertonia in the arms was significantly more prevalent in infants who were later diagnosed with CP. Our results are in line with previous studies stating that it takes time for signs of CP to manifest clinically: they gradually emerge during infancy and their presentation during early life is heterogeneous.[36,37]

Children with CP had a higher prevalence of hypertonia in the arms than their peers without CP and not in their legs. A likely explanation for the relatively early association between hypertonia of the arms and CP is the following. The brain parenchyma of the primary motor areas of the arms – with the arms having a larger cortical representation than the legs – is susceptible to

haemorrhage or infarction, due to its blood and oxygen supply by distal cortical branches of the anterior and middle cerebral arteries.[38,39] The reason that from the second half year of life onwards hypertonia in the arms, and not in the legs, differentiates between children who got diagnosed with CP and those who were not, may be that the larger cortical area representing the arms offers more opportunity for early recovery of (mildly) affected parts in the children who were not diagnosed with CP, due to the bigger surface area as such, or because of early recruitment of cortical collaterals.[40] Additionally, the high prevalence of hypertonia of the legs throughout infancy in both the group that developed CP and in the group that did not, suggests that the cortical area in charge of motor control of the legs is more prone to early damage than that of the arms, or that damage in the motor area of the legs results more easily and/or for a longer period of time in an atypical muscle tone (i.e., hypertonia). Thus, our study suggests that in VHR-infants hypertonia in the legs during infancy is not a significant measure that distinguishes children who will get the diagnosis of CP and those who are not.

Interestingly, the pattern with hypertonia in the legs was throughout infancy associated with the presence of cystic PVL, the type of brain lesion that is most strongly associated with the diagnosis of CP.[41] The association between cystic PVL and hypertonia in the legs most likely is based on the finding that in cystic PVL especially the parts of the corticospinal tract are damaged that are located near the posterior parts of the brain's lateral ventricles which are responsible for motor control of the legs.[42] Despite the association between hypertonia in the legs and cPVL this muscle tone pattern was in our study not associated with CP. This is probably due to the fact that 11 of the 20 infants diagnosed with CP had a brain lesion other than cystic PVL**.** This relatively large contribution of other brain lesions that were associated with different muscle tone patterns presumably precluded a clear association between hypertonia in the legs and CP.



*Conclusion and clinical implications*

Our study in very high-risk infants supports the finding in our low-risk infant group that muscle tone impairments in 3 or 4 body parts are clinically relevant. It is a marker of an increased risk of a neurodevelopmental disorder.[43-47] Our results underline that virtually all children with CP already show evident muscle tone impairments in infancy, but not all infants with evident muscle tone impairments will be diagnosed with CP.[46] Additionally, during the first half year post term the patterns of muscle tone impairment are heterogeneous and do not predict CP. Based on our results, we recommend that clinicians in well-baby clinics, paediatric physiotherapists, and paediatricians who assess high-risk infants, document the development of atypical muscle tone over time and assess whether the infant shows abnormalities in other neurodevelopmental domains. From the second half of the first year onwards, specific patterns start to be associated with CP: especially the presence of hypertonia in the arms assists the prediction of CP. More generally, infants who present with persisting atypical muscle tone in three or four body parts, persisting hypertonia in arm(s) or leg(s), and/or deviations in other neurodevelopmental domains, warrant referral for further diagnostics, close monitoring and

– in general – early intervention. Our studies focussed on muscle tone. This does however not imply that we discard the evaluation of the quality of spontaneous movements. In fact, it has been well documented that assessment of the quality of spontaneous movements in infancy is a reliable tool for detecting infants at high risk of CP. A proper infant neurological assessment includes both evaluation of the quality of spontaneous movements and assessment of muscle tone (see e.g., [27]). Note that the latter does not only assist in identifying primary disorders of the central nervous system such as CP, but is also essential in identification of peripheral neurological disorders, such as infant hypotonia due to disorders of anterior horn cells, peripheral nerves, neuromuscular junctions or muscles.[48,49]

Our findings of the knee jerk study described in **chapter 5** shed light on possible mechanisms underlying typical and atypical development of the nervous system in terms of hyperreflexia and hypertonia. We found a decrease in prevalence of tonic responses and contralateral phasic responses between infancy and school-age. At school-age, their presence was no longer associated with the diagnosis of CP and their prevalence in VHR-children was similar to that in typically developing (TD) children. Only clonus occurred more often in VHR-children without CP than VHR-children who were diagnosed with CP.

In the knee jerk studies that were carried out during infancy, tonic responses (TRs), clonus and contralateral phasic responses occurred more often in VHR-children than in TD-children.[50,51] The prevalence of these responses decreased in all VHR-children during infancy,[51] yet significantly slower in infants who later got diagnosed with CP, suggesting a possible contribution of atypical knee jerk reflexes in the prediction of CP. In the current study, described in chapter 5, we report that the decrease in prevalence of TRs and contralateral responses continued between infancy and school-age. Our results confirm that hyperexcitability of the reflex pathway decreases with increasing age. This is a well-known phenomenon in typically development.[52-54] In CP, hyperexcitability often persists into childhood and can be expressed as hyperreflexia, one of the main characteristics of spastic CP.[33,34,55] Nevertheless, also our VHR-children, including the children with CP, showed a decrease in hyperexcitability. In contrast to what we expected based on the literature that describes vivid reflexes in children with CP,[33,34,55] we did observe a high threshold and low intensity of the knee jerk reflex in some children with CP with high GMFCS-levels. The clinical observation of lower reflex activity than expected got confirmed and further specified by the EMG-recordings, where we found that VHR-children with the highest GMFCS-levels had a lower clonus prevalence than VHR-children without CP. Our findings are in line with those of Dimitrijevic, who reported that clonus is less likely to occur when the muscle is exceedingly hypertonic.[56] Our counterintuitive finding of children with severe spastic CP showing less clear phasic and clonus reflex responses may be explained by morphological changes in hypertonic muscles in children with severe spastic CP,[57,58] such as a reduced number of sarcomeres or overstretched sarcomeres,[59] which may mask the visibility of phasic and clonic responses and/or may result in a reduced capacity of the muscle to contract in response to stretch activity.

*Conclusion and clinical implications*

Our follow-up study on the knee jerk assessment in the VHR-children yields several clinical implications. First, in contrast to what literature describes, CP is not always characterized by vivid reflexes: we observed that children with spastic CP functioning at high GMFCS levels may have tendon reflexes with a high threshold and low intensity. This observation illustrates the heterogeneity in clinical presentation of children with CP, and underlines the clinical add-on of evaluation of reflexes as part of the neurological examination. Second, we found that at group level, not only in typically developing children but also in children with CP, motoneuronal hyperexcitability decreases with increasing age. This implies that with increasing age, in general less tonic and clonic responses will be observed during the neurological examination. Third, our results suggest that the presence of tonic responses at early age is an indicator of an increased neurodevelopmental risk. TRs' assistive role in prediction of CP is taken over later in childhood by the presence of other clinical signs, such as hypertonia, which takes time to manifest clinically.

In **chapter 6** we found that in VHR-infants, trajectories of specific IMP-scores were associated with functional outcome and - to a minor extent only - to cognitive outcome at school-age. More specifically, better starting conditions reflected by higher initial IMP-scores, and a stronger improvement of IMP-scores in the domains that reflect the size of the motor repertoire (variation) and achievement of motor milestones (performance) were associated with better functional outcome. A higher rate of change of IMP variation scores during infancy was associated with better cognitive outcome.



Assessment of early motor behaviour by means of the IMP is a useful and reliable method in early detection of children at high risk of neurodevelopmental disorders.[29] Impaired infant motor development does not only indicate an increased risk of a neurodevelopmental disorder for example due to early brain injury;[60-62] it often also directly interferes with the infant's abilities to acquire new skills and interact with its environment, which puts the child at an additional risk of a general developmental delay, including motor, cognitive and language domains.[63] Our findings show that not only quantitative (IMP's performance domain) but also qualitative (IMP's variation domain) aspects of infant motor development are associated with later functional outcome, and thus are a helpful marker in early detection of children at high risk of neurodevelopmental disorders. In particular, we found that higher initial IMP variation scores and higher rates of change in variation scores were associated with better functional and cognitive outcome at school-age. IMP's variation domain reflects the size of the child's motor repertoire, and gives an impression about the brain's subcortical-cortical connectivity.[29] Thus, our results suggest that a less severe reduction of the motor repertoire in early infancy - indicating a limited impact of the brain lesion on the child's motor function - is associated with better functional outcome. In addition, the association between the changes in variation score and Vineland scores suggest that children whose variation score decreased, i.e., who grew into a deficit, had a less favourable functional outcome, whereas the children in whom the scores improved, i.e., who showed

signs of growing out of their deficit, had a more favourable outcome.[64,65] We also observed an association between IMP performance scores and later functional outcome. Also here, better initial scores and higher rates of changes were associated with better functional outcome at school-age. Conceivably, better initial performance scores reflect - just as better initial variation scores - a limited impact of the brain lesion on the child's functioning. The association between higher rates of change in performance scores and functional outcome means that children who are able to profit most from experience and who are able to use experience to develop motor skills, are the ones who have the most favourable functional outcome at school-age. This corresponds to the general notion that a slower attainment of motor milestones during infancy is an early indicator of an increased risk of a neurodevelopmental disorder such as CP, in which impairments in functional abilities at different ages are common.[34]

*Conclusion and clinical implications*

Our results indicate that the rate of change and direction, i.e., an increase or decrease, of motor development in infancy in VHR-children are associated with daily and cognitive functioning at school-age. First, we found that early motor development measured with the IMP reflects the effect of an early brain lesion and functional plastic activity on the brain's integrity and functioning.[66-68] Second, our study also elaborates on conclusions of previous studies, showing that the IMP is a sensitive instrument to measure both quantitative and qualitative aspects of motor development, which are both significant markers for later developmental outcome, including impaired cognitive outcomes, in VHR-children.[32,69] Our findings emphasize the need for early intervention programmes for VHR-children that allow children to explore the environment and the possibilities and challenges of their own body, as rates of change in motor development are associated with better functional outcome.[70]

## Methodological considerations

The longitudinal design of the L2M-studies allowed us to evaluate in very high-risk children developmental changes in muscle tone impairments throughout infancy, associations between knee jerk responses in infancy and later neurological outcome, and associations between early motor behaviour and developmental outcome at school-age. The unique longitudinal data collection in this study group at very high risk, which is mainly due to an early brain lesion, made it possible to shed a light on possible pathophysiological mechanisms in children with an atypical neurological development. The inclusion of a control group in our study on the knee jerk assessment allowed us to compare reflex organisation of the VHR-children with that of their typically developing peers. Another strength of the study described in **chapter 6**, is that functioning in daily life was our main outcome. We think that this is a representative measure of how the child deals with daily activities. Its clinical relevance is reflected by the wide application of the International Classification of Functioning, Disability and Health - Child and Youth version (ICF-CY) in both research and clinical practice, indicating that in the evaluation of child development, in particular attention should be paid to outcome in daily living across multiple domains.[71]

The major limitation of the follow-up studies of L2M0-2, described in **chapter 5** and **6**, is the small study group size. The relatively high number of children who were lost to follow-up was to a large extent caused by the COVID-19 pandemic, which interfered with on-site assessment of children during the follow-up period. The pandemic increased the already high care burden of families with a child with special needs. However, the high involvement of caregivers with the project served as a buffer and prevented a still higher lost-to-follow-up rate. Caregivers of most children who could not be assessed on-site, were willing to participated by means of a phone interview. This enabled us to collect data on development of their children. The second limitation of the studies in VHR-children presented in this dissertation restricting the external validity of our findings, is the high heterogeneity in outcomes in both infancy and at school-age. The large interindividual variation among the VHR-children with CP clearly reflects CP's umbrella nature, covering a wide variety of aetiologies, types, and severity of motor and associated impairments.[34] Yet, the approximately equal number of VHR-children with and without CP, provided us with the opportunity to compare neurological parameters between both groups.

## Suggestions for future research

The study groups in the second part of this thesis, consisting of the VHR-children and addressing the fundamental processes underlying atypical neurological development, were relatively small. Hence, I suggest that future research focusses on these processes, in particular on reflex organisation and atypical muscle tone in VHR-children. Such research may facilitate understanding of especially the development of spasticity in CP. This may result in improvement of intervention in children with CP and – ultimately – may facilitate the final goal of intervention, i.e., that children with CP achieve their optimal participation potential both at home and in society.



Young people with primary disorders of the central nervous system, such as CP, experience limitations in muscle strength and selective voluntary muscle control, hyperactive muscle stretch reflexes, and spasticity.[72,73] Until now, it has not been entirely elucidated if and how these mechanisms are mutually related and to which extent they affect specific domains of functional ability (body functions and structures, activities, and participation), as described in the ICF-CY.[71] Additionally, many children with spastic CP receive different forms of treatment - including oral medication, botulinum toxin injections, intrathecal baclofen, selective dorsal rhizotomy-, often in combination with adjunctive interventions such as casting, orthoses and splints. Those treatments may affect the way in which muscle stretch reflexes and spasticity are expressed. In order to get a better insight in how these interventions work on the level of nerve-muscle interaction, and to determine the efficacy of such interventions in prevention of spasticity that interferes with daily functioning, I recommend assessment of associations between those interventions and occurrence of specific reflex responses in children with CP at different ages. This could be established by performing a prospective cohort study or large cross-sectional study, applying a similar methodology to that of ours in the study on knee jerk

reflexes during infancy and at school-age (**chapter 5**), i.e., recording muscle activity by means of surface EMG while eliciting muscle stretch reflexes, in combination with evaluation of the presence and rate of spasticity. Such information may lead to better understanding of atypical reflex organisation and development of spasticity in children with CP, to assess the potential added value of surface EMG in evaluation of this specific group of individuals, and ultimately to further improvement of tailored interventions for children with CP. Currently, surface EMG is already considered a promising tool to evaluate the efficacy of spasticity, but until now studies on application of this method are generally technical, rather than clinical.[74] I therefore encourage the recommendation to perform more research translating technical research findings into clinical practice, that focusses on possibilities to improve practical application and interpretation of the outcomes, so that surface EMG could get a more prominent role in clinical practice of children with CP.

## Concluding remarks

The studies described in this thesis contribute to a better understanding of early neurological signs in typical and atypical infant development, in particular a prevailing head position, muscle tone impairments, atypical responses to the knee jerk reflex, and motor behaviour in infancy. The results showed that it takes developmental time before the significance of the early signs for later outcome gets clear. Persistence of the signs, their occurrence in multiple parts of the body, and the occurrence of signs in multiple neurological domains, increase the predictive value for a neurodevelopmental disorder.

The studies showed that low-risk infants often show some neurological signs. For instance, low-risk infants often have an atypical muscle tone in one or two body parts. This is not associated with perinatal risk or neurodevelopmental status, implying that it may be regarded as belonging to the manifestations of typical development. On the other hand, atypical muscle tone in three or four parts of the body is considered clinically relevant, since it was associated withs specific perinatal risk factors and a suboptimal developmental condition. The studies also showed that many young low-risk infants show a prevailing head position to one side. The head preference to one side generally disappears during the first half year after birth. In the infants who do continue to show a head preference at 4-5 months, head preference is associated with perinatal risk and less optimal neuromotor behaviour. Therefore, I suggest that infants with a prevailing head position at the age of 4 of 5 months, and those with an atypical tone in 3 or 4 body parts deserve further assessment and - if needed - early intervention.

Our studies revealed that in infants at high risk of neurodevelopmental disorders the prevalence of muscle tone impairments and atypical knee jerk reflexes was and remained high during infancy. Atypical muscle tone differentiated children who were later diagnosed with CP from those who were not from the age of 7 months onwards. Atypical knee jerk reflexes, especially the presence of a tonic knee jerk, assisted prediction of CP at school-age when it persisted throughout infancy. TRs at school-age were not associated with the diagnosis of CP. Thus, in

early infancy these neurological signs do reflect the presence of a brain lesion, but they do not assist early detection of CP. In this respect, evaluation of the quality of movements, as is done in the general movement assessment (GMA), the IMP and SINDA, is a better tool to detect children who are at risk of CP.[27,29,67,68,75] From the second part of the first year post term, muscle tone and reflexes do assist the early detection of CP. Therefore, we underline the recommendation to perform the neurological examination multiple times during infancy.

In conclusion, this thesis is a valuable addition to the growing amount of knowledge in the field of early identification of infants at high risk of a neurodevelopmental disorder, in particular CP, since it provides better insight in the prevalence of early neurological signs, possible underlying mechanisms, and their associations with neurodevelopment in both low-risk and high-risk children, therewith offering clues for daily clinical practice of health care professionals working with young children.

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# 8

# Summary
# Samenvatting

# SUMMARY

Neurological development is a fascinating process which is, by definition, characterized by change. This thesis zooms in on neurological signs early in life. Neurological signs may reflect typical, but non-optimal development, but they also may indicate underlying damage of the central nervous system. At early age, the clinical significance of neurological signs is often not clear. The aim of this thesis was to shed light on the prevalence of specific neurological signs early in life and their possibly underlying pathophysiological mechanisms in order to contribute to improvement of early detection of children who are at high risk of neurodevelopmental disorders, in particular cerebral palsy (CP). To this end, we studied two groups of children. The first group consisted of infants who participated in the IMP-SINDA-project, in which normative data on two infant neurodevelopmental assessments were collected: the Infant Motor Profile (IMP) and the Standardized Infant Neurodevelopmental Assessment (SINDA). This group was representative of the general Dutch infant population. The results of the studies that we performed on the basis of this group on a prevailing head position and atypical muscle tone are presented in **chapter 2** and **chapter 3**, respectively. The second group of children had participated in the LEARN2MOVE 0-2 (L2M0-2) years project. Those children were at very high risk of neurodevelopmental disorders such as CP, mainly because of an evident brain lesion. This thesis describes their muscle tone in infancy (**chapter 4**), and a follow-up study at school-age to assess the assistive role of specific knee jerk responses in early detection of CP (**chapter 5**), and to assess associations between early motor development and later functional and cognitive outcome (**chapter 6**).

## Part 1
## Early neurological development in the general infant population

In **chapter 2** we studied the prevalence of a prevailing head position to one side in infants aged 2 to 6 months from the IMP-SINDA project (n=500). In addition, we evaluated associations between a prevailing head position and perinatal risk factors and neurological and functional condition. A prevailing head position was defined as a moderate to strong asymmetry in head position in at least two of the following positions: supine, prone and (supported) sitting. It was assessed with the IMP. We evaluated the infants' neurological condition with the SINDA. We concluded that a prevailing head position during the first half year of life is a frequently occurring phenomenon (20%) with an evident decrease in prevalence with increasing age: at 2 months of age 49% of the infants showed a prevailing head position, whereas none of the infants of 6 months of age did. Throughout the first 6 months of life its presence was only weakly associated with some perinatal conditions. Infants with a prevailing head position at 4 and 5 months showed significantly more often suboptimal reaching and grasping behaviour than their peers without a prevailing head position. The former also had more often a less optimal neurological condition than the latter. Our results are particularly relevant for health professionals in primary health care who work with young children. A prevailing head position

in otherwise healthy infants often belongs to typical development. This observation may help clinicians to reassure caregivers. Our results also provide clues for clinicians in making a well-informed decision about whether or not to refer the infant to physiotherapeutic intervention.

**Chapter 3** describes the results of our study on atypical muscle tone in infants from the general infant population aged 2 to 12 months (n=1100). We assessed muscle tone in four parts of the body: neck/trunk, arms, legs and ankles. An atypical muscle tone was defined as hypotonia, hypertonia or a changing tone at the neurological examination. We found that an atypical muscle tone in one or two parts of the body is a common phenomenon: we observed this in 50% of the infants. This pattern was not associated with perinatal risk factors nor neurodevelopmental condition. Isolated hypotonia of the legs (prevalence 8%) and isolated hypertonia of the arms (prevalence 7%) were the most common specific patterns. Eight percent of the infants had an atypical tone in three or four body parts. This pattern was associated with two perinatal risk factors, namely preterm birth and being too small or too large for gestational age, and also with a less optimal developmental condition. This means that an atypical muscle tone in three or four body parts is clinically relevant. Based on our findings, we recommend further investigation of the infant when neurological signs accumulate in multiple parts of the body and/or across neurological domains.

## Part 2
## Neurological signs and later outcome in children at very high risk of cerebral palsy

In **chapter 4** we evaluated the prevalence and development of muscle tone impairments in infants from the LEARN2MOVE project (n=39) who were at very high risk of neurodevelopmental disorders, in particular CP. In this very high-risk group, muscle tone impairments occurred in a wide variety and with a high prevalence: we observed an atypical tone in three or four body parts in 93% of the assessments. Hypotonia in the neck/trunk combined with hypertonia of the extremities was the most common pattern. During the first half year of life, the prevalence of specific muscle tone patterns did not differ between infants who were and those who were not diagnosed with CP at 21 months corrected age. From the age of 7 months onwards, hypertonia in the arms occurred more often in infants who were later diagnosed with CP than infants who were not. An asymmetry in muscle tone of the arms (for instance hypertonia in one arm and typical tone in the other) was also associated with the diagnosis of CP. Hypertonia in the legs was not associated with CP, but occurred more often in infants with cystic periventricular leukomalacia. Thus, our study shows that major part of the children with CP show significant muscle tone impairments in infancy, but not all infants with evident muscle tone impairments will be diagnosed with CP. Especially during early infancy, the presence of muscle tone impairments in very high-risk infants has limited value in prediction of CP. Our results also underline the clinical relevance of muscle tone assessment as part of the infant neurological examination.

**Chapter 5** describes the clinical meaning of specific reactions of the knee jerk reflex assessed with surface EMG in very high-risk children of LEARN2MOVE (n=31) both during infancy and at school-age. We also assessed typically developing school-aged children (n=24). First, we replicated and extended the finding of Hamer et al. (2018) that the presence of tonic responses during multiple infant assessments was associated with the presence of CP, not only at the age of 21 months, but also at school-age. Second, we found that the presence of tonic responses in infancy was not associated with the severity of CP at school-age in terms of gross motor functioning (GMFCS). In the very high-risk group, the prevalence of tonic responses decreased between infancy and school-age and became similar to that in the typically developing children. At school-age tonic responses were not associated with CP. The study also revealed that very high-risk children without CP had a higher prevalence of clonus than those with CP. This might be explained by masking of clonic responses in the latter group due to continuous muscle contraction and/or changed muscle properties. Lastly, our results indicated that in very high-risk children spinal hyperexcitability decreases with increasing age, a developmental trend that previously had been reported in typically developing children.

In **chapter 6** we evaluated if and how early motor development in children who participated in the LEARN2MOVE-project was associated with functional and cognitive outcome at school-age (n=31). We assessed early motor behaviour with the IMP expressed as total scores, and scores in the domains variation, adaptability and performance. We zoomed in on early IMP-scores (as a marker of the effect of the early brain lesion on neural function), and the rate of change in IMP-scores as a measure of developmental progression. The rate of change was defined as the difference in IMP-scores between the final and initial assessment in infancy divided by the time difference between final and initial assessment. We observed that higher initial total IMP-scores and scores on the variation and performance domain and their rates of change were associated with better functional outcome at school-age. A positive rate of change in IMP variation scores was also associated with better cognitive outcome. Despite the small size of the study group, our results suggest that in children at very high risk of neurodevelopmental disorders, motor development in early infancy reflected by early IMP-scores and the rate of change in motor development during infancy are assistive in prediction of outcome at later age.

## Conclusions

This thesis reports the prevalence of specific early neurological signs, possibly underlying pathophysiological mechanisms, and associations with function in other developmental domains in low-risk and high-risk children. By doing so, this thesis is a valuable addition in the field of early detection of children at high risk of developmental disorders. The six main findings of this thesis are:

- A prevailing head position in low-risk infants at 2 or 3 months is a frequently occurring sign with limited clinical significance. This means that actions of health professionals may be restricted to provision of information on how to promote a symmetrical head position and to reassure caregivers.
- A prevailing head position to one side in low-risk infants aged 4 or 5 months has more clinical significance. It deserves assessment of neurological condition and it may be an indication for early intervention.
- Atypical muscle tone in one or two body parts is a highly prevalent finding in infancy and has little clinical significance, whereas atypical muscle tone in three or four body parts is associated with increased perinatal risk and less favourable neurodevelopmental status.
- Very high-risk infants virtually always present with atypical muscle tone. Yet, it is first in the second half of the first year that specific atypical muscle tone patterns assist prediction of CP.
- In very high-risk children, the presence of a tonic response of the knee jerk during infancy assists the prediction of CP, but not the severity of CP.
- The Infant Motor Profile (IMP) assists prediction of developmental outcome in very high-risk children: scores in early infancy and their rates of change are associated with functional and cognitive outcome at school-age.

# SAMENVATTING

Neurologische ontwikkeling is een fascinerend proces dat continu aan verandering onderhevig is. Dit proefschrift zoomt in op de klinische betekenis van neurologische verschijnselen op jonge leeftijd. Deze verschijnselen kunnen uiting zijn van een normale, maar niet optimale ontwikkeling, maar ze kunnen ook duiden op een beschadiging van het centrale zenuwstelsel. Op jonge leeftijd is de klinische betekenis van vroege neurologische verschijnselen vaak nog niet duidelijk. Het doel van dit proefschrift was om het voorkomen van een aantal van deze verschijnselen op jonge leeftijd en de mogelijk onderliggende pathofysiologische mechanismen verder te onderzoeken, en zo bij te dragen aan verbetering van vroege opsporing van kinderen met een hoog risico op een ontwikkelingsstoornis, in het bijzonder cerebrale parese (CP). Daartoe hebben we twee groepen kinderen onderzocht. De eerste groep betreft zuigelingen die meededen aan het IMP-SINDA-project, waarin normgegevens werden verzameld voor twee meetinstrumenten waarmee de ontwikkeling op de zuigelingenleeftijd kan worden onderzocht: de Infant Motor Profile (IMP) en de Standardized Infant NeuroDevelopmental Assessment (SINDA). Deze groep zuigelingen was representatief voor de algemene Nederlandse bevolking. De resultaten van de studies die we uitvoerden in het IMP-SINDA-cohort over een hoofdvoorkeursstand en spiertonusafwijkingen staan beschreven in **hoofdstuk 2** respectievelijk **hoofdstuk 3**. De tweede groep bestaat uit kinderen die hadden deelgenomen aan het LEARN2MOVE 0-2(L2M0-2)-onderzoek. Deze kinderen hadden een zeer hoog risico op een ontwikkelingsstoornis zoals cerebrale parese (CP) met name door de aanwezigheid van een duidelijke hersenafwijking. Dit proefschrift beschrijft spiertonusafwijkingen bij deze kinderen op de zuigelingenleeftijd in **hoofdstuk 4**, het vervolgonderzoek op schoolleeftijd naar de rol van specifieke reacties bij de kniepeesreflex in vroege opsporing van CP in **hoofdstuk 5**, en verbanden tussen vroege motorische ontwikkeling en functionele en cognitieve uitkomst, eveneens op schoolleeftijd in **hoofdstuk 6**.

## Deel 1
## Vroege neurologische ontwikkeling in de algemene zuigelingenpopulatie

In **hoofdstuk 2** hebben we onderzocht wat de prevalentie is van een hoofdvoorkeursstand in de algemene zuigelingenpopulatie. Dit deden we bij zuigelingen uit het IMP-SINDA-project van 2 tot 6 maanden oud (n=500). Daarnaast onderzochten we associaties tussen een hoofdvoorkeursstand enerzijds en perinatale risicofactoren en neurologische en functionele conditie anderzijds. Een hoofdvoorkeursstand was gedefinieerd als een matig tot sterke asymmetrie in de positie van het hoofd in minimaal twee van de volgende houdingen: rugligging, buikligging, en (ondersteunde) zithouding, gemeten met de IMP. De neurologische conditie beoordeelden we aan de hand van de SINDA. We concludeerden dat een hoofdvoorkeursstand tijdens het eerste halfjaar van het leven een vaak voorkomend verschijnsel is (20%), met een duidelijke afname in prevalentie met stijgende leeftijd: op de leeftijd van 2 maanden vertoonde 49% van de kinderen een hoofdvoorkeursstand, terwijl we dat verschijnsel bij geen enkele

baby op 6 maanden observeerden. Tijdens de eerste 6 levensmaanden was het voorkomen van een hoofdvoorkeursstand slechts zwak geassocieerd met een perinatale omstandigheden. Zuigelingen van 4 en 5 maanden met een hoofdvoorkeursstand vertoonden significant minder goed reik- en grijpgedrag dan hun leeftijdsgenootjes en hadden ook vaker een suboptimale neurologische conditie. De resultaten zijn vooral relevant voor eerstelijnszorgverleners die met jonge kinderen werken. Een hoofdvoorkeursstand bij zuigelingen die verder gezond zijn is vaak onderdeel van de normale ontwikkeling. Deze observatie kan clinici helpen om verzorgers van het kind gerust te stellen, en helpt clinici ook bij het maken van een weloverwogen besluit over het al dan niet verwijzen van het kind naar de kinderfysiotherapeut.

**Hoofdstuk 3** beschrijft de uitkomsten van ons onderzoek naar afwijkende spiertonus bij zuigelingen van 2 tot 12 maanden uit de algemene populatie (n=1100). We beoordeelden de spiertonus in vier lichaamsdelen: de nek/romp, armen, benen en enkels. Een afwijkende spiertonus was gedefinieerd als hypotonie, hypertonie of een wisselende tonus bij het neurologisch onderzoek. We vonden dat een afwijkende spiertonus in een of twee lichaamsdelen vaak voorkomt: 50% van de zuigelingen liet dit zien. Dit patroon was nauwelijks geassocieerd met perinatale risicofactoren en neurologische ontwikkeling. Geïsoleerde hypotonie in de benen (prevalentie 8%) en geïsoleerde hypertonie in de armen (prevalentie 7%) waren de meest voorkomende patronen. Acht procent van de kinderen had een afwijkende spiertonus in drie of vier lichaamsdelen. Dit patroon was geassocieerd met twee perinatale risicofactoren, namelijk vroeggeboorte en een geboortegewicht dat te laag dan wel te hoog was voor de zwangerschapsduur, en lagere ontwikkelingsscores. Daarom beschouwen we een afwijkende spiertonus in drie of vier delen van het lichaam als klinisch relevant. Op basis van onze bevindingen raden we aan om zuigelingen uitgebreider te onderzoeken wanneer neurologische verschijnselen voorkomen in meerdere lichaamsdelen en/of in meerdere neurologische domeinen.



## Deel 2
## Neurologische verschijnselen en latere ontwikkeling in kinderen met een zeer hoog risico op cerebrale parese

In **hoofdstuk 4** hebben we de prevalentie en ontwikkeling van spiertonusafwijkingen onderzocht bij zuigelingen van het LEARN2MOVE-project (n=39). De kinderen hadden een hoog risico op ontwikkelingsstoornissen, in het bijzonder op CP. In deze zeer-hoog-risicogroep kwamen spiertonusafwijkingen in veel verschillende patronen en met een hoge prevalentie voor: in 93% van de onderzoeken vonden we een afwijkende spiertonus in drie of vier lichaamsdelen. Hypotonie in de nek/romp in combinatie met hypertonie in de extremiteiten was het meest voorkomende spiertonuspatroon. Tijdens het eerste halfjaar was er geen verschil in prevalentie van specifieke spiertonuspatronen tussen zuigelingen die op de gecorrigeerde leeftijd van 21 maanden wel of niet de diagnose CP kregen. Vanaf 7 maanden kwam hypertonie in de armen vaker voor bij kinderen die later gediagnosticeerd werden met CP dan bij kinderen die de diagnose niet kregen. Een asymmetrie in spiertonus van de armen (bijvoorbeeld hypertonie in

de ene arm en normotonie in de andere) was ook geassocieerd met de diagnose CP. Hypertonie in de benen kwam niet vaker voor bij zuigelingen met CP, maar was wel geassocieerd met de aanwezigheid van cysteuze periventriculaire leukomalacie. Ons onderzoekt laat zien dat een groot deel van de kinderen met CP duidelijke spiertonusafwijkingen laat zien op de zuigelingenleeftijd, maar dat niet alle kinderen met duidelijke spiertonusafwijkingen CP zullen ontwikkelen. Vooral tijdens de eerste maanden van het leven heeft het voorkomen van spiertonusafwijkingen bij hoog-risicokinderen een beperkte rol in opsporing van CP. Niettemin benadrukken onze resultaten het klinische belang van evaluatie van spiertonus als onderdeel van het neurologisch onderzoek.

**Hoofdstuk 5** beschrijft de klinische betekenis van specifieke reacties bij de kniepeesreflex die we op de zuigelingenleeftijd en op schoolleeftijd in de zeer-hoog-risicogroep van LEARN2MOVE in kaart brachten met behulp van oppervlakte-EMG (n=31). Ook hebben we de resultaten van de zeer-hoog-risicogroep vergeleken met die van kinderen met een normale neurologische ontwikkeling (n=24). Als eerste repliceerden we de bevindingen van Hamer et al. (2018) en breidden we deze uit: het voorkomen van tonische reacties op meerdere momenten tijdens de zuigelingenperiode was geassocieerd met CP, niet alleen op de leeftijd van 21 maanden, maar ook op schoolleeftijd. Daarnaast vonden we dat de aanwezigheid van tonische reacties tijdens de zuigelingenperiode niet geassocieerd was met de ernst van CP op schoolleeftijd in termen van grof-motorisch functioneren gemeten met de GMFCS. Bij deze zeer-hoog-risicogroep daalde de prevalentie van tonische kniepeesreacties tussen zuigelingenleeftijd en schoolleeftijd, om vervolgens even vaak voor te komen bij kinderen met een optimale neurologische ontwikkeling. Op de schoolleeftijd waren tonische reacties niet geassocieerd met CP. Het onderzoek liet ook zien dat zeer-hoog-risicokinderen zonder CP vaker clonus lieten zien dan de kinderen met CP. Een mogelijke verklaring hiervoor is dat voortdurende spiercontractie en/of veranderde eigenschappen van de spieren van kinderen met CP voorkomen dat clonus tot uiting komt. Tot slot duiden onze resultaten erop dat in zeer-hoog-risicokinderen spinale hyperexcitabiliteit afneemt naarmate het individu ouder wordt. Deze ontwikkelingstendens werd al eerder beschreven bij kinderen met een normale neurologische ontwikkeling.

In **hoofdstuk 6** onderzochten we of en hoe vroege motorische ontwikkeling van kinderen die meededen aan LEARN2MOVE (n=31) gerelateerd was aan de functionele en cognitieve status op de schoolleeftijd. Het motorisch gedrag van de baby's brachten we in kaart met de IMP, uitgedrukt als de totaalscore en scores in de domeinen *variatie*, *adaptabiliteit* en *performance*. We keken daarbij specifiek naar 1) de IMP-scores op het eerste meetmoment tijdens de zuigelingenperiode omdat we verwachtten dat ze een afspiegeling zijn van het effect van een vroege hersenlaesie op het functioneren van het zenuwstelsel, en 2) de mate van verandering in IMP-scores (berekend als het verschil in IMP-scores tussen het laatste en eerste meetmoment op zuigelingenleeftijd gedeeld door het tijdsverschil tussen het laatste en eerste meetmoment) als maat voor ontwikkeling. We vonden dat hogere vroege IMP-totaal-, variatie- en performancescores en hun mate van verandering geassocieerd waren met betere functionele ontwikkeling op de schoolleeftijd. Een

grotere positieve verandering in IMP-variatiescores bleek ook samen te hangen met een betere cognitieve uitkomst. Hoewel onze studiegroep klein was, wijzen de resultaten van dit onderzoek erop dat bij kinderen met een hoog risico op ontwikkelingsstoornissen de motorische ontwikkeling in de eerste levensmaanden en de mate van verandering in motorische ontwikkeling op de zuigelingenleeftijd behulpzaam is in het voorspellen van ontwikkelingsuitkomst op latere leeftijd.

## Conclusies

Dit proefschrift beschrijft de prevalentie van een aantal vroege neurologische verschijnselen, mogelijk onderliggende pathofysiologische mechanismen en relaties met functioneren in andere ontwikkelingsdomeinen, bij zowel kinderen met een laag risico als kinderen met een hoog risico op een ontwikkelingsstoornis. Daarmee is dit proefschrift een waardevolle toevoeging op het gebied van vroege opsporing van ontwikkelingsstoornissen. Onze zes belangrijkste bevindingen zijn:

- Bij laag-risicokinderen van 2 of 3 maanden komt een hoofdvoorkeursstand veel voor. Het verschijnsel heeft beperkte klinische betekenis. Dit betekent dat de handelingen van zorgverleners beperkt kunnen blijven tot het geven van informatie over hoe een symmetrische hoofdpositie kan worden bevorderd en tot het geruststellen van verzorgers.
- Bij laag-risicokinderen van 4 of 5 maanden heeft een hoofdvoorkeursstand meer klinische betekenis. We raden aan om deze kinderen neurologisch te onderzoeken en eventueel te verwijzen voor vroege interventie.
- Een afwijkende spiertonus in een of twee lichaamsdelen komt vaak voor bij zuigelingen en heeft beperkte klinische betekenis, terwijl een afwijkende spiertonus in drie of vier lichaamsdelen geassocieerd is met een verhoogd perinataal risico en een minder optimale neurologische conditie.
- Zuigelingen met een zeer hoog risico op een neurologische ontwikkelingsstoornis vertonen bijna altijd een afwijkende spiertonus. Toch helpen specifieke afwijkende spiertonuspatronen pas vanaf het tweede halfjaar bij de voorspelling van CP.
- Bij kinderen met een zeer hoog risico op een ontwikkelingsstoornis helpt de aanwezigheid van een tonische reactie bij de kniepeesreflex op de zuigelingenleeftijd bij het voorspellen van CP, maar niet bij het voorspellen van de ernst van CP op schoolleeftijd.
- De Infant Motor Profile (IMP) helpt bij het voorspellen van ontwikkelingsuitkomst bij zeer-hoog-risicokinderen: IMP-scores op vroege zuigelingenleeftijd en hun mate van verandering zijn geassocieerd met de functionele en cognitieve ontwikkeling op schoolleeftijd.

## ABBREVIATIONS

| | |
|---|---|
| **ADHD** | attention deficit hyperactivity disorder |
| **AGA** | appropriate for gestational age |
| **AIMS** | Alberta Infant Motor Scales |
| **CA** | corrected age |
| **CFCS** | Communication Function Classification System |
| **CI** | confidence interval |
| **COPCA** | COPing with and CAring for Infants with special needs |
| **CP** | cerebral palsy |
| **(c)PVL** | (cystic) periventricular leukomalacia |
| **(c)US** | (cranial) ultrasound |
| **DCD** | developmental coordination disorder |
| **EMG** | electromyography |
| **GA** | gestational age |
| **GMFCS** | Gross Motor Function Classification System |
| **GMs** | general movements |
| **HINE** | Hammersmith Infant Neurological Examination |
| **IMP** | Infant Motor Profile |
| **IQ** | intelligence quotient |
| **L2M** | LEARN2MOVE |
| **LGA** | large for gestational age |
| **MACS** | Manual Ability Classification System |
| **MND** | minor neurological dysfunction |
| **MRI** | magnetic resonance imaging |
| **NGST** | neuronal group selection theory |
| **NICU** | neonatal intensive care unit |
| **OR** | odds ratio |
| **PHP** | prevailing head position |
| **PIC** | persistent inward current |
| **PMA** | post-menstrual age |
| **PR** | phasic response |
| **PVL** | periventricular leukomalacia |
| **RAKIT** | Revisie Amsterdamse Kinder IntelligentieTest |
| **RCT** | randomized controlled trial |
| **SD** | standard deviation |
| **SES** | socioeconomic status |
| **SGA** | small for gestational age |
| **SINDA** | Standardized Infant NeuroDevelopmental Assessment |
| **TD** | typically developing |
| **TIP** | traditional infant physiotherapy |
| **TR** | tonic response |
| **UMCG** | University Medical Center Groningen |
| **VABS** | Vineland Adaptive Behaviour Scales |
| **VHR** | very high risk |
| **WMI** | white matter injury |

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# DANKWOORD

Hoewel mijn naam op de voorkant van dit proefschrift staat, had ik mijn promotietraject nooit alleen kunnen voltooien. Het was een proces met vallen en opstaan. Graag wil ik in dit gedeelte van mijn proefschrift dan ook iedereen bedanken die mij de afgelopen jaren heeft bijgestaan in mijn wetenschappelijke, klinische en persoonlijke ontwikkeling. Een aantal personen noem ik in het bijzonder. Mijn hart maakt een sprongetje bij het schrijven van dit dankwoord omdat ik zoveel fijne mensen om mij heen heb!

Prof. dr. Hadders-Algra, beste Mijna, onder jouw zorgvuldige begeleiding kreeg ik op de Ontwikkelingsneurologie (ON) de mogelijkheid me verder te verdiepen in de wondere wereld van het zich ontwikkelende kind: van zuigeling tot schoolkind, van typically developing tot het hoogste GMFCS-niveau. Jouw supervisie was altijd vol geduld en aandacht voor details. Maar ook persoonlijk heb ik veel van je geleerd. Trial and error - dat is voor mij het mantra geworden van de periode die ik met het afronden van dit proefschrift afsluit, maar dat ik zeker meeneem in de toekomst. Het is een geruststellende gedachte dat het niet erg is als iets niet in één keer lukt. Bedankt voor jouw niet aflatende geduld, je persoonlijke bemoedigingen, snelle reacties, en je (digitale) deur die altijd open staat. Ook in tijden van een wereldwijde pandemie, waardoor we noodgedwongen onze onderzoeksplannen moesten aanpassen en we veel op afstand hebben gecommuniceerd, liet je zien hoe flexibel je bent in je denken en doen. Diezelfde pandemie zorgde er helaas ook voor dat het laatste jaar van je werkzame carrière anders was dan je je had voorgesteld, en je ten tijde van Nederland in lockdown je emeritaat inluidde. Niettemin wens ik je, samen met Roelof, veel plezier en het allerbeste voor deze volgende fase van je leven. Dankjewel, Mijna!

Dr. Heineman, beste Kirsten en Dr. Hamer, beste Elisa, dankjulliewel dat jullie mij de afgelopen jaren als copromotoren hebben bijgestaan. En dat naast jullie werk als kinderneuroloog (in opleiding) en gevulde gezinsagenda's. Wat was het fijn om met jullie samen te werken! Kirsten, al tijdens mijn wetenschappelijke stage zag ik met hoeveel plezier en geduld jij kinderen onderzoekt. Ze zijn bij jou op je gemak, en zo voelde ik mij ook als promotiestudent onder jouw copromotorschap. Jouw enthousiasme en positiviteit zijn aanstekelijk. Elisa, wij hebben de gevoelsmatige afstand tussen Groningen en Nijmegen aanzienlijk verkleind door ons vele digitale contact. Jouw kennis van de LEARN2MOVE-groep en klinische ervaring hebben erg geholpen bij het tot stand laten komen van de artikelen in mijn proefschrift. Ook kon ik altijd bij je terecht voor persoonlijke vragen. Hartelijk dank, lieve dames!

Prof. dr. M.A.A.P. Willemsen, Prof. dr. E.E.A. Rameckers en Prof. dr. C.K. van der Sluis, ik wil jullie hartelijk danken voor het zitting nemen in de beoordelingscommissie, en het kritisch beoordelen en goedkeuren van dit proefschrift!

Mijn grote dank gaat vervolgens uit naar alle ouders en kinderen die hebben meegedaan aan de onderzoeken die in mijn proefschrift staan beschreven. Zonder jullie had dit proefschrift er nu niet gelegen. Jullie oprechte interesse en enthousiasme om mee te doen hebben mij als persoon geraakt. De korte maar zo persoonlijke kijk in jullie leven hebben mij in zowel mijn professionele als persoonlijke leven veel nieuwe inzichten opgeleverd. Bedankt voor jullie deelname en vertrouwen!

De Junior Scientific Masterclass Groningen wil ik bedanken voor het mogelijk maken van het volbrengen van dit MD/PhD-traject.

Anneke, tijdens een groot deel van mijn onderzoeksproject bemande je het secretariaat van de ON, maar de term 'secretaresse' vond je maar niets. Je bent van alle markten thuis: van grafische ondersteuning bij het maken van figuren (we zaten geregeld samen héél dicht bij het computerscherm om te kijken of alle lijnen wel écht recht stonden) tot het bieden van een luisterend oor. De follow-up-metingen van LEARN2MOVE waren telkens een dagje uit. We hebben in de Volvo samen ruim 3600 km gereden (dat is meer dan van Groningen naar Rome en weer terug). Afgezien van zo nu en dan een gedurfde inhaalactie, heb ik relaxed op de bijrijdersstoel gezeten. Bedankt voor je hulp, onze fijne gesprekken en de gezelligheid! En wie weet kunnen we daadwerkelijk eens een stedentrip naar Rome maken.

Linze, bedankt voor je hulp bij mijn projecten, waaronder de technische voorbereidingen van de LEARN2MOVE-onderzoeken en het klaarmaken van Excelspreadsheets met zoveel outputgetallen dat het mij soms duizelde. Je hebt mij ook het begrip van een slapende server bijgebracht. Dat klinkt lief, maar zo onschuldig was het niet want alle bestanden die ik tijdens de slaap had bewerkt, waren niet opgeslagen en moesten dus opnieuw verwerkt worden. Jouw rustige houding gaf mij altijd het vertrouwen dat het goed zou komen.

Sacha, bedankt voor je hulp bij de statistische analyses, je geduld om mijn vragen te beantwoorden en extra uitleg te geven als dat nodig was. Jouw kritische vragen hielpen mij om de boodschappen van de artikelen scherper voor ogen te krijgen en daarmee de manuscripten beter te maken.

Ying-Chin, we got to know each other during the IMP-SINDA project. Thank you for your help in data collection, especially with Excel and SPSS. Together, we enthusiastically started the BAMBI-project, which we unfortunately had to stop because of the worldwide pandemic. I wish you all the best for your career and family back in Taiwan!

Vera, kort maar krachtig waren wij collega's. Met veel enthousiasme begon je met het BIRD-onderzoek, waarin een groot deel van de kinderen van het IMP-SINDA-project opnieuw wordt onderzocht. Ik kijk met een fijn gevoel terug op onze koffiepauzewandelingen. Hopelijk heb je een fijne werkplek gevonden die bij je past en waar je je verder kunt ontwikkelen. Selena, jij volgde Vera op en je zet nu het BIRD-onderzoek voort. Wat vond ik het leuk om in mijn

laatste maanden de kleuters die ik als baby heb onderzocht, over de afdeling te zien lopen onderweg naar de onderzoeksruimte waar jij ze met veel gedrevenheid, geduld en zichtbaar plezier onderzoekt. Bedankt voor je gezelligheid, inclusief de spontane door-de-weekse borrels in de stad. Ik wens je heel veel succes en plezier met jouw PhD-traject.

Anke en Derk, mijn voormalige MD/PhD-collega's op de ON: we hebben slechts een korte periode direct met elkaar samengewerkt. Bedankt dat jullie me op weg hebben geholpen en dat ik met mijn vragen bij jullie terecht kon. Ik wens jullie heel veel succes met jullie opleiding! Andere collega's en studenten die mij hebben geholpen met mijn projecten, waaronder Kilian, Lotte, Carlijn, en Tessa; jullie waren mijn praktische hand maar ook mijn sparringspartners bij de projecten waar jullie je wetenschapsstage liepen. Fijn dat ik tijdens mijn ontwikkeling ook jullie op weg mocht helpen. Kim, je werkte via de studentenpool een tijdje op het secretariaat van de ON. Bedankt voor je hulp bij het IMP-SINDA-project en de gezellige koffie- en lunchpauzes! Tjitske, Raymond, Machiel, Mart, Darlene, Patricia, de samenwerking met jullie heb ik als erg prettig ervaren. Ik wens ieder van jullie het allerbeste!

Mariël, Ilse en Manouk (met later Truls en Hanne), we begonnen ongeveer tegelijk met onze projecten op de ON. Ik vind het mooi om te zien hoe we, vanuit onze gezamenlijke interesse, allemaal ons eigen pad weten te vinden. En toch troffen we elkaar steeds opnieuw voor een kop thee, een wandeling door Groningen, samen eten, of zomaar even een belletje. Ik hoop van harte dat we onze vriendschap kunnen voortzetten! Mariël, vanaf het begin konden we goed samenwerken, maar ook naast het werk is het fijn om met je te zijn. Wat een cadeautje dat jij vandaag als paranimf naast me staat!

Lieve vriendinnen uit de polder; lieve Lisette, Sascha, Lian, Eline, Maaike, Karin en Ilse, jullie brengen me terug naar mezelf en laten me allerlei mooie kanten van het leven zien. Wat is het waardevol om deel te zijn van een vriendinnengroep waarin we lief en leed met elkaar kunnen delen en zonder terughoudendheid onszelf kunnen zijn, ondanks onze onderlinge fysieke afstand. Bedankt dat jullie er zijn! Lisette, al vanaf het begin van de middelbare school zijn wij vriendinnen. Ondanks onze verschillende levens hebben we vaak aan een half woord genoeg. Wat voelt het vertrouwd om jou als paranimf aan mijn zijde te hebben!

Marcel Kroes en Judith Luiken, wat fijn dat we na de middelbare school in contact konden blijven. We hebben elkaar afgelopen jaren niet veel gezien, maar jullie moedigden me aan om door te gaan met mijn project. Bedankt voor de fijne ontmoetingen!

Lieve Mirna en meiden van het Groninger Studentenkoor - tegenwoordig Nova - ; tijdens de repetities op vrijdagavond kon ik mijn hoofd helemaal leegmaken. Bedankt voor de bijzondere muzikale verbondenheid die ik met jullie heb mogen ervaren. Ik kijk daar met heel veel dankbaarheid en plezier op terug!

Lieve mensen die ik in de loop van de jaren bij Encounter Nederland heb leren kennen, dankjulliewel dat jullie mij naar mezelf laten kijken en me steeds weer doen inzien dat ik enig, uniek, waardevol maar ook beperkt ben. Onze ontmoetingen zijn mij heel veel waard.

Herzlich danken möchte ich auch dem Team der Ärztinnenpraxis in Glattbrugg, Schweiz. Habt vielen lieben Dank für Euren herzlichen Empfang und das Vertrauen, das Ihr mir als beginnende Ärztin entgegenbringt.

Liebe Elena, du zeigst mir, dass so viel mehr möglich ist, als ich immer gedacht habe. Es bedeutet mir sehr viel, mit Dir zusammen unterwegs zu sein. Ich danke Dir herzlichst für Deine Unterstützung und Dein ständiges Vertrauen in mich!

Opa en oma, jullie zijn voor mij als een extra paar ouders. Met veel liefde op afstand, maar toch dichtbij door de vele telefoongesprekken tussen Groningen en Ter Aar, en onze bezoekjes in het weekend. Oma, na opa's overlijden bleven we in regelmatig belcontact. U vroeg me vaak naar de stand van zaken rondom mijn proefschrift, maar bent ook steeds persoonlijk betrokken. Uw steun betekent veel voor me. Ik weet zeker dat opa vanaf boven deze bijzondere dag met ons meeviert.

Tot slot papa, mama en Thomas, bedankt dat jullie thuis altijd echt thuis laten zijn. Hoewel jullie me inhoudelijk vaak niet direct konden helpen (ik heb jullie wat moeilijke termen om de oren gegooid...), staan jullie altijd voor me klaar met raad en daad, een wandeling in het bos, een kop koffie, een goed gesprek, of een spelletje als ik mijn hoofd wil leegmaken. Ogenschijnlijk simpele activiteiten, maar voor mij zo betekenisvol. Bedankt voor jullie onvoorwaardelijk vertrouwen en de liefde die jullie me geven!

*Lilian Straathof*

# OVER DE AUTEUR

Lilian Straathof werd op 7 september 1994 geboren in Haarlem na een zwangerschapsduur van 37+4 weken met een geboortegewicht van 3080 gram. Op jonge leeftijd verhuisde ze met haar ouders naar Marknesse, een dorp in de weidse Noordoostpolder. Samen met haar jongere broer Thomas groeide ze op in een warm gezin. In 2012 behaalde Lilian haar vwo-diploma op het Zuyderzee College in Emmeloord. Ze verhuisde naar Groningen, waar ze met de studie Geneeskunde aan de Rijksuniversiteit Groningen begon. Vanaf het begin van de opleiding was ze geïnteresseerd in het samenspel tussen de patiënt, de medische aandoening en de omgeving. Lilian liep haar coschappen in het Universitair Medisch Centrum Groningen (UMCG) en het Antoniusziekenhuis in Sneek. De behoefte om zichzelf breder te ontwikkelen en zich in te zetten voor haar omgeving vervulde ze met enthousiasme middels verschillende activiteiten naast haar opleiding. Zo was ze onder andere een jaar secretaris van Studentenpopkoor Estrellas, deed ze vrijwilligerswerk als taalcoach bij Humanitas Groningen en gaf ze bijles aan middelbare scholieren. Na haar coschappen begon Lilian in het najaar van 2017 aan haar wetenschapsstage bij het Instituut voor Ontwikkelingsneurologie van het Beatrix Kinderziekenhuis in het UMCG. Hier raakte ze gefascineerd door het zich ontwikkelende zenuwstelsel. Omdat ze zich verder wilde verdiepen in de neurologische en motorische ontwikkeling van kinderen solliciteerde ze voor een MD/PhD-traject bij de Ontwikkelingsneurologie via de Junior Scientific Masterclass Groningen en werd aangenomen. Lilian liep haar semi-artsstage op de afdelingen Dwarslaesierevalidatie en Kinderrevalidatie in het UMCG Centrum voor Revalidatie, locatie Beatrixoord en het UMCG. Ze behaalde haar masterdiploma in het voorjaar van 2019, waarna ze zich volledig kon toeleggen op haar MD/PhD-project. De vijf artikelen in haar proefschrift zijn allen gepubliceerd in wetenschappelijke tijdschriften. Momenteel werkt Lilian als arts-assistent in een huisartsenpraktijk in Zürich, Zwitserland.

# ABOUT THE AUTHOR

Lilian Straathof was born on September 7th, 1994 in Haarlem, the Netherlands, at a gestational age of 37 weeks and 4 days with a birth weight of 3080 grams. At a young age, she moved with her parents to Marknesse, a village in the Noordoostpolder. Together with her younger brother Thomas, she grew up in a loving family. Lilian completed secondary education (vwo) at the Zuyderzee College in Emmeloord. In 2012, she started studying Medicine at the University of Groningen. From the onset of her medical training, Lilian was intrigued by the interplay between patient, medical condition and the environment. She completed her internships at the University Medical Center Groningen (UMCG) and Antoniusziekenhuis in Sneek, Friesland. During that time, Lilian fulfilled several extracurricular activities, e.g., she was secretary of Studentenpopkoor Estrellas (a student choir), volunteered as a language coach at Humanitas Groningen, and tutored high-school pupils. After the first two years of her clinical internships, Lilian started her research internship at the Institute of Developmental Neurology in the Beatrix Children Hospital of the UMCG in 2017. Eager to learn more about children's typical and atypical neurodevelopment, she successfully applied for an MD/PhD position at the Developmental Neurology via the Junior Scientific Masterclass Groningen. Lilian completed her final clinical internships at the UMCG Center for Rehabilitation, location Beatrixoord and the UMCG at the departments of Spinal Cord Rehabilitation and Paediatric Rehabilitation. After obtaining her master's degree in spring 2019, she devoted her time to her MD/PhD degree. The five articles in her thesis are all published in peer-reviewed journals. Currently, Lilian works as a junior doctor in a practice for general medicine in Zurich, Switzerland.

# LIST OF PUBLICATIONS

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