Chapter 4

Prognostic predictors for ambulation in children with cerebral palsy

Publication of short communication in this chapter is listed below.

Keeratisiroj O, Thawinchai N, Siritaratiwat W, Buntragulpoontawee M. Prognostic predictors for ambulation in Thai children with cerebral palsy aged 2 to 18 years. J Child Neurol. 2015;30:1812-8.

Keeratisiroj O, Thawinchai N, Siritaratiwat W, Buntragulpoontawee M., Pratoomsoot C. Prognostic predictors for ambulation in children with cerebral palsy: a systematic review and meta-analysis of observational study. Disabil Rehabil. 2016: 1-9. [Epub ahead of print]

1. Gross motor function

Five decades ago, the history of the motor outcome among children with CP has been studied.[1] The gross motor function is one in motor outcome of this impairment. Several approaches for measuring the impact of CP on gross motor function have been developed, but there are two important measurements, including the GMFM and GMFCS.

1.1 Gross motor function measure (GMFM)

In children matured 5 months to 16 years with CP, GMFM is a measure referenced observational instrument that was developed and validated to evaluate change in gross motor function. There are two versions of GMFM, including the original 88-item version and the newer 66-item version. The GMFM-88 is the original version, and tests 88 items. This assessments have been developed by Russel et al. since 1980. The limitation of the GMFM-88 is long evaluation time. In practice, there is a selection of some dimensions that the goal of treatment. However, the selection of some dimensions is not appropriate due to the validity and reliability is low. In order to reduce this limitation GMFM-88 has been updated. GMFM-66 is a new version, which reduced to 66 items by Rasch analysis and items on the GMFM-88 was converted from ordinal scale to interval scale. It is also used in the new calculation of the total score based on computer program, called the Gross Motor Ability Estimator. The total score ranges from 0 to 100.[2-5]

GMFM is a gross motor function instrument among children with CP has been used by clinicians in many studies to evaluate the effectiveness of treatment such as physical therapy,[6-11] the use of orthoses,[12] hippotherapy,[13, 14] selective dorsal rhizotomy,[15] intrathecal baclofen therapy,[16] and electrical stimulation.[17, 18] It is particularly useful for children with more severe levels of 3, 4, and 5 on the GMFCS. It comprises of five measurements of estimation include: (1) lying and rolling; (2) sitting; (3) crawling and kneeling; (4) standing; and (5) walking, running, and jumping.[4] Both GMFM-66 and GMFM-88 had great reliability and validity in the assessment of gross motor function.[3, 4, 19, 20] A study on the reliability of the GMFM-66 in Thailand[21] found that the inter-rater and intra-rater reliability were high among Thai children with CP. The intra class correlation (ICC) for inter-rater reliability was 0.93 and for intra-rater reliability was 0.99 to 1.00 for the total score, which was assessed by Thai pediatric physical therapists.

1.2 Gross motor function classification system (GMFCS)

GMFCS was developed in 1997 by Palisano and colleagues.[22] They define it as "GMFCS is a 5 level classification system that describes the gross motor function of children and youth with CP on the basis of their self-initiated movement with particular emphasis on sitting, walking, and wheeled mobility". The GMFCS was used to classify children and youth with CP in four age groups (<2 years, 2-4 years, 4-6 years and 6-12 years). Later in 2007, it has been improved by increasing an age band 12-18 years and focus on the ICF concept of WHO is called GMFCS - Expanded and Revised (GMFCS-E&R).[23]

GMFCS is expected to enhance correspondence amongst families and experts in the child's gross motor function, setting objectives, and settling on administration choices. GMFCS was produced for use in clinical practice, and a gathering variable for the database, registries, program assessment, and clinical research.[23] Children with CP will be delegated in one of five levels of the GMFCS. Children in level I can do all things with their companions, in spite of the challenges with speed, balance, and coordination. Children in level V have the trouble in controlling the head and trunk to control voluntary movement. To recognize GMFCS levels concentrate on practical confinements and the requirement for assistive innovation including mobility devices and wheeled mobility than the quality of the movement.[22, 23] General heading for each level of GMFCS is shown in Table 4.1.

Table 4.1 General heading for each level of Gross motor function classification system (GMFCS)

GMFCS Level	General heading
I	Walks without Limitations
II	Walks with Limitations
III	Walks Using a Hand-Held Mobility Device
IV	Self-Mobility with Limitations; May Use Powered Mobility
V	Transported in a Manual Wheelchair

Data from: Palisano R et al. (1997)[22]; Palisano RJ (2008)[23]

There are many studies that support the validity and reliability of the original GMFCS and GMFCS-E&R. The original GMFCS, inter-rater reliability was analyzed among 51 physical and occupational therapists, which were not trained. Overall kappa coefficient was 0.75 for children 2 to 12 years of age and 0.55 for children less than 2 years of age.[22] Wood and Rosenbaum's study[24] shows that the GMFCS is relatively stable over time with the overall test-retest reliability

was 0.79 and inter-rater reliability is very high as well (generalizability coefficient=0.93). For GMFCS-E&R has been conducted to validate using group consensus methods. The results of this study provide evidence of content validity.[23] Health team is familiar with the movement of children with CP, for example, physical therapists, occupational therapists, doctors, and other wellbeing administration can dependably utilize the GMFCS with no preparation essentially by perusing the criteria. Nowadays, with the development of GMFCS Family and Self Report Questionnaire (GMFCS-FR) to parents of children with CP aged 2 to 18 years and children with CP, aged 12 to 18 years can be assess the GMFCS by themselves.[25] The reliability between teachers, physical therapists, and caregivers of the Thai GMFCS-FR was reported by Ramrit et al.[26, 27] In year 2013, they reported high inter-rater reliability (weight kappa = 0.90) between physical therapists and caregivers and intra-rater reliability (weight kappa = 0.89) of physical therapists.[26] And in year 2016, they reported high intra-rater reliability (ICC=0.91 to 1.00), teacher's inter-rater reliability (ICC=0.69 to 0.97), and caregiver's inter-rater reliability (ICC=0.70 to 0.97).[27] Morris and colleagues[28] reported excellent inter-rater reliability between the classification of children with CP aged 6 to 12 years, by families and by health professionals (ICC=0.94). In children aged 4 to 18 years found that the agreement between the classification of children with CP by the parent and research physiotherapist was good (weighted kappa=0.75).[29] Moreover, inter-rater reliability amongst parent and specialist assessors for children with CP matured 2 to 4 years and 4 to 6 years with kappa coefficient were 0.66 and 0.73, respectively.[30]

The GMFCS and GMFCS-E&R are utilized broadly all through the world as the basic dialect to portray the gross motor function of children with CP. The GMFCS has had a variety of applications in both the research and clinical practice and has been used increasingly over time.[31-33] Now, versions of the GMFCS-E&R have no less than 20 languages around the world, including Thailand.[34] For GMFCS-E&R © 2007 (Thai version) was translated by Siritaratiwat and Thomas[35] and GMFCS © 1997 by The Liabsirinon et al.,[36] which has been permitted by CanChild Centre for Childhood Disability Research. Thai version of GMFCS was found that the inter-rater reliability (kappa coefficient) for overall age (0 to 12 years), age of 0 to 2 years, age of 2 to 4 years, age of 4 to 6 years, and age of 6 to 12 years were 0.77, 0.67, 0.76, 0.76, and 0.79, respectively.[36]

2. Ambulation

2.1 Gait

Children with CP often have difficulty walking. Therefore, understanding pathological gait in these children will help them to walk at full capacity, or help themselves as much as possible. The first thing to understand is the normal gait to analyze abnormal gait in these children and to take corrective action.[37-39]

2.1.1 Normal gait

Human gait is a form of complex functions of the body, which requires a complex interaction between the nervous system and peripheral nervous system. It requires a balance, propulsion, shock absorption, and energy consumption. Gait cycle was characterized as the time from the minute when the foot hits the ground to the time. At the point when a similar foot hits the ground once more. The gait cycle is isolated into the position and swing stages. For normal walking, the stance phase is the period of foot contact with the ground and swing phase is when the feet are not touching the ground. The stance phase time is 60% and swing phase time is 40% on comfortable speed (Figure 4.1).[37-40] Gait of a child is different from adult and adolescent. Toddler walks with short and wide steps. When children grow up heel strike starting at about 3 years of age. Stance phase knee flexion and external rotation has the shortest walk of adults. Also, Step width narrows and reciprocal arm movements begin for about four years old. Rhythm, step length, and speed are mature at about 15-18 years old.[38]

2.1.2 Gait analysis

Gait analysis is a method for analyzing the components of human walking patterns. This analysis is important in understanding the abnormal gait of children with CP. Gait analysis assumes an immense part in research, training, and the decision to treat. It comprises of the extra testing, including recording, kinematic, and kinetic evaluation, understanding muscle enactment designs with electromyogram and pediabarograph, and the energy requirements of walking. Consideration of history taking and physical examination is fundamental preceding performing step investigation.[37-40]

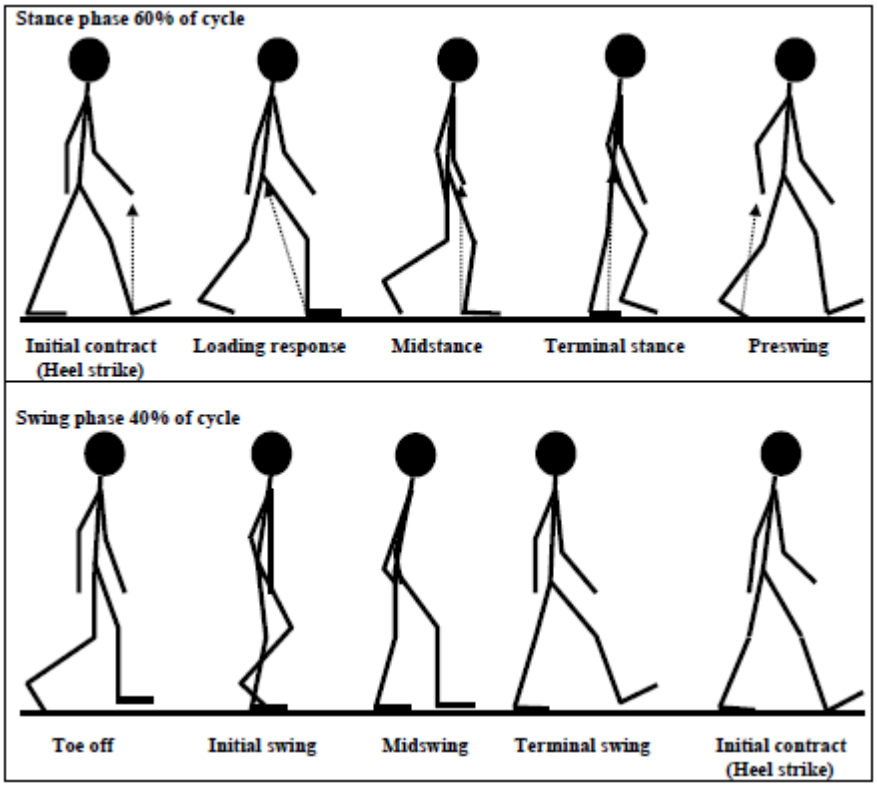

Figure 4.1 Normal human gait. (Adaptation from: Miller F, Browne E. Cerebral Palsy: Springer; 2005.[37]; Nadire B, Selim Y. The HELP Guide to Cerebral Palsy: Avrupa Medical Bookshop Co. Ltd. & Global-HELP Organization; 2005.[38])

2.1.3 Abnormal gait in CP

Steadiness in position, movement and foot leeway in swing is essential for ambulation. However, children with CP often lack stability because of the lack of balance, increased muscle tone, leading to abnormal gait in these children. The regular issues are expanded hip adduction tone can bring about scissoring and trouble propelling the appendage in swing stage. Expanded tone in the iliopsoas can prompt to expanded hip flexion, bringing about a front pelvic tilt and a crouched gait.[37-41] The retrospective study of specific gait abnormalities in children with CP found that firm knee in swing, equinus, and intoeing were altogether found in over half of the subjects in each of the hemiplegic, diplegic, and quadriplegic children.[42]

2.2 Prognosis for ambulation

The prognosis for ambulation in children with CP is still a main subject for both caregivers and health care professionals involved in their management.[43] These children may have started walking at age 2 to 7 years or more. There are some real occasions in motor control must happen all together for the child to walk. He should have the capacity to hold his head before he can sit and he will have the capacity to sit freely before he can walk all alone.[38] A Study on ambulatory prognosis has been reviewed for decades by Sala and Grant.[44] They are divided into three main groups: (1) primitive reflexes and postural reactions; (2) gross motor skills; and (3) type of CP. In addition to these factors, other factors (e.g. epilepsy, intellectual disability, visual impairment, and hearing impairment) have been considered in several studies are as follow.

2.2.1 Personal factors

(1) Primitive reflexes and postural reactions: The discovery of Bleck,[45] Molnar and Gordon,[46] Watt et al.[47], and Trahan and Marcoux[48] pointed out that the existence of primitive reflexes and the absence of improvement of postural reaction have been related with poor prognosis for ambulation. These primitive reflexes and postural reactions include: (1) the asymmetrical tonic neck reflexes (ATNR); (2) the symmetrical tonic neck reflexes (STNR); (3) the Moro reflex; (4) the neck righting reflex; (5) the tonic labyrinthine reflex (TLR); (6) the extensor thrust; and (7) the positive supporting reaction. In a prospective study of 73 children with CP, Bleck[45] has additionally settled a scoring framework to predict ambulatory children with CP aged more than one year. He documented the persistence of five primitive reflexes and the absence of two postural reactions at 12 to 18 months of age. Each abnormal response was scored as one point. The foundation for walking was the capacity to walk no less than 15 meters freely on a level surface. The main outside backings allowed were crutches (usually forearm crutches). A zero score showed a decent anticipation for walking, a one-point score was characteristic of a guarded prognosis and a two-point score or more noteworthy demonstrated a poor guess. Of 49 subjects with a total score of 0, 46 inevitably walked. Of 17 subjects with a score more prominent than two, just a single walked. Of seven subjects with a score of one, all walked, however five utilizing crutches. The accuracy of prediction using Bleck's scoring system method was 94.5%.[44, 49] However, a recent study in Japan[50] found that there was no significant in Bleck's

scores between children with spastic quadriplegic CP who ambulation and non-ambulation groups. Findings from this study does not support using primitive reflexes alone as a clinical predictor as there are other clinical predictors affecting prognosis for walking

(2) Gross motor skills or Motor mile stone: The gross motor skill that is most noted as the best predictors of walking is independently sitting at aged 2 years.[49, 51-53] In prospective study of 31 spastic diplegia or triplegia CP,[53] the quantity of gross motor skills accomplished and the rate of accomplishment before 2 years old, capacity to put weight on the hands while prone, and move from supine to prone position by 18 months of age were observed to be related with walking status at 3 to 5 years old. A retrospective study of Wu and co-workers[51] concluded that the independent predictors of successful ambulation at 6 year of age included early motor milestones such as sitting and pulling to a stand. And most recently, Kulak et al.[52] found that inability to sit at 2 years of age had a negative effect on the free walking of children with CP. Therefore, children who are able to sit after reaching aged 2 years will have little opportunity to walk independently and require ambulatory aids.

(3) Type and distribution of CP: Type and distribution of CP varied with the different prognosis for ambulation. Hemiplegics and diplegics have good prognosis among all other types of CP, while quadriplegics have poorer prognosis.[38, 44, 54, 55] In one study, spastic diplegia was the most common type of ambulatory children with CP.[52] As the review of literature by Montgomery found that spastic hemiplegic children were the best predictor for ambulation.[49] In a retrospective study of all children with CP found that ataxic and dyskinetic CP were a better predictors for ambulation than spastic and hypotonic CP.[51]

(4) Comorbidities: Lack of visibility and intelligence influence learning in the walking of children with CP. There are many studies that support this as well.[51, 53, 56] In prospective study, Fedrizzi and colleagues[53] found that the majority of children who achieved ambulation have normal intelligence (86%), while walking with the help of children and those who do not have walking the normal intelligence level is 55% and 27%, respectively. In addition, all walking children have normal vision while 46% of non-walking children have severe visual defect. A retrospective study of Wu and colleagues[51] also found similar relationship. In addition, they also found that the better hand function, being able to independently eating, being able to say simple word, and absence seizures are associated with a better chance of ambulation. As well as one large retrospective study by Beckung et al.[56] in children with CP found that ambulation potentiality was fundamentally identified with IQ levels, the presence of severe

visual impairment, and other impairment, including hearing impairment, and epilepsy. The factors that predict ambulation in spastic quadriplegic CP by Simard-Tremblay et al.[57] found that the seizures in the initial 24 or 72 hours of life was related with a possible failure to accomplish ambulation. And a retrospective study of Lee et al.[54] clearly confirmed the effects of seizure on ambulation in diplegics.

(5) Demographic characteristics: CP children tend to walk at later age. Bleck[45] was critical about discontinuing ambulation-oriented treatment for CP at the age of 7 years old. In fact, some children may walk at later age given they have continuous ambulation training.[49] The age of children with CP to start walking, it is not clear. In a retrospective study among adult with CP,[58] reported median age for starting walking was 3 years old, with a range from 1 to 14 years old. Other factors include gender, ethnicity, growth and nutrition. A retrospective study by Wu and co-workers,[51] they found that gender and ethnicity did not affect the ambulation in children with CP. But the study by Simard-Tremblay[57] found that presence of Caucasian mother significantly associated with successful independent ambulation. However, this causal cannot be explained. It may be associated with many socioeconomic factors. Gokkaya and colleagues[59] studied the relationship between anthropometric measurements and ambulatory status. They found that higher level of ambulation (community walker) associated with high percentiles of growth parameters. In addition the nutrition status and skinfold measurement correlated significantly with ambulatory status, but the relationship was not statistically significant.

(6) Perinatal factors: The relationship between perinatal factors on ambulatory children with CP is less clear and controversial among many studies. Some studies found a clear relationship between the Apgar score,[52] administration of antibiotics during pregnancy or delivery,[57] hyperbilirubinemia,[57] gestational age,[57] and birth weight[57] with ambulation achievement. But some studies have found little correlation. One retrospective study from SCPE database found weak association between birth weight, gestational age and walking ability.[56] Other studies found no independent influence of birth weight and gestational age on ambulation for each type of CP.[54]

(7) MRI finding: In retrospective study, Kulak and co-workers[52] studied neuroimaging findings of children with CP who experience issues ambulation contrasted with ambulant patients. They found that non-ambulation children (27.8%), brain atrophy than ambulation children (7.0%). The results were observed by MRI are factors that affect the ability to independently walking of children with CP.

2.2.2 Environmental factors

Intervention: Medical, surgical, and physical therapy interventions are intended to improve ambulatory function in children with CP.[60] Various treatment strategies, for example, physical therapy, orthotics, serial casting are used sequentially or in combination for ambulation training in CP children. The purpose of these strategies is to simulate the stretch their muscles usually get from regular physical activities and encourage muscle development. These are frequently joined by measures to deduct muscle tone by chemical neurolysis using phenol, alcohol or botulinum toxin A or neurosurgical methods such as selective dorsal rhizotomy, or intrathecal baclofen.[61] When the child develops soft-tissue contractures of the lower extremities, orthopedic surgery for soft-tissue release can help the child to walk better. A study in Thailand by Thamkunanon[62] found that lone event multilevel soft tissue surgery was effective in upgrading the GMFCS level ordinary one level in spastic diplegic CP. He stated that surgery in children aged less than likely have better results.

3. Supporting research

3.1 Thai children with cerebral palsy

The study entitled "Prognostic predictors for ambulation in Thai children with cerebral palsy aged 2 to 18 years" by Keeratisiroj et al.[63] To my current knowledge, this is the first to find out prognostic predictors based on clinical predictors in Thai children with CP (Appendix B). Summaries of this study show the following.

Rationale of the study: The factors to predict ambulation in children with CP have been informed for decades by Sala and Grant.[44] The factors are divided into three main groups: (1) primitive reflexes and postural reactions, (2) gross motor skills, and (3) type of CP. In addition to these factors, other factors (e.g., epilepsy, intellectual disability, visual impairment, and hearing impairment) have been considered in several studies,[47, 49, 51, 53, 56, 57, 59, 64-67] although with no consensus to date on their contribution. Some previous studies about predictors of ambulation in children with CP had a relatively small number of patients recruited from a single clinic,[47, 48, 57, 59, 65, 66] studied only a subgroup of CP,[48, 53, 57, 65] and/or used only univariable analysis,[57, 64-67] with sometimes conflicting results.

Previous studies differing on the definition of “ambulation” made comparisons difficult. In addition, important operational definitions did not provide enough information to determine whether the term “ambulation” can be used to achieve the function. The GMFCS is the functional assessment that has been widely accepted.[22] However, only two recent studies used this to classify ambulatory status.[57, 67] Additionally, there are no studies about prognostic predictor for ambulation in children with CP in Thailand.

Objectives of the study: To fine prognostic predictors for ambulation among Thai children with CP and identify their ambulatory status.

Study settings: Rajanagarindra Institute of Child Development Chiang Mai Province, Srisangwanchiangmai School, Srisangwankhonkaen School, Special Education Center Region 7, Special Education Center Region 8, and Special Education Center Region 9, Thailand.

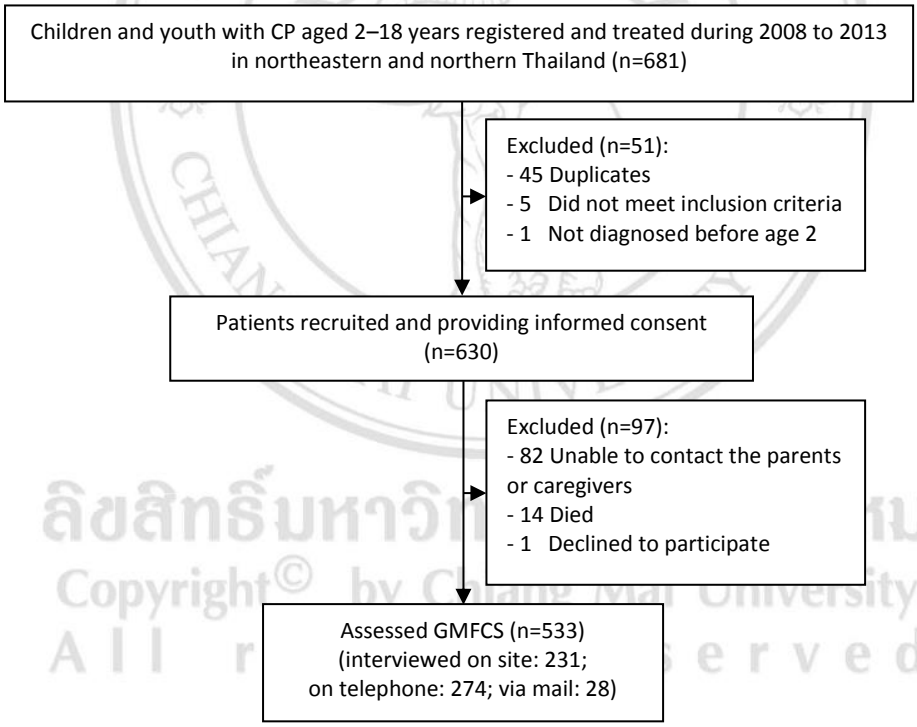

Figure 4.2 The flow chart of patients included in study I

Recruitment: All children with CP registered at the six special schools or hospitals for children with physical disabilities in northeastern and northern Thailand during the period from 2008 to 2013 were recruited. The children had to be 2 to 18 years old and diagnosed with CP by

a physician, with the CP first appearing before age 2 were included. After eliminating duplicates and those not meeting the inclusion criteria, 630 participants were enrolled, and they provided informed consent. This number was subsequently reduced to 533 participants because some participants could not be evaluated using GMFCS (Figure 4.2).

Outcome measures: The GMFCS-E&R[23, 34] was used to classify the ambulatory status. The GMFCS-E&R family and self-report questionnaires (Thai version) have been licensed for translation into Thai by Siritaratiwat and Thomas.[25, 35] This tool has five locomotor scales for each age group (Table 6). The ambulatory status was classified as three ordinal groups: (1) independent ambulation (GMFCS I-II); (2) assisted ambulation (GMFCS III); and (3) non-ambulation (GMFCS IV-V).

Data collection: The baseline characteristics (age, gender, weight, height, and caregiver) and clinical data (type of CP, gestational age, birth weight, hyperbilirubinemia, epilepsy or seizure, sitting independently at age 2 years, intellectual disability, visual impairment, hearing impairment, hand function, eating, speech, medication, history of orthopedic surgery, and orthotics use) were reviewed from the medical and physical therapy records. These were confirmed by interview on site, on telephone, or via mail. Accompanying impairments were obtained through interview with the child's caregivers or observation of the child when possible, just to make sure whether the child has disability or not. Some baseline and clinical data, including gender, body mass index, type of CP, gestational age, birth weight, hyperbilirubinemia, epilepsy or seizure, sitting independently at age 2 years, intellectual disability, visual impairment, hearing impairment, hand function, eating, and speech, were analyzed as factors predicting ambulation. Age and history of orthopedic surgery were treated as confounding factors. Medication and orthotics use were found no effect on walking, therefore, they were not imported into the data analysis.

Statistical analysis: Descriptive statistics were used to characterize participants according to the three ambulatory statuses. Nonparametric tests for the trend across ordered groups were applied to the different distributions. The outcomes were estimated using descriptive and inferential statistics: frequencies, percentages, and 95% CI. Univariable ordinal continuation ratio logistic regression analysis was used to identify the association between each independent factor and ambulatory status. Variables that had *p*-value ≤0.20 were selected as

candidate predictors for the multivariable ordinal continuation ratio logistic regression analysis using backward elimination and adjusting for covariate factors. The possible interaction terms were considered. The results presented the crude and adjusted odds ratios (OR) with 95% CI. All levels of significance were set at *p*-value 0.05.

Results and discussion: A total of 533 children with CP were included and their levels of GMFCS were classified into three groups: (1) independent ambulation (34.9%); (2) assisted ambulation (n=13.3%); and (3) non-ambulation (n=51.8%). The distribution of ambulatory status in this study is not consistent with reports from several European countries. A large project of the collaboration, "Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers"[56] showed that of children with CP at 5 years old, 54% were independently ambulatory, 16% walked with assistance, and 30% could not walk at all. This is similar to the findings of two previous studies, which reported that more than half of children with CP could walk without an assistive device.[68, 69] In contrast, our study showed that Thailand had a burden of disability from non-ambulatory children with CP. However, our study was conducted at special schools or hospitals for children with physical disabilities. It is possible that most Thai children with CP who can walk independently are not enrolled or admitted in these institutions.

There are three strongest positive predictors of ambulatory status after adjusting for confounders (Table 4.2). These three predictors were the following: (1) type of CP, including spastic diplegia, spastic hemiplegia, dyskinesia, ataxia, hypotonia, and mixed type; (2) sitting independently at age 2 years; and (3) eating independently. These predictors confirmed the findings of previous studies. The type of CP has been considered as a predictor of ambulation since Sala and Grant,[44] in 1995. In addition, Montgomery[49] concluded that spastic hemiplegia was the best predictor of ambulation in children, while children with spastic diplegia were most likely to require an assistive device and those with spastic quadriplegia had the worst prognosis for ambulation. This conclusion is consistent with the findings of the present study: most of the CP children in the independent ambulatory group had spastic hemiplegia; in the assisted ambulatory group, most of the CP children had spastic diplegia; and in the non-ambulatory group, most of the CP children had spastic quadriplegia. Therefore, spastic quadriplegia was selected as the reference group to compare with others in this study. Other types of CP, including dyskinesia, ataxia, hypotonia, and mixed, were smaller and they rarely got discussed. The present study found that ataxia has a better prognosis than the others; all 13 ataxic children

in this study walked with assistance or independently. This concurs with Wu et al.,[51] who found that ataxic CP has a better prognosis for ambulation than spastic and dyskinetic CP.

Table 4.2 Univariable and Multivariable Analysis of Predictors for Ambulatory Status

Predictors	OR_{crude} (95% CI)[a]	*p*-value	$OR_{adjusted}$ (95% CI)[b, c]	*p*-value
Type of CP[d]				
Spastic quadriplegia	1.00		1.00	
Spastic diplegia	13.10 (6.94–24.76)	<0.001	8.96 (3.47–23.16)	<0.001
Spastic hemiplegia	62.89 (31.08–127.25)	<0.001	44.44 (16.19–121.97)	<0.001
Dyskinesia	10.64 (5.13–22.04)	<0.001	12.28 (4.39–34.36)	<0.001
Ataxia	70.57 (18.49–269.37)	<0.001	101.81 (16.87–614.47)	<0.001
Hypotonia	3.81 (0.90–16.21)	0.070	10.56 (1.99–55.95)	0.006
Mixed	2.99 (1.08–8.27)	0.035	4.59 (1.24–16.99)	0.023
Sitting independently at age 2	13.96 (9.60–20.31)	<0.001	7.74 (4.83–12.40)	<0.001
Eating independently	7.47 (5.19–10.77)	<0.001	2.59 (1.44–4.64)	0.001
Male gender	1.17 (0.87–1.56)	0.302	Not selected	
Body mass index	1.09 (1.04–1.14)	0.001	Not selected	
Gestational age	1.01 (0.98–1.05)	0.484	Not selected	
Birth weight	1.00 (1.00–1.00)	0.285	Not selected	
No hyperbilirubinemia	0.86 (0.61–1.21)	0.384	Not selected	
No epilepsy/seizure	1.25 (0.93–1.67)	0.141	Not selected	
No intellectual disability	0.69 (0.48–0.99)	0.043	Not selected	
No visual impairment	2.22 (1.40–3.52)	0.001	Not selected	
No hearing impairment	1.29 (0.62–2.67)	0.492	Not selected	
Have functional use of hands	24.42 (9.74–61.22)	<0.001	Not selected	
Can say single words, sentences	3.41 (2.48–4.69)	<0.001	Not selected	

Notes: [a]Univariable ordinal continuation ratio logistic regression. [b]multivariable ordinal continuation ratio logistic regression. [c]adjusted for covariate (current age and history of orthopedic surgery). [d]spastic quadriplegia included spastic triplegia; spastic diplegia included spastic paraplegia; spastic hemiplegia included spastic monoplegia and spastic double hemiplegia; and mixed type included spastic athetosis and spastic ataxia.
The abbreviations are as follows: CP = cerebral palsy; CI = confidence interval; OR = odds ratio.

The ability to sit independently by age 2, in this study, was a strong predictor for ambulation, as with previous studies.[47, 51, 65, 67] Montgomery[49] reviewed the literature to identify predictors of ambulation in children with CP, in the years 1970 to 1995; he concluded that the best gross motor skills to predicting ambulation was sitting. Later studies confirmed that the ability to sit without support at 2 years of age was a good prognosis for ambulation.[51, 53, 67] Previous studies also examined different ages (1 year and 3 years) for sitting independently.[66, 70]

Finally, this study found that eating independently (functional use of the hands with no oromotor dysfunction) was a significant predictor for ambulation. More recent studies have looked at accompanying impairments. In one large study of children with CP who were not yet walking at 2 years of age,[51] the ability to feed themselves was a univariable predictor for ambulation, but not a multivariable predictor. Kulak et al.[64] found that more than half of the non-ambulatory group was eating with assistance. It is well known that children with CP are associated with poor growth, the main reason being feeding problems.[59, 71] The ability to eat, therefore, affects the gait of these children.

This study found that body mass index, intellectual disability, visual impairment, hand function, and speech were associated with ambulatory status in univariable analysis. However, these variables were not statistically significant predictors for the multivariable model. Some previous research studies have found that these variables are related to walking ability. It has long been known that intellectual disability is a factor determining lack of independent walking of children with CP.[47, 53, 56, 66, 67] Several studies have shown an association between visual acuity and ambulation in children with CP.[51, 53, 56] As with our results, Wu et al.[51] found that increasing hand function was associated with achieving ambulation in univariable analysis, but not in multivariable analysis. It is likely that the hand function is connected with other covariates, such as the ability to eat independently. Additionally, Kulak et al.[64] reported that lack of speech development was a predictor for independent ambulation. Some variables, such as seizure or epilepsy, for which the present study found no association with ambulation, were predictors in other studies.[48, 51, 56, 57, 67] This may be due to this classifying the data into those with a history of seizures or not, rather than specifying the severity and frequency of seizures. Routine data were used in this study, so other variables related to ambulation of children with CP, such as primitive reflexes and postural reactions, were not analyzed.

3.2 Worldwide children with cerebral palsy

The study entitled “Prognostic predictors for ambulation in children with cerebral palsy: a systematic review and meta-analysis of observational study” by Keeratisiroj et al.[72] To my current knowledge, this is the first to conclude prognostic predictors by systematic review and meta-analysis in worldwide (Appendix C). Summaries of this study show the following.

Rationale of the study: There are many factors affecting ambulation in children with cerebral palsy.[44, 49, 51, 53, 56, 57, 59, 63, 73] However, there was no consensus that these factors may have contributed to the success of walking independently. The present, amount of research for predicting ambulation in children with cerebral palsy has increased.[47, 48, 51, 53, 56, 57, 63, 73-77] Yet, no quantitative synthesis of the evidence could be found. There was only a literature review by Montgomery[49] which concluded from seven studies that the persistence of primitive reflexes at 18-24 months were poor prognostic predictors for ambulation while early motor milestones were the best prognostic predictors.

Objectives of the study: To investigate the prognostic predictors for ambulation in children with cerebral palsy using meta-analysis of observational studies.

Search strategies: The meta-analysis of observational studies in epidemiology (MOOSE) was used in this study.[78] It also reports the content guidelines for systematic review and meta-analysis protocol (PRISMA-P).[79] A systematic literature search was performed in PubMed, SCOPUS, CINAHL, ProQuest, Ovid, Wiley InterScience, and ScienceDirect databases. These databases were searched from their start dates to December 2015. A search strategy was produced and adjusted for every database with a blend of free content and controlled vocabulary terms. This search employed the Medical Subject Headings (MeSH) “cerebral palsy”, “predict*”, and “ambula*”, and explored these keywords with slight modifications based on the source. The extra strategies were hand searching of journals not recorded in the electronic sources, online searches, and screening of reference arrangements of retrieved studies for further possibly pertinent articles, with no limitations to the study design and language. The first reviewer (OK) retrieved and performed the primary screening of the titles and abstracts; a second reviewer (NT) checked for accuracy. If there were disagreements regarding eligibility, the article was judged by a third reviewer (WS). Then, the full-text articles were assessed for eligibility by the same method.

Selection criteria: The inclusion criteria for the current study were as follows: studies using cross-sectional, case-control, or cohort (including longitudinal studies) designs; the participants consisted of children or youth from 0 to 18 years of age who were diagnosed with cerebral palsy by physicians or physiotherapists; definitions and measurements of outcomes were reported; and either relative risks (RRs) or raw data were reported to enable their calculation. The exclusion criteria consisted of the following: articles other than original articles

such as comments, letters, reviews, meta-analyses, case reports, surveys, or editorials; and articles not reporting effect estimates or with information that is insufficient to compute effect estimates.

Data extraction, quality assessment and qualitative synthesis: All the included studies were independently assessed by two investigators (OK and NT) using the Newcastle-Ottawa Scale[80] for evaluating the quality of non-randomized studies in meta-analyses. The score was calculated based on three main components: selection (0 to 4 points), comparability (0 to 3 points), and outcome (0 to 2 points). A higher score represented high methodological quality. Any inconsistencies between two specialists were settled by discussion and consensus. The first reviewer (OK) extracted data for the study setting, study design, number and characteristics of participants, outcomes, predictors, and results; a second reviewer (NT) checked for accuracy. Potential predictors were subsequently extracted, and qualitatively synthesized. From which, the selected potential predictors were used in quantitative synthesis.

Quantitative synthesis (Meta-analysis): The meta-analysis was performed using ambulatory status as the binary outcome (ambulation and non-ambulation). The pooled RRs with 95% CI for predicting ambulatory status were calculated using random-effects models, which were most suitable for both random variation within the study and between different studies.[81] The presence of heterogeneity was assessed using the Cochran's Q-test: when *p*-value <0.10, it was considered as evidence of heterogeneity. Furthermore, the effect of heterogeneity was quantified by I^2 which presents the rate of aggregate variety over the investigations of heterogeneity rather than by chance. A value of 0% indicates no observed heterogeneity, with $I^2 \geq 50\%$ represent substantial heterogeneity.[82, 83] Publication bias was assessed using Egger's test for asymmetry with a visual inspection of the funnel plot.[84] The shape of asymmetry indicates the existence of bias, and the accompanying *p*-value <0.05 was suggestive of publication bias. Forest plots were created to show RR with corresponding CI for every study and the overall random-effects pooled estimates. Likely sources of heterogeneity were further investigated by visual examination of the information, forest plots, and subgroup analyses. Finally, sensitivity analyses were used to investigate the robustness of the pooled results.

Results and discussion

A total of 1,123 potentially relevant articles were retrieved. Of these, 273 were excluded as they were duplicates. After reviewing the titles and abstracts of the 850 records, 827 studies were excluded due to the fact that they were not relevant, not original articles, or not regarding children with cerebral palsy, thus 23 were retrieved for full text review. Among the full texts, 11 articles were excluded for the following reasons: it was not possible to translate into English language, it was not possible to access the full texts, they did not answer the research question, the participants were aged over 18 years, or they did not report the definitions and measurements for outcomes. Consequently, 12 studies were deemed suitable for qualitative synthesis.[47, 48, 51, 53, 56, 57, 63, 73-77] Finally, eight studies were selected for meta-analysis, which consisted of four prospective cohort studies,[47, 53, 56, 57] three retrospective cohort studies,[48, 63, 75] and one case-control study.[73] Two studies were excluded from the meta-analysis because they did not report effect estimates or there was inadequate data to calculate effect estimates,[51, 74] the other two were excluded because of data duplication,[76] and different scales were used to report outcomes[77] (Figure 4.3).

The prognostic predictors were considered eligible for both qualitative and quantitative syntheses of supporting evidence regarding strong ambulatory predictors in children with cerebral palsy. The characteristics of the 12 eligible studies in the qualitative synthesis are shown in Table 4.3. The potential predictors for ambulation in these studies were synthesized from multivariable analysis and were shown to be statistically significant (Table 4.4). The studies which did not report the estimated effects or reported insufficient data for the calculation of the estimated effects were excluded from the quantitative synthesis. The results from meta-analysis confirmed that sitting independently at the age of two years, absence of visual impairment, absence of intellectual disability, and absence of epilepsy or seizure are positive predictors for ambulation (Table 4.5 and Figure 4.4). Although it provides new strong quantitative evidence about these prognostic predictors, this seems to be expected. As children with more severe cerebral palsy would likely have more concomitant impairments and less likelihood of independent ambulation, these impairments may reflect severity as much as they are predictors for non-ambulation. Hence, it is recommended to always assess for the presence

of the aforementioned impairments. These should be detected or resolved as early as possible to prevent or impede the development of physical disability.[85, 86]

Furthermore, while some other studies pointed out a few other prognostic predictors including type of cerebral palsy,[47, 48, 51, 56, 63, 73, 75, 76] primitive reflexes and postural reactions,[47, 48, 74] gestational age,[48, 56, 57, 73, 75] birth weight,[56, 57, 73, 75] gender,[51, 73] ability to self-feed,[51, 63] hand function,[51, 63] expressive language,[51, 63] maternal ethnicity,[51, 57] antibiotic use,[57] APGAR score,[73] hyperbilirubinemia,[57] hearing impairment,[56] body mass index,[63] postural control,[77] reciprocal lower limb movement,[77] microcephaly,[48] and magnetic resonance imaging abnormality,[73] these prognostic predictors were not statistically significant or were not pooled estimates in this thesis (Table 4.4).

The high quality of 12 observational studies included in the qualitative synthesis was assessed using the Newcastle-Ottawa Scale (scores obtained; 6 to 9). Only one case-control study[73] was found to have very low quality. The RRs were used for pooled effect estimates in this meta-analysis because most studies were cohort studies, with only one case-control study. In addition, the prevalence of ambulatory outcome was more than 10%. Therefore, the use of RR is more appropriate than the use of OR.[87] We explored the possible sources of heterogeneity by subgroup analyses. The heterogeneity in this study was caused by study designs which included both hospital-based and population-based studies and types of cerebral palsy, which differed from study to study. However, there was a possibility of occurrence of bias because we were unable to exclude some studies since the number of studies were limited. In addition, the interpretation of the Q-test and I^2 should be performed with care since the meta-analysis of a few studies can pose a problem of reducing the power of the test.[82] Furthermore, although the RRs of each study were different, they were of the same direction. Plus, subgroup analyses were used to identify source of heterogeneity were found not to affect the overall findings. The result of egger's test indicated no significant publication bias (Table 4.5 and Figure 4.5).

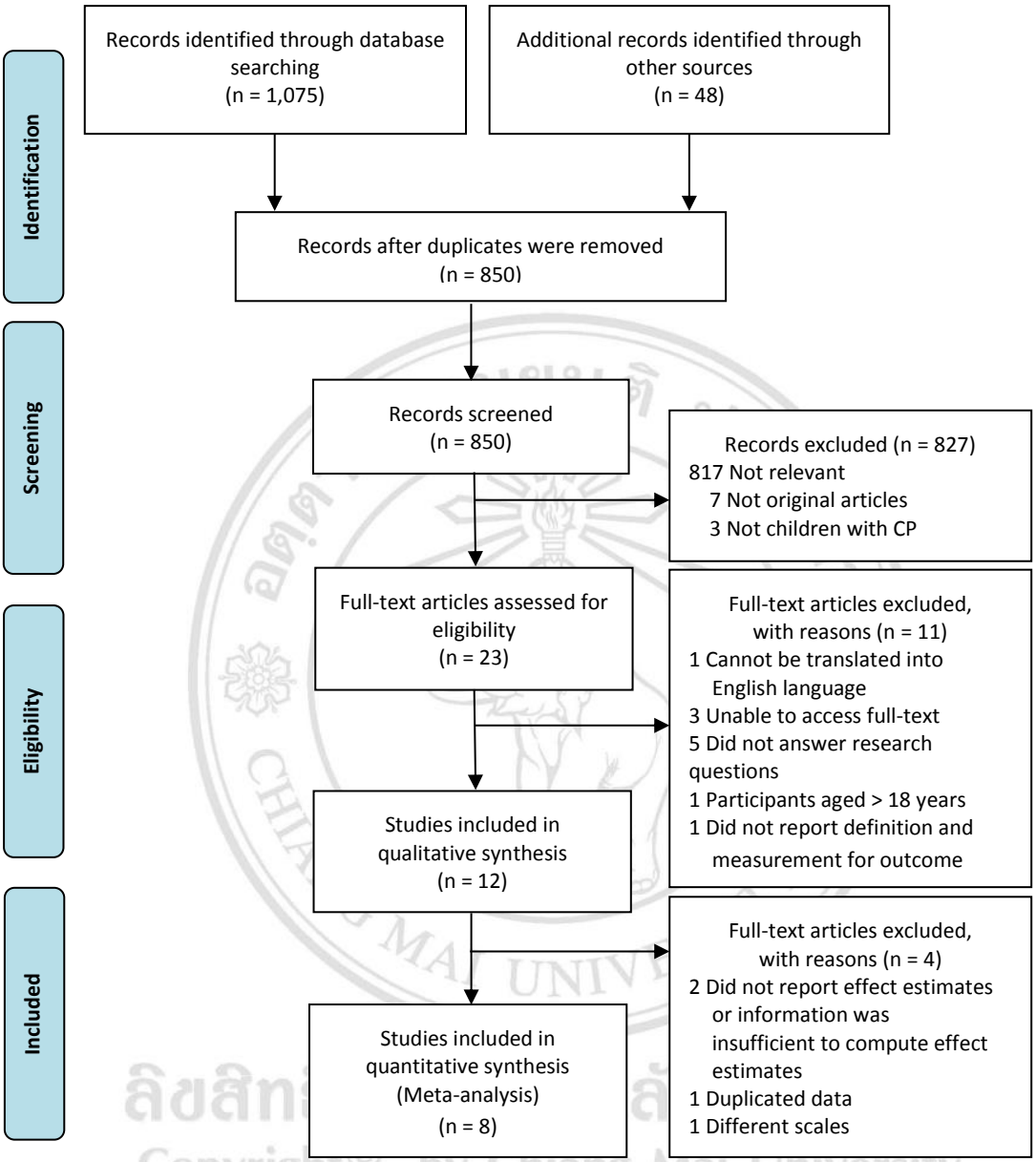

Figure 4.3 The PRISMA flow chart of the study selection process

Table 4.3 Characteristics of studies included in qualitative synthesis

First author (year)	Study design	Study based on	Country	Participants (n)	Enrollment and follow-up period (year)	% Event	Outcome	Adjustment for covariates	Quality
Beck (1975) [a]	Pro. cohort	Hospital based	USA	children with all types of CP (73)	1 to 5	74.0 (54/73)	Ambulatory status: "ambulation" (The ability to walk at least 15 m independently on a level surface [i.e., a carpeted or uncarpeted floor, a clipped lawn, or an outdoor smooth surface] without falling.)	- Age - Therapy	Selection: 4 comparability: 2 outcome: 2
Watt (1989)	Pro. cohort	Hospital based	Canada	children with all types of CP (74)	1 to 6	63.5 (47/74)	Ambulatory status: "ambulation" (community ambulators). If they are able to walk independently for 15 m on a level surface, with or without ankle-foot orthoses and/or upper extremity aids (Bleck 1975). Crutches, rollator walkers, and ankle-foot orthoses were allowed. All others, including household and exercise "ambulators," were regarded as non-ambulators, along with those confined to wheelchairs.	- Age - Therapy	Selection: 4 comparability: 2 outcome: 3
Trahan (1994)	Retro. cohort	Hospital based	Canada	children with quadriplegia or diplegia CP (264)	< 2 to > 8	53.0 (140/264)	Ambulatory status (the child's locomotion level at age six describes the way the child usually moves about at home or at school): - "able to walk," if he or she could walk (with or without crutches or walkers) when performing all his or her daily activities (community ambulator) - "unable to walk," if he or she depended on a wheelchair (self-propelled or motorized) for all or some activities	- Age - Therapy - Type of CP	Selection: 4 comparability: 2 outcome: 3
Fedrizzi (2000)	Pro. cohort	Hospital based	Italy	Children with spastic diplegia or triplegia (31)	2 to 6	58.1 (18/31)	Ambulatory status (as determined at the most recent follow-up examination): - independent ambulation - ambulation only with assistance (sticks, crutches, or walkers) - ambulation not achieved	- Age - Therapy - Type of CP	Selection: 4 comparability: 2 outcome: 3

Table 4.3 Characteristics of studies included in qualitative synthesis (continue)

First author (year)	Study design	Study based on	Country	Participants (n)	Enrollment and follow-up period (year)	% Event	Outcome	Adjustment for covariates	Quality (NOS score)
Wu (2004) [a]	Retro. cohort	Population based	USA	Children with all types of CP who were not yet walking at 2 to 3 ½ years of age (2,295)	< 3 to 7	31.2 (716/2,295)	Ambulatory status: - "full ambulation," as the child has the ability to walk well alone at least 20 feet without assistive devices, on the basis of the CDER definition for ambulation at level 4; also, the child balances well. Clients who have an unusual or awkward gait but who are not in danger of stumbling or falling should also be rated at this level - "no ambulation," if a client typically uses a wheelchair; rate at level 1	- Age - Therapy	Selection: 4 comparability: 2 outcome: 2
Lee (2006)	Retro. cohort	Hospital based	Korea	Children with all types of CP (385)	0 to 5	58.2 (224/385)	Ambulatory status: "independent" (walking aids or independently walking, regardless of the distance.)	- Age - Therapy	Selection: 4 comparability: 2 outcome: 3
Beckung (2008)	Pro. cohort	Population based	14 European centers in 8 countries	Children with all types of CP (9,012)	2 to N/A	69.9 (6,301/9,012)	Ambulatory status (walking at 5 years of age): - unaided walking - walking with aids - unable to walk	- Age - Therapy	Selection: 4 comparability: 2 outcome: 2
Shevell (2009) [a]	Pro. cohort	Population based	Canada	Children with all types CP (243)	2 to N/A	66.3 (161/243)	Ambulatory status: - ambulant group (GMFCS ≤ III) - non-ambulant group (GMFCS ≥ IV)	- Age - Therapy	Selection: 4 comparability: 2 outcome: 2
Simard-Tremblay (2010)	Pro. cohort	Population based	Canada	Children with spastic quadriplegia (85)	Age of outcome = 6	23.5 (20/85)	Ambulatory status: - ambulant group (GMFCS ≤ III) - non-ambulant group (GMFCS ≥ IV)	- Age - Therapy - Type of CP	Selection: 4 comparability: 2 outcome: 2
Kułak (2011)	Case control	Hospital based	Poland	Children with all types of CP aged 6–17 years (345)	2 to 8	61.4 (212/345)	Ambulatory status: - ambulant group (GMFCS ≤ III) - non-ambulant group (GMFCS ≥ IV)	Age, therapy	Selection: 3 comparability: 2 outcome: 1

Table 4.3 Characteristics of studies included in qualitative synthesis (continue)

First author (year)	Study design	Study based on	Country	Participants (n)	Enrollment and follow-up period (year)	% Event	Outcome	Adjustment for covariates	Quality (NOS score)
Keeratisi-roj (2015)	Retro. cohort	Hospital based	Thailand	Children with all types of CP aged 2-18 years (533)	NA	48.2 (257/533)	Ambulatory status: - ambulant group (GMFCS I- II) - Assisted ambulation (GMFCS III) - non-ambulant group (GMFCS IV-V)	- Age - Therapy	Selection: 4 comparability: 2 outcome: 2
Begnoche (2015) [a]	Retro. cohort	Population based	USA and Canada	Children with all types of CP in GMFCS II-III aged 2-6 years (80)	NA	26.3 (21/80)	Ambulatory status: "Independent walking ability" The ability to walk ≥ 3 steps independently, was measured using item 69 on the Gross Motor Function Measure (GMFM-66).	- Age - Therapy	Selection: 4 comparability: 2 outcome: 2

Notes: [a]Studies were excluded from the meta-analysis. The abbreviations are as follows: CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measurement; NOS, Newcastle–Ottawa Scale; Pro., prospective; Retro., retrospective.

Table 4.4 Prognostic predictors of studies included in qualitative synthesis

Prognostic predictor	Bleck (1975) [a]	Watt (1989)	Trahan (1994)	Fedrizzi (2000)	Wu (2004) [a]	Lee (2006)	Beckung (2008)	Shevell (2009) [a]	Simard-Tremblay (2010)	Kulak (2011)	Keeratisi-roj (2015)	Begnoche (2015) [a]
Type of cerebral palsy		*	**		**	#	*	*		#	*, **	
Early motor milestones (1–2 years)												
Prone weight on hands				**								
Rolling			*	*	**							
Crawling			*		*							
Sitting independently		*	**	*	**					*	*, **	
Pull to stand					**					*		**

Table 4.4 Prognostic predictors of studies included in qualitative synthesis (continue)

Prognostic predictor	Bleck (1975) [a]	Watt (1989)	Trahan (1994)	Fedrizzi (2000)	Wu (2004) [a]	Lee (2006)	Beckung (2008)	Shevell (2009) [a]	Simard-Tremblay (2010)	Kulak (2011)	Keeratisi-roj (2015)	Begnoche (2015) [a]
Primitive reflexes and postural reactions												
Tonic labyrinthine reflex	*	*	*									
Asymmetrical tonic neck reflex	*	*	**									
Symmetrical tonic neck reflex	*	*	*									
Moro reflex	*	*	**									
Extensor thrust	*											
Foot placement reaction	*	*										
Parachute reaction	*	*										
Visual impairment		#	*	**	**		**				*	
Intellectual disability		#		*		*	**			*	*	
Epilepsy/seizure		#	**		*	*	**		*	*		
Ability to self-feed					*						*, **	
Gestational age			*			#	*		*	*		
Birth weight						#	*		*	*		
Gender					*					#		
Hand function					*						*	
Expressive language/say simple words					*						*	
Maternal ethnicity					*				*			
Antibiotic use									*			
APGAR score										*		
Hyperbilirubinemia									*			
Hearing impairment							*					
Body mass index											*	
Postural control (GMFM, 53)												*
Reciprocal lower limb movement (GMFM, 45)												*
Microcephaly			*									
Magnetic resonance imaging abnormality										*		

Note: [a]Studies were excluded from the meta-analysis. *Significance for univariable analysis; **significance for multivariable analysis; #influence.

The abbreviations are as follows: GMFM, Gross Motor Function Measurement.

Table 4.5 Meta-analysis and subgroups analysis of significant predictors for ambulation

Total or subgroup	Study (n)	Heterogeneity		Meta-analysis, subgroup analysis		Egger's test
		I^2 (%)	Q-test *p*-value	Pooled RR (95% CI)	*p*-value	*p*-value
Sitting independently at 2 years	4	43.8	0.148	4.82 (3.20 to 7.24)	< 0.001	0.877
Absence of visual impairment	5	68.0	0.014	2.62 (1.70 to 4.03)	< 0.001	0.061
Study design						
Hospital based	4	0	0.785	2.01 (1.45 to 2.77)	< 0.001	
Population based	1	-	-	3.63 (3.22 to 4.09)	< 0.001	
Absence of intellectual disability	4	97.4	0.001	2.12 (1.35 to 3.34)	< 0.001	0.496
Study design						
Hospital based	3	0	0.541	1.75 (1.59 to 1.93)	< 0.001	
Population based	1	-	-	3.08 (2.88 to 3.29)	< 0.001	
Absence of epilepsy/seizure	7	74.8	0.001	1.68 (1.41 to 2.01)	< 0.001	0.235
Subject						
All type of CP	5	79.2	0.001	1.59 (1.32 to 1.91)	< 0.001	
Some type of CP	2	20.7	0.262	2.69 (1.27 to 5.70)	0.010	

Note: The abbreviations are as follows: RR, relative risk; CI, confidence interval; CP, cerebral palsy.

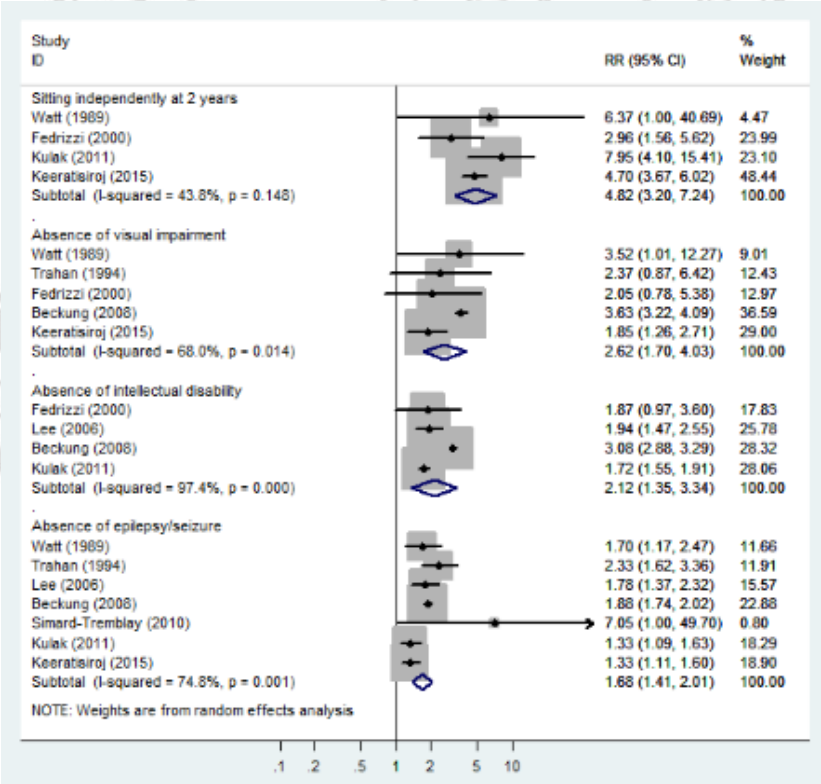

Figure 4.4 Forest plots displaying the meta-analysis of significant predictors for ambulation in children with cerebral palsy.

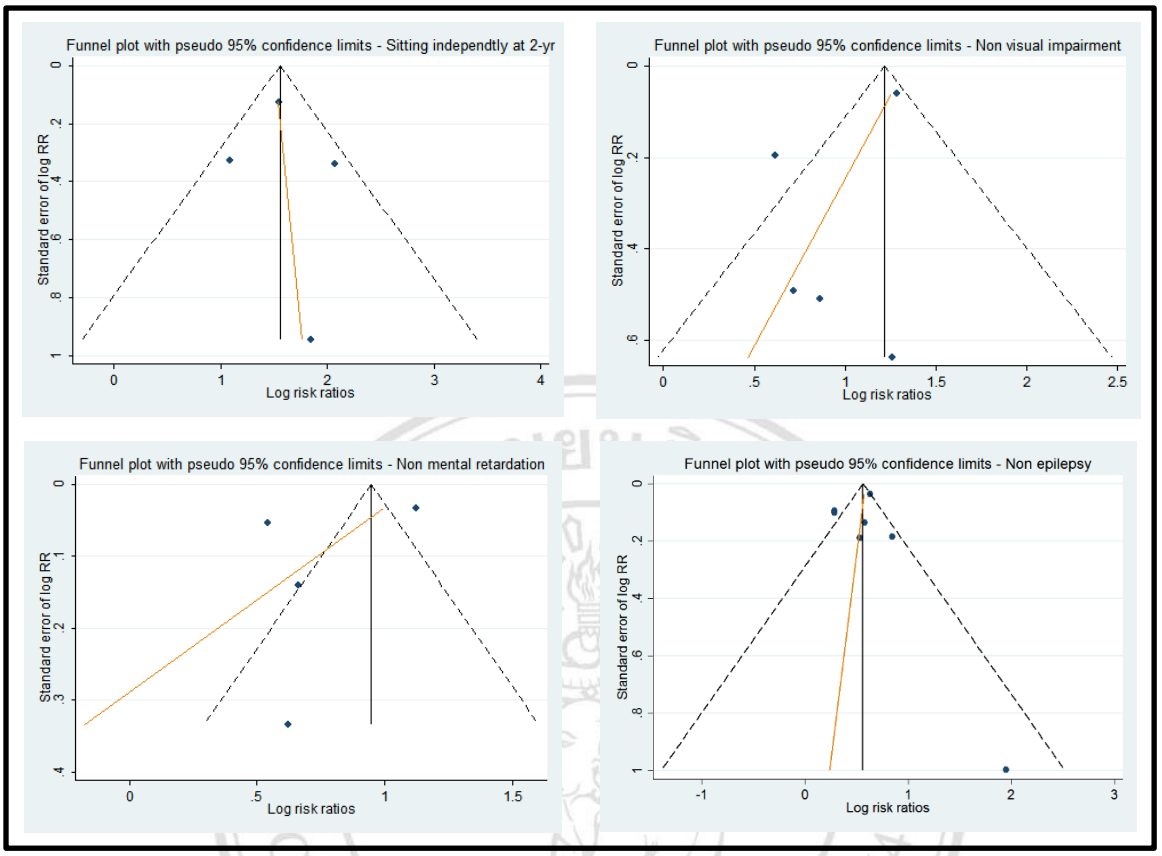

Figure 4.5 Funnel plots displaying the meta-analysis of significant predictors for ambulation in children with cerebral palsy.

4. Conclusion

Study I, the findings in Thailand indicate that good predictors for ambulation among children with CP include the type of CP (spastic diplegia, spastic hemiplegia, dyskinesia, ataxia, hypotonia, and mixed type), sitting independently at age 2 years, and eating independently. The children were classified as follows: capable of independent ambulation (GMFCS I-II, 34.9%), dependent on assisted ambulation (GMFCS III, 13.3%), and affected with non-ambulation (GMFCS IV-V, 51.8%). These predictors were used to develop the clinical scoring scale for predicting the ability to walk in future among Thai children with CP (article 3). The results are potentially beneficial in the long-term treatment and rehabilitation of children with CP in Thailand.

Additionally, the systematic review and meta-analysis from worldwide studies (study II) confirm that sitting independently at 2 years of age, absence of visual impairment, absence of intellectual disability, and absence of epilepsy or seizure are good predictors for ambulation in

children with CP. These factors should be taken into consideration in order to encourage children with CP to walk with their full potential. In addition, the next study should include two reviewers for search strategies to increase the reliability of systematic review.

Although evidence suggests that the likelihood of walking independently in children with independent sitting after 2 years is less than children who can sit autonomously at 2 years, children in the former group are still able to practice walking independently since there are other prognostic predictors for ambulation.

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