Walking problems in patients with neurological impairments due to cerebral palsy:

- Gait: progressive, characterized by reduced energy expenditure and specific participation.
- Balance: often impaired, affecting posture and stability.
- Mobility: limited due to muscle weakness and joint stiffness.
- Coordination: disrupted, leading to difficulties in maintaining and changing body positions.
- Communication: speech and language may be affected, impacting daily interactions.

Research life experiences and quality of life are significantly impacted by these impairments.
Introduction
The first indications of MS date from 1838, in which drawings of autopsies clearly show what would now be recognized as MS.\textsuperscript{[5,6]} In the 21\textsuperscript{st} century, MS has become what is probably the most common neurological disease of young adults. MS is characterized by lesions in all parts of the central nervous system,\textsuperscript{[7,8]} which cause a wide variety of neurological symptoms. The complexity of the disease is explained by symptoms affecting eight

\textsuperscript{a} In this thesis walking ability is used as the standard term for walking as daily activity.
neurological systems, classified as visual, brainstem, pyramidal, cerebellar, sensory, blow/bladder, cerebral and mental. The severity of MS is based on symptoms in these areas and assessed with the so-called Expanded Disability Severity Scale (EDSS).\cite{9} Due to these symptoms, MS patients experience walking problems in daily life as well as severe fatigue, leading to severe effects on social functioning.

The incidence rate of MS in Western Europe ranges between the 2 and 9 per 100,000 and prevalence is approximately 120 per 100,000.\cite{10} MS affects twice as many women as men and disease onset is usually between 20 and 40 years of age.\cite{7,6,10}

The clinical course of MS is classified into three different disease courses, characterized by either (i) episodic acute periods of worsening, (ii) gradual progressive deterioration of neurologic function, or (iii) a combination of both. The most severe disease course is characterized by a nearly continuously disease progression from onset with occasional plateaus and minor temporary improvements, the so-called primary progressive MS (PPMS). Around 80\% of the patients present with relapsing-remitting MS (RRMS), characterized by clearly defined disease exacerbations, with full or partial recovery in the periods between exacerbations.\cite{11} The relapsing-remitting phase is often followed by the secondary progressive phase (SPMS). In this phase a gradual progression is seen, with or without exacerbations and remissions, and 65\% of RRMS patients will eventually enter this secondary progressive phase.\cite{6,11}

The immune-mediated destruction of myelin sheaths in the central nervous system is considered to be the primary pathology of MS, but it is well established that progressive axonal loss is a major cause of irreversible neurological disability.\cite{12,13} This neurodegeneration explains the neurological decline in patients without evidence of inflammatory demyelination and the non-response to current disease modifying anti-inflammatory therapies.\cite{13}
FUPRO MS PROJECT

This thesis is a component of the longitudinal FuPro MS study. This MS study is one of the follow-up studies of the Dutch national rehabilitation research programme ‘Long-term prognosis of functional outcomes in neurological disorders’ (FuPro), supervised by the Department of Rehabilitation Medicine of the VU University Medical Center, Amsterdam. More details about the project can be found in the appendix.

FuPro MS-I was planned as a 3-year follow-up study with five measurement moments, and began in 1998. Five outpatient neurology departments invited all newly diagnosed patients to participate, which resulted in an incidence cohort of 156 MS patients.

All measurements were repeated 6 years and 10 years after diagnosis (respectively, FuPro MS-II and FuPro MS-III). The results of FuPro MS-II showed a steady decline in walking ability in MS patients, often associated with gait related problems, such as impairments in stability, kinematics and energy cost. In order to plan effective rehabilitation strategies, a more detailed knowledge of MS-related gait abnormalities was required. Therefore, FuPro-MS III was launched in 2007 and the measurements were extended with additional physical tests concentrating on the determinants of walking ability, such as balance, muscle strength, coordination tests and clinical gait analysis.

FRAMEWORK

The International Classification of Functioning, Disability and Health, known as the ICF, is used in rehabilitation medicine as a theoretical framework to describe and measure health and disability. The domains of the ICF are classified as body functions & structures, activities (individual) and participation (social perspectives). The three domains are related to health condition (disorder or disease) and two external domains, environmental and personal factors (figure 1.1).[14]

In this thesis gait abnormalities is used as the standard term for impairments in the gait cycle.
The purpose of the ICF is to describe the functioning of an individual based on the three domains. The domain *body functions and structures* represents the functioning of an individual at the level of physiology functions and anatomical parts of the body. Loss of function at this level is referred to as ‘impairment’ and constitutes the symptoms of the pathology. MS patients experience a variety of impairments, which may include spasticity, ataxia, paresis, sensory loss or hypersensitivity, vision problems, memory problems and articulation problems.

The *activity* domain concerns the ability to perform general daily tasks and fulfil the requirements of daily life, such as mobility, self-care and communication; the inability of an individual to perform such a task is assessed as an activity limitation.

*Participation* is defined as ‘involvement in a life situation’, and concerns attainment of meaningful goals, such as participating in education, visiting the supermarket and performing work. Restrictions to participation and

![Figure 1.1 The ICF model](image-url)
involvement in daily life are common problems amongst individuals living with MS.

The wide variety of neurological impairments in MS, together with the progressive nature of the disease, result in diverse activity limitations that will increase over time. Long-term follow-up studies of such effects on activities are therefore essential to healthcare and rehabilitation medicine, as both treatment planning and the allocation of financial resources are dependent on the physical and cognitive abilities of the patient. Chapter 2 describes the ten-year course of daily functioning of the FuPro MS cohort, with an emphasis on physical functioning, cognitive functioning, social functioning and general health. The activity domains were simultaneously measured with neurological deficits (impairments in body functions and structures).

The focus of this thesis is on the walking ability of MS patients, since an activity limitation in walking has a major impact on all activities of daily living, as well as on the levels of participation. A description of gait and the limitations in walking ability on the level of impairments in MS patients follows in the next section.

The ICF defines participation as containing the following topics: education, work, community life, recreation/leisure, religion, civic life, and child care. Since reduced walking ability has an effect on the level of participation, as well as on the level of activity, a mobility outcome measure should cover both fields. In Chapter 3 a community walking scale is introduced as an outcome measure for participation. The level of community walking was derived from items and domains from several questionnaires. The advantage of this type of community-based walking scale is that it offers the possibility to immediately generalize limitations in mobility to the level of activity and participation, and to identify the specific problems that patients experience in daily life. A valid assessment of community walking currently requires a large number of aspects to be covered and all should be measured or detailed in questionnaires. This level of detail can be inconvenient for the patients and time-consuming for clinicians, making a method for quick classification of the level of community walking an important goal. Chapter 3 studies whether gait speed is related to a certain level of community walking.
WALKING LIMITATIONS IN MULTIPLE SCLEROSIS

Walking is the most basic form of human movement, consisting of a repetitious sequence of leg movements that move the body forward and simultaneously maintain stance stability. This cyclic motion of both legs can be sub-divided into different gait phases (see figure 1.2). The gait cycle begins when one of the legs hits the ground, referred to as initial contact, and ends when the same leg hits the ground again (one stride). The first part of the gait cycle is the stance phase, which endures for approximately 60% of the gait cycle. The stance phase is followed by the swing phase of the leg, which begins as the foot is lifted from the ground. Both phases can be sub-divided into further distinct phases and all phases make a functional contribution to the gait cycle.[17-19]

The complexity of walking becomes especially apparent when the ability to walk is reduced as a result of a central neurological disorder such as MS. Limitations which might disturb community walking include reduced walking speed,[1,3] the inability to walk long distances,[20] an increased risk of falling,[21-23] and an elevated energy cost of walking.[24,25] Limited walking ability may be caused, amongst others, by balance problems, MS-related fatigue, muscles weakness, and/or spasticity in the lower limbs.

Figure 1.2 The phase of the gait cycle according to Perry[16]
In order to structure the problems associated with walking, we used the five prerequisites of normal gait that are frequently lost in pathological gait: (1) energy conservation, (2) stability in stance, (3) sufficient clearance during swing, (4) appropriate swing phase pre-positioning of the foot, and (5) adequate step length.\textsuperscript{17,18}

During walking healthy individuals are able to minimize the energy cost of walking and mediate this energy conservation through (1) joint stability provided by ligaments instead of muscles, (2) minimal excursion of the center of mass during walking and (3) optimal use of muscle forces. These requirements can often not be met in pathological gait, due to impairments in body functions such as muscle weakness, balance problems, spasticity and contractures. Consequently, energy conservation in pathological gait may not be as efficient as in normal gait.\textsuperscript{17} Moreover, this inefficiency may lead to fatigue. MS patients may experience one or more of the above impairments and although the resulting fatigue is one of the most disabling symptoms of MS, its aetiology remains unclear.\textsuperscript{26-28} A better understanding of fatigue requires that we consider whether the fatigue experienced by MS patients is related to an inefficient manner of walking. Energy expenditure during walking has been used as an outcome measure in studies of children with cerebral palsy and in cases of post poliomyelitis, and these studies demonstrated that fatigue is directly caused by physical inefficiency during walking.\textsuperscript{29,30} In Chapter 4, we investigate the relationship between self-reported fatigue in MS patients and the energy cost of walking, with the intention to explain a substantial proportion of the experienced fatigue.

The most important requirement in gait is stability during the stance phase. Stability is a prerequisite to maintain a stable position during walking. In order to maintain static balance, the projection of the body center of mass (CoM) on the support surface should be within the base of support (BoS).\textsuperscript{31} However, during walking, stability in stance is challenged by two major elements: (1) the body is top-heavy, and (2) walking continually alters segment alignment.\textsuperscript{17} It is therefore nearly impossible to maintain the body center of mass within the base of support in a dynamic situation such as walking. To maintain stability on a surface, not only should the stance foot be stable on the surface, but the lower-extremity joints must function to allow
advancement of the limb in swing, maintain balance, provide propulsion, and ensure appropriate position of the body.\[^{17}\] This is a complicated task because multiple systems have to work together to accomplish a stable situation during walking. Balance control is characterized by a complex interaction between musculoskeletal and neuromuscular systems, including sensory, vestibular and visual components.\[^{32,33}\] One or more of these systems can be affected by demyelination and cause balance problems. Earlier research showed that balance impairments were most apparent when patients had to respond to internally and externally generated perturbations to their CoM.\[^{34-36}\] This indicates that impaired balance is mainly a problem during walking and not during standing or sitting activities. Most tests used to measure balance in MS patients measure static situations and are therefore not sufficiently sensitive for use with minimally impaired patients.\[^{33,37}\] The importance of capturing balance during walking presents the challenge of finding a reliable dynamic balance measurement for patients with MS. In Chapter 5 the margin of stability, from the model of Hof,\[^{38,39}\] is used as a dynamic balance outcome. The relationship between the margin of stability and static balance is explored in a first attempt to investigate whether this represents a valuable dynamic balance measurement in MS patients.

The other three prerequisites, sufficient clearance, appropriate positioning of the foot in swing, and an adequate step length, are all important to a correct leg advancement in the swing phase and to prepare the leg for the stance phase. Impairments in coordination, muscle strength and spasticity are the most common MS symptoms affecting these requirements.\[^{3,1,40}\] As a result of these symptoms, insufficient push-off, reduced clearance, knee flexion in stance and an inadequate range of motion in hip, knee or ankle could affect the gait pattern. Although MS patients may resort to compensating strategies, this will elevate the energy cost, reduce gait speed, and decrease step length. The progressive course of MS causes a decline in walking ability, indicating that targeted and early clinical treatment is necessary. Gait analysis is a common method to plan and evaluate treatment of gait disorders in other patient groups, such as those with cerebral palsy or stroke,\[^{17,41}\] and categorization of gait patterns has facilitated targeted, individualized treatment in these patients.\[^{42}\] However, due to differences in impairments
and development over time, gait patterns cannot be duplicated between pathologies. In Chapter 6, we explore the possibility of categorizing gait patterns or distinct gait parameters, in order to identify specific gait problems in patients with MS.

**AIM**

The aim of this thesis is twofold: the first aim is to study the 10-year course of daily functioning in the domains of neurological deficits, physical functioning, mental health, cognitive functioning, social functioning and general health in patients with MS, in order to capture the functional decline in this progressive disease. The second aim focuses on the relationship between impairments and walking ability, in order to enhance clinical and scientific knowledge and to gain insights into the walking problems of MS patients.

**OUTLINE**

Chapter 2 describes the 10-year course of daily functioning of the FuPro MS cohort in the domains of neurological deficits, physical functioning, cognitive functioning, social functioning and general health.

In Chapter 3, gait speed is used to assign MS patients to a specific level of community walking. Furthermore, this chapter describes the investigation of whether a minimal important change on a community walking scale is related to an absolute change in gait speed.

In Chapter 4, the relationship between self-reported fatigue and the energy cost of walking is investigated, using structural equation modelling. The same model examines how self-reported fatigue and the energy cost of walking are related to physical functioning in patients with MS.

In Chapter 5, the relationship between balance during walking, the so-called dynamic balance, and static balance measured with posturography is investigated. Earlier studies have shown that static balance measurements are not sufficiently sensitive for use with minimally impaired MS patients,
i.e. are not able to differentiate between the levels of disease severity. Therefore, a further aim was to evaluate whether the Margins of Stability (MoS) during walking, i.e. dynamic stability, could distinguish between severity levels of MS.

**Chapter 6** investigates whether gait patterns can be defined based on walking characteristics such as joint kinematics, push off, and clearance, as well as by muscle activity assessed with clinical gait analysis.

The general discussion in **Chapter 7** highlights some methodological and clinical issues. Furthermore, recommendations are made for future research and the implications for clinical practice are discussed.
APPENDIX

FuPro MS project

The FuPro MS study formed part of the rehabilitation research programme ‘Long-term prognosis of functional outcome in neurological disorders’ (FuPro), supervised by the Department of Rehabilitation Medicine of the VU University Medical Center, Amsterdam. The FuPro programme investigated which measures were most appropriate measures for the description of functional outcomes in patients with neurological disorders and investigated the determinants of functional prognosis. Four separate neurological disorders were included: multiple sclerosis, stroke, traumatic brain injury and neuromuscular disorders.

FuPro MS-I was planned as a 3-year follow-up study with five measurement moments, and began in 1998. Five outpatient neurology departments invited all consecutive, potentially eligible patients to participate, resulting in an incidence cohort of 156 MS patients diagnosed less than six months previously. To facilitate participation, patients were visited at home at the start of the study, at six months, and after one, two and three years following diagnosis.\cite{43} The participants received a questionnaire two weeks prior to the home visit. The measurements at both assessments focused on the level of activity, e.g. daily functioning, physical, social and cognitive functioning, and included a neurological examination.\cite{44} The results showed that, from onset of the disease, social functioning, physical functioning, mental health and general health were all aberrant when compared to the healthy population.\cite{43,45} After three years neurological deficits and physical functioning showed a clinically relevant deterioration. Although mental health also showed a significant deterioration, this deterioration was not clinically relevant.

In 2004, FuPro MS-II was launched as an extension of FuPro MS-I, since MS is a progressive disease, more severe disability problems were expected some years after diagnosis. An extension of the follow-up of the incidence cohort was therefore required and would provide additional insights into the long-term prognosis. Patients were again measured, six years after definite diagnosis,
with patients receiving both a questionnaire and a home-visit during which the same assessments were done. The mobility-related outcome measures showed a significant decline after 6 years. As mobility problems are often related to gait abnormalities and in order to plan effective rehabilitation strategies a detailed knowledge of MS-related walking problems is required.

FuPro MS-III began in 2007 and included an extra follow-up measurement at 10 years. The FuPro MS-III measurements were extended with additional physical tests concentrating on the determinants of walking ability such as balance, muscle strength, coordination tests and clinical gait analysis. FuPro MS-III focused on the relationship between MS-related symptoms and walking ability, and aimed to enhance the understanding of the mechanism behind this relationship and thus improve rehabilitation strategies.
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