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MEASUREMENT INSTRUMENTS FOR THE EARLY DETECTION OF UNILATERAL CEREBRAL PALSY AND EVALUATION OF BIMANUAL PERFORMANCE

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Measurement Instruments for the Early Detection of Unilateral Cerebral Palsy and Evaluation of Bimanual Performance

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To all the children and families who
have contributed to this work enabling others to benefit from these findings in the future

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles and manuscript, which will be referred to by their Roman numerals I-IV:

I. Early prediction of unilateral cerebral palsy in infants with asymmetric perinatal brain injury – model development and internal validation

   Ryll UC*, Wagenaar N*, Verhage CH, Blennow M, de Vries LS, Eliasson AC

   Eur J Paediatr Neurol. 2019;23(4):621-628. doi:10.1016/j.ejpn.2019.04.004

II. Predictive validity of the Hand Assessment for Infants (HAI) in infants at risk of unilateral cerebral palsy

   Ryll UC, Krumlinde-Sundholm L, Verhage CH, Sicola E, Sgandurra G, Bastiaenen CHG, Eliasson AC

   Submitted for publication in Dev Med Child Neurol

III. Assisting Hand Assessment (AHA) and Children's Hand-use Experience Questionnaire (CHEQ): observed versus perceived bimanual performance in children with unilateral cerebral palsy

   Ryll UC, Bastiaenen CHG, Eliasson AC

   Phys Occup Ther Pediatr. 2017;37(2):199-209. doi:10.1080/01942638.2016.1185498

IV. To explore the validity of change scores of the Children's Hand-use Experience Questionnaire (CHEQ) performance in children with unilateral cerebral palsy

   Ryll UC, Eliasson AC, Bastiaenen CHG, Green D

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SUMMARY

Infants with early brain lesions are at risk of developing unilateral cerebral palsy (CP) and valid and reliable measurement instruments for their early detection as well as evaluation of their bimanual performance at later age are needed. Such identification allows for early family support and intervention, while evaluation of hand function at later ages enables to tackle primary challenges children and adolescents with unilateral CP face continuously while performing everyday activities that require the use of both hands.

This thesis focuses on two measurement instruments, *the Hand Assessment for Infants (HAI) and the Children's Hand-use Experience Questionnaire (CHEQ),* as applied to infants at risk of developing unilateral CP and children and adolescents with this condition, respectively. The overall aim was to determine the validity of HAI scores to predict unilateral CP and the ability of the CHEQ scores to capture perceptions of bimanual performance, both at a single point in time and over time, in comparison to other assessments serving as external criteria.

The HAI is the first standardized test designed to evaluate both uni- and bimanual functions in infants from 3-12 months of age at risk of developing unilateral CP. In combination with neonatal magnetic resonance imaging, and considerations of gestational age and sex, the HAI can predict unilateral CP in infants with asymmetric perinatal brain injury as young as 3.5-4.5 months of age. In addition, HAI scores exhibit very good to excellent overall accuracy in predicting the development of unilateral CP in infants at risk at various time-points from 3.5-12 months of age.

Impaired hand function presents a continuous challenge when performing daily activities requiring the use of both hands, especially as children with unilateral CP grow older. The CHEQ, is an online patient-reported questionnaire of how children and adolescents with unilateral hand impairment experience the use of the affected hand in connection with activities requiring both hands. The AHA is a standardized test based on observation of the use of the affected hand by children with unilateral CP during bimanual activities. The CHEQ and the AHA were found to measure different constructs that are only related to a minor extent, emphasizing the need to utilize both of these complementary tools to obtain a more complete picture of the perceived and observed performance of bimanual activities by children and adolescents with unilateral CP. The CHEQ scores captured some change in perceived bimanual performance, with good accuracy for the scale *feeling bothered*, but only limited accuracy for the scales *grasp efficacy* and *time utilization*. Consequently, CHEQ scores can be recommended primarily for describing perceived bimanual performance.

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LIST OF ABBREVIATIONS

AHA	Assisting Hand Assessment
AI	Asymmetry index of the HAI
BGT	basal ganglia and/or thalamus
BoHM	Both hands measure of the HAI
CA	corrected age
CHEQ	Children's Hand-use Experience Questionnaire
CI	confidence interval
CP	cerebral palsy
CST	corticospinal tract
EaHS	Each hand sum score of the HAI
GAS	Goal Attainment Scale
HAI	Hand Assessment for Infants
MRI	magnetic resonance imaging of the brain
PLIC	posterior limb of the internal capsule

1 INTRODUCTION

1.1 MEASUREMENT PROPERTIES

Accurate prediction or evaluation of outcomes over time in clinical practice and research must be based on reliable and valid measurements. This is increasingly important in terms of reporting to and negotiating for patients with providers of health insurance, but also crucial for the assessment of research subjects. Choosing the most appropriate measurement instrument for any given situation can be challenging and must take both reliability and validity into consideration. These properties are dependent on the situation and population under investigation and alternation in the target population and/or methodological modifications (e.g., the use of single items rather than the complete scale) require re-evaluation of reliability and validity [1,2].

This thesis focuses on the validity of the Hand Assessment for Infants (HAI) for predicting the clinical outcome of unilateral CP (Studies I and II) and the validity of change scores of the Children's Hand-use Experience Questionnaire (CHEQ) which is based on the perceptions of children and adolescents concerning their performance of bimanual activities (Study IV). In addition, the relationship of the CHEQ to and its agreement with the observation-based Assisting Hand Assessment (AHA) was examined in a cross-sectional setting (Study III). The present chapter provides a brief introduction to the measurement properties, touching on two widespread theories, as well as short descriptions of patient-reported outcome measures and the target population children with unilateral CP.

1.1.1 Reliability

Reliability refers to the degree to which the scores of a measurement instrument are free from measurement error (both systematic and random) and, consequently, can differentiate between individuals [1,3]. Reliability involves consistency, as well as agreement in the scores obtained by the same assessor on different occasions, so-called *intrarater reliability*; by different assessors on the same occasion, *interrater reliability*; or in connection with repeated assessments over time, *test-retest reliability*, as well as the interrelatedness of items being assessed, *internal consistency*.

1.1.2 Validity

Validity can be defined as "the degree to which an instrument truly measures the construct(s) it purports to measure" [3], i.e. to which extent inferences made about individuals on the basis of the scores obtained are valid [1]. The three main types of validity are described as content, construct and criterion validity which again encompass several different subtypes of validity. *Content validity* refers to whether the content of the measurement instrument represents the

construct to be measured adequately, i.e., the relevance and comprehensiveness (e.g., of test items). *Construct validity*, often understood to reflect overall validity, refers to whether the instrument actually measures what it was designed to measure, or more precisely "the degree to which the scores of a measurement instrument are consistent with hypotheses" concerning the underlying construct [3].

Criterion validity is evaluated when a validated external criterion, a so called 'gold standard' is available for comparison. However, such a gold standard rarely exists and surrogates that are assumed to capture a similar construct must often be used instead. A proposed definition for the criterion validity is "the extent to which a measurement instrument relates to the construct of the gold standard" [3]. Criterion validity can be evaluated in relation to the external criterion either at one time-point *(concurrent validity)* or over time *(predictive validity)*. The concept of criterion validity will be applied to the predictive validity of the HAI (Study III) and to explore the validity of change scores of the CHEQ (Study IV).

The validity of change scores

The concept of validity encompasses both single scores in a cross-sectional setting and change scores in a longitudinal setting, also referred to as responsiveness or longitudinal validity. Responsiveness is of particular importance in connection with measurement instruments utilized to evaluate changes during the natural course of development, as well as following interventions [1,2,4]. As yet, there is no consensus concerning the definition and evaluation of the responsiveness of instruments to measure health, and accordingly this has been investigated employing many different approaches [2,5–82,5–8]. According to the definition proposed by the COSMIN (COnsensus-based Standards for selection of health Measurement INstruments) group, responsiveness is " the degree to which an instrument measures changes in the construct it intends to measure" [3]. Consequently, if an individual changes on the construct of interest, the investigated measurement instrument assessing the same or a similar construct should reflect this [2].

1.1.3 Theories of measurement

Many constructs in rehabilitation medicine are not directly observable, e.g., the perceived bimanual performance evaluated by the Children's Hand-use Experience Questionnaire (CHEQ). Such constructs are usually assessed instead on the basis of multiple items that can be observed and are often combined in multi-item tests or questionnaires. Such an approach requires an underlying theory concerning how the scores generated are related to the underlying construct, theories such as the well-known classical test and item response theories.

The *classical test theory (CTT)* is based on the concept that any individual's observed item score is composed of a 'true' score and an associated error, both of which are unobservable [1]. All

items of the assessment or questionnaire can be considered to be repeated measurements of the construct [2]. When the several assumptions on which the CTT is based are valid, the average of an individual's observed score is considered to approach the 'true' score if the assessment or questionnaire were to be administered an infinite number of times [1].

The *item response theory (IRT)* provides a framework that encompasses several models that describe the relationship between an individual's ability and the probability of a particular response to any given item [1,2]. This theory assumes that the underlying construct (latent trait or latent ability), and thus, the items form a continuum. The items (location or difficulty) and the individual (location or ability) are ordered on the same scale, which provides information about both [2]. The aim is to measure the ability of the individual by estimating her/his location on the scale on the basis of her/his responses to the test items.

Among IRT models, the Rasch measurement model is widely employed to evaluate the extent to which the scores on a measurement instrument (responses) describe a unidimensional construct, that is one underlying trait. This is the case when the scores of a measurement instrument fulfil two criteria: (I) all individuals are more likely to perform less difficult items than more challenging ones, and (II) all items are likely to be managed more effectively by individuals with higher ability than those with less ability [9]. The measurement instruments investigated here, that is the HAI, CHEQ and AHA, were all developed from the Rasch measurement model and as such are based on the item response theory.

1.1.4 Patient-reported measures of outcome

As healthcare has become more patient-centred patient-reported outcomes (PROs) have become increasingly important as they provide evidence on health care effects from the perspective of the patient [10]. Patient-reported outcome measures (PROMS) are typically single- or multi-item questionnaires thought to capture perceptions concerning certain aspects of an individual's health [11]. PROMs can be either generic, assessing general health-related quality of life, or disease-specific and involve patients in decision-making and treatment planning regarding their own health. Such inclusion of patients' opinions enhances both motivation and participation in therapy [12–14]. Moreover, it provides clinicians with insight into the concerns and priorities of patients regarding certain activities, a valuable complement to standardized observational assessments considered to be objective and comparable.

In the case of PROMS concerning younger children, their guardians, who are assumed to have good insight into the health of their child, are often requested to act as proxy-raters. Regarding the CHEQ, adolescents about 13 years of age or older are considered capable of completing the questionnaire, which demands a certain degree of comprehension and attention, themselves [15]. It has been reported that what is thought to be important by pediatric patients and health care

professionals and should be prioritized in therapy can differ [16,17]. Therefore, understanding the perceptions of children and adolescents themselves, or their proxies is crucial to optimizing motivation and involvement in their own treatment, especially long-term.

1.2 CEREBRAL PALSY

The term cerebral palsy (CP) covers a group of permanent, non-progressive disorders of movement and posture that result from an insult or lesion in the developing brain. In addition to affecting motor function, these conditions can also exert an impact on sensation, perception, cognition, communication, and behaviour [18,19]. The likelihood and severity of associated impairments, such as learning difficulties (40-50%), epilepsy (30-33%) and severe visual impairment (5-19%), are positively correlated to the severity of motor impairment [20,21].

Although the most frequent cause of physical disability in early childhood, the overall prevalence of CP in Europe is fortunately declining. The prevalence is estimated to be about 2.08 (95% CI 2.02-2.14) per 1000 live births, but significantly higher among infants born very preterm or with very low weight [22,23]. Other risk factors include genetic predispositions, maternal and neonatal infections, and asphyxia at birth (Bax et al., 2006; Mc Intyre et al., 2013; McIntyre, Morgan, Walker, & Novak, 2011).

On the basis of neurological criteria, CP can be divided into three subtypes: spastic (uni- or bilateral), dyskinetic (dystonic or chorea-athetotic) and ataxic CP [19]. Children affected by these different subtypes can also differ with respect to motor development, cognition, communication, hearing, vision and epilepsy, as assessed by different classification systems such as the Gross Motor Function Classification System (GMFCS) [25], the Manual Ability Classification System (MACS) for handling of objects [26], IQ testing and the Communication Function Classification System (CFCS) [27] or Viking Speech Scale [28].

1.2.1 Unilateral cerebral palsy

Unilateral spastic CP is the second most common subtype, accounting for approximately 30-40% of the cases, in Europe [22,23,29]. This form of CP is due predominantly to an asymmetric lesion in the brain resulting from infarction of the middle cerebral artery, periventricular lesions, posthemorrhagic porencephaly, brain malformation, or hemi-brain atrophy. These lesions often affect corticospinal tracts, leading to motor and sensory impairments, primarily on one side of the body. Individuals with unilateral CP often experience more difficulties with their arms than their legs and hand dysfunction becomes apparent. Indeed, preferential use of the right or left hand is often the first indication of unilateral CP [21]. The most affected arm is often weak and movements of the fingers less selective, impairing coordination of fingertip forces that causes difficulties in grasping and releasing of objects [30]. These impairments and the limited control of movement cause difficulties in performing bimanual actions associated with

many daily activities that require the use of both hands [31]. This becomes more apparent as these children grow up and learn to take responsibility for an increasing number of activities themselves, such as moving around, self-care (e.g., washing, going to the toilet, dressing, and eating), assisting in household tasks, education and play, leisure activities, and peer relationships. In this context, extensive training in form of constraint-induced movement therapy or bimanual intensive training can improve the motor function of children with unilateral CP [32–37].

Imaging techniques are being applied increasingly to understand the pathological mechanisms underlying CP, imaging techniques are increasingly used. Most children with CP (80-90%) exhibit atypical neuroradiology when examined with conventional magnetic resonance brain imaging or computer tomography [38,39]. The use of a classification system based on pathogenic patterns observed with MRI is recommended by the SCPE network and involves five major types of brain injury: (a) maldevelopments; (b) predominant white matter injury; (c) predominant grey matter injury, including arterial infarctions, mostly of the middle cerebral artery; (d) miscellaneous injuries such as cerebellar atrophy or delayed myelination; and (e) lack of any abnormalities [22]. In a population-based study, white matter damage of immaturity was found to be the most common MRI finding on children with CP, followed by basal ganglia lesions, cortical and subcortical lesions, malformations, focal infarcts and miscellaneous lesions, and normal presentation [23].

1.3 EARLY DETECTION OF CEREBRAL PALSY

Although magnetic resonance imaging (MRI) is widely used in standard medical care and its use to help understand the etiology and pathogenesis of CP, including the timing and extent of the insult has been recommended, diagnosis of CP is based primarily on the clinical presentation and medical history of the child [23,38,40]. To facilitate accurate reporting of this diagnosis, the Surveillance of Cerebral Palsy in Europe (SCPE) has proposed utilizing several standardized classification systems (mentioned above in section 1.2) to describe the clinical presentation [19]. Commonly, CP is diagnosed at the earliest between 18-24 months of age and often later in milder cases, since the typical neurological symptoms may be transitionary or change during the development and only become manifest over time [40–42].

The ability to identify infants at risk of developing unilateral CP at an early stage would enable clinicians to inform and counsel guardians concerned about their child's development, as well as to assess the infant's eligibility for health care services and promising early interventions. Currently, a combination of approaches for early detection of CP is recommended, e.g., MRI together with a neurological examination or neurodevelopmental assessment [40,43,44].

1.3.1 Brain imaging

The timing and extent of lesions in the developing brain are related to clinical outcomes and lesions in specific regions such as the corticospinal tracts and basal ganglia are associated with abnormal motor development and the occurrence of unilateral CP [45–47]. *Neonatal MRI* detects preterm infants at risk of developing CP with good accuracy during their first weeks of life, and is even more accurate at the term-equivalent age, when myelination in the posterior limb of the interior capsule (PLIC) becomes evident on MRI [45,47–51]. The overall diagnostic accuracy of conventional MRI and diffusion tensor imaging (DTI), performed soon after birth or at term-equivalent age, in predicting motor development at the age of two years and CP or unilateral CP is estimated to be moderate to excellent, although with limited precision, as indicated by the wide confidence intervals (CI). The corresponding overall sensitivity is between 71-100% (95% CI 30-100%) and specificity 88-100% (95% CI 60-100%) [48,49,52].

1.3.2 Neurological examinations and neurodevelopmental assessments

Neurological examinations and neurodevelopment assessments designed to quantify abnormal patterns of movement in infants and predict the development of neurodevelopmental disorders during the first year of life, are essential for an early prognosis or "interim diagnosis" of CP [40]. A great deal is known about early parameters in preterm infants that are related to atypical motor development and the development of CP in general [48,53–59]. Two tools recommended for the prediction of CP in general are the Prechtl's Qualitative Assessment of General Movements (GMA) and the Hammersmith Infant Neurological Examination (HINE) [40]. However, these instruments provide little information concerning asymmetric behaviour and their ability to predict unilateral CP is thereby limited.

Assessments of the quality of motor behaviour and movement variability, such as the general movements assessment [60,61], provide the best prediction for CP in general [40,62,63]. The *Prechtl's Qualitative Assessment of General Movements* (GMA) assesses movement variability through observation of the spontaneous movements of the infant. From birth until 20 weeks of age, these movements are normally writhing in character, followed by fidgety movements as the infants matures, and subsequently by more intentional, goal-directed movements [60].

Fidgety movements, observed most clearly at about 12-16 weeks of corrected age, are "small movements of moderate speed with variable accelerations of the neck, trunk, and limbs in all directions" [60,64]. Infants displaying normal fidgety movements develop normally, whereas absent, abnormal or sporadic fidgety movements around three months of term-equivalent age are indicative of a considerable risk for neurological disorders. In particular, infants who never show fidgety movements are likely to develop CP later [40,65]. The pooled sensitivity of 98% (95% CI 74-100%) and specificity of 91% (95% CI 83-93%) reported in a review on tools for

the prediction of CP in high-risk populations including infants born preterm and with low-birth weight [48], were similar to other studies predicting CP based on fidgety movements at three months of term-equivalent age in very preterm and late-preterm infants with neonatal cerebral infarction [58,59].

The *Hammersmith Infant Neurological Examination* (HINE), which takes into account movement quality, is a widely used neurological examination [40]. HINE scores are reported to be very accurate to predict walking ability and CP at the age of two years in preterm infants at different from 3-12 months of corrected age, with movement quality and quantity being the items most predictive [48,53,54,56,66], however, cut-off values for the detection of CP were found to be inconsistent [55].

Moreover, the separate application of the HINE and likewise the GMA with respect to predicting development of CP in preterm infants at two years of age, showed only a low-to-moderate association between HINE or GMA and the occurrence of CP, respectively, whereas the application of these methods together showed a very strong relationship [55]. For this combined use of HINE and GMA at three months of corrected age in infants born preterm, a sensitivity of 96% and a specificity of 87% were reported for a HINE cut-off score of 57 indicating a potential for the HINE to early identify the development of CP [55]. Similarly, HINE and GMA in combination with MRI at three months of corrected age demonstrated excellent accuracy in discriminating between high-risk infants from a neonatal intensive care unit with and without CP (area under the curve, AUC=0.99) compared to the mere application of HINE (AUC=0.85) or GMA (i.e., absent versus normal fidgety movements; AUC=0.98) alone, respectively [66].

1.4 EARLY INTERVENTIONS

In connection with the development during the first years of life, the plasticity of the nervous system is highly pronounced, particularly when the development of the brain has been affected by disruptions [67–70]. Several studies on small cohorts indicate that interventions for infants at risk of developing CP may be beneficial if provided during the first months of life, even before the diagnosis is confirmed [34,35,37,40,71,72]. Interventions based on motor-learning that engage both the infant, and her/his parents and involve environmental modifications appear to be promising [37,73]. However, little is presently known about the impact of interventions with infants below 12 months of age on motor development. Treatment of infants with early hand asymmetry at risk of developing unilateral CP, during their first year of life with constraint-induced movement therapy for infants (baby-CIMT), designed to specifically facilitate the development of hand function, demonstrated more beneficial effects than massage in a small randomized controlled

trial [34]. Favourable interventions are task-specific, motivating, and of high intensity and long duration, incorporating daily home training involving active participation by the infant [37,73].

Evaluation of the effects of such early interventions involves many challenges [37,43], a main one being selection bias due to recruitment of many infants who do not eventually develop unilateral CP and most likely did not need early intervention. In addition, differences between interventions in randomized controlled studies are often relatively small since it is unethical to provide treatment with little or no effect to the control group and this may mask significant differences in effect. This is also related to the predominant use of frequency statistics that focus on significant differences, rather than comparison of improvement with different treatments. Consequently, methods that accurately identify infants that will actually develop unilateral CP are needed not least in connection with research on the effects of early interventions.

Although there is no convincing evidence for significant lasting benefits at the present time, it seems likely that early interventions can be beneficial for infants with CP [37,43,73], in particularly in light of research demonstrating a likely relationship between adequate stimulation, and environmental enrichment during childhood and normal development [43].

1.5 EVALUATION OF BIMANUAL PERFORMANCE

1.5.1 Evaluation of bilateral hand use and hand asymmetry in infants

Most measurement instruments for infants presently available lack specific evaluation of fine motor skills and do not evaluate each hand individually, as well as the interplay between both hands, which is essential to quantifying the degree of asymmetric hand use. Only a few measurement instruments that do evaluate bilateral hand use and can potentially quantify asymmetry between the arms of infants below 12 months of age were identified by a review [74]. Those that do evaluate the fine motor skills in infants on a separate scale include the Bayley Scale of Infant and Toddler Development Version III, the Peabody Developmental Motor Scales Version II, and the Postural and Fine Motor Assessment [74–77]. Although, all three of these include items concerning uni- and bimanual function, they evaluate the performance of the preferred hand, which for infants with unilateral CP will most likely be the non-affected hand. As a result, these assessments lack information on the use of each hand separately during bimanual activities and thereby seem inappropriate for the assessment of potential asymmetric behaviour.

At the time at which that earlier review was published, two assessments considered relevant to the specific challenges that infants at risk of unilateral CP encounter in performing bimanual tasks, the Hand Assessment for Infants and the Grasp and Reach Assessment of Brisbane [78,79],

were still under development, but these have now been described. Both are designed to evaluate bimanual activity and asymmetric hand use represented by assessing each hand separately.

The *Hand Assessment for Infants (HAI)* is the first standardized test designed to quantify hand function in terms of asymmetry and the use of both hands in interplay by infants from 3-12 months of age and at high risk of developing unilateral CP [78]. Indeed, asymmetric spontaneous hand and finger movements can already be observed as early as at three months of age in children with suspected CP [78,80]. The assessment involves a semi-structured, video-recorded, 10-15-minute session of play with toys selected carefully and presented to the infant to encourage exploration, allowing observation of a wide range of motor actions. The HAI is a criterion- and norm-referenced test, and its scores demonstrate excellent validity, test-retest and interrater reliability of scores for the evaluation of bilateral hand use in infants from 3-12 months of corrected age and at risk of unilateral CP and with signs of asymmetric hand use [78,81]. Moreover, results from Rasch measurement modelling indicate that the HAI has considerable potential for measuring change over time [78,81].

The *Grasp and Reach Assessment of Brisbane (GRAB)* is a criterion-referenced, video-recorded assessment in an experimental setting, and is designed to detect and quantify asymmetry in the use of the upper limbs by infants from four months of age affected by asymmetric brain injury [79]. Its complex scoring system evaluates uni- and bimanual behaviour, including the number of occasions and duration in seconds, and an asymmetry index is calculated. GRAB scores exhibit moderate-to-strong validity of the construct concerning the quantification of uni- and bimanual reaching and grasping behaviours, by infants with asymmetric brain injury and those developing typically at 18 weeks of age. Furthermore, strong inter- and intrarater reliability has been reported for a small sample of the same target group at 14-18 weeks of age [79].

Of these assessments, the HAI, which has been developed further, appears to provide the most detailed information concerning fine motor skills, in particular on differences between the use of the upper limbs by infants at risk for unilateral CP in a clinical setting [78,81]. However, all methods have their limitations and assessment of unilateral CP, a complex disorder with a wide range of symptoms requires a combination of different approaches and assessments [40], to enhance the accuracy of the prognosis and minimize false-positives, and, even more important, avoid false-negatives as effectively as possible.

1.5.2 Evaluation of bimanual performance in children and adolescents

A number of activity measures that focus on capacity and performance according to the ICF framework [82], were recommended for a comprehensive evaluation of hand function in children and adolescents with unilateral CP. These include the Melbourne Assessment, and the Assisting Hand Assessment, as well as the ABILHAND-Kids and the Children's Hand-use Experience

Questionnaire, patient-reported outcome measures [15,83–86]. In addition to these tools, the recently published Hand-Use-at-Home Questionnaire is also of interest [87].

The *Melbourne Assessment 2 (MA2)* which had been extended and refined using the Rasch measurement model, evaluates the quality of unilateral movements of the upper limb in children with neurological impairments from 2-15 years of age [88–90]. From the video-recordings, each of the 14 items on reaching, grasping, releasing, and manipulating objects is scored on four subscales: range of motion, accuracy, dexterity, and fluency. The scores of the MA2 demonstrate improved validity and reliability [89,91]. However, this assessment focuses on unilateral movements, and does not provide information on activities that require the use of both hands.

A widely used, observation-based, and standardized tool that assesses how effectively children from 1.5-18 years of age with unilateral upper limb dysfunction (obstetric brachial plexus palsy or unilateral CP) use their affected hand in connection with bimanual activities is the *Assisting Hand Assessment (AHA*) [92]. This Rasch-based assessment involves a video-recorded, semi-structured play session with the AHA test kit, and evaluates general use, arm use, grasp and release, fine motor adjustment, coordination and pace of the affected limb [92,93]. Excellent validity, test-retest and interrater reliability of these scores have been reported in several studies [94,95]. Thus, the AHA offers a useful tool to evaluate bimanual performance of children with unilateral upper limb impairment and follow their development over time.

The *ABILHAND-Kids* is a parent-reported Rasch-based questionnaire consisting of 21 items designed to evaluate the manual ability of children from 5-16 years of age to perform certain daily activities [96]. Its scores demonstrate unidimensionality of the construct and moderate evidence of test-retest validity [83,96,97]. However, the majority of these items can actually be performed using one hand only, and scoring does not take into consideration whether the affected or non-affected hand was used to perform the activity [15,86]. Consequently, this questionnaire provides only limited information on the actual performance of the affected hand in bimanual activities.

The *Children's Hand-use Experience Questionnaire* (CHEQ), also a Rasch-based patient-reported outcome measure, explores the experiences and perceptions of the child or adolescent in connection with the performance of daily activities that require the use of both hands [15,98]. Although this questionnaire is designed for children and adolescents 6-18 years of age with unilateral CP, upper limb reduction deficiency and obstetric brachial plexus palsy, it is recommended to be completed by the parents or guardians of children below the age of 13. The CHEQ scores for children with unilateral CP demonstrate very good validity and test-retest reliability [15,98].

Another recently developed parent-reported outcome measure is the *Hand-Use-at-Home Questionnaire (HUH)* quantifying the amount of spontaneous hand use of the affected upper limb concerning 18 bimanual activities of daily living by children with unilateral CP or neonatal brachial plexus palsy from 3-10 years of age [87]. The HUH was developed based on the Rasch measurement model and its scores demonstrate good internal validity (unidimensionality of the construct) and excellent test-retest reliability [87,99].

Although observational assessments of performance aim to be objective and comparable, information concerning the child's perceptions of her/his own performance can be valuable for identifying concerns and setting priorities for treatment. Indeed, the benefits of incorporating objectives identified by the children and their guardians into treatment have been confirmed by a meta-analysis on the efficacy of upper limb therapies for children with unilateral CP [100–102].

1.6 DAILY LIFE ACTIVITIES AND UNILATERAL CEREBRAL PALSY

Many activities of daily life such as getting dressed or eating require the use of both hands. One such example is opening a milk carton at the breakfast table, where one hand holds the carton while the other unscrews the lid. Individuals with unilateral CP have impairments primarily on one side of the body, with the upper extremity generally being more impaired than the lower extremity. The non-affected hand is often used to compensate for the limitations of the affected hand, utilizing more numerous advanced movements than those performed by the dominant hand of children who develop typically [103]. This, consequently, has an effect on the coordination between both arms, in particular during asymmetric bimanual activities [103–105].

In children with unilateral CP, the motor abilities of the upper extremity range from being able to perform most activities independently to requiring extensive assistance [106–108]. In this context, hand function is usually described employing the Manual Ability Classification System (MACS) [26]. Even though most individuals with unilateral CP, especially with MACS levels I or II, are quite capable of performing activities of daily living independently, including self-care, performance of bimanual activities can be challenging [31,94,107,109]. For individuals with unilateral CP, planning an activity that requires the use of both hands involves complex decision-making that is influenced by both personal and environmental factors [31]. To manage activities of daily living and to participate in leisure activities together with others, these individuals utilize a repertoire of strategies, but none of these is ideal and the alternative with the least negative consequences is usually chosen [31]. In addition to their impairments in motor function, the learning difficulties and perceptual disturbances that often accompany CP can hinder the accomplishment of complex activities involving several sequential tasks [110].

Designed to promote independence in activities of daily living, activity-based training directed towards specific goals of the children utilizing meaningful and motivating tasks have a positive

impact on hand function and bimanual performance [111,112]. In addition to occupational and physical therapy, such training can involve specific intensive interventions, such as constrained-induced movement therapy or bimanual intensive training designed to intensify practice of particularly challenging activities over a specified period of time, as well as home-based training incorporating guardians, possibly, educators [110]. Moreover, approaches that primarily focus on the children and their families, considering their specific needs and involving them in decision-making, enhance well-being and satisfaction, as well as the efficacy of the training [13,113].

In addition, as demonstrated by longitudinal investigations using the HAI and the AHA, hand function generally improves with age [106,108,114]. Distinct patterns of improvement and differences in the rate of development by children with different initial levels of hand function were observed, with infants and children demonstrating greater initial manual ability reaching a higher level of performance [106,108,114].

2 RELEVANCE OF THE PRESENT STUDIES

Valid assessment of the hand function of individuals with unilateral CP from infancy into adolescence is crucial for a number of reasons. First of all, early and accurate identification of infants at high risk for unilateral CP provides support to them and their families, reducing the uncertainty associated with brain injuries and atypical patterns of movement. Secondly, such assessment allows follow-up and early evidence-based interventions during the sensitive period of brain development, as well as facilitating further research into the effectiveness of early interventions through accurate identification of those who will indeed develop unilateral CP. Furthermore, longitudinal follow-up of these children ensures that they receive the support they need as they develop from infancy into adulthood. Incorporation of their own perceptions and experiences concerning their performance of daily activities that require the use of both hands into individualized interventions becomes increasingly important as they grow older and become more aware of potential limitations in their daily life.

3 AIMS OF THE THESIS

The overall aim here was to investigate two measurement instruments, the Hand Assessment for Infants (HAI) and the Children's Hand-use Experience Questionnaire (CHEQ), applied to infants at risk of developing unilateral CP and to children and adolescents with unilateral CP, respectively. Of particular interest was the validity of their scores for predicting unilateral CP (HAI) and for capturing perceptions of bimanual performance (CHEQ), both at a single point in time and over time, in relation to other assessments serving as external criteria.

The specific aims were:

(I) to investigate whether combining neonatal brain imaging (MRI) with early assessment based on HAI and other patient characteristics can predict the development of unilateral CP in infants with asymmetric perinatal brain injury;

(II) to evaluate the predictive validity of the Hand Assessment for Infants (HAI) to the clinical diagnosis of unilateral CP in infants at risk;

(III) to explore the similarities, relationship, and extent of agreement between the Children's Hand-use Experience Questionnaire (CHEQ) and the Assisting Hand Assessment (AHA) and

(IV) to explore the validity of change scores of the Children's Hand-use Experience Questionnaire (CHEQ) in the construct of perceived bimanual performance in comparison to the Goal Attainment Scale (GAS).

4 METHODS

4.1 MEASUREMENT INSTRUMENTS

The two primary measurement instruments utilized were the Hand Assessment for Infants (HAI) and the Children's Hand-use Experience Questionnaire (CHEQ). The Assisting Hand Assessment (AHA) and the Goal Attainment Scale (GAS) are also described below, since these served as external criteria for studying the relationship of the CHEQ to the AHA in order to improve the understanding of the construct of CHEQ and for evaluating the validity of changes scores of the CHEQ.

4.1.1 The Hand Assessment for Infants (HAI)

The Hand Assessment for Infants (HAI) is a criterion- and norm-referenced standardized observation-based assessment of infants 3-12 months of age at risk of developing unilateral CP [78]. It evaluates the quantity, as well as the quality of manual abilities such as contacting, reaching, grasping, and manipulating objects (toys), as performed by each hand individually or both together. In a semi-structured, video-recorded 10-15-minute session of play, 12 uni- and five bimanual items are tested and scored on a 3-point scale [78]. The sum score is Rasch-transformed into an interval level logit-based Both hands measure, BoHM (0-100 HAI-units) with higher scores demonstrating a more proficient performance. In addition, unimanual items are scored for each hand separately to obtain the Each hand sum score, EaHS (0-24 points). On basis of the EaHS, an asymmetry index, AI (0-100 percentage difference), is calculated automatically based on the EaHS by relating the difference in ability between both hands to the ability of the better-functioning (ipsilesional) hand [78].

4.1.2 The Children's Hand-use Experience Questionnaire (CHEQ)

The Children's Hand-use Experience Questionnaire (CHEQ) is a patient-reported outcome measure that evaluates the child's experience of using the affected hand in bimanual activities of daily living. This 29-item online questionnaire is designed for children 6-18 years of age with upper limb impairment (unilateral CP, upper limb reduction deficiency, or obstetric brachial plexus palsy) and is available online free of charge (www.cheq.se). Its main features are three scales that assess the efficacy of grasping by the affected hand when both hands are involved (*grasp efficacy*), the time required to perform the activity in comparison to peers (*time utilization*), and the feeling of being bothered while performing the activities (*feeling bothered*). The CHEQ also assesses whether children perform the activities independently and whether one or two hands are used on a binary scale. Higher scores represent more activities being performed (*grasp efficacy*) or a greater satisfaction with the performance (*time utilization* and *feeling bothered*). This questionnaire can be completed by guardians acting as proxies for their children and adolescents below the age of 13 years. After completion of the questionnaire

online, the website automatically summarizes the answers graphically. The raw scores of the four-point CHEQ scales can be transformed by Rasch measurement analysis to logits and, further, into a 0-100 scale (CHEQ-units) [15,98].

4.1.3 The Assisting Hand Assessment (AHA)

The Assisting Hand Assessment (AHA) is a standardized observational test designed to evaluate bimanual performance of the affected hand by children from 1.5-18 years of age with unilateral upper limb dysfunction, unilateral CP or obstetric brachial plexus palsy [92,115]. Its scoring criteria are the same for the entire age range [92]. The AHA 4.4 utilized here comprised 22 items that assess general use of the affected hand, arm use, grasp and release, fine motor adjustment, coordination, and pace of use of the affected hand on a four-point scale. This ordinal scale, with higher scores indicating greater ability, is transformed by Rasch measurement analysis into AHA-units on interval scale level ranging from 0-100 [93]. The AHA was administered by a certified rater, blinded to the CHEQ results.

4.1.4 The Goal Attainment Scale (GAS)

The Goal Attainment Scale (GAS) measures the extent to which an individual achieves goals set during intervention. The goals are formulated individually for each child and are assumed to be reached, but the procedure for setting these goals and evaluating their achievement is standardized [116]. Actual performance is judged against the a priori formulated levels of goal achievement [117]. GAS scores are valid for defining goals to evaluate changes in gross motor function in response to physical therapy, and have demonstrated good reliability, in particular when applied by the child's own therapist [118,119]. In addition, the GAS has been reported to be more sensitive in evaluating function than standardized measures [118,120–122].

4.2 STUDY DESIGN

To facilitate future implementation and strengthen the ecological validity of this research, all studies were performed in a clinical setting. A longitudinal prospective design was employed to investigate the performance of the predictive model developed (Study I), assess the predictive validity of the HAI (Study II) and evaluate the validity of change scores of the CHEQ (Study IV). A clinical diagnosis of unilateral CP (yes/no) at ≥24 months of age served as external criterion to evaluate the predictive model and predictive validity of the HAI (Studies I and II). The Goal Attainment Scale (GAS) was used as external criterion (anchor) for changes in the construct of the CHEQ (Study IV). Finally, a cross-sectional validity study served to explore the relationship between the CHEQ and the AHA as the external criterion (Study III).

4.3 PARTICIPANTS

4.3.1 Recruitment

All infants, children and adolescents who agreed to participate in the according studies and their proxies were recruited through convenience sampling at neurological clinics in Sweden, the Netherlands, Italy and Australia from 2006 - 2016.

For Studies I and II, 203 infants were recruited from neurological clinics at the following locations: the Astrid Lindgren Children's Hospital and Södersjukhuset in Stockholm, Sweden; the Wilhelmina Children's Hospital of the University Medical Center in Utrecht, The Netherlands; the Stella Mares Hospital, Pisa, Italy; and the Cerebral Palsy Alliance, Sydney, Australia. In Stockholm, all infants were recruited on the basis of neurological signs and MRI findings from the national follow-up program for perinatal stroke. In Utrecht, in contrast, only infants considered to be at high risk of developing unilateral CP based on evidence of asymmetric perinatal brain injury obtained through visual inspection of MRI were recruited. A subsample of 52 infants with asymmetric perinatal brain injury belonging to this latter cohort was analysed separately in Study I.

In Study III, children and adolescents from 6-18 years of age and affected by unilateral CP were recruited via their occupational therapists from the Astrid Lindgren Children's Hospital in Stockholm over a period of one year.

The data on children and adolescents with unilateral CP analysed in Study IV were retrieved from an investigation of an intensive bimanual training intervention applied during a two-week day camp in England [123].

4.3.2 Eligibility criteria for participants

For the first two studies, the target population were infants at risk of later developing unilateral CP due to a neonatal event such as an asymmetric perinatal brain injury or who demonstrated early neurological signs of hand asymmetry.

In Study I, only infants with an asymmetric perinatal brain injury verified by MRI within one month of term-equivalent age and for whom a HAI assessment at 3.5-4.5 months of age was available were included.

Study II involved a broader population of infants considered to be at risk of developing unilateral CP on the basis of a clinical diagnosis of perinatal stroke, an asymmetric perinatal brain injury verified by MRI, or neurological signs of hand asymmetry alone without a confirmed neonatal event at the time of their first HAI assessment. Hand asymmetry was defined as a difference of at least three points between the two HAI Each hand sum scores (EaHS), since 98% of infants that develop typically have a side difference of less than three points [124]. Since the aim was to determine the predictive validity of the HAI, the target

population represented a broad variety of groups at risk for unilateral CP, with abilities of hand function varying as evaluated by the HAI.

Similarly, Studies III and IV involved individuals whose bimanual abilities varied widely in order to cover the full range of activities evaluated by the assessment tools. Both of these studies included children and adolescents 6-18 years of age and diagnosed with unilateral CP. In the case of Study III, participants were required to complete the CHEQ and perform the AHA within the same three-month period. Hand function was assumed to be stable during this period, even though participants may still have been receiving standard care at their local rehabilitation centre in Sweden, which involves at most one session of occupational therapy per month [125,126]. The children and adolescents in Study IV had to have participated in a two-week intensive intervention designed to improve performance of activities involving both hands [123]. Their progress had to have been measured using the GAS both before and after the intervention. The detailed inclusion and exclusion criteria for each study are presented in Table 5.1.

Table 5.1 The criteria for inclusion and exclusion of participants

Study	Inclusion criteria	Exclusion criteria
I	▪ neonatal MRI within one month term-equivalent age, ▪ assessment by HAI between 3.5-4.5 months, ▪ presence or absence of unilateral CP after 24 months of age, as verified by a child neurologist	▪ major congenital malformation or surgery before appearance of the first symptoms ▪ early signs of other forms of CP ▪ severe visual impairment that hinderd completing the assessment
II	▪ 3-12 months of corrected age with risk of developing unilateral CP due to ▪ either an image of asymmetric perinatal brain injury, a clinical diagnosis of perinatal stroke, or neurological signs of hand asymmetry alone (≥3 points difference in the two HAI EaHS), and ▪ documentation of whether the child has a diagnosis of unilateral CP or not after 24 months of age verified by medical records	▪ early signs of other forms of CP ▪ severe visual impairment that hindered taking the test
III	▪ 6-18 years of age with ▪ unilateral CP and ▪ subsequent CHEQ and AHA evaluation	▪ intensive treatment ▪ surgery of the upper limb during collection of the data
IV	▪ 6-18 years of age with ▪ unilateral impairment of the upper limb ▪ assessments with the CHEQ and GAS at baseline and immediately following the two-week program of hand-arm bimanual intensive therapy	▪ other severe impairments that limited participation in the training program

HAI - Hand Assessment for Infants, EaHS - Each hand sum score of the HAI, CP - cerebral palsy, CHEQ - Children's Hand-us Experience Questionnaire, AHA - Assisting Hand Assessment, GAS - Goal Attainment Scale

4.4 SAMPLE SIZE

For a study developing a prediction. model, in order to obtain sufficient power it is recommended that 10 participants (i.e., in the present case individuals with unilateral CP) per model predictor be included [127]. The prediction modelling study (Study I) included 52 infants, 18 of whom developed unilateral CP, which would strictly speaking allow analysis of only two predictors. This should be the two predictors of major interest, i.e. HAI and corticospinal tract (CST) involvement as confirmed by neonatal MRI. However, it is well known that other factors, such as young gestational age and male sex, also are related to the development of unilateral CP.

A further consideration in this context, is the type of statistical analysis that is appropriate for the data being examined. CST involvement proved to be a quasi-complete separator in our sample, i.e., no infants without such involvement developed unilateral CP (100% sensitivity). This situation requires a specific type of logistic regression, namely Firth logistic regression, which does not allow selection of variables, but considers all predictors available for modelling instead. In addition, gestational age and sex are readily available. Therefore, we decided to include all possibly relevant predictors that were available. Another general aspect of prediction models is that the greater the number of relevant predictors included, the better the prediction can be expected to be.

In general, a minimum of 50 individuals is considered to be sufficient for a validity study, a condition met well in connection with the analysis of the subgroups in Study II [2]. However, Studies III and IV, on the Children's Hand-use Experience Questionnaire (CHEQ*)* are explorative in nature and include a smaller number of participants. Consequently, the results of these studies must be interpreted with care and understood as pieces in the puzzle on the validity of scores generated by the CHEQ. In addition, Study IV involved secondary analysis of data from an intensive intervention already completed, so the number of participants could not be increased [123]. A predictive validity study must include participants of the same population both with and without the expected outcome, in order to evaluate whether the instrument can distinguish between these. Likewise, for investigating the validity of change scores of a measure, the study population should include individuals whose scores changed and some whose scores did not.

4.5 PROCEDURES AND DATA COLLECTION

For Study I, *magnetic resonance imaging of the brain (MRI)* was performed within one month of reaching term-equivalent age, as part of routine clinical follow-up of a neonatal event. The MRI protocols included T1- and T2-weighted images (T1WI, T2WI) and, in Utrecht, DWI as well. More detailed information on the scanning procedure is presented in the related article [128]. Two clinicians with expertise in the field of neonatal neurology, both unaware of the clinical

outcome, re-evaluated all MR images by visual inspection. This evaluation focused on specific areas of the brain known to predict atypical motor outcomes, i.e. the corticospinal tracts (CST) at the level of the posterior limb of the internal capsule (PLIC) and the cerebral peduncle [47,129], as well as the basal ganglia and thalamus region (BGT) [45,130].

The *Hand Assessment for Infants (HAI)* was performed between 3.5-4.5 months of corrected age, depending on the clinical routine at the hospital involved (Study I). In Study II, infants affected by perinatal stroke or another asymmetric perinatal brain injury were assessed with the HAI during their regular follow-up visits to the hospitals at approximately 3, 6, 9, and 12 months of corrected age. For infants at risk of developing unilateral CP as judged on the basis of solely neurological signs of asymmetry between hands and without known neonatal event, the HAI was performed after referral to their hospital. All HAI assessments were videotaped and subsequently scored in accordance with the manual by experienced occupational therapists blinded to the clinical outcome (Studies I and II). In Study II, the HAI assessments were grouped into six age intervals for analysis: early assessment at 3 months of age, additional assessments at 3.5-4.5, 4.5-5.5, 5.5-6.5, and 6.5-7.5 months, and a combined assessment at 7.5-12 months. The infants could be assessed at somewhat different exact ages, due to variations in the clinical routines of the participating hospitals, i.e., one or more times across all age intervals. No more than one assessment per infant per age interval was included.

The *clinical outcome of unilateral CP* (yes/no) was determined at ≥24 months of age, either through a clinical assessment by a child neurologist (Study I) or on the basis of medical records (Study II). This diagnosis was determined following international European guidelines [19].

The *Children's Hand-use Experience Questionnaire (CHEQ)* was completed online either by the children or adolescents themselves or their guardians during a hospital visit or at home (Study III) or before and after an intensive two-week intervention (Study IV) [123].

The *Assisting Hand Assessment (AHA)* was performed in the hospital by a certified assessor who was also an occupational therapist (Study III). In addition, information of the Manual Ability Classification System (MACS) was provided by the occupational therapists involved (Studies III and IV) [26]. The MACS describes on five different levels how children with CP handle objects in their everyday life: from 'independent handling of objects with minor difficulty' (level 1) to 'need for assistance for managing objects' (level 5).

Prior to the start of the intervention in Study IV, goals for bimanual performance were formulated and set by the children and their guardians together with the therapist using the *Goal Attainment Scale (GAS)*. After the intervention, the achievement of these goals was evaluated in accordance with predefined scaling parameters and based on consensus between observations by a therapist and a report from the child and guardian.

As described in the Introduction, responsiveness is understood as the validity of change scores and is accordingly, investigated in a manner similar to validity, but in a longitudinal setting. Changes in the construct of interest indicated by the measurement instrument under study, in this case the CHEQ, are compared to those observed with an external criterion or construct (anchor) [2]. The *Goal Attainment Scale (GAS)* was chosen here as the *anchor* for changes in the construct of bimanual performance based on the perceptions of children and their guardians (Study IV). In this context, the GAS goals and CHEQ items were assumed to be sufficiently related, since the involvement of participants and therapists in formulating and evaluating personal goals enabled combining of standardized procedures and perceptions of bimanual performance, which reflects parts of the construct being measured by the CHEQ. On the basis of the GAS, participants were classified as improved when there was a minimal increase of two scale steps in two or more GAS goals, an extent of change reported to be meaningful [121].

4.6 STATISTICAL METHODS

An overview of the statistical methods applied in each individual study is given in Table 5.2. *Descriptive summary measures* were reported either as mean with standard deviations (SD) or median values with interquartile ranges (IQR), depending on the distribution of data and level of measurement. The *Shapiro-Wilk tests* and *scatterplots* were used to check for normality and possible outliers.

Firth penalized regression was employed to construct the multivariable prediction model (Study I) based on all available and relevant clinical predictors (CST, BGT, HAI, gestational age, sex). At the same time, this approach took the quasi-complete separation with respect to CST involvement (i.e., no infants without CST involvement detectable by MRI, developed unilateral CP) into consideration. To limit overfitting of the model, we applied *ten-fold cross-validation* (i.e., division of the data into ten subsets) where nine are utilized to construct the model and the tenth to evaluate its accuracy. This procedure, repeated with each subset of the tenth, reduces the magnitude of model coefficients.

Receiver operating characteristic (ROC) curve analysis was performed and the area under the curve (AUC) was calculated to evaluate the overall accuracy of the prediction model (Study I) and of the HAI (Study II) to discriminate between infants with and without unilateral CP. The ROC curve plots the sensitivity over 1-specificity (false-positive rate) for every single value of the measure or method and the *area under the curve (AUC)* represents the overall accuracy of this measure over a range of possible thresholds. An AUC close to 1.0 indicates excellent discrimination (accuracy), whereas an AUC of 0.5 is no better than chance.

To investigate the predictive validity of the HAI (Study II), *sensitivity and specificity, predictive values, accuracy, and likelihood ratios* of specific cut-off values were obtained from the ROC curve analysis (Study II).

Sensitivity is defined as the proportion of infants with unilateral CP correctly identified by the test (the prediction model in Study I, the HAI in Study II); where *specificity* is the proportion without unilateral CP classified correctly by the test [131].

The *positive predictive value (PPV)* is the proportion of infants with positive test results (high probability of developing unilateral CP according to the prediction model in Study I; limited hand function in Study II) who are later diagnosed with unilateral CP; while the *negative predictive value (NPV)* is the proportion with negative test results correctly identified as not developing unilateral CP [132]. *Accuracy*, the proportion of correctly classified infants (true-positives and true-negatives), was calculated for several cut-off values of the HAI in Study II using several cut-off values.

A positive test result refers to impaired hand function as measured by the HAI in Study II, while a negative test result indicates adequate hand function on HAI in Study II. A positive clinical outcome means the presence of unilateral CP and negative, absence of this condition.

To facilitate clinical use of the HAI for diagnosing unilateral CP in clinical practice, *cut-off values* (Study II) were retrieved from the ROC curve analysis. The choice for appropriate cut-off values for each HAI scale at different ages was based on a balance between sensitivity and specificity at maximal or near-maximal accuracy. When multiple cut-off values were possible, clinical experience, and knowledge concerning hand development in infants, as well as normative values for the HAI were also considered [106,124].

		Diagnosis +	–	
Test	+	**TP**	FP	*PPV* *TP/(TP+FP)*
	–	FN	**TN**	*NPV* *TN/(TN+FN)*
		Sensitivity *TP/(TP+FN)*	*Specificity* *TN/(TN+FP)*	*Accuracy* *(TP+TN)/(TP+TN+FP+FN)*

positive likelihood ratio (LR+) = sensitivity/(1-specificity)
negative likelihood ratio (LR-) = (1-sensitivity)/specificity

Modified from Fletcher and Fletcher (2005) [133]

The *likelihood ratios* refer to how many fold more or less likely a particular HAI result is observed among infants with unilateral CP than those without. The positive likelihood ratio (LR+) is defined as the ratio between the likelihood of having a positive test result when the clinical outcome is positive (unilateral CP) to the corresponding likelihood with a negative clinical outcome (no unilateral CP), with the negative likelihood ratio (LR-) being the ratio between the likelihood of having a negative test result when the clinical outcome is positive to the corresponding likelihood with a negative clinical outcome. LR values of less than 1 indicate

less likelihood of the disease, LR values greater than 1 more likelihood, an LR=1 no change. An LR+ >10 is a strong indicator of the presence of unilateral CP, and a LR- <0.1 strong evidence for the absence of this condition [134].

The predictive values are dependent on the prevalence of disease in the cohort and, consequently, only applicable to populations where the prevalence is similar to that among the study subjects. Sensitivity and specificity, as well as likelihood ratios, are much less dependent on disease prevalence, but are influenced by the characteristics of the patients and the spectrum of disease severity. Accordingly, tests for the detection of disease are more sensitive when the condition is more severe. Thus, sensitivity, specificity and likelihood ratios for one group of patients are only applicable to other groups with comparable characteristics and disease severity.

To analyse the *strength of the relationships* between the scales of the CHEQ and AHA, on the one hand, and the anchor GAS on the other hand, scatterplots were inspected visually and *Pearson correlation coefficients (r)* (study III) or *Spearman rank correlation coefficients (ρ)* (Study IV) calculated, depending on the level of the data. Large correlation coefficients were considered to indicate greater similarity between the measurement instruments, and small correlation coefficients less similarity.

In Study IV, the Spearman rank correlation coefficients (ρ) between the CHEQ scales and the anchor GAS were calculated in order to investigate to which extent changes in the construct (i.e., bimanual performance based on the perception of participants) measured by CHEQ relate to changes determined by the GAS, and thereby determining the appropriateness of utilizing GAS as an anchor in this context.

The *coefficients of determination (R^2)* were calculated to facilitate interpretation of the correlation coefficients in Study III. R^2 is a measure of the variability shared by two variables, but provides no information about the agreement or disagreement between two methods of measurement. Consequently, the level of agreement between CHEQ and AHA was examined employing *Bland-Altman plots* and the *limits of agreement* [2,135]. In Bland-Altman plots, the difference between the scores obtained by the two measurement instruments, i.e., the AHA and each of the three CHEQ scales (Study III), were plotted against their mean values with 95% limits of agreement reflecting the spread of observations for each individual [2,136].

Two-tailed paired-samples t-tests at a significance level of p <0.05 were performed to determine whether mean differences between demographic variables (Study I) or between the scales of the CHEQ and AHA in the Bland-Altman plots (Study III) differed significantly from zero.

In the case of Study IV, an anchor-based approach was applied to compare changes in the construct of CHEQ to those indicated by the anchor GAS. In connection with the construct of

bimanual performance concerning participants' perceptions, *effect sizes* based on a priori defined hypotheses about the magnitude of their change were calculated for both the group that improved and those that did not according to the GAS, using Cohen's d and the standardized response mean (SRM). In addition, a ROC analysis was performed and the *AUC* calculated to analyse the ability of the CHEQ to discriminate between participants who improved and those that did not.

All statistical analyses in this thesis were performed utilizing the Stata IC 15, SPSS 22.0, MedCalc, and Excel 2013 software.

Table 5.2 Methodological overview of the studies

Objective	Design	Target population	Statistical analysis
Study I: Prediction model for unilateral CP			
To develop and internally validate a prediction model for unilateral CP in infants at risk at 3.5-4.5 months of age	Prediction modelling study in a hospital-based setting; convenience sampling	Infants with asymmetric perinatal brain injury	Firth penalized regression with ten-fold cross-validation; Receiver operating characteristic (ROC) curve analysis; calculation of sensitivity, specificity, predictive values, and likelihood ratios; Paired-samples t-test
Study II: Predictive validity of HAI scores			
To investigate the predictive validity of the HAI for unilateral CP in infants at risk from 3-12 months of age	Predictive validity study in a hospital-based setting; convenience sampling	Infants from 3 months of age at risk of unilateral CP due to a history of a neonatal event, or an asymmetric brain injury confirmed by MRI, or neurological signs of hand asymmetry	ROC curve analysis; calculation of sensitivity, specificity, predictive values, and likelihood ratios
Study III: The CHEQ versus the AHA			
To explore the differences, relationship and extent of agreement between the CHEQ and AHA	Cross-sectional validity study; convenience sampling	Children and adolescents from 6-18 years diagnosed with unilateral CP	Pearson correlation coefficient; Bland-Altman plot; Paired-samples t-test
Study IV: Validity of CHEQ change scores			
To explore the validity of change scores of the CHEQ in relation to the anchor GAS	Longitudinal study of the validity of change scores; convenience sampling; secondary analysis	Children and adolescents from 6-18 years with unilateral CP who underwent a two-week intensive intervention	Spearman rank correlation coefficient, ROC curve analysis

CP - cerebral palsy, HAI - Hand Assessment for Infants, AHA - Assisting Hand Assessment, CHEQ - Children's Hand-use Experience Questionnaire, MRI - magnetic resonance imaging, GAS - Goal Attainment Scale

* These infants were also included in study II.

5 REFLECTIONS ON ETHICAL CONSIDERATIONS

Consent to participate in these studies was obtained from both the children and adolescents themselves and their parents/guardians after providing detailed information in form of a letter or, if required personal conversation. The assessments have been developed for clinical practice and their application was not reported to cause harm or unease to the participants. The Hand Assessment for Infants (HAI) and the Assisting Hand Assessment (AHA) both involve non-invasive 10-15-minute sessions of play. Both support the development of the child and can also help families to facilitate the development of their child's hand function. The Children's Hand-use Experience Questionnaire (CHEQ) asks about bimanual activities of daily life, with a focus on the affected hand. To reflect on one's own performance can be challenging, but can also provide detailed insight concerning activities that can be performed well and those that need further attention. All families received feedback on the results of the assessments and if this led to additional questions regarding their healthcare, were guided appropriately through the healthcare system. Participants were informed about the study through an information letter and personal conversation, if requested. The participants were also informed that they could withdraw at any time without consequences. Ethical approval was granted by the relevant ethics committee for all aspects of this research.

6 RESULTS

6.1 CHARACTERISTICS OF THE PARTICIPANTS

All participants were at risk of developing unilateral CP (Studies I and II) or had developed unilateral CP (Studies III and IV). The 52 infants with asymmetric perinatal brain injury involved in Study I took also part in Study II. The characteristics of all of the participants are summarized in detail in Table 7.1.

Table 7.1 Characteristics of the participants

	Median [IQR] or mean (SD)	Frequency (%)
Study I: Prediction model for unilateral CP (n=52)		
Gestational age at birth in weeks	39.3 [33.5, 40.5]	
Female/male		25(48)/ 27(52)
Preterm (<37 weeks of gestation)		19 (37)/ 33 (63)
Unilateral CP at ≥12 months CA		18 (35)
Laterality of lesion: left/right/asymmetric bilateral		25 (48)/ 24 (46)/ 3 (6)
Corrected age at the time of the HAI assessment	16 [15; 18]	
Study II: Predictive validity of HAI scores (n=203)		
Female/male		106 (52)/ 97 (48)
Gestational age at birth (weeks)	38.1 [32; 40.4]	
Term/preterm/very preterm[§]		130 (64)/ 37 (18)/ 36 (18)
Age at first HAI: 3-5/6-8/9-10 months CA		155 (76)/ 45 (22)/ 3 (2)
Unilateral CP at ≥12 months CA: yes/no		103 (51)/ 100 (49)
Study III: The CHEQ versus the AHA (n=34)		
Age (years)	12.1 (3.9)	
Female/male		16 (47)/ 18 (53)
Affected hand right/left		18 (53)/ 16 (47)
MACS level* I, II, II		7 (21)/ 23 (67)/ 3 (9)
Respondent child/parent or guardian/both		18 (53)/ 10 (29) /6 (18)
Days between CHEQ and AHA assessment	33.2 (82.4)	
AHA-units	58 (14.4)	
Study IV: Validity of CHEQ changes scores (n=44)		
Age in years	9.7 (2.4)	
Female/male		14 (32)/ 30 (68)
Affected hand right/left		23 (52)/ 21 (48)
MACS level I/II/III		7 (16)/ 22 (50)/ 15 (34)
GMFCS level I/II/III		30 (68)/ 13 (30)/ 1 (2)
Respondent child/parent or guardian		42 (96)/ 2 (4)

CP - cerebral palsy, HAI - Hand Assessment for Infants, MRI - magnetic resonance imaging, CA - corrected age, AHA - Assisting Hand Assessment, CHEQ - Children's Hand-use Experience Questionnaire, GMFCS - Gross Motor Function Ability Classification System, MACS - Manual Ability Classification System;
* MACS level missing for one participant;
[§] term: ≥37 weeks gestational age (GA) at birth, preterm: 36-30 weeks GA, very preterm: <30 weeks GA

6.2 THE PREDICTION OF UNILATERAL CEREBRAL PALSY

The *Hand Assessment for Infants* (HAI) showed very good to excellent overall accuracy for the prediction of unilateral CP from 3.5-12 months of age (Study II). The specific cut-off values demonstrated very good sensitivity and specificity for the clinical application of the HAI to contribute to clinical diagnosing of unilateral CP from 3.5-12 months of age. A *multivariable prediction model* that combines both, the qualitative evaluation based on neonatal MRI and the contralesional Each hand sum scores (EaHS) of the HAI with gestational age and sex, can predict unilateral CP in infants at risk from 3.5-4.5 months of age with excellent accuracy.

6.2.1 Prediction model

The multivariable prognostic model based on all relevant predictors available, i.e.,

- ✓ CST and BGT involvement as indicated by neonatal MRI within one month of term-equivalent age (no involvement = 0, involvement = 1)
- ✓ the contralesional HAI EaHS score between 3.5 and 4.5 months of age
- ✓ gestational age, and
- ✓ sex (female = 0, male = 1),

was developed to predict unilateral CP in infants from 3.5-4.5 months of age and internally validated. The model discriminated with excellent accuracy between infants who did and did not develop unilateral CP, with an area under the curve, AUC, of 0.98 (95% CI 0.95-1.00). The strongest predictors appeared to be CST involvement and the contralesional HAI EaHS score as demonstrated by exploring alternative models excluding either MRI parameters or the HAI and univariate analyses. The results of the final model can be applied by using the nomogram suggested to estimate the prognostic risk (probability) of an infant developing unilateral CP based on individual values for each predictor at certain time-points (Figure 7.2).

Application of the nomogram to a clinical case [128]:

A baby *girl* was born at *25+3 weeks of gestation* after an emergency Caesarean section indicated by decelerations on cardiotocography. Her birth weight was 900 grams and Apgar scores after 1, 5 and 10 minutes 4, 7 and 9. Her MRI at approximately term-equivalent age showed clear *asymmetry of the corticospinal tracts (CST)* at the level of the posterior limb of the internal capsule (A). Similarly, the *basal ganglia and thalamus (BGT)* also clearly exhibited *asymmetry*. She was discharged from the neonatal unit and returned for a follow-up at 17 weeks of corrected age, at which time the HAI was performed. Her *HAI Each hand sum score (EaHS)* for her left (contralesional) hand was *7 points*.

The nomogram in Figure 7.2 illustrates by drawing a dotted line from each predictor scale to the 0-11 'Score' scale

- ✓ her score of **0** for being female
- ✓ the score of **0.6** for her age at birth of 25 gestational weeks
- ✓ a score of **1.5** for basal ganglia involvement
- ✓ a score of **7.1** for contralesional HAI EaHS of 7 points
- ✓ a score of **2.8** for corticospinal tract involvement

The sum of these scores is 12 indicated by the 'Total score' at bottom line and her Probability of developing unilateral CP is displayed above being 0.94.

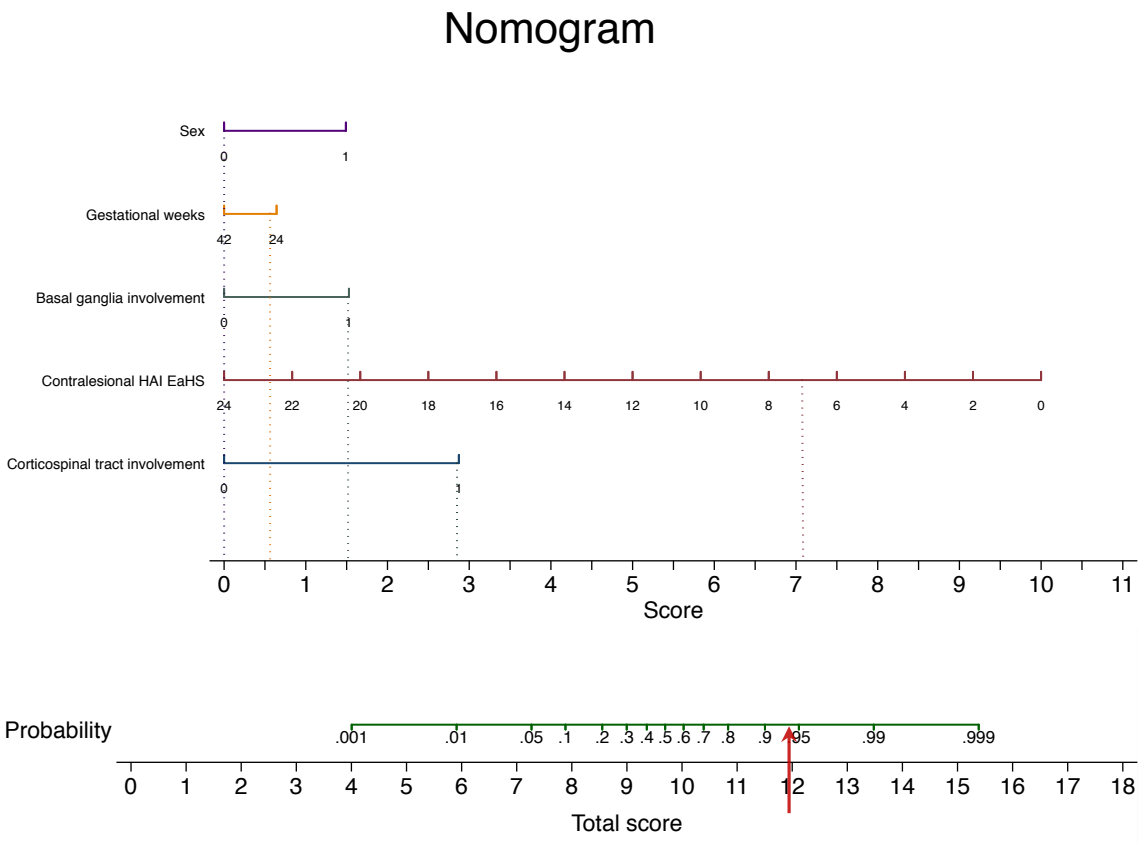

Figure 7.2 Nomogram illustrating the prognostic risk of developing unilateral CP based on the sum of the scores of individual predictors;
sex: female = 0, male = 1, basal ganglia/corticospinal tract involvement: no = 0, yes = 1

The sensitivity and specificity associated with the range of cut-off values for the prognostic risk of unilateral CP at a later age are displayed in Figure 7.3. Here, sensitivity refers to the proportion of infants correctly predicted to develop unilateral CP by the model, while specificity represents the proportion correctly predicted not to develop this condition. Deciding on a threshold for the prognostic risk depends strongly on the actions to follow. In connection with very intense interventions, it might be desirable to limit the number of false-positives by choosing a higher cut-off value associated with higher specificity, whereas for information and support to families the cut-off chosen may be lower providing higher sensitivity, so that as few cases as possible are missed.

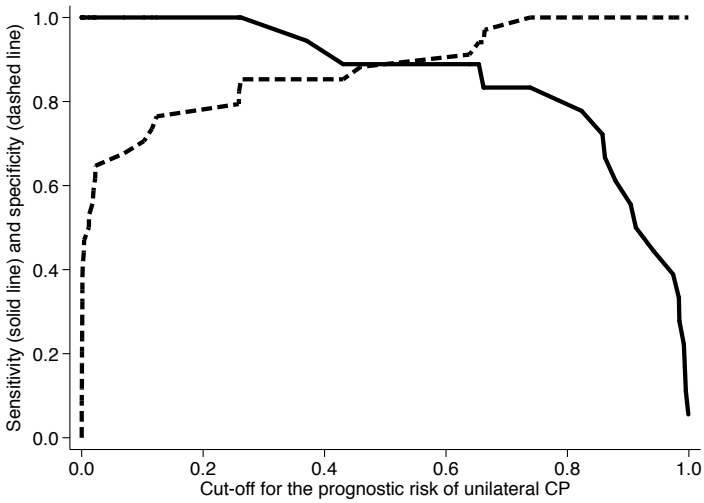

Figure 7.3 Sensitivity and specificity associated with the prognostic risk of unilateral CP [128]

6.2.2 The predictive validity of the HAI

In summary, the Hand Assessment for Infants (HAI) exhibited excellent overall accuracy in predicting whether infants would develop unilateral CP or not between 3.5-12 months of age. For all of the HAI scales, this accuracy increases with age.

Thus, the HAI can be helpful for clinical diagnosing of unilateral CP from as early as 3.5 months of age, as indicated by the very good areas under the curve *(AUC*>0.8*)* in Figure 7.4 and its *sensitivity* (79%) and *specificity* (88%) at this age, especially with respect to the contralesional EaHS (with a cut-off ≤10) and AI (cut-off ≥30). The contralesional EaHS and AI showed the best predictive performance across age intervals. In contrast, the BoHM did not attain similar predictive ability until 5.5-6.5 months of age, presumably because this is when bilateral movements begin to develop. However, the BoHM never exhibited predictive performance as accurate as the contralesional EaHS and AI. Prediction of unilateral CP about 3 months of age remains difficult, since goal-directed movements have not yet emerged fully.

Similar to the values for sensitivity and specificity, the *predictive values* of the HAI ranged from 80-91% between 3.5-12 months of age for a group among whom 40-62% developed unilateral CP, again with the highest values being associated with the contralesional EaHS and AI at an early age.

Moderate *positive likelihood ratios* (LRs) were associated with the contralesional EaHS from 3.5-6.5 months of age with excellent positive LRs for the AI from 4.5-6.5 months of age indicating a moderate-to-large probability of observing impaired hand function, a positive test result on the HAI, in an infant who will develop unilateral CP than one who will not. With the BoHM, moderately positive LRs were only reached at later ages.

In general, the AUCs obtained are in line with the values of sensitivity and specificity, predictive values, accuracy and likelihood ratios that were derived from the ROC curve analysis and are reported for specific cut-off values for each HAI scale.

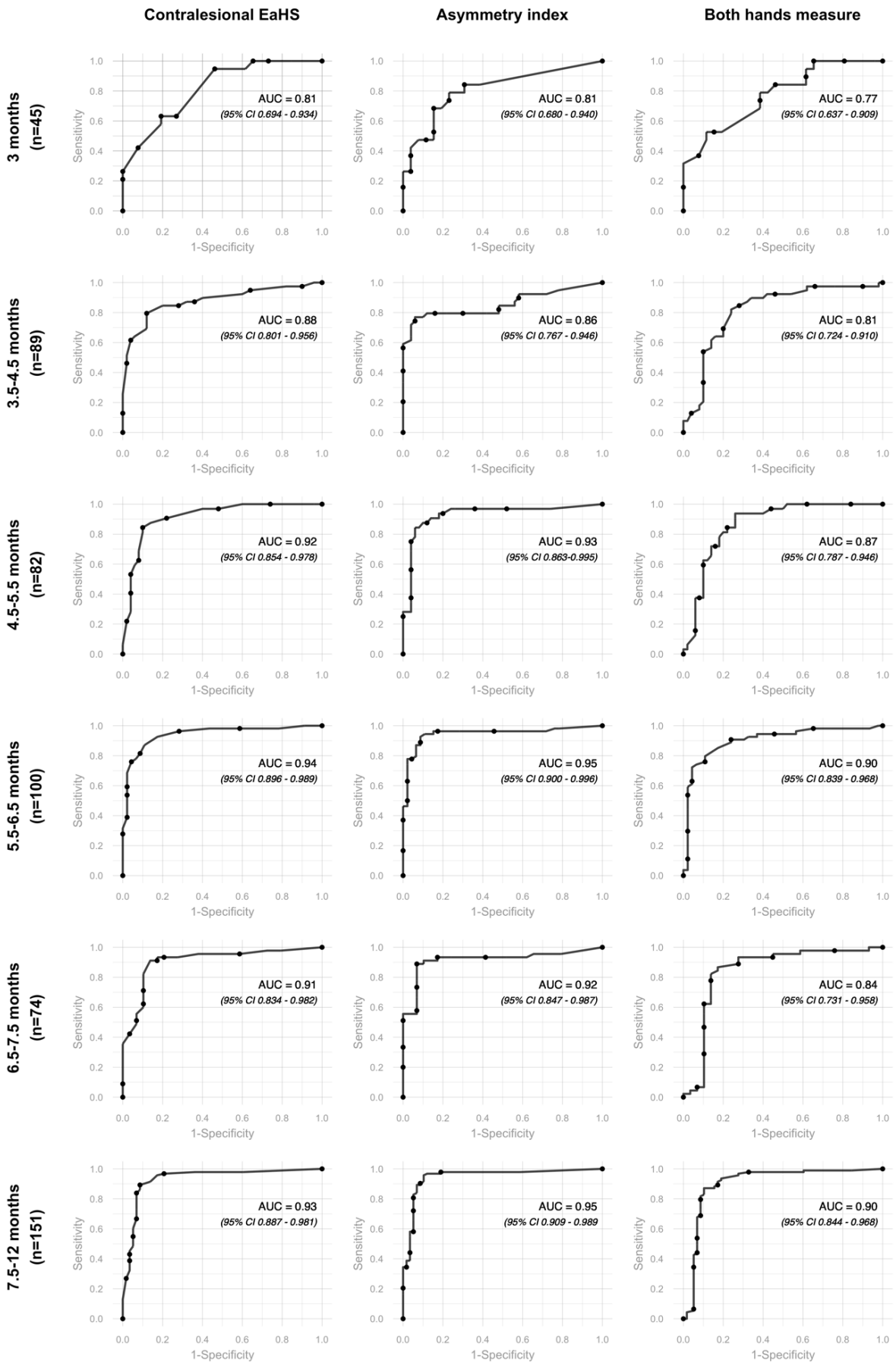

Figure 7.4 Receiver operating characteristic curves displaying the areas underneath (AUC) for the contralesional HAI EaHS, AI and BoHM at various ages

7 EVALUATION OF BIMANUAL PERFORMANCE IN CHILDREN AND ADOLESCENTS WITH UNILATERAL CEREBRAL PALSY

7.1.1 Perceived versus observed bimanual performance: comparison of the CHEQ to the AHA

In summary, the Children's Hand-use Experience Questionnaire (CHEQ) and Assisting Hand Assessment (AHA) measure different constructs that are partially related. The CHEQ scales and AHA share a minor extent of their variance with each other. In addition, there was considerable disagreement between these instruments indicated by very wide limits of agreement.

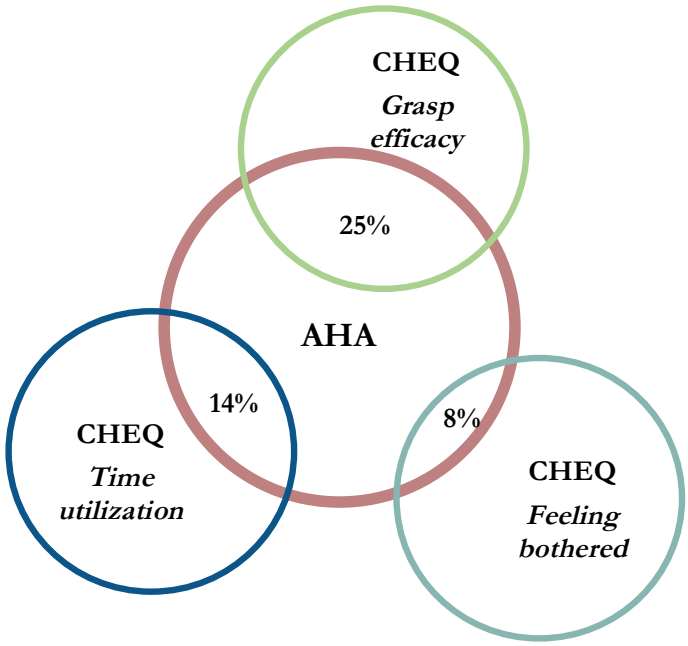

Figure 7.3 The variance (R^2) shared by the CHEQ scales and AHA

The CHEQ scales and the AHA were weakly-to-moderately related with Pearson correlation coefficients ranging from 0.28-0.50. As Figure 7.3 demonstrates, the CHEQ scale *grasp efficacy* shares 25% of its variance (R^2) with the AHA, the CHEQ scale *time utilization* 14%, and the CHEQ scale *feeling bothered* 8%.

The large width of the limits of agreement shown in the Bland-Altman plots (Figure 7.4), indicate considerable disagreement between the three CHEQ scales and the AHA. The estimated mean difference *d* (solid line) between the CHEQ scales and AHA was not significantly different from zero; e.g., the mean difference between the CHEQ scale *grasp efficacy* and AHA was only 1.4 units (on a scale of 0-100). However, the large 95% confidence intervals (CI), presented as dotted lines around the mean difference, imply that the 'true' mean difference could actually lie somewhere between -4.4 and 7.2 units. The outer dashed lines are the 95% limits of agreement and represent the spread of the difference scores for each individual. For 95% of the observations, the differences between the CHEQ scales and the AHA are as large as ± 1.96 times the standard deviation (SD) on either side of the mean difference. Concerning the example, this means that for 95% of the observations the AHA measurements are between 33.8 units above and 31 units below the scores of the CHEQ scale *grasp efficacy* (on a scale of 0-100). Similar disagreement is indicated by the limits of

agreement for the other two CHEQ scales, *time utilization* and *feeling bothered*, as well (Figure 7.4).

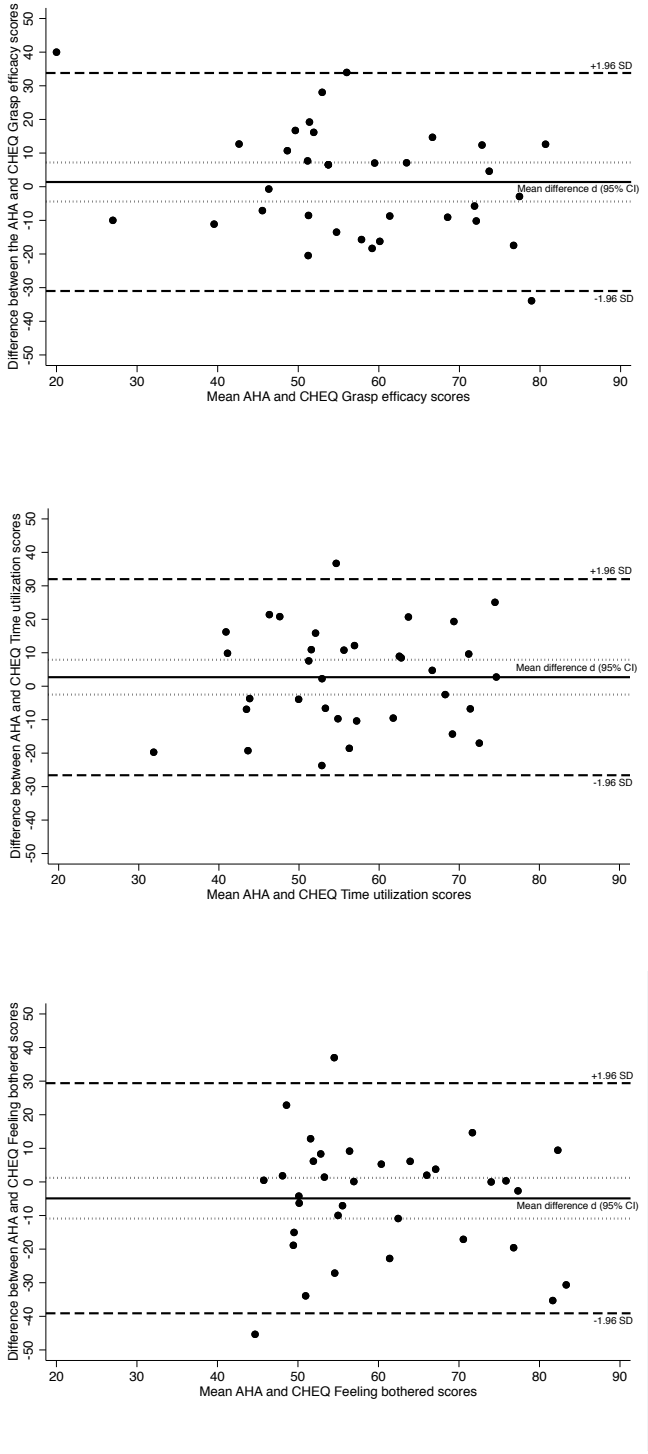

Figure 7.4 Bland-Altman plots illustrating the limits of agreement for the AHA and CHEQ scale (in 0-100 units); each individual is represented by a dot in the graph

7.1.2 The validity of change scores of the CHEQ

Limited evidence was found for the validity of change scores of the Children's Hand-use Experience Questionnaire (CHEQ) in the construct of bimanual performance based on the perception of children and adolescents with unilateral CP and their guardians.

Change scores of the CHEQ were found to correlate sufficiently with these indicated by the GAS to allow the latter to be used as anchor for the CHEQ. According to the GAS, 34 children had improved after the two-week intensive intervention and 44 had not. Hypotheses concerning the magnitude of the effect sizes (Cohen's d and SRM) associated with changes in the construct of CHEQ according to the GAS were met with larger changes for those who improved than those who did not. Though the CHEQ scores for *grasp efficacy*, *time utilization*, and *feeling bothered*, appeared to capture some change in perceived bimanual performance with the GAS as anchor, the accuracy of the CHEQ in discriminating correctly between children that improved (n=34) and did not improve (n=10) in this respect after a two-week intensive intervention was limited in the case of the *grasp efficacy* and *time utilization* scale, with only feeling bothered discriminating sufficiently (Figure 7.5). This may reflect the fact that in many cases the CHEQ was completed by proxy raters (guardians), who may not yet have observed the newly acquired bimanual skills of their children in daily life.

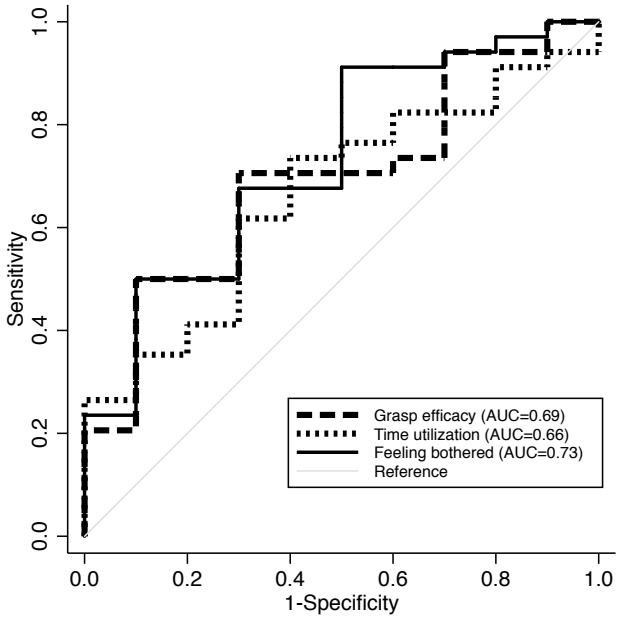

Figure 7.5 Receiver operating characteristic curves for CHEQ scales illustrating the AUC associated with discriminating between the children who improved (n=34) and did not (n=10) after the intervention, according to the GAS

Table 7.6 Overview of the major findings of the present thesis

Objective	Main results	Conclusion
Study I: Prediction model for unilateral CP		
To develop and internally validate a prediction model for unilateral CP for infants at risk from 3.5-4.5 months of age	Study sample: 52 infants with asymmetric perinatal brain injury, of whom 18 developed unilateral CP, were analysed. The model showed excellent accuracy in predicting unilateral CP (AUC=0.98).	The combination of neonatal MRI and the HAI with infants' characteristics can identify the prognostic risk of unilateral CP at 3.5-4.5 months CA with excellent accuracy.
Study II: Predictive validity of HAI scores		
To investigate the predictive validity of the HAI for unilateral CP in infants at risk from 3-12 months of age	Study sample: 203 infants between 3-10 months CA at risk, of whom 103 developed unilateral CP, were included. The AUC ranged from 0.77-0.95 across different HAI scales and age intervals. Regarding specific HAI cut-off values, sensitivity ranged from 63-93%, specificity from 62-91%, and accuracy from 73-94%.	HAI scores predict unilateral CP from 3.5-12 months of age with very good-to-excellent overall accuracy. Prediction accuracy increases with age. Accuracy was best for the contralesional EaHS and AI.
Study III: The CHEQ versus the AHA		
To explore the differences, relationship and extent of agreement between the CHEQ and AHA	Study sample: 34 children and adolescents with unilateral CP. The CHEQ scales *grasp efficacy, time utilization,* and *feeling bothered* share 8-25% of their variance with the AHA. Considerable disagreement between these instruments was demonstrated by very wide limits of agreement.	The CHEQ and AHA measure different constructs, perceived and observed bimanual performance, respectively, and are only related to a minor extent. The use of both tools to capture a comprehensive picture of bimanual performance is recommended.
Study IV: Validity of CHEQ changes scores		
To explore the validity of change scores of the CHEQ in relation to the anchor GAS	Study sample: 44 children and adolescents with unilateral CP; The GAS was used as anchor for change in the construct. The median change for children that improved according to the GAS was 6.4-10.0 CHEQ-units and 0.4-1.9 CHEQ-units for those who did not improve. Accordingly, effect sizes were larger for the improved than non-improved group, as hypothesized, and the AUCs ranged from 0.67-0.73 across CHEQ scales.	CHEQ scores captured some change of perceived bimanual performance according to the GAS. The accuracy for the scale *feeling bothered* was good, but limited for *grasp efficacy* and *time utilization*. Therefore, use of CHEQ scores is mainly recommended to describe perceived bimanual performance in a cross-sectional setting.

CP - cerebral palsy, HAI - Hand Assessment for Infants, CA - corrected age, CI - confidence interval, AUC - area under the receiver operating characteristic curve, EaHS - Each hand sum score of the HAI, AI - asymmetry index of the HAI, AHA - Assisting Hand Assessment, CHEQ - Children's Hand-use Experience Questionnaire

8 DISCUSSION

The major novel findings of these investigations were as follows: (1) By using neonatal MRI in combination with the Hand Assessment for Infants (HAI), unilateral CP can be predicted in infants as early as 3.5 months of age, HAI scores alone are valid for the same purpose at various ages up to 12 months. (2) The perceptions captured by the patient-reported Children's Hand-use Experience Questionnaire (CHEQ) and observations provided by the Assisting Hand Assessment (AHA) are based on unique constructs and thus, provide separate perspectives on the perceived bimanual performance of infants with unilateral CP, demonstrating only minor overlap. (3) In addition, in comparison to the Goal Attainment Scale as an anchor, CHEQ scores capture to some extent changes in the perceptions of children and adolescents with unilateral CP concerning their bimanual performance, with good accuracy in the case of the *feeling bothered* scale, but limited accuracy for *grasp efficacy* and *time utilization*.

Early identification of unilateral CP using the HAI

The conclusion based on the first two studies described here that unilateral CP can be predicted in infants as young as 3.5-4.5 months of age agrees well with developmental studies on upper extremity skills, in particular with the onset of grasping and reaching around 4 months of age and early signs of asymmetric hand usage [78,80,137,138]. Application of neonatal MRI alone for very early prediction within one month of term-equivalent age is less accurate, although this can provide early indications of a development of unilateral CP.

Thus, the model proposed here can be used to predict with excellent accuracy whether an infant with asymmetric perinatal brain injury will develop unilateral CP at a later age. The clinical application of the nomogram requires assessment of the potential involvement of corticospinal tract and basal ganglia/thalamus involvement by MRI within one month of term-equivalent age and determination of the contralesional HAI Each hand sum score (EaHS) between 3.5-4.5 months of age, as well as knowledge of the infant's gestational age and sex.

Furthermore, the same age range concerning the prediction model seems also appropriate for an initial HAI assessment in infants at risk to obtain valid information about a possible diagnosis of unilateral CP at later age as well as beyond this age up to 12 months. Clinical cut-off values for the HAI determine a potential development of unilateral CP at various ages from 3.5-12 months. Thus, when an infant is suspected to develop unilateral CP after an initial HAI assessment because hand function does not meet the suggested thresholds, monitoring of the upper extremity may be indicated by additional follow-up assessments, in order to accumulate evidence about a potential diagnosis of unilateral CP in addition to history taking, neurological examinations, neonatal MRI and other standardized motor assessments. Moreover, the HAI offers a unique tool to preliminarily establish the topography of unilateral CP, which is crucial

with respect to resources concerning individualized intensive interventions such as constrained-induced movement therapy or bimanual intensive training, from the perspective of both the families of the infants and the health care system. In addition, such accurate identification of infants who will most likely develop unilateral CP will provide a firmer foundation for future research on the effectiveness of early interventions.

Although the scores on the contralesional HAI EaHS and the AI both proved to be valid for predicting the development of unilateral CP at a later age, the HAI EaHS is preferable for use in clinical practice, since it is independent of the ability of the non-affected hand and thus provides a more direct indicator of potential asymmetric hand function. Even though the BoHM demonstrated adequate predictive performance with infants around 5.5-5.6 months of age, it was never as accurate as the contralesional EaHS and the AI, perhaps because the BoHM, being based on the scores of the affected and non-affected hands, is diluted by the score of the latter.

Assessments for the accurate prediction of CP in general and unilateral CP in particular

The combination of knowledge provided by MRI and the HAI with findings from other assessments of overall early motor development, such as the General Movements Assessment (GMA) and Hammersmith Infant Neurological Examination (HINE) (described in section 1.3.2), as well as clinical information may allow earlier and more accurate diagnosis of unilateral CP than is currently possible. Such a combined approach has been recommended internationally [40] and for example, the combined use of MRI, the GMA and HINE at three months of age is strongly related to the development of CP in general at two years of age and discriminates more accurately whether or not preterm infants develop CP than does application of these tools individually [55,56,66].

With respect to detection of infants with unilateral CP in particular, the additional information provided by the HINE asymmetry score and a higher cut-off for the total HINE score have been recommended [55,139]. However, the predictive validity of HINE scores remains to be determined in a prospective longitudinal study. The HINE as well as the GMA are used to detect CP in general, but do not specifically target unilateral CP [40,48,140].

The role of sensitivity, specificity, predictive values and likelihood ratios for the prediction of unilateral CP

The choice of an appropriate measurement instrument for the prediction of unilateral CP must be based on sensitivity and specificity of the tool, as well as on the characteristics of the population for which it has been validated. The ideal situation of a test demonstrating 100% sensitivity and specificity is, unfortunately, seldom attainable and a certain amount of misclassification is therefore unavoidable. Depending on the actions that follow, a more sensitive or specific test is required, concerning the identification of unilateral CP both qualities are desirable. On the one hand, high sensitivity of the HAI ensures that only few infants who

will later develop unilateral CP will be missed (i.e., there will be few false-negatives). On the other hand, a high specificity is sought because one does not want to cause concern in families by communicating that their infants will develop unilateral CP when they will not (i.e., to limit the number of false-positives).

The strength of the HAI here is that it can be applied across the first year of life, and thereby gives the possibility to monitor early signs of hand asymmetry. An initial assessment could be performed early about 3.5-4.5 months of age followed by one or more follow-up assessments if needed at later age, e.g., at 5.6-6.5 months in order to accumulate evidence about a potential diagnosis of unilateral CP. At present, the HAI is the only tool available that allows valid and reliable assessment of each hand individually, as well as both in interplay, and such detailed information can help to interpret ambiguous findings when they occur [78,81].

Moreover, predictive values and likelihood ratios are of specific importance in clinical practice and enable individualized decision-making. The positive predictive values, e.g., play a role after the HAI has been performed and inform the clinician about the proportion of infants that will develop unilateral CP given a positive test result, i.e., limited hand function or a considerable asymmetry between hands. It is important to remember even with almost optimal sensitivity and specificity, the predictive values for cohorts in which the prevalence of the disease is not comparable may differ [132,141].

Likelihood ratios provide an indication of the extent to which the HAI can contribute to a preliminary diagnosis of unilateral CP for any individual infant. The positive likelihood ratios associated with the contralesional EaHS or AI performed between 3.5-6.5 months of age indicate a moderate-to-large increase in the probability of a diagnosis of unilateral CP when a limited hand function or an asymmetry is indicated by the HAI. Consequently, the performance of the HAI during this period increase the probability of detecting this disorder. Likelihood ratios can be calculated for any test on the basis of its sensitivity and specificity, and then employed to compare predictions of the probability of disease before (pre-test probability) and after the test is performed (post-test probability). Such comparisons exert a major impact on decisions concerning whether a certain test should be administered at a certain age [142].

Patient-reported outcome measures for daily bimanual performance

Among the combination of tools recommended to provide a broader understanding of the difficulties and challenges encountered by children and adolescents with unilateral CP in connection with the performance of bimanual activities [83,84], self-reports are particularly helpful. These can reveal potential discrepancies between the perspectives of the patients and professionals concerning the activities that are challenging and important to the individual to tackle. In this context, the perception-based questionnaire CHEQ is a valuable complement to

the observation-based AHA, and both tools contribute with their unique constructs to a comprehensive picture of the individual's performance of everyday activities that are commonly executed using both hands. The more pronounced association between the *grasp efficacy* scale than the *time utilization* and *feeling bothered* scales of the CHEQ and the AHA may reflect a greater similarity between that first scale and actual performance. Differences in the relationship between the individual CHEQ scales and the AHA can also be understood as a reflection of the different qualities of bimanual performance that CHEQ is measuring [15]. In addition to assessing how children perceive the grasping skills of their affected hand in connection with everyday activities, the CHEQ also evaluates the efficiency of their performance in relationship to that of their peers, as well as whether they have negative feelings about the performance of their affected hand during bimanual activities.

The validity of CHEQ change scores

A major challenge connected with attempts to examine the validity of change scores of a measurement tool involves the choice of an appropriate external criterion, a suitable anchor to measure change in the construct of interest, that demonstrates adequate measurement properties. Moreover, several different definitions of the validity of change scores (responsiveness) have been proposed and numerous ways are described to investigate this aspect of validity [1,2,5]. Consequently, the interpretation of results obtained utilizing different approaches is most likely to differ depending on the understanding of responsiveness [1]. Furthermore, information about the validity of change scores are often missing or limited, due to poor methodological quality or differences in the characteristics of the populations under investigation [97].

Although GAS scores provide evidence of good validity and reliability [118–122], the use of the GAS as an anchor for change concerning bimanual performance based on perceptions and experiences of children with unilateral CP or their guardians is debatable. The mode of application and the design of the scales of these two tools differ essentially. At the same time, the perception and reflection on one's own performance of daily activities are key aspects of the CHEQ that are also shared by the GAS when involving children and families in goal setting and in the evaluation of their performance [117,143], so that GAS scores that assess bimanual performance of everyday activities can be linked specifically to CHEQ items that concern this same performance. Beneficial for linking the GAS to the construct of the CHEQ was the majority of children and adolescents that formulated their GAS goals after completing the CHEQ, which resulted in 81% of the GAS goals reflecting a majority of CHEQ items. This indicates the strength of applying the GAS as an anchor in this explorative study, especially since no other comparable tool providing adequate measurement properties, including the validity of change scores, was available at the time this study was performed.

As reported earlier, the assessment of bimanual performance by the CHEQ based on the perceptions of participants agreed to only a minor extent with the AHA based on observations by professionals [144]. At first glance, the ABILHAND-Kids questionnaire might appear to offer a good alternative external criterion, but this questionnaire concerns a majority of unimanual activities which limits the interpretation of the scores with regard to the performance of everyday activities commonly performed using both hands [96]. Another alternative, recently described, might be the HUH, which measures the amount of hand us of the affected upper limb in bimanual everyday activities in the home [87]. However, the HUH was not available at the time of this research and, moreover, has been reported to be only moderately related to the amount of activities involving the affected hand, which is quantified by the opening questions of the CHEQ, however, its relationship to the actual CHEQ scales concerning the perception of bimanual performance was not investigated [99].

8.1 METHODOLOGICAL CONSIDERATIONS

Inclusion of participants in all of the studies of this thesis was based on convenience sampling, which involves a risk of selection bias. For example, in Study I all infants involved in the Swedish stroke follow-up program who demonstrated neurological signs and MRI evidence of an asymmetric perinatal brain injury were included; whereas in the Netherlands, only infants with a high risk of unilateral CP as indicated by MRI were considered. At the same time, these different criteria for inclusion resulted in a more varied population that could allow identification of various risk factors and help develop a model for clinical prediction of unilateral CP. Furthermore, post-hoc analyses indicated very similar performance of our model in both countries.

Another aspect in Study I that may have influenced the performance of the prediction model involved the differences in diagnoses of perinatal asymmetric brain injury, since the outcome of unilateral CP due to different types of brain injury differs. Periventricular haemorrhagic infarction and perinatal arterial ischemic stroke are observed more commonly among preterm [145–147] and term infants [46,47,148], respectively; whereas other diagnoses such as white matter injury are less likely to result in unilateral CP. To take such differences into consideration, MRI parameters such as involvement of the corticospinal tract and basal ganglia/thalamus, which can be applied to several different types of brain injury, were used as predictors.

Unilateral CP among the infants included in Studies I and II was diagnosed clinically from two years of age, as a result of which mild cases or a change in topography from unilateral to bilateral disorder at a later age may have been missed. However, compliance of participants is also a crucial aspect that also needs to be considered when performing longitudinal studies. Moreover, although the SCPE recommends that the diagnosis of CP and, in particular, the

subtype be confirmed at the age of five, the actual average age of diagnosis in high-income countries is between 1-2 years [40].

In addition, in Study II selection bias may have arisen from the fact that some infants are more often represented across age intervals than others due to a variation in age at which the infants were assessed with the HAI. Thus, within any given age interval, some of the infants were assessed for the first time, while others being assessed had already one or more assessments at previous age intervals inducing a relation between HAI measurements across time which may have inflated the predictive values of the HAI.

It must be emphasized that our findings on the prediction model (Study I), as well as the cut-off values established for the HAI (Study II) need to be confirmed by investigations on a comparable population (external validation) before their implementation in clinical practice, as is always the case for studies on the sensitivity and specificity of a method [149].

Commonly, children and adolescents with unilateral CP represent a heterogeneous population which may be considered a limitation, but does reflect the target group to be assessed here for the investigation of measurement properties. Nonetheless, the generalizability of findings of Studies III and IV may be limited due to small sample sizes. Despite the inclusion of children and adolescents who varied widely with respect to the abilities assessed by the CHEQ and AHA, fewer children with independent manual abilities and no severely affected individuals were included according to MACS (Study III). This, however, realistically reflects manual abilities of the population of children and adolescents with unilateral CP (Study III). Similarly, in Study IV, the data employed to analyse the validity of CHEQ changes scores were retrieved from an intervention study with more homogeneous eligibility criteria, which may have led to an overestimation of effect sizes.

As both Studies III and IV were explorative in nature and aimed to further understand the construct of the CHEQ, the findings must therefore be considered as only of the accumulating body of evidence on the validity of CHEQ scores in children and adolescents with unilateral CP.

9 CONCLUSIONS AND CLINICAL IMPLICATIONS

By combining the HAI with MRI and individual characteristics of infants, development of unilateral CP in infants with asymmetric perinatal brain injury can be predicted as early as 3.5-4.5 months of age. By applying the nomogram, shown in Figure 7.2, clinicians can thus inform families about this risk when their infant is still quite young, and refer infants with a particularly high probability of developing unilateral CP to early intervention. In addition, HAI scores can be of value for diagnosing unilateral CP in infants at risk at various ages between 3.5-12 months of age.

The differences in the constructs of the CHEQ and AHA emphasize the necessity of utilizing both these tools to capture the perceptions of the child or adolescent concerning her/his bimanual performance comprehensively, as a complement to observations on performance of bimanual tasks made by the professionals.

CHEQ scores capture some change in the construct of perceived bimanual performance, as indicated by the GAS as an anchor, with good accuracy in the case of the *feeling bothered* scale, but limited accuracy for *grasp efficacy* and *time utilization*. On the basis of these findings, the CHEQ can at present only be recommended for describing how children and adolescents with unilateral CP experience the performance of their affected hand in activities of daily life. In this respect, the CHEQ complements standardized observation-based measures in a cross-sectional context. Not only can such information assist in planning treatment, it can also facilitate the involvement of the children and their families in this process.

10 FUTURE PERSPECTIVES

External validation and possibly refinement of the prediction model, as well as the cut-off values for the HAI in another comparable population is desirable before incorporating the nomogram and those cut-off values into clinical practice. Further validation research to compare the HAI with different tools that are currently used to predict CP (e.g., the GMA and HINE) in infants at risk of unilateral CP is another interesting next step to learn more about their constructs and see how much information they have in common and contribute to each other. Another important aspect is the sequential application of different tools that are recommended for early detection of infants with (unilateral) CP. Moreover, the results described here may stimulate interest in the use of prediction modelling to detect CP, combining various predictors in particular different assessment tools that have shown to be relevant for this target group.

Further investigation of potential differences in the perceptions of bimanual performance by children and adolescents with unilateral CP and their guardians is of interest, especially when applying the CHEQ. Moreover, the limited evidence for the validity of changes scores of the Children's Hand-use Experience Questionnaire (CHEQ) following a short-term intensive intervention as well as the availability of a revised version of the CHEQ demands further research employing a wider population that includes children and adolescents with obstetric brachial plexus palsy and upper limb reduction deficiency over a longer period of time.

11 ACKNOWLEDGEMENTS

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