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DISABILITY AND PHYSICAL EXERCISE IN ADULTS WITH MYOTONIC DYSTROPHY TYPE 1

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Life is not a problem to be solved,
but a reality to be experienced.

Søren Aabye Kierkegaard

ABSTRACT

Background: Myotonic dystrophy type 1(DM1) is an inherited, slowly progressive, multi-system disease. There is no overall picture of its effect in individuals, and there is a lack of scientific evidence to support recommendations on physical exercise.
Aim: The aims of the work described in this thesis were to explore aspects of functioning, disability and contextual factors in adults with DM1 with regard to different stages of the disease; to describe the reliability and feasibility of the six-minute-walk test (6MWT), and to evaluate the feasibility and effects of a physical exercise programme.
Methods: Seventy adults with DM1 were assessed using various methods and measures, including a modified ICF checklist, tests and questionnaires. The reliability of the 6MWT was evaluated in 12 persons with DM1, and its feasibility in another 64. A comprehensive group exercise training programme, the Friskis&Svettis® Open Doors programme, was evaluated in 35 adults with DM1. They were assigned by lot to either a training group (18 persons) or a control group (17 persons). The training group participated in the exercise programme for 60 minutes twice a week during 14 weeks. The 6MWT was the primary outcome measure. Stages of disease progression were in all the studies based on the disease-specific muscular impairment rating scale.
Results: Excessive daytime sleepiness, muscle weakness and fatigue were common body-function impairments. Activity limitations were most frequently found in physically-demanding mobility activities. Few reported participation restrictions. Support from the immediate family was the most important facilitator for functioning. The individual's total number of impairments, limitations and restrictions was high and persons with severe muscular impairment had more impairments and limitations/restrictions than did those with mild. The 6MWT was reliable and feasible. The better of two possible trials was identified for use as test result. A difference of 33 metres or 6% for an individual with DM1 for a change not to be ascribed to measurement error is suggested .The Open Doors programme was well tolerated and no detrimental effects were found. Intention-to-treat analyses revealed no significant between-group differences in the primary outcome measure. Six persons in the training group and two controls increased their 6MWT distance by ≥6%. Many participants in the training group experienced subjective improvements and could recommend this form of physical exercise to others with the same disease
Conclusion: The finding of a wide variety of body-function impairments, activity limitations and participation restrictions underlines the multi-systemic nature of the disease and the vast impact it has on health. It further implies that a multi-professional approach is needed for optimal care. The information can be used for developing clinical practice and for health promotion for people with DM1. The 6MWT was reliable and feasible, and can be used as an outcome measure in adults with DM1. The Friskis&Svettis® Open Doors programme was feasible for adults with DM1 who had been screened for cardiac involvement, had distal or mild-to-moderate proximal muscle impairment and no severe cognitive impairments.

Keywords: classification, disability, functioning, ICF, myotonic dystrophy, physiotherapy, physical exercise, rehabilitation, reliability

SAMMANFATTNING

Bakgrund: Dystrofia myotonika typ 1 (DM1) är en ärftlig, långsamt progressiv multisystemsjukdom. Det saknas en samlad bild av de effekter sjukdomen har på individer, och det råder en brist på vetenskaplig evidens för rekommendationer gällande fysisk träning vid DM1.
Syfte: Avhandlingens syfte var att undersöka aspekter av funktionstillstånd, funktionshinder och kontextuella faktorer hos vuxna med DM1 med hänsyn till olika stadier av sjukdomen; att beskriva reliabilitet och genomförbarhet av sex minuters gångtest (6MWT), och att utvärdera genomförbarhet och effekter av ett fysiskt träningsprogram.
Metod: Sjuttio vuxna med DM1 bedömdes med hjälp av olika metoder, bl.a. en modifierad ICF checklista och olika tester och frågeformulär. I undersökningen av reliabilitet och genomförbarhet av 6MWT ingick 12 respektive 64 personer med DM1. För att utvärdera ett allsidigt program för motionsträning i grupp, Friskis & Svettis ® Öppna dörrar, lottades 35 vuxna med DM1 till antingen en träningsgrupp (18 personer) eller en kontrollgrupp (17 personer). Träningsgruppen deltog i motionsträning i 60 min, två ggr/vecka under 14 veckor. Den primära effektvariabeln var 6MWT. Den diagnosspecifika skalan ”muscular impairment rating scale” användes i alla studier för att beskriva olika stadier av sjukdomen.
Resultat: Dagtrötthet, muskelsvaghet och fatigue var vanligt förkommande funktionsnedsättningar. Aktivitetsbegränsningar förekom oftast i fysiskt krävande aktiviteter inom ICF-domänen förflyttning. Få personer uppgav delaktighetsinskränkningar. Stöd från närstående var den viktigaste underlättande omgivningsfaktorn. Det sammanlagda antalet funktionsnedsättningar, aktivitetsbegränsningar och delaktighetsinskränkningar per individ var högt, och personer med svår grad av sjukdomen hade fler nedsättningar och begränsningar/inskränkningar än de med mild grad. Testet 6MWT var reliabelt och genomförbarheten var god. Det bästa av två försök ska användas som testresultat. För en individ med DM1 föreslås en skillnad på 33 meter eller 6% överstiga mätmetodfelet. Motionsträningen tolererades väl och det förekom inga skadeverkningar. Det var ingen skillnad mellan grupperna avseende den primära effektvariabeln, 6MWT. Sex personer i träningsgruppen och två kontroller ökade sin 6MWT gångsträcka med ≥ 6%. Många deltagare i träningsgruppen upplevde subjektiva förbättringar och kunde rekommendera denna form av träning till andra med samma sjukdom.
Slutsats: Fynden av en mängd olika funktionsnedsättningar, aktivitetsbegränsningar och delaktighetsinskränkningar understryker att DM1 är en multisystemsjukdom som har stor inverkan på hälsan. Resultatet indikerar vidare att ett multiprofessionellt förhållningssätt krävs för optimal vård. Informationen kan användas för att utveckla klinisk praxis och för hälsofrämjande arbete för individer med DM1. Testet 6MWT var reliabelt, och kan användas som ett utvärderingstest hos vuxna med DM1. Friskis & Svettis ® Öppna dörrar-program var lämpligt för vuxna med DM1 som hade undersökts avseende hjärtfunktion, hade distal eller mild till måttlig proximal muskelsvaghet och inga svåra kognitiva funktionsnedsättningar.

Nyckelord: klassifikation, funktionshinder, funktionstillstånd, ICF, dystrofia myotonika, sjukgymnastik, fysisk träning, rehabilitering, reliabilitet

LIST OF PUBLICATIONS

I. Kierkegaard M, Harms-Ringdahl K, Widén Holmqvist L, Tollbäck A. Perceived functioning and disability in adults with myotonic dystrophy type 1: A survey according to the International Classification of Functioning, Disability and Health. J Rehabil Med 2009;41:512-520.

II. Kierkegaard M, Harms-Ringdahl K, Widén Holmqvist L, Tollbäck A. Functioning and disability in adults with myotonic dystrophy type 1. Submitted.

III. Kierkegaard M, Tollbäck A. Reliability and feasibility of the six minute walk test in subjects with myotonic dystrophy. Neuromuscul Disord 2007;17:943-949.

IV. Kierkegaard M, Harms-Ringdahl K, Edström L, Widén Holmqvist L, Tollbäck A. Feasibility and effects of a physical exercise programme in adults with myotonic dystrophy type 1 – a randomised controlled pilot study. In manuscript.

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CONTENTS

LIST OF ABBREVIATIONS

6MWT	Six-minute-walk test
ADL	Activities of daily living
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CTG	Cytosine-thymine-guanine
CV	Coefficient of variation
DM1	Myotonic dystrophy type 1
ECG	Electrocardiogram
ESES	Exercise self-efficacy scale
ESS	Epworth sleepiness scale
FAI	Frenchay activities index
FSS	Fatigue severity scale
HAD	Hospital anxiety and depression scale
HRQoL	Health-related quality of life
ICC	Intraclass correlation coefficient
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile range
Katz I-ADL	Katz instrumental ADL index
Katz P-ADL	Katz personal ADL index
MIRS	Muscular impairment rating scale
NHPT	Nine-hole peg test
RMI	Rivermead mobility index
ROC	Receiver operating characteristic
SD	Standard deviation
SEM	Standard error of measurement
SF-36	Short-form 36 health survey
TST	Timed-stands test
TUG	Timed up-and-go test
VC	Vital capacity
WHO	World Health Organization

1 BACKGROUND

1.1 INTRODUCTION

Imagine you had a disease that slowly made you weaker and weaker. That weakness and wasting first affected muscles in your face, neck, hands and feet, making it difficult for you to do ordinary daily things like opening a jar, carrying home your groceries, climbing the stairs or running to the bus. Wouldn't you like to know whether physical exercise was good for you? Well, I would!

The scenario just described could be the one for a person with myotonic dystrophy type 1, the most common form of inherited muscular dystrophy in adults. As a physiotherapist, working at the Neurological Physical Therapy Department at Karolinska University Hospital, I meet people with this neuromuscular disease at our outpatients' clinic. They often ask whether physical activity and exercise are of any use. This question was actually the starting point for the work presented in this thesis, because when I turned to the literature for guidance, I could not find any answers! There were few studies of the effects of physical activity and exercise on myotonic dystrophy. Further, at that time, studies giving an overall picture of the effect of the disease on individuals were few and far between.

1.2 MYOTONIC DYSTROPHY TYPE 1 (DM1)

Neuromuscular diseases encompass many disorders caused by disturbances at any part of the motor unit and can, depending on pathology, broadly be divided into neuropathies and myopathies. One subgroup in the myopathies consists of muscular dystrophies, which form a group of inherited disorders characterised by muscle wasting and weakness [1]. Included in this group are the myotonic dystrophies which are currently presented as two different clinical and genetic types, i.e. myotonic dystrophy type 1 which is most common, and myotonic dystrophy type 2, also known as proximal myotonic myopathy [2].

Myotonic dystrophy type 1 (DM1) is a slowly progressive disease first described as a separate disorder in 1909 [3-4]. Characteristic symptoms are myotonia (a delayed relaxation after muscle contraction), and muscle weakness and wasting in neck and facial muscles, and in a distal-to-proximal progression order in the limb muscles. Other organs and systems can also be affected, such as the ocular, cardiovascular, respiratory, digestive, metabolic and endocrine systems, and the central nervous system (CNS); and DM1 is therefore recognised as a multi-system disorder [5-6]. It is one of the most common neuromuscular diseases, with an estimated worldwide prevalence of 5-20 per 100 000 [7]. However, the prevalence figures vary widely according to geography, e.g. 0.5/100 000 in Taiwan [8], 10-18/100 000 in various European regions [9-11], 37/100 000 in Norrbotten, northern Sweden [12] and 189/100 000 in the Saguenay-Lac-Saint-Jean region in Quebec, Canada [13]. Life expectancy is reduced in persons with DM1, especially in those who have early onset of the disease. Mean age at death is reportedly 45 years for those with childhood onset and approximately 55 years for those with adult onset [14-15]. The most common causes of mortality are respiratory and cardiac problems [14-15].

The mutation causing DM1 is an unstable expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the 3´-untranslated region of the myotonic dystrophy protein kinase (DMPK) gene in chromosome 19q [16-17]. Different models have been proposed to explain how and why an expanded CTG repeat in a non-coding region of a gene can cause DM1, and evidence is accumulating that DM1 is an RNA-mediated disease [18-19].

The number of CTG repeats in healthy individuals can vary from five to 37, and people with repeat sizes between 38 and 49 are said to carry the pre-mutation. They are unlikely to have symptoms, but there is an increased risk that their offspring will inherit larger repeat sizes and thereby the disease [20-22]. The number of CTG repeats in persons affected with DM1 varies from 50 to several thousand [17, 21-22]. Mutations in these regions are highly unstable and biased toward further expansions, which can explain the phenomenon of anticipation, i.e. the occurrence of increasing disease severity and decreasing age onset in successive generations, seen in DM1 [17, 22-23]. In addition to the genetic instability over successive generations, the CTG repeat is also somatically unstable within and between body tissues and with an age-dependent expansion process [22, 24-27]. The diagnosis is nowadays based on genetic testing with PCR analysis to detect CTG repeat sizes up to approximately 100 repeats and TP-PCR and/or Southern blot analyses to detect larger expansions [21, 28]. There is a rough correlation between CTG expansion size and disease severity and age at onset, in that individuals with larger expansions have earlier onset and more severe symptoms [23, 29-30]. At the same time, the prognosis for an individual in terms of age at onset, kind of symptoms and their severity, or rate of progression, cannot be made on the basis of the measured CTG expansion size [21, 24].

The inheritance pattern is autosomal dominant, meaning that one copy of the mutated gene is sufficient to cause the disease and that it is passed on to both sexes with equal frequency. There is, however, a sex-specific inheritance difference. Women transmitting DM1 have a significant risk of having a severely affected child, while this is rarely seen when the affected parent is the father [22].

DM1 can be subdivided into four forms based on the clinical presentation, i.e. age at onset and symptoms, and CTG repeat size: 1) the congenital form, 2) the childhood form, 3) the classic adult form, and 4) the mild adult form [2, 30-32]. Congenital DM1 is the most severe form and symptoms are present *in utero* (lack of foetal movements, and polyhydramnios) or from birth (hypotonia, contractures of large joints, breathing and feeding difficulties, mental retardation) [32]. The childhood form is without neonatal symptoms and development is normal within the first year. Age onset is before 10 years and reported symptoms include abdominal and mild motor problems, indistinct speech, variable degree of mental retardation, behavioural problems with learning disability and difficulties in relationships [32-33]. Autism spectrum conditions and anxiety disorders are also associated with both the congenital and the childhood form of DM1 [34-35]. With time, people with the childhood form also develop the same symptoms as in the classic adult-onset form. In this form clinical signs such as myotonia and muscle weakness, and/or symptoms from the ocular, cardiovascular, respiratory, digestive, metabolic, endocrine, and the central nervous system, generally appear between the ages of 10 and 30 years. This is in contrast to the mild adult form where onset is at older age (>40

years) and symptoms are few; only cataract and/or mild myotonia [36]. There is however no absolute distinction between the different forms which, rather, form a continuum [37]. The present work encompasses adults (defined as a person ≥ 18 years of age) with either the childhood form, the classic adult form or the mild adult form.

1.3 ICF

The International Classification of Functioning, Disability and Health (ICF) was developed by the World Health Organization (WHO) as a conceptual framework and a classification system providing a unified and standardized language to describe people's health and health-related states from the perspective of body, individual and society [38]. The ICF is a "components-of-health classification" and supplements the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [39], which provides an etiological framework and a "diagnosis" of diseases or disorders. By classifying functioning and disability associated with health conditions, i.e. diseases or disorders, a broader and more meaningful picture is given of individuals' and populations' experience of health [40].

The ICF comprises two parts, see Figure 1. Part 1, Functioning and disability, includes the components body functions and body structures, and activities and participation. Part 2, Contextual factors, includes the components environmental factors and personal factors. Functioning is an umbrella term indicating non-problematic or neutral aspects of health, comprising all body functions, activities and participations. Disability, on the other hand, is used to indicate problems and summarizes body-function and body-structure impairments, activity limitations and participation restrictions.

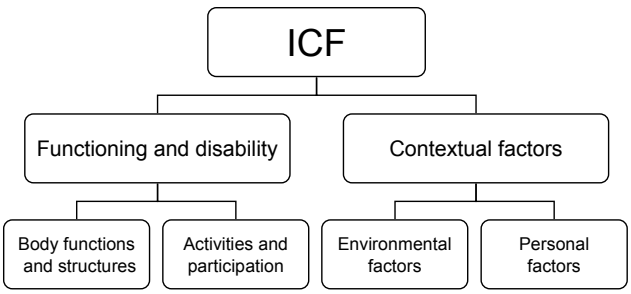

Figure 1. Parts and components of the ICF.

In the ICF, body functions relate to physiological and psychological functions of body systems, and body structures to anatomical parts of the body. Activity is defined as a person's execution of a task or action, and participation as a person's involvement in a life situation. Environmental factors refer to the physical, social and attitudinal environment in which a person lives and conduct his/her life. Personal factors are the individual background of a person's life and living.

The ICF is based on a "bio-psychosocial" approach, which is an integration of two different conceptual models of disability, i.e. the medical model and the social model. In the medical model, disability is seen as a feature of the person caused by disease,

trauma or other health conditions. Disability in the social model is viewed as a socially-created problem and not at all an attribute of an individual. By synthesising these models, the ICF attempts to give a coherent view of different aspects of health. Functioning or disability is always an interaction between contextual factors, i.e. features of the person and of the overall context in which the person lives, and the health condition. Figure 2 represents the ICF model and illustrates the multiple interactions among the components.

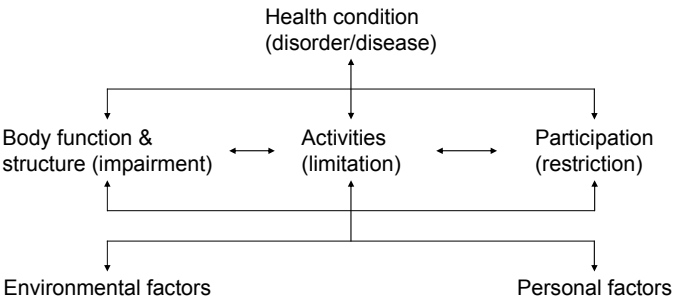

Figure 2. The ICF model: interactions between the components of the ICF.

Except for personal factors, all the components can be classified and coded. An ICF component consists of domains, which incorporate categories, the units of the classification. The domains are arranged hierarchically (chapter, second, third and fourth level), which is reflected in the coding. The ICF categories are designated by a letter; b for body function, s for body structure, d for activity and participation (or a for activity; p for participation), and e for environmental factor. These are followed by a number where the first digit indicates the chapter, the next digit the second level and so on. See example below.

Table 1. Organization and structure of the ICF coding.

Level	Example	Coding
Component	Body functions	b
Domain (chapter)	sensory functions and pain	b2
second level	sensation of pain	b280
third level	pain in body part	b2801
fourth level	pain in back	b28013
Component	Activities and participation	d
Domain (chapter)	mobility	d4
second level	walking	d450
third level	walking long distances	d4502

By adding qualifiers, numeric codes that specify the extent or magnitude of functioning or disability in that category or how far an environmental factor is a facilitator or barrier, an individual's health and health-related state can be described. A generic scale is used to indicate a problem which may mean an impairment, limitation or restriction; 0 = no problem, 1 = mild problem, 2 = moderate problem, 3 = severe problem, 4 = complete problem. Environmental factors are quantified either as barriers or facilitators using a 0-4 scale, where the sign + is used to denote facilitator, ranging from no to complete barrier/facilitator.

The ICF model and classification are proposed for use both in clinical practice and in research [38, 40-44]. In the clinic, the ICF can be applied as a tool for patient assessment, goal-setting, intervention management, and evaluation [41, 43-44]. In research, it can provide a framework or structure, and a standard taxonomy for functioning, disability and health, thereby contributing in both research planning and reporting [42].

However, a problem when using the ICF is the size of the classification system – over 1400 categories. The ICF checklist [45] and several ICF core sets [46-47] have therefore been developed. The checklist [45] consists of 123 second-level categories, and a Swedish version is available from the National Board of Health and Welfare [48]. Core sets are short lists of domains considered relevant for describing health conditions, and can be generic [47], condition-specific [46, 49-50] or developed for different settings [51-52]. A searchable online version of the ICF, (http://apps.who.int/classifications/icfbrowser/), is provided by the WHO to facilitate the use of the classification.

The ICF has been criticized as being too complex for daily use [53]; that it lacks the subjective dimension [54-55]; and is ambiguous concerning the differentiation of activity and participation [56-57]. Pointed out is also the need for a classification of the personal factors [57] and that the ICF model should be expanded to include the concepts quality of life and human development [58].The conceptual platform of the ICF and the view of health expressed in the ICF have also been questioned by Nordenfelt [59-60]. He argues that the distinction between activities and participation is not coherent, that the ICF lacks the concept of will, and that an opportunity qualifier would be more relevant than the ICF performance qualifier.

In the present work, the ICF was used as a conceptual framework and taxonomy to explore functioning, disability and health, and the effects of a physical exercise programme, in adults with DM1.

1.4 FUNCTIONING AND DISABILITY IN DM1

Below are presented some aspects of functioning and disability in DM1 that, based on current research and clinical experience, are considered to be relevant. The vocabulary of the ICF is used in the headings and corresponds to the list of chapters, and the order in which they are presented, of the components body functions, and activities and participation.

1.4.1 Body functions

1.4.1.1 Mental functions

Excessive daytime sleepiness or hypersomnia is a prominent symptom of DM1. It occurs both in the childhood form [32, 61] and in the adult forms [62-64]. The reported prevalence ranges from 20% to 52% [32, 61-65]. Fatigue can be defined as "an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion" that should be distinguished both from symptoms of depression and from muscle weakness [66]. Fatigue is a problem in DM1, present in over 60% in both the childhood- and the adult-onset forms [32, 61, 63, 67]. The causes of excessive daytime sleepiness and/or fatigue are not fully understood. It seems likely, however, that they include hypoventilation, central and obstructive sleep apnoea, hypercapnia, direct central mechanisms and other pathophysiological mechanisms [65, 68-70]. Psychostimulants, i.e. drugs that increase alertness, are used to treat excessive daytime sleepiness, although there is limited evidence to support their routine use [71].

Cognitive function is remarkably varied among the DM1 population, ranging from normal function to severe mental retardation, the latter being associated with the congenital form. In the childhood form, mental retardation has been classified as borderline/mild to moderate [32, 37, 72]. Persons with the adult form usually perform within the normal range on tests, although often lower than controls/normative data [33, 73-74]. The cognitive profile is, however, uneven and problems are reported in executive functions, visuospatial and visuouconstructive functions, memory and attention [34, 73-77]. There is a tendency to progression with age [75-76]. Personality disorders associated with apathy and social avoidance [33, 78-79], and reduced ability to recognise facial emotions [80], are also present.

The occurrence of depression and anxiety is somewhat unclear. The reported prevalence of depression in DM1 ranges from 2.5% to 32% [64, 81-82], and of anxiety disorders from 8% to 40% [81, 83]. These discrepancies might be due to different assessment methods and criteria for classification of depression and anxiety disorders. Depression is not a significant problem according to some studies [64, 81], whereas others report that mild-to-moderate depression is more common in adults with DM1 than in controls [82, 84]. An increased frequency of anxiety disorders is reported in the childhood form [32, 34, 83], but does not seem to be a prominent feature in the adult forms [85].

1.4.1.2 Sensory functions and pain

Visual impairment in adults with DM1 is often due to cataract, and can be the only symptom in the mild form [5]. A higher prevalence of visual impairments, such as low visual acuity, hyperopia and astigmatism, was found in children with congenital and childhood DM1 than in controls [86].

Pain is a common and frequent problem for persons with neuromuscular disease [87-91]. Approximately 60-70% of studied adults with DM1 have reported pain, mainly of moderate intensity and with back and legs as the most frequent sites [88-91]. Another frequent complaint is abdominal pain, reported by both children and adults [32, 92].

1.4.1.3 Voice and speech functions

Speech problems in DM1 are mainly due to muscle weakness and myotonia [5, 93]. A nasal and indistinct speech, with poor articulation, is often present in the childhood form [32].

1.4.1.4 Functions of the cardiovascular and respiratory systems

Impaired heart functions are frequent in DM1 and are progressive over time [94-95]. Most common are conduction system abnormalities and arrhythmias, and less often ventricular and myocardial dysfunctions [95]. The reported prevalence of abnormal electrocardiogram (ECG) recordings varies between 26% and 65% [94, 96-97]. Clinical symptoms are, however, often absent, and regular cardiac investigations are therefore recommended [95, 98]. It is recognized that persons with DM1 risk arrhythmia and sudden death [99-100], even children and adolescents with no other symptoms [101-102]. Holter monitoring, i.e. 24-48-hour ambulatory ECG monitoring, should also be performed in addition to the annual conventional ECG, since many with a normal resting ECG show abnormalities on the Holter monitoring [95, 103].

Persons with DM1 often have hypotension. A marked reduction in both systolic and diastolic blood pressure, even in persons classified as minimally affected, and a reduced age-related rise in blood-pressure, have been reported [5, 104].

Respiratory impairments are common and are due mainly to ventilatory muscle weakness, even though myotonia of these muscles, and mechanical changes in chest wall and pulmonary compliance, also contribute [105-107]. Pulmonary function tests reveal reductions in total lung capacity, vital capacity, forced vital capacity and in forced expiratory volume [69, 94, 105, 108]. Mild-to-moderate restrictive lung disease was reported in 44% and severe in 14% of 57 persons with DM1 [108].

1.4.1.5 Functions of the digestive, metabolic and endocrine systems

Gastrointestinal symptoms are common, and there are multiple reasons for these, including impairments of the nervous and neuroendocrine systems, and smooth and striated muscle weakness [109-111] Chewing and swallowing problems, caused by muscle weakness and myotonia [111-113] are frequent, and 30-55% reportedly perceive difficulties [92, 111]. Other common symptoms from upper and lower digestive tracts are heartburn, dyspepsia, nausea, vomiting, regurgitation, abdominal pain, bloating, constipation and diarrhoea [109-111]. Anal incontinence can also be present both in children and in adults [109, 111]. A high incidence of gallstones has been stated to be a feature of DM1, although there is limited data to support this [5].

Metabolic disturbances seen in DM1 include hyperinsulinaemia, insulin resistance and abnormal blood-lipid levels with high levels of triglycerides [114-115]. Increased body fat mass and increased leptin levels are also present [114-116]. Even though few studies document incidence or prevalence rates of diabetes mellitus in the DM1 population, a slightly increased incidence is reported [5].

Endocrine disturbances are widespread in DM1, involving several endocrine systems, and often with a sex discrepancy, males being more severely affected [115]. Primary hypogonadism in males can give symptoms such as small testis with decreased sperm production, weak secondary sex characteristics, and breast enlargement [5, 115]. Disturbances at several levels of the hyopothalamopituitary-adrenal system, with abnormal regulation of cortisol and androgens, disturbed secretion of growth hormone, and increased levels of cytokines, are reported [114-115].

1.4.1.6 Genitourinary and reproductive functions

Reduced fertility can occur in both sexes [5]. Pregnancy complications are not uncommon and many are a direct consequence of uterine muscle involvement [117].

1.4.1.7 Neuromusculoskeletal and movement-related functions

Myotonia, which is a delayed relaxation after a muscle contraction, is often the first symptom of DM1 in adults [118-119]. It is common in the hand muscles, making it difficult to release following a forceful grip. Myotonia is frequently described as a feeling of stiffness, and is aggravated by cold weather and diminished by repeated contractions, the warm-up phenomenon [5, 120]. Other areas where myotonia occurs are jaw and tongue muscles [5], and respiratory muscles such as the diaphragm [106]. Myotonia is reportedly most marked in persons with minor muscle weakness and a problem of less extent [5, 119]. Different drugs, mostly sodium channel blockers, have been used to treat myotonia, even though a systematic review concludes that there is not enough evidence to determine whether any drug treatment of myotonia is safe and effective [121].

Muscle weakness and wasting are the main features of DM1. Typical is the weakness of facial and jaw muscles and anterior neck muscles, and the distal-to-proximal progression of upper- and lower-limb muscle weakness [5, 119, 122]. The facial weakness and wasting contributes to the typical facial characteristics of DM1 with ptosis (drooping eyelid), hollowing of the temples and a jaw that might hang open. Palate and pharyngeal muscle weakness is also common and can cause considerable problems, for example with swallowing and speech. Although distal weakness in hand and foot muscles is an early and prominent symptom, proximal muscles are also affected both in children and in adults with DM1 [108, 123-124]. The isometric strength in distal and proximal muscles is reduced compared to normative reference values or the strength of controls [108, 123, 125]. Longitudinal studies confirm the progression of muscle weakness [124-126]. However, there is a considerable individual variation in both muscle weakness [118, 123, 127] and rate of progression [118-119].

The gait pattern is typical, due to foot drop; and was in a gait analysis study of five persons with DM1 described as a “foot-slap” pattern with reduced toe-off plantarflexion and abnormal hip motion [128].

1.4.1.8 Functions of the skin and related structures

Premature balding, with hair loss that may be both frontal and temporal, is common and is seen mainly in men with DM1 [5].

1.4.2 Activities and participation

1.4.2.1 Learning and applying knowledge

Learning difficulties are a prominent symptom in the childhood form [32, 34, 37, 72], often being the cause of the first medical consultation; and many children with DM1 require special education [32].

1.4.2.2 General tasks and demands

Although not exclusively studied, people with DM1 may have difficulties with general tasks, for example when undertaking multiple tasks, carrying out daily routines, and handling stress and other psychological demands.

1.4.2.3 Communication

Communication difficulties are common in children and adolescents with DM1 [35, 72, 129]. The dysarthric speech seen in adults can also lead to communication difficulties [119].

1.4.2.4 Mobility

Limitations in mobility are common in DM1 and increase over time [94, 130-133]. Walking and balance difficulties, and a high risk of falls, have been shown in adults [134-135].

1.4.2.5 Self-care

Both children and adults can have limitations in activities related to self-care, although most adults seem to be independent in personal activities of daily living (ADL) [72, 129-130, 133]. Longitudinal studies show that the dependency in ADL increase with time [133, 136].

1.4.2.6 Domestic life

Examples of areas included in the ICF domain domestic life are; "acquiring a place to live, food, clothing and other necessities; household cleaning and repairing; caring for personal and other household objects; and assisting others" [38]. Activity limitations and participation restrictions in areas of domestic life are reported mainly in adults [130-131, 133, 136], but can also be present in children with DM1 [72].

1.4.2.7 Interpersonal interactions and relationships

It is commonly reported that children with DM1 have social difficulties [32, 34-35, 72, 79]. A deterioration in social interaction, which increases over time, has also been shown in adults [94, 133, 136].

1.4.2.8 Major life areas

Participation restrictions concerning work and employment seem common in DM1 [130-131, 137-138]. Persons with DM1 are reported to have lower education levels, reduced employment rates, lower family income and higher reliance on social assistance, compared to a general reference population [138].

1.4.2.9 Community, social and civic life

Activity limitations and participation restrictions in community, social and civil life, are not uncommon. Adults report difficulties concerning recreation and leisure [130, 133, 136], and there is deterioration over time [133, 136]. Notable shortcomings in community areas are reported in children with DM1 and few attend leisure-time activities [72].

1.5 CONTEXTUAL FACTORS IN DM1

Disability, as the term is used in the ICF, denotes the phenomenon resulting from the interaction between a person and his/her physical and social environment [38]. This implies the importance of contextual factors, and they should also be covered to provide a complete picture of the effect of a disease. What follows summarizes aspects of environmental and personal factors in DM1.

1.5.1 Environmental factors

Environmental factors can be thought of as either barriers to or facilitators of functioning [38]. Although the literature is scarce on how persons with DM1 perceive environmental factors, the following ICF environmental factor domains can act as facilitators: products and technology; support and relationships; attitudes; and services, systems and policies. Examples of these are drugs for alleviating impairments such as excessive daytime sleepiness and fatigue; pain; cardiovascular, gastrointestinal and endocrine problems; and myotonia [5]. Further examples are assistive devices such as orthotic, mobility, ADL and technological aids; home adaptations; and public services, which all aim to enhance activity and participation. Negative support and attitudes from family and friends, obstacles related to access and use of technology and to government and public services, were in a study of 200 persons with adult onset found to form barriers which were identified as predictors of participation limitations in domestic life, mobility, employment and recreation [139].

1.5.2 Personal factors

Personal factors are attributes of the individual such as age, gender, social background, education, life experience and coping styles. They are important to survey as they may affect the outcome of interventions. Low education level is a common factor that partly explains disrupted participation in domestic life, mobility, employment, and recreation in adults with DM1 [139]. Further, persons who were married/common-law partners were less likely to be social-assistance recipients, and men were more likely than women to have low support from family [138]. Age, gender and educational levels were predictors of employment status in DM1. Most likely to be employed were younger men with higher education levels [140]. Coping has been evaluated in persons with various neuromuscular diseases, including DM1 [131, 133, 141]. Emotion-focused coping, i.e. ways in which a person handles emotions associated with stressful situations, is reportedly used more often than problem-focused coping, i.e. dealing with the problem itself [141]. Further, coping strategies remain stable over time [133].

1.6 HEALTH-RELATED QUALITY OF LIFE

1.6.1 General aspects

Although it is possible to give a comprehensive view of a person's health using the WHO classifications, no description of health status is complete without reference to quality of life (QoL). The term is ill-defined according to Fayers and Machin [142], and the concept depends on the theoretical perspective and the context in which it is used. QoL can be thought of as a construct of well-being. In the ICF, well-being is defined as a general term that includes all human life areas – physical, mental and social aspects – that make up a "good life" [38].

Health has been defined by the WHO as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. Health is a resource for everyday life, not the object of living. It is a positive concept emphasizing social and personal resources as well as physical capabilities" [143]. This implies that health is multidimensional and points to the complexity of the concept. Health is a personal experience and can therefore only be rated by the person him- or herself. Self-rated health is an overall assessment of a person's perception of his/her general health status and is a predictor of clinical outcome and mortality [144]. The difference between QoL and health is not clearly defined in the literature. It is generally agreed that QoL is a multidimensional construct and includes components of happiness and satisfaction with life [142]. The term health-related quality of life (HRQoL) is a pragmatic delimitation from QoL in its more general sense, and is concerned mainly with functioning and well-being in relation to illness and treatment [145]. HRQoL refers perhaps to aspects of QoL that may be affected by health status and health care. There is no universal agreement on what dimensions of QoL should be included in HRQoL, and the concept may therefore vary between studies. In general, HRQoL questionnaires reflect the multidimensional construct, and include at least items focusing upon general health, and physical, emotional and social functioning [142].

1.6.2 Health-related quality of life in DM1

Reduced HRQoL in physical functioning [133, 136, 146] and in psychosocial functioning, and deterioration over time [133, 136] have been shown in adults with DM1. Overall HRQoL is also significantly lower than in healthy controls and the general population [84].

1.7 HEALTH CARE AND REHABILITATION IN DM1

As there is no curative therapy for DM1, management of the disease symptoms is essential to overall well-being. The complexity and the variability of DM1 call for a coordinated multidisciplinary team approach for achievement of optimal outcomes [98, 147-148]. The overall aims are to relieve impairments, reduce limitations and optimise participation. There are no national Swedish guidelines or standards for provision of specialist care. There is, however, a Scandinavian consensus programme [98] with recommendations on health care including habilitation/rehabilitation. Regular yearly structured follow-ups and collaboration between specialists are advocated [98]. The availability of specialist care usually depends on where you live. Hill and Philips describe specialist care for persons with neuromuscular disease in the United Kingdom

as concentrated in areas of high population density [149]. They also point out that most neuromuscular disease clinics are not a result of local or national planning, but rather due to clinicians with a special interest. The same probably applies in Sweden. To improve health care for people with DM1, nursing case management on a disease-management model has recently been proposed [150]. The model's components include "population identification processes, evidence-based practice guidelines, collaborative practice, patient self-management education, and process outcome evaluation".

Few multidisciplinary rehabilitation programmes have been scientifically evaluated and there is therefore limited data to support this form of rehabilitation for people with DM1. A rehabilitation programme in a hospital setting showed some positive effects on balance in gait in 20 adults with DM1 [151]. In the county of Örebro, Sweden, adults with muscular dystrophy are offered a comprehensive rehabilitation programme that is tailored to their medical, physical and psychosocial needs. The effects on ADL, coping and QoL of this programme were assessed in a quasi-experimental controlled clinical study [152]. Although no significant effects were shown, the results indicate that the participants reduced maladaptive coping patterns [152]. Physiotherapy was included in the programme, and physiotherapists are commonly involved in both the evaluation and management of persons with DM1.

1.8 PHYSIOTHERAPY

1.8.1 General aspects

Hislop proposed a model of pathokinesiology, the science of abnormal human movement, as the basis for physiotherapy [153]. A hierarchical pattern at six different levels of the human organism; cell, tissues, organs, systems, persons and family, was used to define the science of physiotherapy and its application. Physiotherapy was described as a profession that uses therapeutic exercises to prevent, evaluate, and treat disorders of human motion [153]. In Sweden, this model has been further developed as a model of human movement by Tyni-Lenné [154], who describes the movement hierarchy as expressing three aspects ; movement prerequisites, movement capacity and movement behaviour; and how they interact. Tyni-Lenné has also presented a problem-solving model, the "physiotherapy process" [155], which describes the clinical reasoning and decision-making process on which physiotherapy interventions are based.

Building on Hislop's pathokinesiology model, the movement continuum theory of physical therapy [156] was published in 1995 and presented as a grand theory of physiotherapy. Movement is the key concept here and is conceptualised as a continuum from micro (molecular) level to macro (person in society) level influenced by external and internal factors. Every person is said to have a maximum, current and preferred capability to move at each level of the movement continuum determined by biological, psychological and social factors [156]. The aim of physiotherapy practice is to maintain, improve or prevent deterioration of current movement capability with interventions directed at minimising the difference or gap between preferred and current movement capability [156]. An extension of the movement continuum theory has been proposed by Allen [157]. A model subdividing movement into six dimensions, i.e. flexibility, strength, accuracy, speed, adaptability and endurance, and a self-report measure with focus on movement, are described [157-158]. Although the model has been questioned [159], the

measure provides evidence supporting the theoretical construct of the preferred and current movement capability gap described by the movement continuum theory [160].

Physiotherapy is currently defined by the World Confederation for Physical Therapy (WCPT) in a position statement from 2007 [161] as services to persons to "develop, maintain and restore maximum movement and functional ability throughout the lifespan" when "threatened by ageing, injury, disease or environmental factors" [161]. Movement is considered an essential element of health and well-being. Physiotherapy is "concerned with identifying and maximising quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation. This encompasses physical, psychological, emotional, and social well-being" [161]. An integral part of physiotherapy is the interaction process between the physiotherapist and the patient/client, his/her family, and others. Included in this process are both the assessment of movement potential and the agreement upon goals. At the request of the Swedish Association of Registered Physiotherapists, the WCPT document was further developed for Swedish conditions. "Physiotherapy as science and profession" by Broberg and Tyni-Lenné [162] gives a comprehensive view of the historical development, the fields of knowledge, the core concepts, the professional autonomy, the physiotherapy process, and areas and fields of application within physiotherapy. Both the movement continuum theory [156] and the ICF framework [38] are integrated in this definition of physiotherapy [162].

1.8.2 Physiotherapy in DM1

The literature describing physiotherapy in DM1 is scarce. Nitz [163] advocates a holistic approach to management and asserts that understanding all the patient's problems is important for compliance with treatment. Suggested interventions include respiratory physiotherapy, exercise programmes, and the prescription of mobility aids and orthoses [163]. The aims of physiotherapy in neuromuscular diseases in general are to prevent complications, and to maintain and/or improve functioning and quality of life [164-165]. Regular contact with physiotherapists is emphasised for persons with DM1 in the Scandinavian consensus programme [98]. Regular adapted physical activity is also recommended [98]. In summary, depending on the level of function and disability, physiotherapy for persons with DM1 varies and may consist of individual training and treatment, prescription of orthoses and mobility aids, and of advice on, and the prescription of, physical activity and exercise [98, 163-166].

1.9 PHYSICAL ACTIVITY AND EXERCISE

1.9.1 General aspects

Physical activity is defined as "any bodily movements produced by skeletal muscles that result in energy expenditure" [167]. Accordingly, physical activity encompasses almost everything a person does during his/her waking hours, and can in daily life be categorised into occupational, sports, conditioning, household, and other activities. Exercise, on the other hand, is "a subset of physical activity that is planned, structured, and repetitive" with the purpose of improving or maintain physical fitness [167]. Whereas physical activity is related to the movements performed, physical fitness is health- or skill-related attributes that a person has or achieves. Cardiorespiratory endurance,

muscular endurance, muscular strength, body composition and flexibility are the five health-related components of physical fitness [167].

Physical activity is an important factor for general health. Physically active people have higher health-related fitness, lower risk of developing medical conditions, and lower rates of chronic diseases, than the physically inactive [168]. Regular physical activity in adults and older adults (men and women age ≥ 65 years), lowers the rate of all-cause mortality, and reduces the risk of coronary heart disease, cardiovascular disease, stroke, hypertension, type 2 diabetes, metabolic syndrome, colon cancer, breast cancer and depression [168]. Further, being physically active is associated with better-quality sleep and health-related quality of life, and, in older adults, with a reduced risk of falling and with better cognitive function [168]. Evidence is also accumulating for the prescription of physical activity in the treatment of a number of chronic diseases such as metabolic syndrome-related disorders; heart and pulmonary diseases; muscle, bone and joint diseases; cancer; and depression [169-171].

The recommendation of the physical activity needed to promote and maintain health among healthy adults is: moderately intense aerobic physical activity for a minimum of 30 minutes a day, five days a week, or vigorously intense aerobic physical activity for a minimum of 20 minutes a day, three days a week; and eight to 10 strength-training exercises, each repeated eight to 12 times, twice a week [172]. It is possible to combine moderately and vigorously intense physical activity to meet the recommendation [172]. The guidelines for older adults and adults with chronic conditions are basically the same as for healthy adults, although emphasis is put on moderately intense aerobic activity, strength-training exercises, flexibility and balance exercises, reducing sedentary behaviour, and the development of an activity plan [173].

1.9.2 Physical activity and exercise in DM1

People with progressive neuromuscular diseases, such as DM1, are less active than healthy people [134, 174-176]. The reduced physical activity can be due to the disease itself or to a sedentary lifestyle [177], and there is a risk of secondary chronic conditions such as cardiovascular diseases and diabetes [174-175, 177]. The role of physical activity and exercise has not been extensively studied in DM1. Recent reviews conclude that existing studies are limited both in regard to number and quality [178-182]. Exercise programmes, in which at least five people with DM1 have participated, consist of resistance training [183-188], aerobic training [189-190] and qigong [191-192]. The programmes have been home-based [183-185, 189-190], individually supervised [186] or a combination of home-based and supervised group training [187-188, 191-192].

Major shortcomings of these studies are that they have included persons with various neuromuscular diseases [183-184, 189, 191-192], thus making it impossible to interpret the results for each separate disorder. Further, sample size is generally small, varying from five to 19 persons with DM1 [183-184, 186-187, 189-192], although two studies [185, 188] included 35 and 33 persons, respectively. Except for these two latter studies of strength training [185, 188] and qigong [191-192], none have been randomised or controlled. Strength training has in several studies been performed in few muscles, e.g. in knee extensors, elbow flexors, and hand/finger extensors/flexors, [183-184, 186-187], and sometimes only on one side

of the body [183-184, 186]. The description of the characteristics of participants with DM1 is generally limited, and information on whether the diagnosis is genetically verified is often lacking. Thus, it is difficult to assess to whom the findings can be generalized.

Despite these limitations, authors of studies analysing persons with DM1 as a group conclude that the exercise regimes have been well tolerated [185-188, 190]. Improvements in muscle strength [186], hand function [187-188] and aerobic capacity [190] are reported. The clinical relevance of these improvements is, however, uncertain and rarely discussed. From the only study with adequate quality, a randomised clinical trial of a 24-week, home-based, progressive resistance exercise programme in 33 DM1 patients [185], neither beneficial nor negative effects were shown. Although existing evidence is limited, persons with slowly progressive neuromuscular diseases are recommended low-to-moderate-intensity strength and aerobic exercise training, as well as the adoption of an active lifestyle [179, 181, 193]. However, no studies evaluate the effects of a more comprehensive training programme where strength, aerobics, flexibility, and balance exercises are included.

When promoting physical activity and exercise for people with chronic conditions such as DM1, reference settings outside the health care system are important. Friskis&Svettis® is a Swedish non-profit sports association providing different forms of exercise. There are 113 local associations throughout the country and approximately 5% of Sweden's inhabitants are members [194]. The aim is to provide engaging and easily accessible exercise of high quality for everyone. Friskis&Svettis® has – in cooperation with the Swedish Association of People with Mobility Impairments (DHR), the Swedish Association for Persons with Neurological Disabilities (NHR) and the Swedish Association for Survivors of Accident and Injury (RTP) – developed a special form of training programme for persons with disability called "Öppna dörrar" (Open Doors). This group exercise programme is supported with music, and comprises aerobic activities, muscular strength and endurance exercises, and balance and flexibility exercises. Open Doors classes are available at nine of the local associations. This form of exercise seemed to be appropriate for people with DM1, but before referring them to Open Doors classes, an evaluation of the feasibility and effects of the programme was needed.

1.10 VALIDITY, RELIABILITY AND FEASIBILITY

To evaluate the effects of an intervention, tests and measures are needed. They may be designed and used for different purposes; to discriminate, predict or evaluate [195]. Evaluative tests and measures can measure changes over time in an individual or group, and are therefore often called outcome measures. When choosing outcome measures, it is important to consider both the measurement properties, i.e. validity and reliability, and the feasibility for the target population [195].

Validity relates to the meaningfulness and usefulness of a test or measure, how far it assesses what it is supposed to measure. The main types of validity are face validity, content validity, construct validity, and criterion validity; although additional terms have been used in connection with construct validity [195]. Validity is not an inherent

property of a test or measure, but rather a matter of degree [196]: it is context-specific, and a test or measure is never just valid, it is valid for making certain measurements.

Reliability has to do with the consistency, reproducibility and repeatability of a test or measure. It can be defined as the degree to which a test or measure is free from measurement error. The two main components of reliability are the ability to differentiate among patients/persons who are being tested or measured, and consistency, i.e. to provide consistent values with small measurement errors [195]. Systematic and random errors are the main sources of variability associated with measurement error. Systematic errors are predictable, constant and biased, occurring in one direction only, such as learning or fatigue effects [197-198]. Random errors are unpredictable and can be caused by inherent biological or mechanical variation, or by inconsistencies in the measurement procedures [198].

Reliability also comes in different types: internal consistency, test-retest reliability, intra-rater and inter-rater reliability. Internal consistency is most often associated with questionnaires and relates to the homogeneity, i.e. how well items that reflect the same construct yield similar results [195]. Test-retest reliability concerns the consistency of repeated measurements over time, when patients/persons are believed to be stable concerning the measured attribute. Intra-rater reliability refers to how far measures obtained by the same rater on different occasions will be consistent, and inter-rater reliability concerns the agreement between two or more raters.

The reliability of a test or measure can be expressed as relative or absolute [195]. Relative reliability refers to the ability to distinguish among patients/persons and when based on interval/ratio level data, is usually assessed with intra-class correlation (ICC) methods. Absolute reliability describes the degree to which repeated measurements vary for individuals and is expressed either in the actual units or as a proportion of the values measured [198]. Common methods of assessing absolute reliability when based on interval/ratio level data, are calculation of the standard error of measurement (SEM), the repeatability coefficient, and coefficients of variation (CV%, SEM%, repeatability%) [199-201]. Absolute reliability results can be used to determine limits for the smallest difference that indicates a real change in an individual or a group [199].

Tests and measures should not only be reliable, but also show sensitivity to change and responsiveness. These are two important and closely-related, although different, measurement properties. Liang [202] has defined sensitivity to change as "the ability of an instrument to measure change in a state regardless of whether it is relevant or meaningful to the decision-maker. Sensitivity to change is a necessary but insufficient condition for responsiveness". Responsiveness, on the other hand, is defined as "the ability of an instrument to measure a meaningful or clinically important change in a clinical state" [202]. It is the patient/person, his/her proxy or the health professional who defines what a clinically meaningful or important change can be, and it is therefore evaluated from that individual's perspective. According to Liang [202], the change should be noticeable, of value, and exceed variation attributable to chance.

Feasibility is an important aspect when choosing outcome measures. Ideally, a test or measure is time-efficient, inexpensive, and easy to administer and score. The

respondent burden, i.e. the time and difficulty it imposes on the patient/person, must also be considered. Further, it should also be possible to interpret the data gathered into information that can be evaluated and used in the clinical and/or research setting.

1.11 RATIONALE

Assessment of human functioning, disability and health is a unique feature in physical and rehabilitation medicine – which includes physiotherapy – and is used to understand a person's experience of disability, so that health services can be selected aiming at optimizing function [203]. Some studies describe functioning and disability in DM1, but few give a comprehensive view of concurrent body-function impairments, activity limitations and participation restrictions in the same sample of adults with genetically confirmed DM1. It is therefore unknown how the individual is affected. Further, the influence of environmental factors has not been extensively explored. Thus, we lack an overall picture of the effect of the disease in a DM1 population.

Tests and measures are used to gather information about patients/persons in rehabilitation and physiotherapy. If the effects of services in these fields are to be evaluated, outcome measures that are valid, reliable, and feasible are needed. Studies exploring these aspects in persons with DM1 are, however, scarce. Consequently, studies on the feasibility and reliability of outcome measures are required.

In summary, physical activity and exercise are acknowledged as an important factor for general health [168]. The scientific evidence supporting recommendations on physical activity and exercise in neuromuscular disease in general, and in DM1 in particular, is, however, limited due to lack of research. Accordingly, there is a need for studies that explore type and amount of physical activity and exercise programmes for persons with DM1.

2 AIMS

2.1 GENERAL AIMS

The overall aims of the work presented in this thesis were to explore aspects of functioning, disability and contextual factors in adults with DM1; to describe the reliability and feasibility of the six-minute-walk test, and to evaluate the feasibility and effects of a physical exercise programme.

2.2 SPECIFIC AIMS

The specific aims of the work were

- to describe and analyse self-rated perceived functioning, disability and environmental facilitators/barriers with regard to different stages of the disease, i.e. disease severity, using the modified ICF checklist, in adults with DM1 (Study I),

- to describe and analyse functioning and the presence of concurrent body-function impairments, activity limitations and participation restrictions with regard to different stages of disease progression, using data from tests and questionnaires, in adults with DM1; further to explore associations of measures of manual dexterity and of walking capacity with measures of activities and participation (Study II),

- to describe the test-retest reliability and feasibility of the six-minute-walk test in adults with DM1; in particular to investigate possible learning effects of repeated tests, to describe relative and absolute reliability, to determine limits for the smallest differences that indicate a real change, and to describe feasibility (Study III), and

- to investigate the feasibility and effects of a comprehensive group exercise training programme, the Friskis&Svettis® Open Doors, on functioning and health-related quality of life in adults with DM1 (Study IV).

3 METHODS

3.1 DESIGN

Studies I and II have a cross-sectional design, Study III a test-retest design, and Study IV a randomized controlled trial design.

3.2 PARTICIPANTS

To recruit as many persons with DM1 as possible in the Stockholm County Council area, all the major hospitals and private practitioners with neurological speciality were contacted and informed about the studies by mail (I, II). This resulted in a list of 128 persons, mainly from the outpatient clinic at the Department of Neurology, Karolinska University Hospital, Stockholm, Sweden. The inclusion criteria were diagnosed DM1, 18 years of age or older, and living in the Stockholm County Council area. Twenty-one of the 128 persons did not fulfil these (14 had other muscular dystrophies or myotonic disorders, five lived outside the area, one had died and one was under 18 years). Thus, 107 persons were eligible for the studies and they were first contacted by mail and then by telephone. Of these 33 declined participation and four did not reply, so 70 persons with DM1 were included in Studies I and II.

Study III consisted of a reliability and a feasibility part, with different participant recruitments. From the 107 eligible persons with DM1 in the first two studies, 12 were recruited to the reliability part. Inclusion criteria were: diagnosed DM1 and ability to walk at least 30 metres with or without walking aids and/or ankle-foot orthosis. The persons were all well known at the Department of Physical Therapy at Karolinska, and were selected to represent the different sexes, ages and stages of disease progression (muscular impairment).

Data for the feasibility part of Study III were collected in connection with Studies I and II. Of the 70 persons in these studies, six were unable to walk, and thus 64 were included.

In Study IV participants were recruited from the earlier-described 107 persons with DM1. However, three persons had died and 10 new cases had been identified, resulting in 114 eligible persons. Inclusion criteria were the same as in Studies I and II, plus: classified as grade 2-5 on the muscular impairment rating scale (MIRS) [204], ability to walk 50 m without assistance, and permission from a cardiologist to take part in an exercise programme. Exclusion criteria were clinically obvious, severe cognitive impairment, other diagnoses that could interfere with participation, and inability to understand and communicate in Swedish. Of 114 eligible persons with DM1, 35 did not fulfil the inclusion criteria (24 were unable to walk 50 metres, four had no muscular impairment, four had severe cardiac arrhythmia, two had other concurrent diagnoses and one did not speak Swedish). Seventy-nine persons were contacted first by mail and then by telephone. Of these, 41 declined participation and three did not reply. Thus, 35 persons with DM1 were included in Study IV.

All participants had a genetically confirmed diagnosis, either in a first-degree family member (n=1) or in themselves (all other participants). They were classified by DM1 form by their treating neurologist. See Figure 3 for participant recruitment.

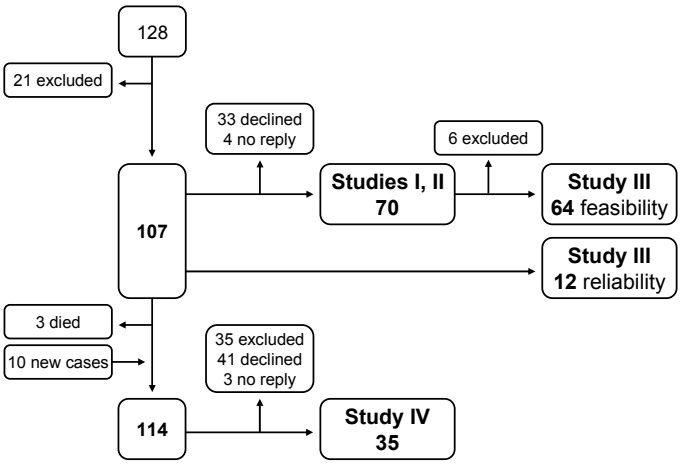

Figure 3. Participant recruitment to the studies.

3.3 PROCEDURES

All data was collected at the Department of Physical Therapy, Karolinska University Hospital, Stockholm, Sweden.

3.3.1 Studies I, II

Data collection for the cross-sectional Studies I and II was divided over two occasions, A and B, in a random order. The order and instructions on each occasion were standardized according to a test protocol. Occasion A consisted of a standard 12-lead ECG recording, and tests of grip strength, lower-extremity performance, manual dexterity and walking, and mobility and ADL questionnaires. A structured interview was used to collect information on personal and environmental factors. Participants were also interviewed for self-rating of functioning/disability and environmental barriers and/or facilitators according to a modified version of the ICF checklist. Occasion B consisted of anthropometric measurements, spirometry, a sub-maximal cardiorespiratory fitness test, and questionnaires. The data presented in Study I was collected on occasion A with structured interviews. The data presented in Study II was collected on occasions A and B, with structured interviews, examinations, tests and questionnaires. Except for the ECG recordings and spirometry tests, which were conducted by an assistant nurse and an experienced biomedical analyst, respectively, all interviews, tests and questionnaire were administered and conducted by the present author (MK).

3.3.2 Study III

In the reliability part of Study III, data was collected on two separate occasions, one week apart, administered by two undergraduate physiotherapy students supervised by the present author (MK). Information, instructions and procedures followed a study protocol. Each student administered the tests to the same participant on the two occasions, and the tests were performed at the same time of day. Data for the feasibility part of study III was collected on occasion A as described above.

3.3.3 Study IV

In Study IV, data was collected within three weeks before the start and within two weeks after the end of the exercise intervention by two independent experienced physiotherapists, blinded to group allocation and each assessing the same participants on both occasions. Information on and instructions for the tests were standardized according to a study protocol and the two physiotherapists were familiar with the tests. In addition to tests and measures, participants answered questionnaires. They gave information on personal and environmental factors in structured interviews. Participants in Study IV were stratified for level of functioning based on the six-minute-walk test (6MWT) [205]. The median value of the 6MWT results from data collection before the start of the exercise intervention was used to divide the participants into two strata from which they were assigned by lot to either a training group or a control group. See Figure 4 for study design. The group training and the data collections were performed at different premises of the hospital (different buildings several blocks apart) and participants were informed not to reveal group affiliation at the evaluation after the exercise intervention.

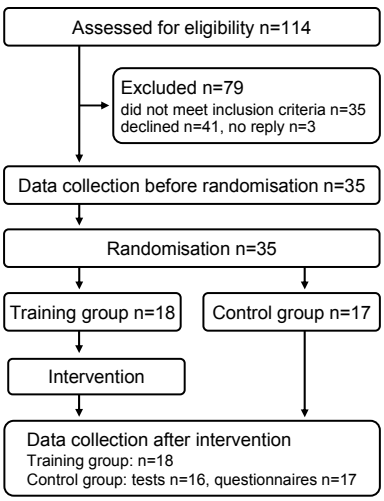

Figure 4. Design of Study IV.

3.4 MEASURES

An overview of used measures in the present work is presented in Table 2.

Table 2. Overview of measures used.

	Study I	Study II	Study III	Study IV
Modified ICF checklist	●			
Epworth sleepiness scale		●		●
Fatigue severity scale		●		
Hospital anxiety and depression scale		●		
ECG recording		●		●
Spirometry		●		
Åstrand-Rhyming test		●		
Grip strength test		●		
Timed-stands test		●		●
Nine-hole peg test		●		
Timed up-and-go test				●
Six-minute-walk test		●	●	●
Rivermead mobility index		●		
Katz Personal ADL index		●		
Katz Instrumental ADL index		●		
Frenchay activities index		●		
Muscular impairment rating scale	●	●	●	●
Anthropometric measures		●	●	●
Physical activity index		●		●
Exercise self-efficacy scale				●
Short-form 36 health survey				●
Study-specific structured interviews on personal and environmental factors	●	●		●
Study-specific questionnaires on perceived effects and experience				●

The ICF checklist

3.4.1.1 The modified ICF checklist (Study I)

The ICF checklist [48] was modified by exclusion of all body-structure categories, by omitting 42 other categories from the original list and by adding 37 categories from the ICF classification, mainly from the activity and participation domain. This was because the checklist was to be used for self-assessment, and should capture information on functioning, disability and environmental factors thought to be relevant for persons with DM1, based on clinical experience and findings in the literature. The modified ICF checklist (see appendix) was used for self-rating of perceived problems in 29 body-function categories, difficulties in 52 activity and participation categories, and barriers and/or facilitators in 23 environmental-factor categories with the following ICF qualifiers:

0=no problem/difficulty/barrier	0= no facilitator
1=mild problem/difficulty/barrier	+1=mild facilitator
2=moderate problem/difficulty/barrier	+2=moderate facilitator
3=severe problem/difficulty/barrier	+3=substantial facilitator
4=complete problem/difficulty/barrier	+4=complete facilitator

The qualifier scale above was transformed to a three-grade scale (0=no, 1=mild to moderate, 2= severe to complete) for descriptive presentation, and dichotomized (0=no problem/difficulty, 1= problem/difficulty) for analysis.

Functioning and disability in activities and participation can be described as a person's capacity and performance. The latter indicates what a person does in his or her current environment, with assistive devices if needed, and was used in the present self-rating of perceived difficulties.

The ICF checklist is not a psychometric measure, but a classification. Nonetheless, an individual's functioning and/or disability is classified using the qualifiers described above. The checklist may be supplemented with any information from written records, the primary respondent, other informants and direct observation [45]. Here primary respondent information was used, as knowledge of persons' own perceptions is of significant value and can assist in the development of health services. The construct validity of the ICF framework has been supported in a retrospective validation study using ICF core sets [206]. Moderate responsiveness has been demonstrated for the ICF core set used with qualifiers on a modified three-point scale for patients with rheumatoid arthritis [207]. Studies of the reliability of the qualifier measurement system have all shown low-to-moderate agreement [208-212]. However, when the scale was reduced from five grades to three, reliability improved [210]. So far, there seem to be no studies of validity or reliability of the ICF checklist, including the qualifiers, in persons with DM1.

3.4.2 Body functions

3.4.2.1 The Epworth sleepiness scale (Studies II, IV)

Excessive daytime sleepiness was evaluated with the Epworth sleepiness scale (ESS) [213-215]. The ESS eight items concern how likely the respondent is to fall asleep/doze off in different situations. Each item is rated on a scale from 0 to 3, and possible scores range from 0 to 24 with higher scores meaning more sleepiness. A score above 10 (≥11) was used to indicate the presence of excessive daytime sleepiness [215] and was classified as a body-function impairment. The scale has a high degree of internal consistency, but there are insufficient data on validity and responsiveness [216]. The ESS is stable over time in persons with DM1, and sufficiently reliable [217]. It is recommended for use in DM1 [218].

3.4.2.2 The fatigue severity scale (Study II)

Fatigue was evaluated with the fatigue severity scale (FSS) [219]. This scale's nine items, concern the effects of fatigue on daily functions, which are rated on a Likert scale ranging from 1 (strongly disagree) to 7 (completely agree). The mean of all item scores constitutes the FSS score, which has a possible range from 1 to 7. A higher score indicates a higher level of fatigue. A score equal to or over 4 (≥4) was used to indicate the presence of fatigue [219-220] and was classified as a body-function impairment. The scale is considered to be valid and reliable in various patient populations [220-222]. It is stable over time in persons with DM1 and has high reliability [217].

3.4.2.3 The hospital anxiety and depression scale (Study II)

Anxiety and depression were evaluated with the Swedish version of the hospital anxiety and depression scale (HAD) [223-224]. The scale's two subscales evaluate the levels of anxiety and depression, respectively. Each subscale consists of seven questions with regard to the person's feelings 'last week', and possible subscale scores range from 0 (no symptoms) to 21 (maximum distress). A score above 10 (≥11) was used to indicate anxiety disorder or depression [223, 225] and was classified as a body-function impairment. The scale is reportedly valid and reliable [223, 226-227], although it has not been tested in persons with DM1.

3.4.2.4 ECG recording (Studies II, IV)

A standard 12-lead ECG (Siemens Sicard 460; Siemens Elema, Germany) recording was used to evaluate cardiac function. The recordings were classified by a cardiologist according to the standards of the Department of Cardiology at the Karolinska University Hospital, and rhythm and conduction abnormalities were documented. An abnormal ECG recording was classified as a body-function impairment.

A 48h ECG examination, i.e. Holter monitoring, was used in Study IV. Participants in the training group were offered this assessment in to ascertain that there were no negative cardiac effects.

3.4.2.5 Spirometry (respiratory function test) (Study II)

Spirometry was used for evaluating respiratory system functions (Spirolab II, MIR, Italy) following the recommendations of the American Thoracic Society/European Respiratory Society (ATS/ERS) [228-229]. These were also used for severity classifications. Vital capacity (VC) when seated, percentage of predicted VC and ATS/ERS severity classification were documented. A spirometric abnormality was classified as a body-function impairment.

3.4.2.6 The Åstrand-Rhyming test (cardiorespiratory fitness test) (Study II)

The Åstrand-Rhyming test [230-231], a sub-maximal cycle ergometer test, was used to evaluate exercise tolerance functions, i.e. cardiorespiratory fitness. Based on estimated maximal oxygen uptake (VO_2-max in ml x kg^{-1} x min^{-1}), each person's cardiorespiratory fitness was classified related to age and sex on a five-grade scale from low to very high [232]. The Åstrand-Rhyming test is considered feasible for health surveys [233], and acceptable reliability has been reported [234]. The validity of the test to predict VO_2-max is somewhat conflicting, both over- and underestimations having been reported [233, 235]. In general, however, data on the psychometric properties of the test are limited [236].

3.4.2.7 The grip strength test (Study II)

A standard hydraulic hand dynamometer (ref 43050, Chattanooga Group USA), equivalent to a Jamar dynamometer, was used for evaluating grip strength. Test procedures were standardized as described by Mathiowetz and co-workers and were in line with recommendations from the American Society of Hand Therapists [237-238]. Three trials were performed for each hand, with a 10-15 s rest between trials. The mean value of the three trials, for each hand, was recorded. Measured mean values were compared to published normative values [237]. Grip strength was considered to be below norm, and classified as a body-function impairment, when less than the mean minus 1 standard deviation (SD) of the predicted hand-, age- and sex- normative value. Measures of grip strength with hand dynamometers are considered to be valid and reliable [238-241]. Further, grip strength is a predictor of mortality, disability, complications and increased length of hospital stay [239]. High reliability of grip strength with another instrument, the Grippit®, has been reported in adults with DM1 [242].

3.4.2.8 The timed-stands test (Studies II, IV)

The timed-stands test (TST) [243] was used to evaluate lower-extremity performance, and thought of as a proxy for lower-extremity strength. Following a practice trial, the time a person took to rise and sit down 10 times as quickly as possible, without using the arms, from a chair without armrest (0.45 m seat height) was recorded. Studies providing normative data are scarce. However, upper time limits have been published and are suggested to separate normal from abnormal performance [243]. The TST was compared to these published time limits. It was considered to be below norm, and classified as a body-function impairment, when the time exceeded the upper time limit of predicted age- and sex- normative values. The TST is reportedly a valid and reliable measure for lower-extremity function [243-244]. There are, however, no published studies of its psychometric properties for persons with DM1.

3.4.2.9 The study-specific questionnaire on perceived effects (Study IV)

To evaluate perceived effects of the exercise intervention in Study IV, participants in the training group answered a study-specific questionnaire after the training period. The questionnaire was developed by the author (MK) exclusively for study IV. Self-rated changes in fitness, strength, flexibility and daytime sleepiness were rated on a five-grade scale ranging from much worse to much better.

3.4.3 Activities and participation

3.4.3.1 The nine-hole peg test (Study II)

The nine-hole peg test (NHPT) was used to evaluate manual dexterity/fine hand use. The standardized test procedures and the test equipment were as described by Mathiowetz and co-workers [245]. Following a first practice trial, the time taken to place nine pegs in a board and then remove them was recorded. The measured time for each hand was compared to published normative values [245]. When the time was greater than the mean plus 1 SD of the predicted hand-, age-, and sex- normative value, the NHPT was considered to be below norm, and classified as an activity limitation. The NHPT is considered valid and reliable in various populations [245-247], although measurement errors are larger when hand function is very limited [247]. Good-to-very-good intra- and inter-reliability were reported in adults with DM1 [242] when manual dexterity/fine hand use was assessed with the Purdue Pegboard, a similar test to the NHPT.

3.4.3.2 The timed up-and-go test (Study IV)

The timed up-and-go test (TUG) [248] was used for evaluation of mobility and balance. Following a practice trial, the time taken to stand up from a chair with armrest (0.45 m seat height), walk three metres, turn, walk back and then sit down, was recorded. The persons sat with their back against a chair and feet behind a tape marker. They were instructed to rise on the word "go" and to walk at their preferred self-selected speed. Timing was begun when their back left the back of the chair and stopped when the buttocks touched the chair seat again. There are no normative values for younger adults. However, an upper time limit for normal performance in persons aged 60-69 years has been set to 9 seconds [249]. The test is considered valid and reliable [235, 248, 250-253] although there are no published studies in persons with DM1.

3.4.3.3 The six-minute-walk test (Studies II, III, IV)

The six-minute-walk test (6MWT) [205, 254] was used to evaluate walking capacity and exercise tolerance [255]. It was administered according to the ATS guidelines [256] on a 30-metre track in a corridor. The beginning and end of the track, the turnaround points, were marked by orange plastic cones. The instruction was to walk as far as possible during the test. Persons were told that they were permitted to stop and rest if they felt too tired or breathless to continue, but to resume walking as soon as possible. Standardized encouragement was provided during the test, and information about the time left was given regularly. After six minutes, the person was told to stop, and the distance walked was measured. In the reliability part of Study III, three 6MWT trials on two separate occasions, one week apart, were performed. On all other test occasions, i.e. in Studies II, the feasibility part of III and in IV, the persons performed two trials, and the longest distance walked of the two was used in the analyses. Immediately

before and after each trial, perceived rate of exertion was rated on the Borg's RPE scale® [257-258], which ranges from 6 (nothing at all) to 20 (maximal). In Studies II and III, the persons also rated their perceived rate of leg effort and shortness of breath on the Borg CR10 scale® [257-258], which ranges from 0 (nothing at all) to 10 (extremely severe). The instructions for the Borg scales were standardized [258] and given before each first trial.

Studies providing normative values for the 6MWT, when administered as described above, are scarce. However, Troosters and co-workers [259] used a similar set-up as in Study II and propose an equation for calculation of predicted age- and sex- normative 6MWT distances. Distances below 82% of the predicted can be considered abnormal according to the authors [259]. Thus, the 6MWT distance was considered to be below norm, and was classified as an activity limitation, when less than 82% of the predicted. The 6MWT is considered valid and reliable in various populations [235, 251-253, 255, 260-261]. There are, however, no studies on the feasibility and reliability of the test in persons with DM1.

3.4.3.4 The Rivermead mobility index (Study II)

The Rivermead mobility index (RMI) [262] was used to evaluate overall mobility. The scale's 15 items range from turning in bed to running. One item, sitting unsupported, is rated by direct observation, and all the others are self-reported. Possible scores range from 0 to 15, a higher score indicating a higher level of mobility function. The RMI scores were dichotomized as independent, i.e. a full score, or dependent, i.e. a score between 0 and 14. The latter was classified as an activity limitation. The scale is considered valid and reliable in various populations [253, 263-265] and is recommended for use in DM1 [218].

3.4.3.5 The extended Katz ADL index (The Katz P- and I-ADL) (Study II)

The extended Katz ADL index, without its continence item, was used to evaluate personal ADL (P-ADL) and instrumental ADL (I-ADL), as described by Sonn and Åsberg [266-268]. The Katz P-ADL index consists of five items; feeding, bathing, dressing, toileting and transfer, and the Katz I-ADL index of four items; shopping, cleaning, cooking and transportation. Each item is assessed based on level of dependency and scored 0 if the person is dependent, and 1 if independent. Thus, the Katz P-ADL sum score range from 0 to 5, and the Katz I-ADL sum score from 0 to 4. Persons with a full score were categorised as independent. Any score less than full sum score was categorised as dependent, and was classified as an activity limitation. The scales are generic, and reliability and validity are considered to be sufficient [269].

3.4.3.6 The Frenchay activities index (Study II)

The Frenchay activities index (FAI) [270-271] was used to evaluate social and lifestyle activities. The scale consists of 15 items mainly concerning domestic chores, work/leisure and outdoor activities. Each item is rated on a 4-point scale (0-3) and scoring is, for most items, based on the frequency with which the activities are carried out, (activities which require involvement and initiative from the person). Possible sum scores range from 0 (inactive) to 45 (active). The FAI scores were compared to

published norms [272] and were considered to be below norm when less than the 25th percentile of the predicted age- and sex-norm value. The FAI scores were dichotomized as within-norm or below-norm, and the latter was classified as a participation restriction The scale is considered valid and reliable [265, 271-272], although Rasch analyses suggest revisions of items [273-274]. The psychometric properties of the scale have not been evaluated in persons with DM1.

3.4.4 Environmental factors

3.4.4.1 Structured interview (Studies I, II, IV)

Information on environmental factors was collected in structured interviews. Questions were asked about medicines, aids, home adaptations and personal care assistance.

3.4.5 Personal factors

3.4.5.1 Structured interview (Studies I, II, IV)

Information on personal factors was also collected in structured interviews. Questions elicited age at diagnosis, inheritance pattern, additional health disorders, education level, civil and employment status.

3.4.5.2 Form of DM1 (Studies I, II, IV)

Persons were classified by form by their treating neurologist using the criteria described in the literature [2, 30-32].

3.4.5.3 The muscular impairment rating scale (Studies I, II, III, IV)

The muscular impairment rating scale (MIRS), a DM1-specific scale assessing muscular impairment [118, 204], was used for monitoring major stages of disease progression (expressed as disease severity in Study I). The MIRS is based on manual muscle testing, according to the modified medical research council scale (MRC) [275], of the neck flexors-, and six proximal and four distal muscle groups bilaterally. Severe weakness is defined as a MRC score <3/5. The five-point scale tallies with the usual distal-to-proximal progression of the muscular involvement where 1=no muscular impairment, 2=minimal signs, 3=distal weakness, 4=mild-to-moderate proximal weakness and 5=severe proximal weakness. Mild muscular impairment was defined as MIRS grades 1-3 and severe as MIRS grade 4-5. The validity and reliability of the MIRS have been supported by studies in persons with DM1 [118, 204], and the scale is recommended for use in DM1 [218].

3.4.5.4 Anthropometric measures (Studies II, III, IV)

To calculate body mass index (BMI), weight and height were measured. Classification of adult underweight (BMI<18.5 kg/m^2), normal weight (BMI=18.5-24.9 kg/m^2) and overweight (BMI≥25 kg/m^2) was based on reference values from the WHO [276].

Waist circumference was measured with a plastic measuring-tape midway between the lowest rib and the iliac crest. The sex-specific waist circumference cut-off values (women ≥0.88 m and men ≥1.02 m) from the WHO were used for classifying persons with a substantially increased risk of metabolic complications [276].

3.4.5.5 The physical activity scale (Study IV)

Physical activity levels during the previous summer and winter half-years were evaluated on a six-grade scale [277-279], ranging from hardly any physical activity to heavy or very heavy exercise regularly and several times a week.

3.4.5.6 The exercise self-efficacy scale (Study IV)

The exercise self-efficacy scale (ESES) questionnaire [280-282] was used to evaluate self-efficacy beliefs in Study IV. The scale assesses a person's confidence in performing an exercise programme despite potential barriers, e.g. work schedule, physical fatigue, boredom related to exercise, minor injuries, other time demands, and family and home responsibilities. It consists of six items and possible scores range from 6 to 60, higher scores indicating greater confidence. The scale has been used in a Swedish primary care setting and is considered sufficiently reliable [280].

3.4.5.7 The study-specific questionnaire on perceived experience (Study IV)

To evaluate perceived experience of the exercise intervention in Study IV, participants in the training group answered a questionnaire after the training period. The questionnaire was developed by the author (MK) exclusively for Study IV. Perception of the form of the exercise programme was rated on a five-grade scale ranging from very bad to very good, and of the intensity on a five-grade scale ranging from much too easy to far too strenuous. The participants were also asked whether they could recommend the exercise programme to others with DM1. The questionnaire ended with an open question seeking comments and views about the intervention.

3.4.6 Health-related quality of life

3.4.6.1 The Short-form 36 health survey (Study IV)

The Short-form 36 health survey (SF-36), standard Swedish version 1.0 [145], was used to evaluate health-related quality of life (HRQoL). The scale consists of 36 items and all but one, change in health status, are grouped into eight health subscales: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH). Each subscale has a possible score from 0 to 100, a higher score indicating a better health state. Three of the subscales are bipolar, i.e. GH, VT and MH, and their middle values represent no negative evaluation of personal health, lack of symptoms of tiredness and absence of psychosocial disability, respectively. The SF-36 is a generic questionnaire and is considered both valid and reliable [145, 283-284].

3.5 FUNCTIONING AND DISABILITY

3.5.1 Total number of body-function impairments, activity limitations and participation restrictions

In Study I, the individual's concurrent, i.e. total number of, body-function impairments, activity limitations and participation restrictions was calculated for each person by adding up the ICF categories that were rated as problems or difficulties. Thus, the total number could range from zero to 81.

In Study II, the individual's concurrent, i.e. total number of, body-function impairments, activity limitations and participation restrictions was calculated for each person by adding up the results classified as an impairment, limitation and/or restriction from examinations, tests and questionnaires. These were an abnormal ECG; a restrictive classification in spirometry; a below-norm value in grip strength, NHPT, TST and 6MWT; a dependent categorisation in RMI, Katz P-ADL and Katz I-ADL; a below-norm categorisation in FAI; presence of excessive daytime sleepiness in ESS; presence of fatigue in FSS; a case of anxiety disorders in HAD; and a case of depression in HAD. Those unable to perform the grip strength test, NHPT, TST or 6MWT due to their physical condition, i.e. muscular impairment, were classified as having an impairment or limitation in that test. Thus, the total number could range from zero to 14.

3.5.2 Cut-off values associated with functioning

In Study II, associations were explored of measures of manual dexterity and of walking capacity with measures of activities and participation. Cut-off values associated with independence in personal and instrumental ADL, and within-norm participation in social and lifestyle activities were proposed by use of the following tests and questionnaires: NHPT, 6MWT, Katz P-ADL, Katz I-ADL and FAI. The NHPT was expressed as number of pegs per second in the analyses. For those unable to perform the tests, the NHPT was set to zero pegs/s and the 6MWT to zero metres. The Katz P-ADL and I-ADL scores were dichotomized as independent, i.e. full score, or dependent; and the FAI scores as within-norm, i.e. score within normal range, or below-norm.

3.6 EXERCISE INTERVENTION

The intervention in Study IV consisted of individually-adapted group exercise training in the Friskis&Svettis® Open Doors programme. It was supported by music to guide the intensity and included aerobic activities; muscular strength and endurance exercises; balance and flexibility exercises; stretching and relaxation, see Figure 5. The programme could be adapted to the individual's level of physical capability and capacity by for example performing the exercises with different pace and lever arms, and in varied positions, if necessary. Persons in the training group were asked to participate in the 60-minute Open Doors programme twice a week for 14 weeks, and they had two mid-day and two after-noon classes every week to chose between. They were also to take at least one brisk 30-minute walk every week, and to document these in an exercise diary. Acceptable adherence was defined as 75% attendance in the Open Doors programme, i.e. participation in at least 21 of 28 training sessions. Intended

intensity during the aerobic parts of the programmes was set to 60-80% of maximum heart rate, with maximum heart rate defined as 220 minus age. During the training period, actual heart rate was measured with a portable heart-rate recorder (Polar S610i™) on several occasions. To ascertain that there were no negative cardiac effects, persons in the training group were also offered a 48h ECG examination during the intervention period. Persons in the control group were advised to live their normal lives, and not to change physical activity behaviour during the study period.

The 6MWT was chosen as primary outcome measure and the TST, TUG, ESS and SF-36 as secondary outcome measures. The study-specific questionnaire on perceived effects was used to evaluate self-rated changes in fitness, strength, flexibility and daytime sleepiness in the training group. The ESES, the exercise diaries and attendance at Open Doors classes, and information from the study-specific questionnaire on perceived experience were used to explore the feasibility of the exercise regime.

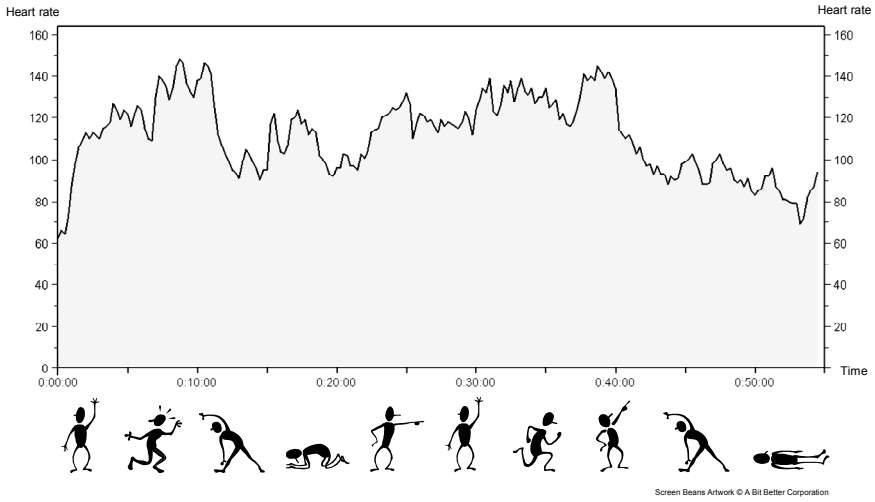

Figure 5. Schematic illustration of the group exercise programme and measured heart rate during a training session from one participant, a 43-year-old man.

3.7 STATISTICAL METHODS

Drop-out analyses were performed with Fisher's exact test for sex and an unpaired *t* test for age. Descriptive statistics were used to present data, i.e. mean and SD, median and interquartile range (IQR), minimum and maximum values, frequency and percentage. The significance level was $p \leq 0.001$ in Studies I and II, and $p < 0.05$ in Studies III and IV. All analyses were performed using SPSS for Windows (release 15.0 or 18.0) except for the two-way repeated measures analysis of variance (ANOVA) in Study III, which used Statistica (release 6.0). See Table 3 for an overview of the statistical methods.

Table 3. Overview statistical methods used.

	Study I	Study II	Study III	Study IV
Descriptive statistics	●	●	●	●
Receiver operating characteristic curves		●		
Bland-Altman plots			●	
Fisher's exact test	●	●		●
Chi-squared test		●		
Mann-Whitney *U* test	●	●		●
Unpaired t test	●	●		●
Wilcoxon matched-pairs signed-rank				●
Paired *t* test			●	
Friedman test			●	
Two-way repeated measures ANOVA			●	
ICC 2.1			●	
Spearman's rank correlation				●
Linear mixed-model repeated-measurement analysis				●

3.7.1 Study I

The qualifier scale was transformed to a three-grade scale for descriptive presentation of the modified ICF checklist results, and dichotomized in between group analyses. Fisher's exact test and the Mann-Whitney *U* test were used to analyse differences in functioning and disability with regard to stages of disease progression (expressed as disease severity in article), i.e. between those with mild (MIRS 1-3) and severe (MIRS 4-5) muscular impairment. The ICF domains were used in the descriptive presentation of persons with self-rated disability, who also rated environmental factors as facilitators. A person was regarded as having a disability if any category within the domain was rated as a problem or difficulty. Likewise, a person was regarded as perceiving the environmental domain as facilitating if any category was rated as a facilitator.

3.7.2 Study II

Fisher's exact test, the Chi-squared test and the Mann-Whitney *U* test were used to analyse differences with regard to stages of disease progression, i.e. between those with mild (MIRS 1-3) and severe (MIRS 4-5) muscular impairment. Descriptive statistics, the Mann-Whitney *U* test, and receiver operating characteristic (ROC) curves were used to explore associations of measures of manual dexterity and of walking capacity with measures of activities and participation.

ROC curves can be used to assess the diagnostic accuracy of a test, to determine a cut-off point at which optimal sensitivity and specificity are achieved and to compare the usefulness of two or more diagnostic tests [285]. An ROC curve is obtained by calculating the sensitivity and specificity of a test at every possible cut-off point and plotting the sensitivity (the proportion of true positive results) on the y-axis against 1-specificity (the proportion of false positive results) on the x-axis [285-286]. The area under the curve (AUC) reflects how well the test can distinguish between persons with and without disease or a certain characteristic [285]. The closer the AUC is to 1, the better the test's discriminative ability, and an AUC of 0.5 indicates that the test is no better than random.

The ROC curves were used to visualise the ability of the NHPT and the 6MWT to discriminate between those who were classified as independent/within-norm and those who were classified as dependent/below-norm. The AUC and 95% confidence intervals (CI) were calculated. Cut-off values in the NHPT and 6MWT associated with independence in Katz P-ADL and I-ADL, and within-norm participation in FAI were identified by choosing those values at which optimal sensitivity and specificity, defined as those yielding the minimal value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$, were achieved [285]. The NHPT was expressed as number of pegs per second in these analyses. A value of zero was set for those unable to perform NHPT or 6MWT due to their physical condition.

3.7.3 Study III

In the reliability part of study III, Bland–Altman plots were used to check for systematic bias, outliers and heteroscedasticity [200-201]. A two-way repeated measures ANOVA with two within factors (occasion and trial) was used to evaluate systematic differences in 6MWT distance and whether there was an interaction effect between occasions and trials. Relative reliability was assessed with $ICC_{2.1}$ [287] and absolute reliability with the SEM (defined as the within-subject standard deviation), the repeatability coefficient (defined as $\sqrt{2} \times 1.96 \times \text{SEM}$) and coefficients of variation, i.e. SEM% (SEM/mean x 100) and repeatability% (repeatability/mean x 100) [199-200]. The paired *t* test was used for analysing systematic changes in the mean between the best of the three trials on each occasion and also for the better of the first two trials on each occasion. The Friedman test [288] was used to test for differences in post-trial ratings on each occasion of perceived rate of exertion, leg effort and shortness of breath.

3.7.4 Study IV

An intention-to-treat analysis approach was applied in Study IV. A linear mixed-model repeated-measurement analysis, using the compound symmetry covariance structure, was used for evaluating within-group, between-group and interaction effects for 6MWT, TST and TUG data. For ESS and SF-36 data, the Wilcoxon matched-pairs signed-ranks test was used for within-group analyses and the Mann-Whitney *U* test for between-group analyses after intervention. Associations between exercise self-efficacy beliefs and attendance were analysed with descriptive statistics and Spearman's rank correlation.

3.8 ETHICAL APPROVAL

Oral and written information was given and all participants gave their signed informed consent before enrolment. They were informed that taking part in the studies was completely voluntary, and that they could at any time, without stating any reasons, terminate their participation without it affecting their care. The studies were approved by the Regional Ethical Review Board in Stockholm and procedures were conducted in accordance with the Helsinki Declaration.

4 RESULTS

4.1 PARTICIPANTS

Drop-out analyses showed that there were no significant differences in sex or age between the persons with DM1 who participated in the studies (I, II, IV) and those who declined. Participant characteristics and personal factors are presented in Tables 4 and 5. Data on environmental factors are presented in Table 6.

The median time between occasions A and B in Studies I and II was four days. One person completed the questionnaires only on occasion B, and another was unable to come to this occasion. In Study IV, one control group member could not attend the data collection occasion after the intervention. He did, however, at that time, complete the questionnaires mailed to him.

Table 4. Participant characteristic and personal factors.

		Studies I, II	**Study III**		**Study IV**	
			reliability	feasibility	training	control
		n=70	n=12	n=64	n=18	n=17
		mean (SD) range	mean (SD) range	mean (SD) range	mean (SD) range	mean (SD) range
Age: years		45 (13) 19-70	44 (12) 28-68	43 (13) 19-70	44 (11) 20-60	41 (15) 20-65
Age diagnosis: years		32 (13) 5-63		32 (14) 5-63		
		n	**n**	**n**	**n**	**n**
Sex:	female	41	6	36	10	10
	male	29	6	28	8	7
Form of DM1:	mild adult	2	0	2	0	0
	classic adult	56	11	50	17	12
	childhood	12	1	12	1	5
Inheritance:	not known	13	3	12	3	3
	maternal	24	3	22	5	7
	paternal	33	6	30	10	7
MIRS grade:	1	3	1	3	0	0
	2	13	3	13	3	1
	3	21	4	21	1	6
	4	13	3	13	12	10
	5	20	1	14	2	0
Additional health disorders:						
	diabetes	3		3		
	goitre	3		2		
	psoriasis	2		2		
	myoma	2		2		

Table 5. Participant characteristics and personal factors.

	Studies I, II	**Study III**		**Study IV**	
		reliability	feasibility	training	control
	n=70	n=12	n=64	n=18	n=17
	n	n	n	n	n
Education level: university	19		19	5	5
high school	35		31	8	3
< high school	16		14	5	9
Civil status:					
cohabiting with partner	31		29	9	9
single	22		20	3	6
divorced, separated, widow	17		15	6	2
Employment:					
work full	18		18	6	2
part time	8		8	2	4
full disability pension	31		27	7	6
other*	13		11	3	5
BMI:	**68**		**63**		
underweight	9	2	9	2	3
normal weight	29	6	29	9	10
overweight	30	4	26	7	4
Waist circumference:	**68**		**63**		
risk metabolic complications	27		22	7	5
Hand dominance:					
right	61		55		
left	9		9		
Smoking/snuff-taking habits:					
smokers	15		12	4	4
snuffers	14		4	1	3
Physical activity summer:	**69**				
mostly sitting to light	45		40	10	13
moderate 1-2 hours/week	17		17	6	3
moderate > 3hours/week to hard	7		7	2	1
Physical activity winter:	**69**				
mostly sitting to light	48		43	13	12
moderate 1-2 hours/week	16		16	4	4
moderate > 3hours/week to hard	5		5	5	5

*other= studying, unemployed, retired

Table 6. Data from structured interviews concerning environmental factors.

	Studies I,II	Study III	Study IV	
		feasibility	training	control
	n=70	n=64	n=18	n=17
	n	n	n	n
Medicines:				
CNS stimulants	26	24	10	3
anti-myotonia	3	3	1	0
Aids:				
ADL	38	32	7	5
orthotic	20	20	5	3
mobility	25	19	1	1
Home adaptations	31	25		
Personal care assistance	18	12		

4.2 FUNCTIONING AND DISABILITY (STUDIES I, II)

Figure 6 presents the total number of categories from the modified ICF checklist rated as a problem and difficulty for each person. The median value was 10, IQR 6-19 for those with mild muscular impairment, and median 30, IQR 20-42 for those with severe. There was a significant difference ($p<0.001$) with regard to stages disease of progression. (Study I)

Figure 7 presents the total number of classified body-function impairments, activity limitations and participation restrictions from tests and questionnaires for each person. The median value was 6, IQR 4-7 for persons with mild muscular impairment, and median 9, IQR 8-10 for those with severe. There was a significant difference ($p<0.001$) with regard to stages of disease progression. (Study II)

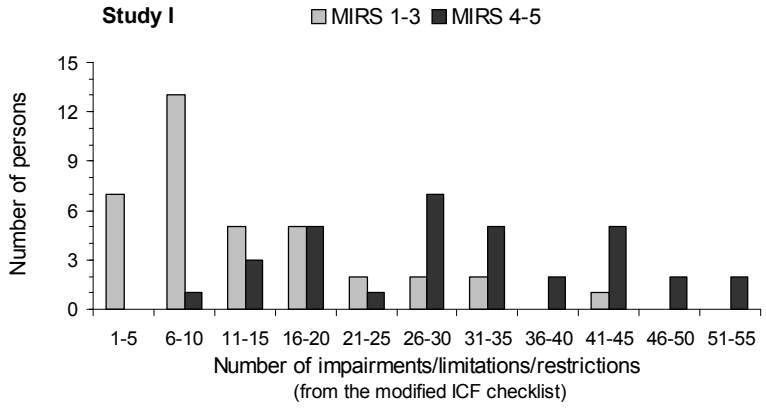

Figure 6. The total number of categories from the modified ICF checklist rated as a problem and difficulty for each person, i.e. body-function impairments, activity limitations and participation restrictions, for those with mild (MIRS 1-3) and severe (MIRS 4-5) muscular impairment in Study I (n=70). The total number could range from zero to 81.

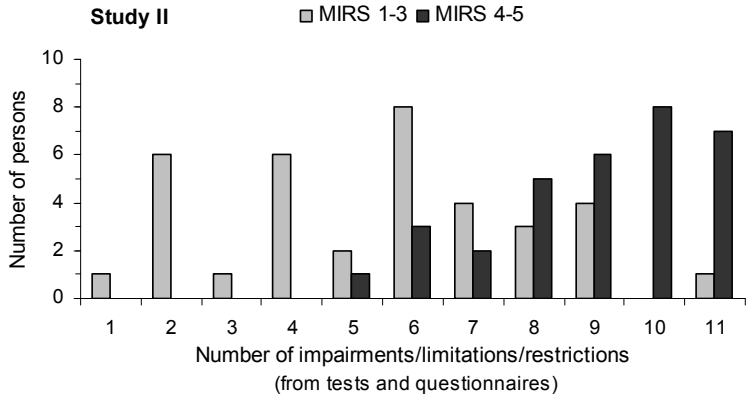

Figure 7. The total number of classified body-function impairments, activity limitations and participation restrictions from tests and questionnaires for those with mild (MIRS 1-3) and severe (MIRS 4-5) muscular impairment in Study II (n=68). The total number of could range from zero to 14.

4.2.1 Body functions

Twenty percent or more of those with DM1 perceived problems in 19 of the 29 body-function categories from the modified ICF checklist. The median number of self-rated body-function impairments per person was 10, IQR 6-13. Excessive daytime sleepiness was rated as a problem by 80%, muscle power functions by 76%, and energy and drive functions by 66%. Further, 30% perceived severe-to-complete problems of muscle power functions and 23% of defecation functions; while 23% perceived pain as a severe or complete problem. Figure 8 presents percentages of perceived problem in the top-seven-rated body-function categories. (Study I)

Impairments of excessive daytime sleepiness and fatigue; cardiac and respiratory functions; grip strength and lower-extremity performance were found (Table 7). There were five cases of anxiety disorders and none with depression. Twenty-eight persons were unable to perform the cardiorespiratory fitness test due to: inability to mount the ergometer cycle (n=10), leg-pain (n=7), unpredictable heart rate recordings (n=6), and perceived exhaustion (n=5). Four were unable to do the grip strength test and 15 the TST due to their physical condition, i.e. muscular impairment. (Study II)

Table 7. Results from measures of body functions (Study II).

	n	median (IQR)	n (%)
Epworth sleepiness scale, (score: 0-24)	69	9 (6-11)	
excessive daytime sleepiness			19 (28)
Fatigue severity scale, (score: 1-7)	69	4 (3-5)	
fatigue			36 (52)
Hospital anxiety and depression scale	69		
Anxiety (score: 0-21)		5 (2-7)	
cases of anxiety disorders			5 (7)
Depression (score: 0-21)		4 (2-6)	
cases of depression			0 (0)
ECG	70		
conduction disturbances			21 (30)
arrhythmias			4 (6)
conduction disturbances and arrhythmias			1 (1)
Respiratory function	68		
VC % of predicted		75 (60-90)	
normal			18 (27)
mild restriction			20 (29)
moderate-to-very-severe restriction			30 (44)
Cardiorespiratory fitness, classified	40		
very low to low			21
average			12
high to very high			7
Grip strength, kg	66		
right hand		8 (4-15)	
body-function impairment, right hand			63 (95)
left hand		8 (4-14)	
Timed-stands test, s	55	24 (18-28)	
body-function impairment			45 (82)

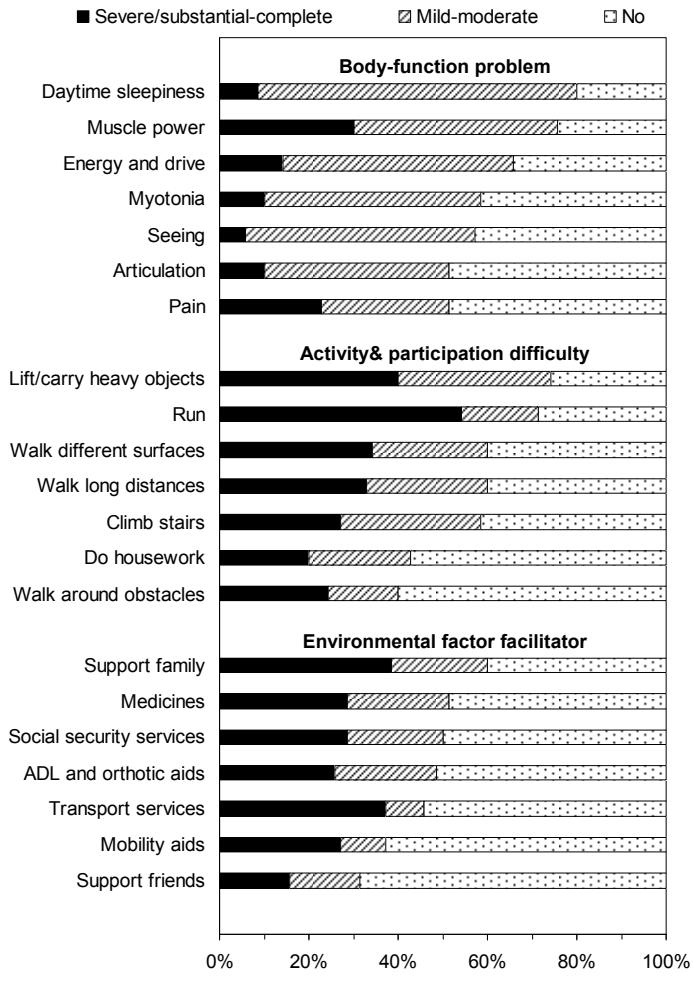

Figure 8. Illustration of relative frequencies of perceived problems, difficulties and facilitators in the top-seven rated-body-function, activity-and-participation and environmental-factor categories, n=70. (Study I)

Persons with mild muscular impairment perceived less body-function problems than those with severe muscular impairment, and significant differences were found in the following four body-function categories from the modified ICF checklist: respiratory muscle, joint mobility, muscle power and gait pattern functions, ($p \leq 0.001$). There was also a significant difference in total number of body-function impairments per person between those with mild muscular impairment, median value 8, IQR 5-10 and those with severe, median value 12, IQR 9-14 ($p < 0.001$). (Study I)

Persons with mild muscular impairment performed better in tests than those with severe muscular impairment, and significant differences were found in tests of grip strength and lower-extremity performance (TST) ($p \leq 0.001$). (Study II)

4.2.2 Activities and participation

Twenty percent or more of the persons with DM1 perceived difficulties in 23 of the 52 activity and participation categories from the modified ICF checklist. The median number of self-rated activity and participation limitations/restrictions per person was 10, IQR 3-19. Between 59% and 74% reported difficulties in physically-demanding mobility activities. The same activities, i.e. lifting and carrying heavy objects, running, walking long distances and on different surfaces, and climbing stairs, were rated as severe-to-complete difficulty by 27% to 54%. Few perceived difficulties in the domain community, social and civic life. Figure 8 presents percentages of perceived difficulties in the top-seven of rated activity and participation categories. (Study I)

Activity limitations in manual dexterity, mobility including walking, and ADL, as well as participation restrictions in social and lifestyle activities were identified (Table 8). One person was unable to perform the NHPT and six the 6MWT due to their physical condition, i.e. muscular impairment. (Study II)

Table 8. Results from measures of activities and participation (Study II).

	n	median (IQR)	n (%)
Nine-hole peg test, s			
right hand	69	22 (20-29)	
activity limitation, right hand			52 (75)
left hand	68	23 (21-31)	
Six-minute-walk test, m	64	465 (371-575)	
activity limitation			49 (77)
Rivermead mobility index, (score: 0-15)	70	14 (13-15)	
dependent			52 (74)
Katz personal ADL index, (score: 0-5)	70	5 (5-5)	
dependent			11 (16)
Katz instrumental ADL index, (score: 0-4)	70	4 (1-4)	
dependent			27 (39)
Frenchay activities index, (score: 0-45)	69	26 (19-32)	
below-norm			36 (52)

Persons with mild muscular impairment perceived less activity and participation difficulties than those with severe muscular impairment, and significant differences were found in 25 activity and participation categories (in the domains mobility, self-care and domestic life) from the modified ICF checklist, ($p \leq 0.001$). There was also a significant difference in total number of activity and participation limitations/restrictions per person between those with mild muscular impairment, median value 3, IQR 1-9 and those with severe, median value 19, IQR 12-29 ($p<0.001$). (Study I)

Persons with mild muscular impairment performed better in tests and questionnaires than those with severe, and significant differences were found in manual dexterity (NHPT), walking capacity (6MWT), mobility (RMI) and ADL (Katz P-ADL and I-ADL) ($p \leq 0.001$). (Study II)

Manual dexterity (NHPT) and walking capacity (6MWT) results for persons categorised as independent or dependent in Katz P- and I-ADL, and as within- or below-norm participation in FAI, are presented in Figure 9. For sensitivity and specificity of the proposed cut-off values, and AUC with 95% CI, see Table 9. The cut-off values in the NHPT were 0.26 pegs/s (test time 35 s) for association with independence in Katz P-ADL, and 0.40 pegs/s (test time 22 s) for association with independence in Katz I-ADL and within-norm participation in FAI. Corresponding cut-off values in the 6MWT were 246 m, 374 m and 486 m. (Study II)

Table 9. Proposed cut-off values in manual dexterity (pegs/s) and walking capacity (m) for independence in personal and instrumental ADL (Katz P-ADL and I-ADL), and within-norm participation in social and lifestyle activities (FAI). Presented also are corresponding sensitivity and specificity values, and area under curve (AUC) with 95% confidence interval (95% CI). (Study II)

	Nine-hole peg test, pegs/s		
	Katz P-ADL	Katz I-ADL	FAI
Cut-off value	0.26	0.40	0.40
Sensitivity	93 %	77 %	70 %
Specificity	82 %	89 %	64 %
AUC (95% CI)	0.94 (0.87-1.00)	0.88 (0.79-0.96)	0.69 (0.57-0.82)

	Six-minute-walk test, m		
	Katz P-ADL	Katz I-ADL	FAI
Cut-off value	246	374	486
Sensitivity	93 %	91 %	61 %
Specificity	100 %	70 %	75 %
AUC (95% CI)	0.98 (0.95-1.00)	0.86 (0.76-0.96)	0.76 (0.64-0.87)

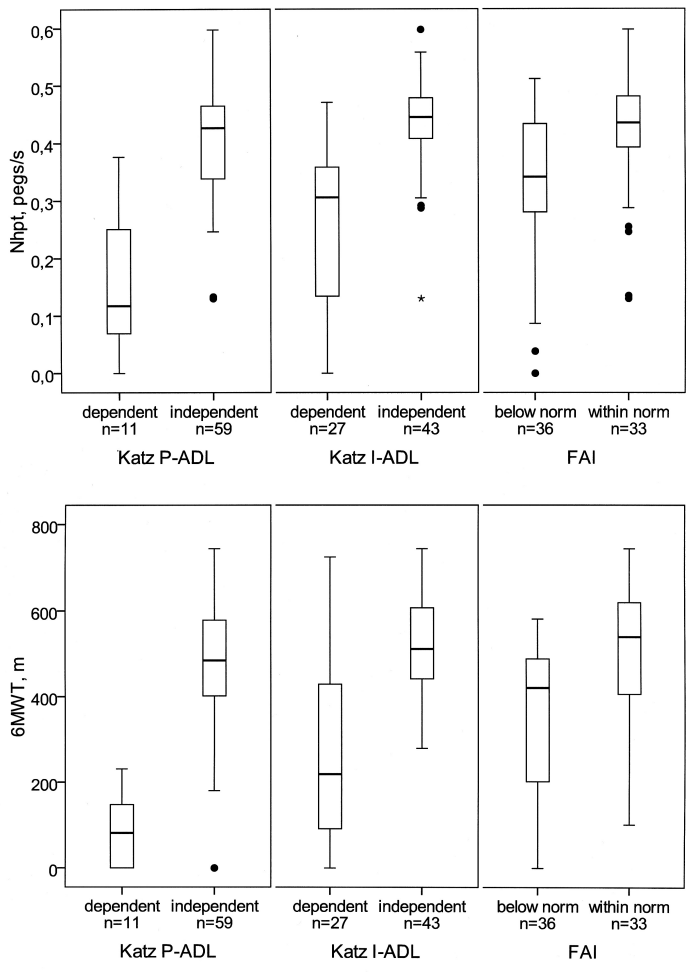

Figure 9. Boxplots of NHPT and 6MWT results for persons categorised as independent or dependent in Katz P- and I-ADL, and as within- or below-norm participation in FAI. The bottom of the box indicates the 25th percentile and the top the 75th percentile. The dark line in the box represents the median. T-bars extend to minimum or maximum value that is not outlier (otherwise to 1.5 times height of box). Outliers (●) are values more than 1.5 times the height of the boxes and extreme outliers (*) are values more than three times the height of the boxes.

4.3 CONTEXTUAL FACTORS (STUDIES I, II)

4.3.1 Environmental factors

Information concerning environmental factors, such as medicines, aids, home adaptations and assistance, collected by structured interviews is presented in Table 6. (Studies I, II)

Twenty percent or more of the persons with DM1 perceived nine of the 23 environmental factors from the ICF checklist as facilitators. Support from the immediate family, medicines, social-security services and aids for personal use in daily living were reported as facilitators by 50-60%. Further, 39% rated support from the immediate family, 37% transport services, 29% medicines and 29% social-security services as a substantial or complete facilitator. None of the 70 persons with DM1 used the barrier qualifiers when rating the 23 environmental factors. Figure 8 presents percentages of perceived facilitators in the top-seven of rated environmental-factor categories. (Study I)

Persons regarded as having disability within a body-function or activity-and-participation domain often rated an environmental domain as facilitating. If expressed as a percentage of the number of persons with disability, between 60% and 100% had rated one or more of the following environmental factor domains as being a facilitator: products and technology, support and relationships, and services, systems and policies. (Study I)

Twenty-one of the 26 persons who reported prescribed CNS stimulants against excessive daytime sleepiness rated medicines as a facilitator. Further, 33 of 38 who had ADL aids, 14 of 20 who had orthotic aids, all 25 who had mobility aids, 20 of 31 who had home adaptations, and 17 of 18 person who had personal care assistance, rated these environmental factors as facilitators. (Study I)

4.3.2 Personal factors

Information concerning personal factors, such as participant characteristics, disease-related and sociodemographic data, collected in structured interviews is presented in Table 3. (Studies I, II)

Overweight was found in 30 persons and 27 had a waist circumference indicative of a substantially increased risk of metabolic complications. Over 60% reported low physical activity levels during summer and winter, and approximately 30% were physically active at least at a moderate level according to the physical activity scale. Persons classified as having severe muscular impairment were less active at this level than persons with mild muscular impairment, especially during summer (four with severe muscular impairment compared to 19 with mild, $p=0.001$). (Study II)

4.4 RELIABILITY AND FEASIBILITY (STUDY III)

4.4.1 Reliability part

Each person's 6MWT distances from the three trials on the two occasions are presented in Figure 10. The two-way repeated measures ANOVA with two within factors (occasion and trial) analyses showed no interaction effect between occasions and trials. There was, however, a systematic difference between occasions (p=0.014), but not between trials (p=0.09). The individual's best trial, that with the longest walked distance, differed between persons and occasions. Therefore, data from the best of the three trials and from the better of the first two trials for each person from both occasions were analysed. There was no systematic difference between occasions when used data came from the best trial (p=0.11) or from the better of the first two (p=0.15). The mean difference was 7 metres, with a 95% confidence interval (CI) of ± 10 metres, and an SD of the differences of 16 metres, with data for the better of the first two trials from each occasion. Using this data, relative reliability was high, with $ICC_{2.1}$=0.99 (95% CI 0.97-1.0). Further, absolute reliability values were low: SEM 12 metres, repeatability coefficient 33metres, and coefficients of variation 2% and 6% for SEM% and repeatability%, respectively.

There was a small, but significant, increase in Borg RPE scores of perceived exertion between trials on both occasions (p<0.05). The median scores increased from 14 to 15 and from 13 to 15 on occasions one and two, respectively. Perceived shortness of breath increased significantly between trials on the first occasion, from a median Borg CR 10 score of 4 to 5 (p=0.009).

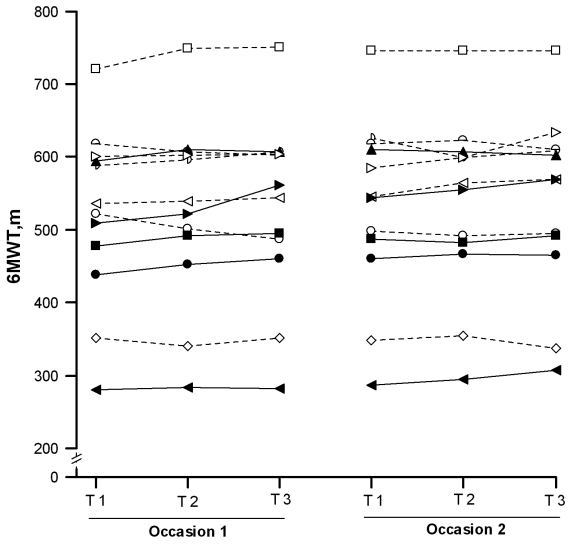

Figure 10. Each person's walking distance on the three trials on the two occasions, n=12.

4.4.2 Feasibility part

All but 12 of 64 persons performed two 6MWT trials in the feasibility part of Study III. The mean walking distance was 501 metres, SD 132 metres, and the individual walking distance varied from 193 to 744 metres. The most common stated reasons for inability to perform the second trial were "feeling too tired" or "lack of energy". Nine of the 12 persons were classified as MIRS 5, i.e. had severe proximal weakness.

4.5 EXERCISE INTERVENTION (STUDY IV)

There were no significant differences in mean 6MWT distance, TST time or TUG time within or between the training group and the control group, nor any interaction effects according to the linear, mixed-model, repeated-measurement analysis. Figure 11 presents 6MWT distances from tests before and after the exercise intervention for training-group participants with acceptable adherence, i.e. at least 75% attendance, and low attendance; and for the control group. Six persons in the training group and two in the control group increased their 6MWT distance by ≥ 6%, while a decrease ≥ 6% was found in three persons in each group. Data from tests collected before and after the exercise intervention are presented in Table 10.

Between-group analyses after the exercise intervention showed no significant differences in excessive daytime sleepiness or HRQoL, except for the MH subscale in favour of the control group (p=0.041). Within-group analyses showed no significant differences in excessive daytime sleepiness or HRQoL, except for a decrease in the vitality subscale in the control group (p=0.027). Data from questionnaires collected before and after the exercise intervention are presented in Table 11.

Table 10. Data from tests before and after the exercise intervention.

	Training group, n=18			**Control group, n=17**		
	mean	SD	min-max	mean	SD	min-max
Six-minute-walk test, m						
before	527	103	398-752	507	100	276-665
after	536	116	363-783	505*	119	173-630
Timed-stands test, s						
before	23.8	6.6	9.9-39.1	22.7	6.7	14.7-36.1
after	23.2	7.2	8.5-36.3	23.1*	9.9	12.5-50.8
Timed up-and-go test, s						
before	7.9	2.2	4.0-12.3	7.1	1.5	4.8-10.2
after	7.4	2.2	4.2-13.0	7.1*	1.9	5.1-12.4

*n= 16

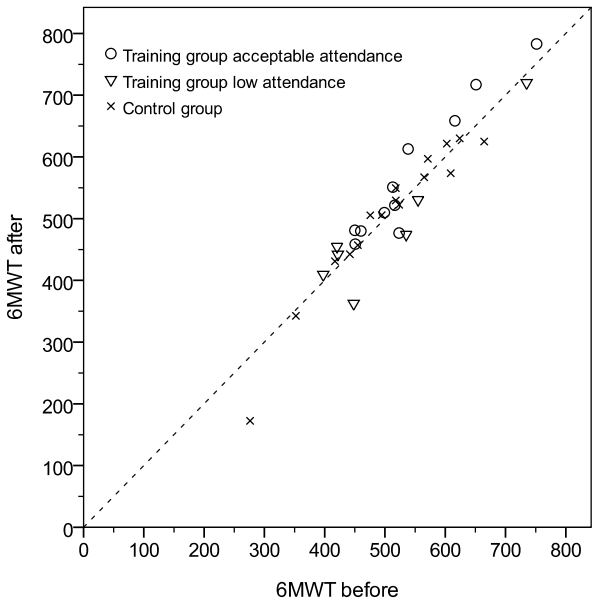

Figure 11. The 6MWT distance from tests before and after intervention, (training group acceptable attendance n=11, training group low attendance n=7, control group n=16).

Eleven of 18 persons in the training group had acceptable adherence to the Open Doors programme, i.e. attended at least 21 of requested 28 sessions, and another three participated between 15 and 17 times. According to the exercise diaries, eight persons took an additional 30-minute weekly walk in at least 11 of 14 weeks. The median time was 32 (IQR 20-44) minutes per session at a heart rate above or equal to 60% of calculated maximum, according to pooled data from 16 persons' heart-rate recordings during training sessions. Analyses of 48h ECG recordings revealed that one person had periods of atrial arrhythmia, however not during or in connection with the training. This person was assessed by a cardiologist, received medical treatment and was allowed to complete the study. No other adverse effects were reported. Exercise self-efficacy scores in the training group correlated positively with attendance, non-significantly before the intervention (r_s=0.38, p=0.117) and significantly after (r_s=0.75, p<0.001).

The training programme was labelled as "good" or "very good" by 16 of the 18 persons in the training group, and 17 could recommend this form of physical exercise for others with the same disease. The intensity was perceived as sufficient by 13, but too strenuous by four persons with proximal muscle impairment, MIRS 4-5. One person reported deterioration in muscle strength, and another perceived a worsening in daytime sleepiness. Improvements in fitness, muscle strength, flexibility and excessive daytime sleepiness were reported by 14, seven, 10 and eight persons, respectively.

Table 11. Data from questionnaires before and after the exercise intervention.

	Training group, n=18			Control group, n=17		
	median	IQR	min-max	median	IQR	min-max
Epworth sleepiness scale (score 0-24)						
before	12	8-15	4-18	8	4-13	1-18
after	12	8-16	2-19	9	6-14	0-21
SF-36 health survey (score: 0-100)						
Physical functioning (PF)						
before	63	48-76	10-95	65	40-90	15-95
after	60	45-84	20-95	60	48-70	20-95
Role physical (RP)						
before	50	0-100	0-100	75	38-100	0-100
after	50	25-100	0-100	100	13-100	0-100
Bodily pain (BP)						
before	73	39-85	20-100	74	41-100	31-100
after	62	41-88	12-100	62	41-92	31-100
General health (GH)						
before	54	34-73	10-87	62	38-72	10-92
after	52	20-68	10-82	65	34-75	10-90
Vitality (VT)						
before	55	39-61	5-80	55	40-68	5-90
after	45	39-58	10-75	40	25-63	5-80
Social functioning (SF)						
before	94	72-100	25-100	88	69-100	50-100
after	75	59-100	0-100	88	63-100	38-100
Role emotional (RE)						
before	67	33-100	0-100	100	67-100	0-100
after	100	58-100	0-100	100	67-100	0-100
Mental health (MH)						
before	80	68-89	44-100	72	66-92	48-96
after	72	67-85	40-92	84	80-92	36-100
Exercise self-efficacy scale (score: 6-60)						
before	35	23-44	10-51	25	21-35	8-49
after	30	21-42	11-49	31	20-34	13-44

5 DISCUSSION

5.1 MAIN FINDINGS

Functioning and disability in adults with DM1 were explored. Measures used included the modified ICF checklist and examinations, tests and questionnaires. Common problems and difficulties, and important environmental facilitators of functioning were described. That a wide variety of body-function impairments and activity limitations, and some participation restrictions were found underlines the multi-systemic nature of the disease and the vast impact it has on health. The individual's concurrent, i.e. total number of, impairments, limitations and/or restrictions was high and differed with regard to stage of disease progression. Persons with severe muscular impairment had more impairments and limitations/restrictions than did those with mild muscular impairment.

The 6MWT was a feasible and reliable outcome measure. Relative reliability, i.e. the ability to differentiate among persons tested, was high as was absolute reliability, i.e. the measurement error was low. Limits for the smallest differences to indicate a real change were suggested. The better of two possible trials on each test occasion was identified to be recommended for use as test result.

The comprehensive group exercise training programme, the Friskis&Svettis® Open Doors programme, was feasible for our adults with DM1 classified as MIRS grade 2-4. The programme was well tolerated and no detrimental effects were shown. Intention-to-treat analyses revealed no harmful or evidently beneficial effects. Many participants in the training group experienced subjective improvements and could recommend this form of physical exercise to others with the same disease.

5.2 FUNCTIONING, DISABILITY AND CONTEXTUAL FACTORS (STUDIES I, II)

Few of the studies on functioning and disability in DM1 describe contextual factors and also give a comprehensive view of concurrent body-function impairments, activity limitations and participation restrictions in the same sample of adults. Some shortcomings of previous reports are the lack of a genetically confirmed DM1 diagnosis and that persons with other muscular dystrophies are included [94, 132-133, 136, 146, 289-290]. Other report mainly activity limitations and participation restrictions [130, 139].

The persons with DM1 included in Studies I and II formed a heterogeneous sample concerning age, onset-forms and stages of disease progression, and this was reflected in the results. Some had multiple body-function impairments, activity limitations and participation restrictions, whereas others were practically unaffected by the disease. That a majority managed their daily activities and few perceived participation restrictions might seem remarkable, and it can be discussed whether this reflected the self-rating procedures and/or other factors. From self-rating you get the individual's opinion or experience on the matter. This might not agree with, for example, a physiotherapist's point-of-view. Further, living with a slowly progressive disease such as DM1 is a process of constant change and adjustment. Part of the adaptation process to a chronic disease consists of coping and a response-shift phenomenon. The response

shift includes a change in internal standards (recalibration), values (reprioritization) and conceptualization (re-conceptualization) [291-292]: changing the way you think about things and adapting expectations, goals and ambitions to the current situation. That few participants in Study I reported difficulties in self-care activities when the modified ICF checklist was used might, consequently, be due to a response shift. The results can also be explained by the fact that performance, and not capacity, was rated. In the ICF, performance indicates what a person does in his or her current environment, with assistive devices if needed. Approximately half of the participants reported that they had ADL- and mobility aids, and home adaptations. The influence of these environmental factors was however unclear, since they were not rated as facilitators or barriers in relation to the activity and participation categories. The use of devices and tricks, as well as a high degree of satisfaction with self-care activities, is on the other hand also reported by others [130-131].

Environmental factors play a central role for the understanding of a person's functioning or disability [293]. As stated in the ICF, disability is not a feature of the individual, but rather the result of the interaction between the person with a disease/disorder and the environment [38]. That environmental factors are important for activity and participation is shown in various cohorts, including neurological and neuromuscular disorders [130-131, 294-295]. That none of the participants in Study I reported any environmental barriers was surprising and in contrast to the findings of Gagnon and co-workers [139] who report barriers to participation only. This disparity might be attributable to differences in assessment methods and to differences between countries concerning the provision of aids, assistance, and government services. A majority of the persons with disability in Study I rated environmental factors as facilitators, and this indicates that they had access to physical and social environmental support.

It is interesting that so few in Study I perceived difficulties in recreation and leisure activities. This is in contrast to Gagnon's and co-workers' [130] report that about a quarter of their DM1 study sample had participation restrictions. They consider participation in a domain to be disrupted if a person accomplishes it with difficulty and/or needs help. The participants in Study I rated if they perceived difficulty in becoming involved in the activities they wanted or chose to do. Thus, the discrepancy might be due to different assessment methods, to difficulties in addressing the role of participants' choices and preferences in ratings, and/or a response shift as outlined above. Such differences might also explain why approximately half the persons with DM1 were classified as having participation restrictions in social and lifestyle activities, i.e. scored below norm FAI (Study II), although hardly any perceived restrictions when interviewed with the modified ICF checklist (Study I). Perhaps the FAI can be seen as an "objective" assessment related to frequency or duration, whereas the modified ICF checklist was a "subjective" assessment evaluating the importance of and the satisfaction with participation in the activities. Reports of satisfaction with recreation and leisure activities are, on the other hand, contradictory: low satisfaction is observed by Gagnon and co-workers [130] whereas Nätterlund and Ahlström [131] conclude that people with muscular dystrophy are satisfied since few wish for an improved situation.

That few participated in social and lifestyle activities while experiencing no participation restrictions might also be explained by the cognitive impairments and personality disorders known to be present in DM1. Examples of such are reduced executive functions, apathy, lack of initiative, indifference to a constrained life situation, avoidance behaviour and difficulties in social interplay [5, 33, 78]. Evaluations of cognitive functions and personal factors such as coping would have been valuable, but were beyond the present scope.

Limitations were found in physically demanding mobility and domestic-life activities, and activity limitations were related to muscle impairment. This was expected, and in line with findings in other studies [130-133, 136, 146, 290]. That few performed within normal range in the walking capacity test might be attributed to the distal foot-muscles weakness present already in the early stage of the disease and to the proximal lower-limb muscle weakness common in later stages. Muscle strength is associated with walking ability in various neurological disorders [296-298], and with balance control and risk of falls in neuromuscular disease [134, 299-300]. Although muscle strength training has positive effects on gait function in other neurological disorders [301-303], this has not been reported in DM1. Some improvements in gait and balance function are, however, reported in the 20 persons with DM1 who participated in a rehabilitation programme incorporating strength training [151].

That muscle weakness is present in DM1 is well documented [122, 124-125, 304], and so far few authors report muscle-strength improvements after strength training [186, 188]. The effect of strength training might, however, depend on initial muscle strength; if it is below 15% of normal, improvements are unlikely [305]. A recent Cochrane review concludes that moderate-intensity strength training in DM1 is not harmful, but there is not enough evidence to state that it offers beneficial effects [182]. Highlighted also is the need for more well-designed research on strength- and comprehensive aerobic exercise training. Exercise programmes might prevent additional disuse muscle atrophy and de-conditioning in people with DM1, and thereby reduce the risk of secondary chronic conditions. Overweight, a waist circumference indicating a high risk of metabolic complications, and low physical activity levels were present in one-third of all participants in Study II, and approximately half of those with severe muscular impairment. This gave indications that these persons were at risk and might benefit from participation in an exercise programme, which was later evaluated in Study IV.

There is no cure for DM1, thus the aim of treatment is to relieve impairments, reduce limitations and optimise participation. Finding factors related to activity and participation is therefore important, so that those at risk of limitations and restrictions can be identified. This gives an opportunity for early interventions. Specific threshold or cut-off values in hand function and mobility associated with functioning may therefore be valuable and useful for occupational therapists and physiotherapists in clinical practice. In Study II, such values were proposed, i.e. cut-offs associated with independence in measures of P- and I-ADL, and within-norm participation in social and lifestyle activities according to the FAI. These values might be used to identify persons risking activity limitation and participation restrictions, and also those with adequate functioning, who might not need interventions. The cut-offs can also serve as “red

flags", indicating that persons below or near these values should be surveyed more closely concerning activities and participation.

Fatigue and sleepiness are said to be two different, but interrelated, complex phenomena [306], and in DM1 are reportedly present both jointly and singly [63]. Over two-thirds reported that they had problems of excessive daytime sleepiness and fatigue (Study I), but fewer were classified as having impairments when the ESS and FSS, two standardized questionnaires, were used for assessment (Study II). The difference was especially large between perceived and classified occurrence of daytime sleepiness, 80% versus 28%. This illustrates, once more, that what is captured certainly differs depending on the measure used for assessment. This might explain why no cases of depression were identified in Study II (the HAD questionnaire), when one-third in another Swedish DM1 sample had signs of clinical depression on the Beck Depression Inventory questionnaire [82]. Excessive daytime sleepiness is reportedly associated with depression in DM1 [63, 307]. The current recommendations for treatment of depression include physical activity and exercise as important parts [170]. That low physical activity levels are associated with fatigue in neuromuscular disease [67, 308], and with daytime sleepiness in e.g. older adults [309] and sleep apnoea patients [310], implies that physical exercise programmes might be a non-pharmacological approach worth considering for these impairments.

Although cardiac and respiratory impairments were identified in approximately 40% by ECG and spirometry assessments (Study II), few participants perceived problems in these functions when the modified ICF checklist was used (Study I). This indicates that they were unaware of their impaired functions. Since both cardiac and respiratory impairments are known causes of mortality in DM1, patient education on warning signs, e.g. syncope, dizziness, palpitations and recurrent chest infections, should be emphasized. Whether chest physiotherapy and respiratory exercises can improve respiratory function in DM1 is uncertain. Two small studies report short-term effects of improved oxygen saturation [311-312], but there is so far no strong evidence to support various respiratory therapies in neuromuscular disease [313].

In the present work functioning and disability were explored with regard to different stages of DM1, and the MIRS [118, 204] was used to categorize participants into two groups depending on degree of muscular impairment: MIRS grades 1-3 for mild muscular impairment and MIRS grades 4-5 for severe. It was no surprise that significant between-group differences were found in tests and questionnaire reflecting functions where muscle strength is important. More interesting was the lack of significant differences in cardiac and respiratory functions, and in excessive daytime sleepiness and fatigue. This result is in line with others' findings [65, 70, 96, 99] and has implications for assessment and management in clinical practice. Consequently, these functions should be monitored regardless of the degree of muscular impairment.

There was a lack of significant differences between the groups in ratings of myotonia and pain when the modified ICF checklist was used. That myotonia was rated as a problem by approximately two-thirds in Study I contrasts to the notion that it is a problem of less extent occurring mostly in mildly affected persons [5]. That pain, and even severe pain, was so frequent in participants regardless to stages of the disease

stage, was somewhat unexpected. On the other hand, pain is currently recognized as a common problem in people with neuromuscular disease [90-91] and the causes are said to depend on type of disease and level of muscle impairment and mobility [314]. The causes and management of pain in DM1 have, however, not been studied in detail, and there is a need for additional research.

The individual's total number of body-function impairments, activity limitations and participation restrictions was high, especially in those with severe stages of the disease. This implies that a multi-professional approach is needed for optimal care. Special centres exist for adults with neuromuscular disease in some parts of Sweden, for example Gothenburg, but there may be a lack of appropriate health-care services for persons with DM1 elsewhere in Sweden. It would therefore be valuable if national guidelines on the standard of care were to be formulated and implemented for people with DM1.

5.3 RELIABILITY AND FEASIBILITY (STUDY III)

The performance of many repeated trials of the 6MWT on one test occasion is not desirable in the clinic or in research. The findings in Study III, that two trials were sufficient, and that the trial with the longest walking distance should be used as the test result, are therefore of significant value. Many studies report that practice trials are needed to get reliable test results [205, 254-255, 315], and a practice trial should be considered according to the ATS guidelines for the 6MWT [256]. Despite the small study sample in Study III, relative reliability tallied with findings in other neurological disorders, where ICC coefficients range from 0.96 to 0.99 [251-252, 260-261]. Absolute reliability results were used to describe the minimal amount of change that was not due to variation in the measure, and thus might indicate a real change for an individual or a group of persons with DM1. Both SEM and repeatability% values were a bit lower than in other neurological disorders where SEM varies from 19 to 31 metres and repeatability% from 13% to 20% [251-252, 260-261]. This might be due to the lack of practice trials [251-252, 260-261] and standardized encouragement [251] in the other studies. The present Study III findings suggest that a difference of 33 metres or 6% might indicate a real change for an individual with DM1.

The 6MWT was feasible in DM1: the test was easy to administer and score, took little time, the cost was low, it was considered safe, and all those able to walk could perform it. However, nine persons classified as MIRS 5, i.e. having severe muscular impairment, felt too tired or lacked the energy to perform two trials on the same occasion. This important finding suggests that persons with severe proximal weakness need sufficient rest between trials, or perhaps should be tested on different occasions.

5.4 EXERCISE INTERVENTION (STUDY IV)

Evidence-based recommendations regarding physical exercise in DM1 must be based on knowledge of feasibility and the effects of various exercise programmes. Study IV therefore addressed these aspects by evaluating a comprehensive group exercise training programme, the Friskis&Svettis® Open Doors programme. That many characterised the training programme as "very good", would recommend it to others with DM1, and reported subjective changes for the better in fitness, strength, flexibility

and excessive daytime sleepiness indicate that this type of exercise regime may be appropriate. The aim and advantage of the programme were that participants could adapt exercises and intensity to their own level of physical capability and capacity. This might explain why participants with such varied muscular impairment, i.e. MIRS grades 2 to 4, rated the intensity level as sufficient. Four persons with proximal weakness, however, found the programme too strenuous. Two of these had severe proximal weakness and participated in one and three sessions, respectively. Although the reason for their low attendance is not known, it can be speculated that the ambition of individualising the group training programme was not fulfilled, and that there might be a need for either special introductions or groups for persons classified as MIRS grade 5.

To improve exercise adherence in Study IV, a number of strategies were applied such as positive reinforcement, exercise diaries and regular contact with participants for feed-back. These were the same as some of the reported strategies that enhance exercise adherence in adults with chronic musculoskeletal pain [316]. However, the time and place for the group exercise training sessions might have hampered adherence, since it was not possible to have evening classes or to use other locations than the hospital. Adherence is a possible threat to the validity and efficacy of any exercise intervention study. This is especially true in DM1, where cognitive and behavioural problems, such as lack of motivation and initiative, fatigue and avoidance behaviour, are common aspects of the disorder [33, 78]. Adherence is better in supervised group training than in home-based training [191-192], and supervised training is therefore recommended [186, 317]. Thus, it was not surprising to find better adherence with the Open Doors classes than with the requested additional weekly walks. The most common reason for not attending classes was illness, and the overall impression was that the motivation level for group training was high. A benefit of group training, besides being cost-effective, was the opportunity for the participants to meet others with the same disease. This is recognised as important for persons with muscular dystrophies [191, 318]. At the same time, meeting persons with worse symptoms, and perhaps then realising the possible course of the disease, can also be bothersome. This might have been the reason for the low attendance of a newly-diagnosed person with few symptoms of the disease. However, most participants in the training group seemed to appreciate the access to social support. Social support, in the shape of social persuasion and comparison, also influences self-efficacy beliefs, which operate as important personal determinants of human behaviour [319-320].

Self-efficacy refers to a person's confidence and beliefs about his or her capability to organize and execute the actions required to attain a wide range of goals [321]. These beliefs are influenced by previous experience, observation of successful or unsuccessful attainment by others, persuasion by others, and by how associated experience, i.e. somatic and emotional states, are interpreted [321]. Self-efficacy correlates with participation in physical activity, and is a determinant of exercise adherence and exercise behaviour in adults [282, 322-324], and a predictor of exercise adoption [322]. Self-efficacy beliefs should be assessed against gradations of challenges or barriers to successful performance [321]. In Study IV, the persons' exercise self-efficacy beliefs were evaluated by assessing their confidence in performing an exercise programme despite potential barriers such as work schedule, physical fatigue, boredom related to exercise,

minor injuries, other time demands, and family and home responsibilities. The pattern of change in exercise self-efficacy scores differed between the two groups. Whereas the median score increased in the control group, a decrease was found for the training group. That a high positive correlation was found between attendance and exercise self-efficacy scores rated after the intervention in the training group indicates that they changed their beliefs over time. Perhaps participants in the training group became more aware of their abilities to engage in exercise under varying conditions. Further, their self-efficacy beliefs at that point were influenced by the experience of the exercise intervention, and this might have made their assessments more realistic. It is important to examine exercise self-efficacy in conjunction with other personal and environmental variables to identify persons likely to adhere to exercise programmes, and to identify potential barriers. Recently, such barriers to and constraints on exercise and physical activity have been reported for neuromuscular disease [176], and for long-term neurological conditions [320]. Lack of energy and motivation, pain, feeling self-conscious at leisure centre/gym, and economics, are specific barriers to exercise in persons with neuromuscular disease [176]. Low exercise self-efficacy beliefs, lack of supporting physical environment and lack of support and understanding from the social environment are factors that limit engagement in physical activity for people with long-term neurological conditions [320].

That the Friskis&Svettis® Open Doors programme included endurance, strength, flexibility and balance components indicates that it was a well-rounded physical activity programme. This is in line with what is recommended for general health and well-being in older adults with chronic disease, and for those with low physical activity levels [325]. Important factors for producing training effects are frequency, intensity and duration of exercise [172]. The necessary overload stimulus is provided by a combination of these factors, and the higher the stimulus the higher the training effect, and vice versa. To reach the recommended volume and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness [172, 326], participants in the training group were asked to attend the Open Doors classes twice a week and to take at least one 30-minute brisk walk every week. The intensity during the aerobic parts of the programme was targeted to be at least moderate, 60-80% of maximal heart rate, and pooled data from heart-rate recordings indicates that the desired intensity was achieved. It can, however, be argued that both frequency and intensity were too low to generate training effects. At the same time, the aim was to study feasibility and effects of a programme that would apply in the real world, and reflect a frequency level that persons with DM1 could incorporate and maintain in their daily lives. Further, the achieved intensity was really up to the participant, even if the music and the group-leader guided and encouraged participants to work up to the intended intensity in the various parts of the training programme.

No adverse events were reported during the study. However, the 48h ECG examinations revealed that one person had periods of atrial arrhythmia, although not connected to the training sessions. This implies the importance of thorough cardiac examinations, and that both conventional and 48h ECG monitoring should be performed regularly. Important findings were, however, that no negative cardiological effects were found, and that the training programme seemed to be well tolerated.

Despite a significant between-group difference in the SF-36 mental health subscale, no significant within-group differences were found. The mental health subscale is, however, bipolar, any value above 50 indicating absence of psychosocial disability. The clinical value of the difference was therefore uncertain. The observed changes in subscale scores were not interpreted as an effect of the exercise intervention. The lack of other statistically significant differences does not *per se* mean that there were no effects, but merely that an effect of zero cannot be ruled out [327]. Even if significant differences were to be found, this is not the same as clinically important or relevant differences. There are no exact rules for how to decide what makes a difference clinically important. It is arguably what clinicians and/or patients judge as clinically important. Sometimes such judgements are based on knowledge of an outcome measure's clinometric property. Based on the results in Study III, a difference equal to or over 6% in 6MWT distance was chosen to indicate a real change for an individual with DM1. Using this cut-off six persons, of whom five had at least 75% attendance, increased their walking distance in the training group compared to two controls. Although no sub-group analyses have been performed, a possible dose-response relationship might explain some of our results.

It is essential to evaluate exercise regimes that are available outside the health care system. With limited resources, it is not possible or even desirable that all persons with DM1 perform their physical exercise at a physiotherapy clinic. Study IV is therefore unique, as it evaluated the feasibility and effects of a comprehensive group exercise programme that is available at many local Friskis&Svettis® sport associations in Sweden. The group exercise training programme seemed to be well tolerated, although some persons with proximal muscle impairment found it too strenuous. However, barriers such as costs and feeling self-conscious in leisure centres or gyms, are identified constraints to exercise in persons with neuromuscular disease [176], implying that it might be difficult for some persons with DM1 to participate in exercise regimes outside the health care system. That persons with mild muscular impairment can be recommended exercise regimes such as the Friskis&Svettis® Open Doors programme is an experience from the exercise intervention. However, it might be better for persons with severe muscular impairment to perform physical exercise within a health-care setting.

5.5 METHODOLOGICAL CONSIDERATIONS

5.5.1 Study sample

Although there is no neuromuscular centre in the Stockholm County Council area, many persons with DM1 have contact with neurologists at the Karolinska University Hospital. A majority of the present participants were identified from the outpatient clinics at this hospital's Department of Neurology. With an estimated prevalence of 10 per 100 000, approximately 200 persons would be expected to be found in the Stockholm County Council area. Thus, many persons with DM1 living in the region did not participate. Whether these persons, or the persons who declined participation, differed significantly from the participants is not known. It can be speculated that persons who lack contact with a neurologist might be less affected by the disease, and that those declining participation might be either less or more severely affected. Drop-out analyses could, however, only be performed on the variables sex and age, due to the

ethical permission. The inclusion of persons with childhood or adult-onset forms resulted in a heterogeneous sample, which can be thought of as a shortcoming. Despite this, the study sample seemed representative of adults with DM1 in comparison with previously reports from Swedish and Canadian cohorts [130, 132, 136, 139, 146].The selection of participants in the reliability part of Study III was intentional: persons were selected to represent the different sexes, ages and stages of disease progression, which supports the idea that the findings may also be relevant for other adults with DM1, even though the study sample was small, only 12 persons.

A major problem in clinical trials of rare diseases is sample size and sample selection. Adults with DM1, also those with the childhood form, were eligible for Study IV in order to recruit as many participants as possible. However, only 35 of those fulfilling the criteria for participation were interested. This resulted in a heterogeneous group with respect to onset form and muscular impairment. This may be a shortcoming, but it reflects reality and the aim was to explore the feasibility of the Friskis&Svettis® Open Doors programme for the DM1 population. The consequence of this small and heterogeneous sample was an underpowered study. Multi-centre studies are therefore currently recommended for exercise intervention research on persons with physical and cognitive disability [328]. However, underpowered studies are not without value since their results can contribute to the larger body of evidence [329].

There is always a risk of selection bias in intervention studies, and especially in those involving physical activity and exercise. People who are willing to participate in exercise-related research are often younger and/or have a better functional level than the entire relevant population [328]. This might also be true for participants in Study IV. However, examples of reasons for declining were “already exercising”, “lack of time or interest”, implying that both physically active and inactive persons chose to not take part. The results from Study IV cannot, however, be extrapolated to the entire DM1 population, since this was not represented. However, the findings may be representative of persons with DM1 who have been screened for cardiac involvement, have distal-to-mild/moderate proximal muscle impairment and no severe cognitive impairment.

5.5.2 Design and procedures

Cross-sectional design studies contribute to research evidence by identifying the occurrence and severity of various health problems. This design was therefore chosen in Studies I and II to gather information on functioning, disability and contextual factors in adults with DM1. However, changes occurring over time cannot be captured with this design nor is it applicable to studying cause-effect relations. The test-retest design, with repeated trials on two occasions, used in Study III might seem unnecessarily complex. It was, however, applicable and adequate for its purpose since learning and/or fatigue effects, and the need for familiarisation trials were to be explored. To provide the most reliable and highest form of evidence for evidence-based practice, a randomized controlled trial (RCT) design was chosen for evaluating the feasibility and effects of the exercise intervention in Study IV. The RCT design is considered the gold standard for evaluating the effectiveness of interventions. Great care was taken to fulfil the criteria for a high quality RCT considering design, conduct,

and analysis; hence the guidelines from the CONSORT (Consolidated Standards of Reporting Trials) Statement [330] were applied for reporting in Study IV.

That the structured interviews and the standardized tests and questionnaires, in Studies I and II, were administered by the same person ensured that variations in outcomes were not likely to be caused by differences in administration. The data collected was, however, fairly extensive. This might have been tiring for the participants, even though evaluations were spread over two occasions, and the day and time were suited to their requests. Thus, it is possible that the large number measures influenced the results. Information and instructions were given, and procedures were performed, according to study-specific protocols in Studies I-IV. This shows that precautions were taken to ensure that any measured variability would not be due to bias caused by external factors such as the test situation and evaluators. The evaluators, two experienced physiotherapists, in Study IV were blinded to group allocation and had no further involvement in the study. The group training and the data collections were performed in different premises at the hospital (different buildings several blocks apart), so it was unlikely that the evaluators were aware of group allocation. Participants were also informed that they were not to reveal group affiliation at the evaluation after the exercise intervention period.

The lack of standardized outcome measures, evaluated concerning validity, reliability and responsiveness in the DM1 population, resulted in a selection of measures based on previous knowledge and experience, literature reviewing, and psychometric properties found in the general population and in people with other neurological disorders. This can be considered a limitation, but it is not unusual in studies in people with rare diseases. The tests and questionnaires were, however, well-known both in the clinical settings and in the research context. Both floor and ceiling effects were found among the chosen measure. Such effects are present when a high proportion of the study sample have the maximum or minimum score, respectively. It is suggested that these effects are present if more than 15% score the highest or lowest possible score [331]. Ceiling effects were for example found in the RMI, the Katz P- and I-ADL index. It can be argued that the TST and the Åstrand-Rhyming test had floor effects since many participants could not perform these tests.

As for the TST, quite a few of those classified as MIRS 4-5 had difficulties to rise and sit down 10 times in a row. A five-times sit-to-stand test is commonly used in elderly people and it has been suggested that it has the broadest application as a functional strength test [332-333]. This test has a predictive value for recurrent falls in community-living elderly people [334]. Given the impaired function present in DM1, this latter sit-to-stand test might be more appropriate, even though the normative reference values are for adults over 60 years of age [333].That excessive daytime sleepiness was possibly underestimated when the suggested ESS cut-off score of ≥11 was used, indicates that the validity of the scale might be questioned. Even though the scale is recommended as an outcome measure in DM1 [218], several authors point out that the ESS is not the most appropriate and sensitive measure to capture the phenomenon in DM1 [63, 68, 217, 335]. Assessment of grip strength is another recommended outcome measure in DM1 [218] and is reportedly useful for clinical trials [336]. The value of Jamar dynamometer assessments might however be of limited value if persons are as weak as many in Study II. Even

though the measurement error of the test is not known for people with DM1, it is reported to be 4.8 kg in healthy persons [241]. Hence, this method of grip strength assessment might not be sensitive enough for clinical trials. That many persons with DM1 were unable to perform the Åstrand-Rhyming test for reasons such as leg pain, perceived exhaustion and unpredictable heart rate recordings indicates that this test might not suitable for the whole DM1 population.

The FAI was used as a measure of participation in social and lifestyle activities. Whether this scale captures the dimension of participation can be questioned, as scoring is for most items based on the frequency with which the activities are carried out. However, these activities are such that they require involvement and initiative from the person. Participation is in the ICF defined as involvement in a life situation. Thus, it may be argued that FAI can be used for assessment of participation.

That self-rating procedures were applied when the modified ICF checklist and the questionnaires were used might be thought of as a shortcoming. Since mental functions such as intellectual, attention, memory, thought and higher-level cognitive functions were not explored, it is unknown whether all persons with DM1 in the present work had the prerequisites to understand all the questions. However, the individual's own perception should not be disregarded: it is significant and can assist in the development of health services. The overall impression was that most of the questionnaires worked even if the SF-36 had a rather complex language.

Although the ICF checklist was modified to capture information thought to be important for persons with DM1, possibly important categories of mental functions, such as intellectual and emotional functions, and of interpersonal interactions and relationships such as family and intimate relationships, were not assessed. At the same time redundant information was collected in the mobility and self-care domains. ICF core sets are shortlists of domains considered relevant for describing health conditions. Wynia and co-workers [337] propose 68 ICF items considered to be relevant for persons with neuromuscular disease. The modified ICF checklist comprised most of these items. Even if a DM1-specific core-set were developed, a barrier to its clinical use would be the ICF language. Experience from the data collection in Study I was that the ICF categories had to be expressed in everyday language to be understandable. Further, that some symptoms or terms used in the clinic do not really fit the ICF. For example there is no obvious ICF category for excessive daytime sleepiness and fatigue which in Study I were mapped to consciousness functions, and energy and drive functions, respectively. Nor is there a category for balance which might be said to come under the mobility domain, activity and participation component. It would therefore be a good idea to develop specific ICF assessment tools or to use the proposed linking rules [338] and "translate" existing outcome measures to ICF language. The ICF can, however, only be used to identify "what?" but not "how?" to measure.

The selection of primary outcome measure in Study IV was based on the assumption that it would mirror endurance and functional exercise capacity. Although the results from Study III showed that the 6MWT was feasible and reliable in DM1, there are issues to consider. The distance walked is determined by the walking speed. An increase in stride length and/or cadence will increase the walking speed and thereby the

walking distance. Crucial for accomplishing this is distal lower-limb muscle strength. Ankle dorsiflexion and plantar flexion strength correlate significantly with both walking speed and the rate of stumbles and falls in persons with DM1 [134]. Hence, a person with severe distal weakness might not be able to increase walking speed without stumbling and falling. Another aspect of the 6MWT is that motivation and cooperation are important for maximal performance. As lack of initiative and motivation, and apathetic attitudes can be features of DM1, special precautions may be needed when administering the tests. The evaluators therefore stressed that the participants were to seek their best possible performance. The order, instructions, and encouragement were, however, standardized according to a study protocol and the same on both data collection occasions, to avoid biasing the results. All participants understood and completed the tests, but it can be speculated that some might not have performed at their maximal level.

5.5.3 Statistical considerations

Descriptive statistics were employed in the present work to give an overview of functioning, disability and contextual factors. Non-parametric statistical methods were used predominately since the data level was mostly ordinal and the distribution skewed. Parametric statistical methods were, however, used for ratio-data fulfilling the requirements for such tests.

The classification of body-function impairments, activity limitations and participation restrictions from test and questionnaire results in Study II, was based on predicted age- and sex-normative values, which is important in between-group comparisons of variables known to be influenced by age and sex. The rationale for choosing the mean minus-or-plus 1 SD or the 25th percentile as cut-off was that most studies presenting normative values are based on rather small study samples, and if for example 2 SD had been chosen there would have been a risk of underestimating impairments/limitations/restrictions. The significance level was set to $p \leq 0.001$ in Studies I and II since so many analyses were performed and false significance was to be avoided (type I error).

An advantage of linear mixed-model repeated-measurement analysis is that the analysis can handle missing data. The only missing data in Study IV was test results from data collection after the exercise intervention for one person in the control group. That walking distance in the 6MWT, the primary outcome measure in Study IV, ranged from approximately 200 to 800 metres with a mean (SD) around 500 (100) metres is explained by the small and heterogeneous study sample. It is evident that a very large study group is needed if statistically significant differences are to be shown in a sample with such variable distribution. Thus, there is a risk of a type II error in Study IV, i.e. a risk of getting a false statistically non-significant difference between the control and training groups.

5.6 CONCLUSIONS AND CLINICAL IMPLICATIONS

Common body-function impairments, activity limitations and participation restrictions, and facilitators of functioning, were identified in adults with DM1 using various measures and methods. Excessive daytime sleepiness, muscle weakness and fatigue were common impairments and activity limitations were most frequently found in physically demanding mobility activities. Few reported participation restrictions. Support from the immediate family seemed to be the most important facilitator for functioning. The individual's total number of impairments, limitations and restrictions was high and there was a difference with regard to stages of disease progression. Persons with severe muscular impairment had more impairments and limitations/restrictions than did those with mild muscular impairment. Differences with regard to disease progression were found in various body-functions and activity and participation categories, mainly such that required muscle strength. Lack of differences with regard to disease progression was found in functions of the cardiovascular and respiratory systems, and mental functions (excessive daytime sleepiness and fatigue), implying that these functions should be monitored regardless of the degree of muscular impairment. The finding of a wide variety of body-function impairments and activity limitations underlines the multi-systemic nature of the disease and the vast impact it has on health. It further implies that a multi-professional approach is needed for optimal care. The information can be used for developing clinical practice and for health promotion for people with DM1.

The 6MWT was both feasible and reliable for use in adults with DM1. Recommended is a practice trial followed by a second trial on the same test occasion, and that the better of these two possible trials be used as test result. Persons with severe proximal weakness need, however, sufficient rest between trials. It is suggested that the minimal detectable difference for a change not due to measurement error be 33 metres or 6% for an individual with DM1.

A comprehensive group exercise training programme, the Friskis&Svettis® Open Doors programme, was feasible for adults with DM1 who had been screened for cardiac involvement, had distal or mild-to-moderate proximal muscle impairment and no severe cognitive impairments. The programme was well tolerated and no detrimental effects were found. Although intention-to-treat analyses revealed no evident beneficial effects, many participants in the training group perceived improvements and could recommend this form of physical exercise for others with the same disease.

5.7 FUTURE RESEARCH

There is a lack of standardized outcome measures evaluated in the DM1 population. Future studies are therefore needed to assess validity, reliability and responsiveness of existing measures and possibly also to develop new disease-specific measures.

The phenomena of fatigue and excessive daytime sleepiness are complex in DM1 and further studies are required to explore these concepts and to develop possible treatment strategies for people with DM1.

Pain is recognized as a frequent and common problem in people with neuromuscular disease, including DM1. Few studies describe factors and/or situations that might aggravate or lower the level of pain, and there is, accordingly, a need for additional research to improve the understanding and management of pain in DM1.

A major problem in clinical trials of rare diseases is sample size and sample selection. The small and heterogeneous study sample in the present work made it difficult to draw conclusions concerning the effects of the exercise intervention. Consequently, future studies on exercise regimes should be performed as multi-centre studies. National and even international cooperation and networking are therefore to be further developed. It would be interesting to explore facilitators for and barriers to physical exercise in people with DM1, to identify possible targets for interventions. Future studies are also needed to decide how exercise programmes should be designed for achieving optimal effect.

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7 REFERENCES

1. Emery AEH. The muscular dystrophies. The Lancet. 2002;359(9307):687-95.
2. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. J Neurol Neurosurg Psychiatry. 2010;81(4):358-67.
3. Batten FE, Gibb HP. Myotonia atrophica. Brain. 1909;32:187-205.
4. Steinert H. Myopathologische Beiträge 1. Über das klinische and anatomische Bild des Muskelschwunds der Myotoniker. Dtsch Z Nervenheilkd. 1909;37:58-104.
5. Harper PS. Myotonic dystrophy. 3rd ed. London: W.B. Saunders; 2001.
6. Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004.
7. Harper PS. Myotonic Dystrophy. Third ed. London: WB Saunders; 2001, p 350.
8. Hsiao KM, Chen SS, Li SY, Chiang SY, Lin HM, Pan H, et al. Epidemiological and genetic studies of myotonic dystrophy type 1 in Taiwan. Neuroepidemiology. 2003 Sep-Oct;22(5):283-9.
9. Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009 Nov;132(Pt 11):3175-86.
10. Ahlström G, Gunnarsson L-G, Leissner P, Sjödén P-O. Epidemiology of neuromuscular diseases, including the postpolio sequele, in a Swedish county. Neuroepidemiology. 1993;12(5):262-9.
11. Medica I, Markovic D, Peterlin B. Genetic epidemiology of myotonic dystrophy in Istria, Croatia. Acta Neurol Scand. 1997 Mar;95(3):164-6.
12. Rolander A, Floderus S. [Dystrophia myotonica in the Norbotten district.]. Sven Lakartidn. 1961 Mar 10;58:648-52.
13. Mathieu J, De Braekeleer M, Prevost C. Genealogical reconstruction of myotonic dystrophy in the Saguenay-Lac-Saint-Jean area (Quebec, Canada). Neurology. 1990 May;40(5):839-42.
14. Mathieu J, Allard P, Potvin L, Prevost C, Begin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology. 1999 May 12;52(8):1658-62.
15. de Die-Smulders CE, Howeler CJ, Thijs C, Mirandolle JF, Anten HB, Smeets HJ, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain. 1998 Aug;121 (Pt 8):1557-63.
16. Fu YH, Pizzuti A, Fenwick RG, Jr., King J, Rajnarayan S, Dunne PW, et al. An unstable triplet repeat in a gene related to myotonic muscular dystrophy. Science. 1992 Mar 6;255(5049):1256-8.
17. Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. Cell. 1992;69(2):385.
18. Wheeler TM, Thornton CA. Myotonic dystrophy: RNA-mediated muscle disease. Curr Opin Neurol. 2007 Oct;20(5):572-6.
19. Todd PK, Paulson HL. RNA-mediated neurodegeneration in repeat expansion disorders. Ann Neurol. 2010 Mar;67(3):291-300.
20. Martorell L, Monckton DG, Sanchez A, Lopez De Munain A, Baiget M. Frequency and stability of the myotonic dystrophy type 1 premutation. Neurology. 2001 Feb 13;56(3):328-35.
21. New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). The International Myotonic Dystrophy Consortium (IDMC). Neurology. 2000 Mar 28;54(6):1218-21.

22. Monckton DG, Ashiwa T. Molecular aspects of myotonic dystrophy: our current understanding. In: Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic Dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004. p. 14-36.

23. Ashizawa T, Dubel JR, Dunne PW, Dunne CJ, Fu YH, Pizzuti A, et al. Anticipation in myotonic dystrophy. II. Complex relationships between clinical findings and structure of the GCT repeat. Neurology. 1992 Oct;42(10):1877-83.

24. Martorell L, Monckton DG, Gamez J, Johnson KJ, Gich I, Lopez de Munain A, et al. Progression of somatic CTG repeat length heterogeneity in the blood cells of myotonic dystrophy patients. Hum Mol Genet. 1998 Feb;7(2):307-12.

25. Anvret M, Ahlberg G, Grandell U, Hedberg B, Johnson K, Edstrom L. Larger expansions of the CTG repeat in muscle compared to lymphocytes from patients with myotonic dystrophy. Hum Mol Genet. 1993;2(9):1397-400.

26. Wong LJ, Ashizawa T, Monckton DG, Caskey CT, Richards CS. Somatic heterogeneity of the CTG repeat in myotonic dystrophy is age and size dependent. Am J Hum Genet. 1995 Jan;56(1):114-22.

27. Ashizawa T, Dubel JR, Harati Y. Somatic instability of CTG repeat in myotonic dystrophy. Neurology. 1993 Dec;43(12):2674-8.

28. Warner JP, Barron LH, Goudie D, Kelly K, Dow D, Fitzpatrick DR, et al. A general method for the detection of large CAG repeat expansions by fluorescent PCR. J Med Genet. 1996 Dec;33(12):1022-6.

29. Hunter A, Tsilfidis C, Mettler G, Jacob P, Mahadevan M, Surh L, et al. The correlation of age of onset with CTG trinucleotide repeat amplification in myotonic dystrophy. J Med Genet. 1992 Nov;29(11):774-9.

30. Harley HG, Rundle SA, MacMillan JC, Myring J, Brook JD, Crow S, et al. Size of the unstable CTG repeat sequence in relation to phenotype and parental transmission in myotonic dystrophy. Am J Hum Genet. 1993 Jun;52(6):1164-74.

31. Koch MC, Grimm T, Harley HG, Harper PS. Genetic risks for children of women with myotonic dystrophy. Am J Hum Genet. 1991 Jun;48(6):1084-91.

32. de Die-Smulders C. Congenital and childhood-onset myotonic dystophy. In: Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University press; 2004. p. 162-75.

33. Meola G, Sansone V. Cerebral involvment in myotonic dystrophies. Muscle Nerve. 2007;36(3):294-306.

34. Douniol M, Jacquette A, Guile JM, Tanguy ML, Angeard N, Heron D, et al. Psychiatric and cognitive phenotype in children and adolescents with myotonic dystrophy. Eur Child Adolesc Psychiatry. 2009 Dec;18(12):705-15.

35. Ekstrom AB, Hakenas-Plate L, Samuelsson L, Tulinius M, Wentz E. Autism spectrum conditions in myotonic dystrophy type 1: a study on 57 individuals with congenital and childhood forms. Am J Med Genet B Neuropsychiatr Genet. 2008 Sep 5;147B(6):918-26.

36. Arsenault ME, Prevost C, Lescault A, Laberge C, Puymirat J, Mathieu J. Clinical characteristics of myotonic dystrophy type 1 patients with small CTG expansions. Neurology. 2006 Apr 25;66(8):1248-50.

37. Echenne B, Rideau A, Roubertie A, Sebire G, Rivier F, Lemieux B. Myotonic dystrophy type I in childhood Long-term evolution in patients surviving the neonatal period. Eur J Paediatr Neurol. 2008 May;12(3):210-23.

38. World Health Organization. International classification of functioning, disability and health: ICF. Geneva: WHO; 2001.

39. World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems. Geneva: WHO; 1992.

40. Ustun B, Chatterji S, Bickenbach J, Kostanjsek N, Schneider M. The International Classification of Functioning, Disability and Health: a new tool for understanding disability and health. Disabil Rehabil. 2003;25(11-12):565-71.

41. Stucki G, Ewert T, Cieza A. Value and application of the ICF in rehabilitation medicine. Disabil Rehabil. 2002;24(17):932-8.

42. Stucki G. International Classification of Functioning, Disability, and Health (ICF): A promising framework and classification for rehabilitation medicine. Am J Phys Med Rehabil. 2005;84(10):733-40.

43. Rauch A, Cieza A, Stucki G. How to apply the International Classification of Functioning, Disability and Health (ICF) for rehabilitation management in clinical practice. Eur J Phys Rehabil Med. 2008 Sep;44(3):329-42.

44. Escorpizo R, Stucki G, Cieza A, Davis K, Stumbo T, Riddle DL. Creating an Interface Between the International Classification of Functioning, Disability and Health and Physical Therapist Practice. Phys Ther. 2010 Jul;90(7):1053-63.

45. World Health Organization. ICF Checklist, Version 2.1a, Clinician form for International Classification of Functioning, Disability and Health. 2003 [cited;101020 Available from: http://www.who.int/classifications/icf/training/icfchecklist.pdf

46. Cieza A, Ewert T, Ustun B, Chatterji S, Kostanjsek N, Stucki G. Development of ICF core sets for patients with chronic conditions. J Rehabil Med. 2004;36(44 Suppl):9-11.

47. Cieza A, Geyh S, Chatterji S, Kostanjsek N, Ustun BT, Stucki G. Identification of candidate categories of the International Classification of Functioning Disability and Health (ICF) for a Generic ICF Core Set based on regression modelling. BMC Med Res Methodol. 2006 Jul 27;6:36.

48. World Health Organization, Socialstyrelsen [The National Board of Health and Welfare]. ICF Checklista, Version 2.1a, för klinisk användning av International Classification of Functioning, Disability and Health. 2003 [cited;101020 Available from: http://www.socialstyrelsen.se/klassificeringochkoder/koderfunktionshinder/Documents/ICF_checklista.pdf

49. Khan F, Pallant JF. Use of the International Classification of Functioning, Disability and Health (ICF) to identify preliminary comprehensive and brief core sets for multiple sclerosis. Disabil Rehabil. 2007;29(3):205-13.

50. Cieza A, Kirchberger I, Biering-Sorensen F, Baumberger M, Charlifue S, Post MW, et al. ICF Core Sets for individuals with spinal cord injury in the long-term context. Spinal Cord. 2010 Apr;48(4):305-12.

51. Grill E, Ewert T, Chatterji S, Kostanjsek N, Stucki G. ICF Core sets development for the acute hospital and early post-acute rehabilitation facilities. Disabil Rehabil. 2005;27(7/8):361-6.

52. Brage S, Donceel P, Falez F. Development of ICF core set for disability evaluation in social security. Disabil Rehabil. 2008;30(18):1392-6.

53. Allet L, Bürge E, Monnin D. ICF: clinical relevance for physiotherapy? A critical review. Adv Physiother. 2008;10(3):127-37.

54. Ueda S, Okawa Y. The subjective dimension of functioning and disability: what is it and what is it for? Disabil Rehabil. 2003 Jun 3-17;25(11-12):596-601.

55. Hemmingsson H, Jonsson H. The issue is. An occupational perspective on the concept of participation in the International Classification of Functioning, Disability and Health -- some critical remarks. Am J Occup Ther. 2005;59(5):569-76.

56. Perenboom RJM, Chorus AMJ. Measuring participation according to the International Classification of Functioning, Disability and Health (ICF). Disabil Rehabil. 2003;25(11-12):577-87.

57. Jelsma J. Use of the International Classification of Functioning, Disability and Health: a literature survey. J Rehabil Med. 2009;41(1):1-12.

58. McDougall J, Wright V, Rosenbaum P. The ICF model of functioning and disability: incorporating quality of life and human development. Dev Neurorehabil. 2010;13(3):204-11.

59. Nordenfelt L. On health, ability and activity: comments on some basic notions in the ICF. Disabil Rehabil. 2006 Dec 15;28(23):1461-5.

60. Nordenfelt L. Action theory, disability and ICF. Disabil Rehabil. 2003;25(18):1075-9.

61. Quera Salva MA, Blumen M, Jacquette A, Durand MC, Andre S, De Villiers M, et al. Sleep disorders in childhood-onset myotonic dystrophy type 1. Neuromuscul Disord. 2006 Oct;16(9-10):564-70.

62. Laberge L, Bégin P, Montplaisir J, Mathieu J. Sleep complaints in patients with myotonic dystrophy. J Sleep Res. 2004;13(1):95-100.

63. Laberge L, Dauvilliers Y, Begin P, Richer L, Jean S, Mathieu J. Fatigue and daytime sleepiness in patients with myotonic dystrophy type 1: To lump or split? Neuromuscul Disord. 2009 Apr 28;19(6):397-402.

64. Rubinsztein JS, Rubinsztein DC, Holland AJ. Apathy and hypersomnia are common features of myotonic dystrophy. J Neurol Neurosurg Psychiatry. 1998;64(4):510-5.

65. van der Werf S, Kalkman J, Bleijenberg G, van Engelen B, Schillings M, Zwarts M. The relation between daytime sleepiness, fatigue, and reduced motivation in patients with adult onset myotonic dystrophy. J Neurol Neurosurg Psychiatry. 2003 Jan;74(1):138-9.

66. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol. 1996 Dec;9(6):456-60.

67. Kalkman JS, Schillings ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BG, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry. 2005 Oct;76(10):1406-9.

68. Hilton-Jones D, Damian M, Meola G. Somnolence and its management. In: Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004. p. 135-49.

69. Begin P, Mathieu J, Almirall J, Grassino A. Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. Am J Respir Crit Care Med. 1997 Jul;156(1):133-9.

70. Laberge L, Begin P, Dauvilliers Y, Beaudry M, Laforte M, Jean S, et al. A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. J Neurol Neurosurg Psychiatry. 2009 Jun;80(6):642-6.

71. Annane D, Moore DH, Barnes PR, Miller RG. Psychostimulants for hypersomnia (excessive daytime sleepiness) in myotonic dystrophy. Cochrane Database Syst Rev. 2006;3:CD003218.

72. Ekstrom AB, Hakenas-Plate L, Tulinius M, Wentz E. Cognition and adaptive skills in myotonic dystrophy type 1: a study of 55 individuals with congenital and childhood forms. Dev Med Child Neurol. 2009 Dec;51(12):982-90.

73. Sistiaga A, Urreta I, Jodar M, Cobo AM, Emparanza J, Otaegui D, et al. Cognitive/personality pattern and triplet expansion size in adult myotonic dystrophy type 1 (DM1): CTG repeats, cognition and personality in DM1. Psychol Med. 2010 Mar;40(3):487-95.

74. Winblad S, Lindberg C, Hansen S. Cognitive deficits and CTG repeat expansion size in classical myotonic dystrophy type 1 (DM1). Behav Brain Funct. 2006;2:16.

75. Sansone V, Gandossini S, Cotelli M, Calabria M, Zanetti O, Meola G. Cognitive impairment in adult myotonic dystrophies: a longitudinal study. Neurol Sci. 2007 Mar;28(1):9-15.

76. Modoni A, Silvestri G, Vita MG, Quaranta D, Tonali PA, Marra C. Cognitive impairment in myotonic dystrophy type 1 (DM1): a longitudinal follow-up study. J Neurol. 2008 Nov;255(11):1737-42.

77. Angeard N, Gargiulo M, Jacquette A, Radvanyi H, Eymard B, Heron D. Cognitive profile in childhood myotonic dystrophy type 1: is there a global impairment? Neuromuscul Disord. 2007 Jun;17(6):451-8.

78. Winblad S, Lindberg C, Hansen S. Temperament and character in patients with classical myotonic dystrophy type 1 (DM-1). Neuromuscul Disord. 2005 Apr;15(4):287-92.

79. Delaporte C. Personality patterns in patients with myotonic dystrophy. Arch Neurol. 1998 May;55(5):635-40.

80. Winblad S, Hellstrom P, Lindberg C, Hansen S. Facial emotion recognition in myotonic dystrophy type 1 correlates with CTG repeat expansion. J Neurol Neurosurg Psychiatry. 2006 Feb;77(2):219-23.

81. Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BG, Bleijenberg G. Psychiatric disorders appear equally in patients with myotonic dystrophy, facioscapulohumeral dystrophy, and hereditary motor and sensory neuropathy type I. Acta Neurol Scand. 2007 Apr;115(4):265-70.

82. Winblad S, Jensen C, Mansson JE, Samuelsson L, Lindberg C. Depression in Myotonic Dystrophy type 1: clinical and neuronal correlates. Behav Brain Funct. 2010;6:25.

83. Goossens E, Steyaert J, De Die-Smulders C, Willekens D, Fryns JP. Emotional and behavioral profile and child psychiatric diagnosis in the childhood type of myotonic dystrophy. Genet Couns. 2000;11(4):317-27.

84. Antonini G, Soscia F, Giubilei F, De Carolis A, Gragnani F, Morino S, et al. Health-related quality of life in myotonic dystrophy type 1 and its relationship with cognitive and emotional functioning. J Rehabil Med. 2006 May;38(3):181-5.

85. Meola G, Sansone V, Perani D, Scarone S, Cappa S, Dragoni C, et al. Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myotonic myopathy (PROMM/DM-2). Neuromuscul Disord. 2003 Dec;13(10):813-21.

86. Ekström A-B, Tulinius M, Sjöström A, Aring E. Visual Function in Congenital and Childhood Myotonic Dystrophy Type 1. Ophthalmology. 2010;117(5):976-82.

87. Engel JM, Kartin D, Carter GT, Jensen MP, Jaffe KM. Pain in youths with neuromuscular disease. Am J Hosp Palliat Care. 2009 Oct-Nov;26(5):405-12.

88. Guy-Coichard C, Nguyen DT, Delorme T, Boureau F. Pain in hereditary neuromuscular disorders and myasthenia gravis: a national survey of frequency, characteristics, and impact. J Pain Symptom Manage. 2008 Jan;35(1):40-50.

89. Tiffreau V, Viet G, Thevenon A. Pain and neuromuscular disease: the results of a survey. Am J Phys Med Rehabil. 2006 Sep;85(9):756-66.

90. Jensen MP, Abresch RT, Carter GT, McDonald CM. Chronic pain in persons with neuromuscular disease. Arch Phys Med Rehabil. 2005;86(6):1155-63.

91. Jensen MP, Hoffman AJ, Stoelb BL, Abresch RT, Carter GT, McDonald CM. Chronic pain in persons with myotonic dystrophy and facioscapulohumeral dystrophy. Arch Phys Med Rehabil. 2008 Feb;89(2):320-8.

92. Ronnblom A, Forsberg H, Danielsson A. Gastrointestinal symptoms in myotonic dystrophy. Scand J Gastroenterol. 1996 Jul;31(7):654-7.

93. de Swart BJ, van Engelen BG, van de Kerkhof JP, Maassen BA. Myotonia and flaccid dysarthria in patients with adult onset myotonic dystrophy. J Neurol Neurosurg Psychiatry. 2004 Oct;75(10):1480-2.

94. Dahlbom K, Ahlström G, Barany M, Kihlgren A, Gunnarsson L-G. Muscular dystrophy in adults: a five year follow up. Scand J Rehabil Med. 1999;31(3):178-84.

95. Duboc D, Eymard B, Damian MS. Cardiac management of myotonic dystrophy. In: Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004. p. 85-93.

96. Groh WJ, Lowe MR, Zipes DP. Severity of cardiac conduction involvement and arrhythmias in myotonic dystrophy type 1 correlates with age and CTG repeat length. Cardiovasc Electrophysiol. 2002;13(5):444-8.

97. Cudia P, Bernasconi P, Chiodelli R, Mangiola F, Bellocci F, Dello Russo A, et al. Risk of arrhythmia in type I myotonic dystrophy: the role of clinical and genetic variables. J Neurol Neurosurg Psychiatry. 2009 Jul;80(7):790-3.

98. Dystrophia Myotonica (DM1) Scandinavian Consensus Program, version 3, 2010-01-07. 2010 [cited;101020 Available from: http://www.orebroll.se/Files-sv/USO/Kliniker_enheter/Neuro/DM%20koncenesus%202010.pdf

99. Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med. 2008 Jun 19;358(25):2688-97.

100. Breton R, Mathieu J. Usefulness of clinical and electrocardiographic data for predicting adverse cardiac events in patients with myotonic dystrophy. Can J Cardiol. 2009 Feb;25(2):e23-7.

101. Christensen AH, Bundgaard H, Schwartz M, Hansen SH, Svendsen JH. Cardiac myotonic dystrophy mimicking arrhythmogenic right ventricular cardiomyopathy in a young sudden cardiac death victim. Circ Arrhythm Electrophysiol. 2008 Oct;1(4):317-20.

102. Bassez G, Lazarus A, Desguerre I, Varin J, Laforet P, Becane HM, et al. Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1. Neurology. 2004 Nov 23;63(10):1939-41.

103. Merlevede K, Vermander D, Theys P, Legius E, Ector H, Robberecht W. Cardiac involvement and CTG expansion in myotonic dystrophy. J Neurol. 2002 Jun;249(6):693-8.

104. O'Brien T, Harper PS, Newcombe RG. Blood pressure and myotonic dystrophy. Clin Genet. 1983 Jun;23(6):422-6.

105. Phillips MF. Respiratory problems in myotonic dystrophy and their management. In: Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004. p. 104-12.

106. Zifko UA, Hahn AF, Remtulla H, Georg CF, Wihlidal W, Bolton CF. Central and peripheral respiratory electrophysiological studies in myotonic dystrophy. Brain. 1996 Dec;119(Pt 6):1911-22.

107. Fodil R, Lofaso F, Annane D, Falaise L, Lejaille M, Raphael JC, et al. Upper airway calibre and impedance in patients with Steinert's myotonic dystrophy. Respir Physiol Neurobiol. 2004 Nov 30;144(1):99-107.

108. Johnson ER, Abresch RT, Carter GT, Kilmer DD, Fowler WM, Jr., Sigford BJ, et al. Profiles of neuromuscular diseases. Myotonic dystrophy. Am J Phys Med Rehabil. 1995 Sep-Oct;74(5 Suppl):S104-16.

109. Ronnblom A, Danielsson A. Hereditary muscular diseases and symptoms from the gastrointestinal tract. Scand J Gastroenterol. 2004 Jan;39(1):1-4.

110. Bellini M, Biagi S, Stasi C, Costa F, Mumolo MG, Ricchiuti A, et al. Gastrointestinal manifestations in myotonic muscular dystrophy. World J Gastroenterol. 2006 Mar 28;12(12):1821-8.

111. van Engelen B, Brunner HG. Gastrointestinal dysfunction in myotonic dystrophy. In: Harper PS, van Engelen B, Eymard B, Wilcox D, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004. p. 113-25.

112. Ertekin C, Yuceyar N, Aydogdu, Karasoy H. Electrophysiological evaluation of oropharyngeal swallowing in myotonic dystrophy. J Neurol Neurosurg Psychiatry. 2001 Mar;70(3):363-71.

113. Leonard RJ, Kendall KA, Johnson R, McKenzie S. Swallowing in myotonic muscular dystrophy: a videofluoroscopic study. Arch Phys Med Rehabil. 2001 Jul;82(7):979-85.

114. Johansson Å. Immuno-endocrine abnormalities in myotonic dystrophy. Umeå: Umeå University; 2000.

115. Johansson Å, Olsson T. Enocrine changes in myotonic dystrophy. In: Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004. p. 126-34.

116. Rakocevic Stojanovic V, Peric S, Lavrnic D, Popovic S, Ille T, Stevic Z, et al. Leptin and the metabolic syndrome in patients with myotonic dystrophy type 1. Acta Neurol Scand. 2010 Feb;121(2):94-8.

117. Rudnik-Schöneborn S, de Die-Smulders C. Pregnancy and perinatal problems in myotonic dystrophy. In: Harper PS, van Engelen B, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University Press; 2004. p. 153-61.

118. Mathieu J, De Braekeleer M, Prévost C, Boily C. Myotonic dystrophy: clinical assessment of muscular disability in an isolated population with presumed homogeneous mutation. Neurology. 1992;42:203-8.

119. Phillips MF, Mathieu J. Physical disability in myotonic dystrophy. In: Harper PS, van Engelen BG, Eymard B, Wilcox DE, editors. Myotonic dystrophy: present management, future therapy. Oxford: Oxford University press; 2004. p. 68-82.

120. de Swart BJ, van Engelen BG, Maassen BA. Warming up improves speech production in patients with adult onset myotonic dystrophy. J Commun Disord. 2007 May-Jun;40(3):185-95.

121. Trip J, Drost G, van Engelen BG, Faber CG. Drug treatment for myotonia. Cochrane Database Syst Rev. 2006(1):CD004762.

122. Mathieu J, Boivin H, Richards CL. Quantitative motor assessment in myotonic dystrophy. Can J Neurol Sci. 2003;30(2):129-36.

123. Kroksmark A-K. Muscle strength and motor function in neuromuscular disorders. Göteborg: University of Gothenburgh; 2006.

124. Nitz JC, Burns YR, Jackson RV. A longitudinal physical profile assessment of skeletal muscle manifestations in myotonic dystrophy. Clin Rehabil. 1999 Feb;13(1):64-73.

125. Hammaren E, Kjellby-Wendt G, Lindberg C. Retrospective longitudinal study of muscular strength and gait speed in adult patients with myotonic dystrophy type 1. Neuromuscul Disord. 2006 Oct;16(9-10):670-.

126. Lindeman E, Leffers P, Spaans F, Drukker J, Reulen J. Deterioration of motor function in myotonic dystrophy and hereditary motor and sensory neuropathy. Scand J Rehabil Med. 1995 Mar;27(1):59-64.

127. Orndahl G, Grimby G, Grimby A, Johansson G, Wilhelmsen L. Functional deterioration and selenium-vitamin-E treatment in myotonic dystrophy. A placebo-controlled study. J Intern Med. 1994 Mar;235(3):205-10.

128. Wright RB, Yoder DM, Costa JL, Andriacchi TP. Characterization of gait parameters in adult-onset myotonic dystrophy: abnormal hip motion. Arch Phys Med Rehabil. 1995 Jan;76(1):33-8.

129. Sjögren L, Engvall M, Ekström AB, Lohmander A, Kiliaridis S, Tulinius M. Orofacial dysfunction in children and adolescents with myotonic dystrophy. Dev Med Child Neurol. 2007 Jan;49(1):18-22.

130. Gagnon C, Mathieu J, Noreau L. Life habits in myotonic dystrophy type 1. J Rehabil Med. 2007 Sep;39(7):560-6.

131. Nätterlund B, Ahlström G. Problem-focused coping and satisfaction with activities of daily living in individuals with muscular dystrophy and postpolio syndrome. Scand J Caring Sci. 1999;13(1):26-32.

132. Nätterlund B, Ahlström G. Activities of daily living and quality of life in persons with muscular dystrophy. J Rehabil Med. 2001 Sep;33(5):206-11.

133. Nätterlund B, Gunnarsson L-G, Ahlström G. Disability, coping and quality of life in individuals with muscular dystrophy: a prospective study over five years. Disabil Rehabil. 2000;22(17):776-85.

134. Wiles CM, Busse ME, Sampson CM, Rogers MT, Fenton-May J, van Deursen R. Falls and stumbles in myotonic dystrophy. J Neurol Neurosurg Psychiatry. 2006 Mar;77(3):393-6.

135. Hammaren E, Ohlsson J, Kjellby-Wendt G, Lindberg C. Survey of postural balance and quality of life with health aspects in patients with myotonic dystrophy type 1 (DM1). Neuromuscul Disord. 2007 Oct;17(9-10):854-.

136. Boström K, Sjöquist Nätterlund B, Ahlström G. Sickness impact in people with muscular dystrophy: a longitudinal study over 10 years. Clin Rehabil. 2005 Sep;19(6):686-94.

137. Fowler WM, Jr., Abresch RT, Koch TR, Brewer ML, Bowden RK, Wanlass RL. Employment profiles in neuromuscular diseases. Am J Phys Med Rehabil. 1997 Jan-Feb;76(1):26-37.

138. Laberge L, Veillette S, Mathieu J, Auclair J, Perron M. The correlation of CTG repeat length with material and social deprivation in myotonic dystrophy. Clin Genet. 2007 Jan;71(1):59-66.

139. Gagnon C, Mathieu J, Jean S, Laberge L, Perron M, Veillette S, et al. Predictors of disrupted social participation in myotonic dystrophy type 1. Arch Phys Med Rehabil. 2008 Jul;89(7):1246-55.

140. Minis MA, Kalkman JS, Akkermans RP, Engels JA, Huijbregts PA, Bleijenberg G, et al. Employment status of patients with neuromuscular diseases in relation to personal factors, fatigue and health status: a secondary analysis. J Rehabil Med. 2010 Jan;42(1):60-5.

141. Ahlstrom G, Sjoden PO. Coping with illness-related problems and quality of life in adult individuals with muscular dystrophy. J Psychosom Res. 1996 Oct;41(4):365-76.

142. Fayers PM, Machin D. Qulity of life: the assessment, analysis, and interpretation of patient-reported outcomes. second ed. Chichester: Wiley; 2009.

143. World Health Organization. Ottawa Charter for Health Promotion. Geneva: WHO; 1986.

144. Fayers PM, Sprangers MA. Understanding self-rated health. Lancet. 2002 Jan 19;359(9302):187-8.

145. Sullivan M, Karlsson J, Taft C. SF-36 Hälsoenkät: Svensk Manual och Tolkningsguide [Swedish Manual and Interpretation Guide]. 2nd ed. Gothenburg: Sahlgrenska University Hospital; 2002.

146. Ahlström G, Gunnarsson L-G. Disability and quality of life in individuals with muscular dystrophy. Scand J Rehabil Med. 1996 Sep;28(3):147-57.

147. Gagnon C, Noreau L, Moxley R, Laberge L, Jean S, Richer L, et al. Towards an integrative approach to the management of myotonic dystrophy type 1. J Neurol Neurosurg Psychiatry. 2007 Aug;78(8):800-6.

148. Lexell J, Forsberg H, Krylborg E, Wallmark I, Andersson S, Engstrom M, et al. [Rehabilitation in dystrophia myotonica. A successful experiment with an interdisciplinary team in Norrbotten]. Lakartidningen. 1999 Oct 6;96(40):4337-40.

149. Hill ME, Phillips MF. Service provision for adults with long-term disability: a review of services for adults with chronic neuromuscular conditions in the United Kingdom. Neuromuscul Disord. 2006 Feb;16(2):107-12.

150. Chouinard MC, Gagnon C, Laberge L, Tremblay C, Cote C, Leclerc N, et al. The potential of disease management for neuromuscular hereditary disorders. Rehabil Nurs. 2009 May-Jun;34(3):118-26.

151. Missaoui B, Rakotovao E, Bendaya S, Mane M, Pichon B, Faucher M, et al. Posture and gait abilities in patients with myotonic dystrophy (Steinert disease). Evaluation on the short-term of a rehabilitation program. Ann Phys Rehabil Med. 2010 Aug-Sep;53(6-7):387-98.

152. Ahlstrom G, Lindvall B, Wenneberg S, Gunnarsson LG. A comprehensive rehabilitation programme tailored to the needs of adults with muscular dystrophy. Clin Rehabil. 2006 Feb;20(2):132-41.

153. Hislop HJ. The not-so-impossible dream. Phys Ther. 1975;55(10):1069-80.

154. Tyni-Lenné R. Sjukgymnastikens kunskapsområde [The scope of physiotherapy knowledge]. In: Broberg C, Westman Kumlin I, Schön-Olsson C, editors. Vetenskaplig utvecling av sjukgymnastik Internordiskt symposium. Göteborg: Göteborgs Universitet; FoU Rapport 1988:1. p. 83-9.

155. Tyni-Lenné R. Sjukgymnastik - fysioterapiprocessen [Physiotherapy process]. Sjukgymnasten. 1983;41(14):17-20.

156. Cott CA, Finch E, Gasner D, Yoshida K, Thomas SG, Verrier MC. The movement continuum theory of physical therapy. Physiother Can. 1995;47(2):87-95.

157. Allen DD. Proposing 6 dimensions within the construct of movement in the movement continuum theory. Phys Ther. 2007 Jul;87(7):888-98.

158. Allen DD. Validity and reliability of the movement ability measure: a self-report instrument proposed for assessing movement across diagnoses and ability levels. Phys Ther. 2007 Jul;87(7):899-916.

159. Cott CA, Finch E. Invited commentary on the movement continuum special series. Phys Ther. 2007 Jul;87(7):925-6; author reply 30-4.

160. Allen DD, Cott CA. Evaluating rehabilitation outcomes from the client's perspective by identifying the gap between current and preferred movement ability. Disabil Rehabil. 2010;32(6):452-61.

161. World Confederation for Physical Therapy. Description of Physical Therapy. 2007 [cited;101020 Available from: http://www.wcpt.org/sites/wcpt.org/files/files/WCPT_Description_of_Physical_Therapy-Sep07-Rev_2.pdf

162. Broberg C, Tyni-Lenné R. Sjukgymnastik som vetenskap och profession [Physical Therapy as science and profession]. Stockholm: Legitimerade sjukgymnasters riksförbund (LSR); 2009.

163. Nitz JC. Physiotherapy for myotonic dystrophy. Physiotherapy. 1999;85(11):591-6.

164. Kroksmark AK. Physiotherapy in muscular dystrophy. Scand J Rehabil Med Suppl. 1999;39:65-8.

165. Eagle M. Report on the muscular dystrophy campaign workshop: exercise in neuromuscular diseases Newcastle, January 2002. Neuromuscul Disord. 2002 Dec;12(10):975-83.

166. Nilsagård Y, Kånåhols M. Strength training for individuals with myotonic dystrophy (MD) [Swedish]. Nordisk Fysioterapi. 2004;8(1):19-24.

167. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.

168. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report. . Washingtin DC: Department of Health and Human Services; 2008.

169. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports. 2006 Feb;16 Suppl 1:3-63.

170. Socialstyrelsen [The National Board of Health and Welfare]. Nationella riktlinjer för vård vid depression och ångestsyndrom 2010 - stöd för styrning och ledning. 2010 [cited;101020 Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/17948/2010-3-4.pdf

171. Yrkesföreningar för fysisk aktivitet (YFA). Fysisk aktivitet i sjukdomsprevention och sjukdomsbehandling [Physical activity in the prevention and treatment of disease]. 2008 [cited;101020 Available from: http://www.svenskidrottsmedicin.se/fyss/pdf/FYSS_2008.pdf

172. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007 Aug;39(8):1423-34.

173. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007 Aug;39(8):1435-45.

174. McCrory MA, Kim H-R, Wright NC, Lovelady CA, Aitkens S, Kilmer DD. Energy expenditure, physical activity, and body composition of ambulatory adults with heriditary neuromuscular disease. Am J Clin Nutr. 1998 Jun;67(6):1162-9.

175. Aitkens S, Kilmer DD, Wright NC, McCrory MA. Metabolic syndrome in neuromuscular disease. Arch Phys Med Rehabil. 2005 May;86(5):1030-6.

176. Phillips M, Flemming N, Tsintzas K. An exploratory study of physical activity and perceived barriers to exercise in ambulant people with neuromuscular disease compared with unaffected controls. Clin Rehabil. 2009 Aug;23(8):746-55.

177. McDonald CM. Physical activity, health impairments and disability in neuromuscular disease. Am J Phys Med Rehabil. 2002;81 (Suppl 11):S108-20.

178. Ansved T. Muscle training in muscular dystrophies. Acta Physiol Scand. 2001 Mar;171(3):359-66.

179. Ansved T. Muscular dystrophies: influence of physical conditioning on the disease evolution. Curr Opin Clin Nutr Metab Care. 2003 Jul;6(4):435-9.

180. van der Kooi EL, Lindeman E, Riphagen I. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev. 2005(1):CD003907.

181. Cup EH, Pieterse AJ, Ten Broek-Pastoor JM, Munneke M, van Engelen BG, Hendricks HT, et al. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Arch Phys Med Rehabil. 2007 Nov;88(11):1452-64.

182. Voet NB, van der Kooi EL, Riphagen, II, Lindeman E, van Engelen BG, Geurts A. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev. 2010(1):CD003907.

183. Aitkens SG, McCrory MA, Kilmer DD, Bernauer EM. Moderate resistance exercise program: Its effect in slowly progressive neuromuscular disease. Arch Phys Med Rehabil. 1993 Jul;74(7):711-5.

184. Kilmer DD, McCrory MA, Wright NC, Aitkens SG, Bernauer EM. The effect of a high resistance exercise program in slowly progressive neuromuscular disease. Arch Phys Med Rehabil. 1994 May;75(5):560-3.

185. Lindeman E, Leffers P, Spaans F, Drukker J, Reulen J, Kerckhoffs M, et al. Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy: a randomized clinical trial. Arch Phys Med Rehabil. 1995 Jul;76(7):612-20.

186. Tollbäck A, Eriksson S, Wredenberg A, Jenner G, Vargas R, Borg K, et al. Effects of high resistance training in patients with myotonic dystrophy. Scand J Rehabil Med. 1999 Mar;31(1):9-16.

187. Aldehag AS, Jonsson H, Ansved T. Effects of a hand training programme in five patients with myotonic dystrophy type 1. Occup Ther Int. 2005;12(1):14-27.

188. Aldehag AS. The effects of hand training in patients with Welander distal myopathy and Myotonic dystrophy type 1. Stockholm: Karolinska Institutet; 2009.

189. Wright NC, Kilmer DD, McCrory MA, Aitkens SG, Holcomb BJ, Bernauer EM. Aerobic walking in slowly progressive neuromuscular disease: effect of a 12-week program. Arch Phys Med Rehabil. 1996 Jan;77(1):64-9.

190. Orngreen MC, Olsen DB, Vissing J. Aerobic training in patients with myotonic dystrophy type 1. Ann Neurol. 2005 May;57(5):754-7.

191. Wennberg S, Gunnarsson L-G, Ahlström G. Using a novel exercise programme for patients with muscular dystrophy. Part I: a qualitative study. Disabil Rehabil. 2004;26(10):586-94.

192. Wennberg S, Gunnarsson L-G, Ahlström G. Using a novel exercise programme for patients with muscular dystrophy. Part II: a quantitative study. Disabil Rehabil. 2004;26(10):595-602.

193. Fowler WM. Consensus conference summary: Role of physical activity and exercise training in neuromuscular diseases. Am J Phys Med Rehabil. 2002;81(11 Suppl):S187-95.

194. Friskis&Svettis Riks. Friskis&Svettis Emergency Facts 2010. 2010 [cited;100317Available from: http://web.friskissvettis.se/emergencyfacts___6475.aspx

195. Finch E, Brooks D, Stratford PW, Mayo NE. Physical rehabilitation outcome measures: a guide to enhanced clinical decision making. Second ed. Baltimore: Lippincott Williams & Wilkins; 2002.

196. Sim J, Arnell P. Measurement validity in physical therapy research. Phys Ther. 1993;73(2):102-15.

197. Bruton A, Conway JH, Holgate ST. Reliability: what is it, and how is it measured? Physiotherapy. 2000;86(2):94-9.

198. Atkinson G, Nevill AM. Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. Sports Med. 1998;26(4):217-38.

199. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. Am J Phys Med Rehabil. 2005 Sep;84(9):719-23.

200. Bland JM, Altman DG. Measurement error. BMJ. 1996 Sep 21;313(7059):744.

201. Bland JM, Altman DG. Measuring agreement in method comparison. Stat Methods Med Res. 1999 Jun;8(2):135-60.

202. Liang MH. Longitudinal construct validity: establishment of clinical meaning in patient evaluative instruments. Med Care. 2000 Sep;38(9 Suppl):II84-90.

203. Stucki G, Melvin J. The International Classification of Functioning, Disability and Health: A unifying model for the conceptual description of physical and rehabilitation medicine. J Rehabil Med. 2007;39:286-92.

204. Mathieu J, Boivin H, Meunier D, Gaudreault M, Bégin P. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. Neurology. 2001 Feb 13;56(3):336-40.

205. Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six- and twelve minute walking test in respiratory disease. Br Med J (Clin Res Ed). 1982 May 29;284(6329):1607-8.

206. Ewert T, Allen DD, Wilson M, Ustun B, Stucki G. Validation of the International Classification of Functioning Disability and Health framework using multidimensional item response modeling. Disabil Rehabil. 2010;32(17):1397-405.

207. Uhlig T, Moe R, Reinsberg S, Kvien TK, Cieza A, Stucki G. Responsiveness of the International Classification of Functioning, Disability and Health (ICF) Core Set for rheumatoid arthritis. Ann Rheum Dis. 2009 Jun;68(6):879-84.

208. Grill E, Mansmann U, Cieza A, Stucki G. Assessing observer agreement when describing and classifying functioning with the International Classification of Functioning, Disability and Health. J Rehabil Med. 2007 Jan;39(1):71-6.

209. Okochi J, Utsunomiya S, Takahashi T. Health measurement using the ICF: Test-retest reliability study of ICF codes and qualifiers in geriatric care. Health Qual Life Outcomes. 2005 Jul 29;3:46.

210. Uhlig T, Lillemo S, Moe RH, Stamm T, Cieza A, Boonen A, et al. Reliability of the ICF Core Set for rheumatoid arthritis. Ann Rheum Dis. 2007 Aug;66(8):1078-84.

211. Koskinen S, Hokkinen EM, Sarajuuri J, Alaranta H. Applicability of the ICF checklist to traumatically brain-injured patients in post-acute rehabilitation settings. J Rehabil Med. 2007 Jul;39(6):467-72.

212. Hilfiker R, Obrist S, Christen G, Lorenz T, Cieza A. The use of the comprehensive International Classification of Functioning, Disability and Health Core Set for low back pain in clinical practice: a reliability study. Physiother Res Int. 2009;14(3):147-66.

213. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.

214. Johns MW. Reliability and factor analysisi of the Epworth sleepiness scale. Sleep. 1992;15(4):376-81.

215. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000 Mar;9(1):5-11.

216. Miletin MS, Hanly PJ. Measurement properties of the Epworth sleepiness scale. Sleep Med. 2003 May;4(3):195-9.

217. Laberge L, Gagnon C, Jean S, Mathieu J. Fatigue and daytime sleepiness rating scales in myotonic dystrophy: a study of reliability. J Neurol Neurosurg Psychiatry. 2005 Oct;76(10):1403-5.

218. van Engelen BG, Eymard B, Wilcox D. 123rd ENMC International Workshop: management and therapy in myotonic dystrophy, 6-8 February 2004, Naarden, The Netherlands. Neuromuscul Disord. 2005 May;15(5):389-94.

219. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct;46(10):1121-3.

220. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep. 2008 Nov 1;31(11):1601-7.

221. Mattsson M, Moller B, Lundberg I, Gard G, Bostrom C. Reliability and validity of the Fatigue Severity Scale in Swedish for patients with systemic lupus erythematosus. Scand J Rheumatol. 2008 Jul-Aug;37(4):269-77.

222. Rietberg MB, Van Wegen EE, Kwakkel G. Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. Disabil Rehabil. 2010;32(22):1870-6.

223. HRQL gruppen. Hospital Anxiety and Depression scale. 2009 [cited;101020 Available from: http://www.hrql.se/content/frageformular/hospital_scale_default.asp

224. Sullivan M, Karlsson J, Sjöström L, Backman L, Bengtsson C, Bouchard C, et al. Swedish obese subjects (SOS) - an intervention study of obesity. Baseline evaluation of health and psychosocial functioning in the first 1743 subjects examined. Int J Obes Relat Metab Disord. 1993 Sep 17;17(9):503-12.

225. Zigmond A, Snaith R. The hospital anxiety depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.

226. Lisspers J, Nygren A, Soderman E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. Acta Psychiatr Scand. 1997 Oct;96(4):281-6.

227. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002 Feb;52(2):69-77.

228. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319-38.

229. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005 Nov;26(5):948-68.

230. Astrand PO. Ergometri konditionsprov in Swedish [Ergometric aerobic capacity test]. Varberg: Monark Exercise AB; 1964.

231. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol. 1954 Sep;7(2):218-21.

232. Andersson G, Forsberg A, Malmgren S. Konditionstest på cykel [Aerobic capacity test on ergometercycle]. Stockholm: SISU Idrottsböcker; 1999.

233. Tammelin T, Remes J, Kujala V, Oksa J, Nayha S, Zitting P, et al. Cardiorespiratory fitness of finnish adolescents. Int J Sports Med. 2007 Oct;28(10):853-9.

234. Keller A, Hellesnes J, Brox JI. Reliability of the isokinetic trunk extensor test, Biering-Sorensen test, and Astrand bicycle test: assessment of intraclass correlation coefficient and critical difference in patients with chronic low back pain and healthy individuals. Spine (Phila Pa 1976). 2001 Apr 1;26(7):771-7.

235. Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. Phys Ther. 2000;80(8):782-807.

236. Andersson D. The Åstrand-Ryhming test/method under the magnifying glass - a review of research articles. Stockholm: Idrottshögskolan 2004.

237. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985 Feb;66(2):69-74.

238. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. J Hand Surg Am. 1984 Mar;9(2):222-6.

239. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. J Geriatr Phys Ther. 2008;31(1):3-10.

240. Mathiowetz V. Comparison of Rolyan and Jamar dynamometers for measuring grip strength. Occup Ther Int. 2002;9(3):201-9.

241. Coldham F, Lewis J, Lee H. The reliability of one vs. three grip trials in symptomatic and asymptomatic subjects. J Hand Ther. 2006;19(3):318-27.

242. Aldehag AS, Jonsson H, Littorin S, Ansved T. Reliability of hand function testing instruments in patients with muscular dystrophies. Int J Ther Rehabil. 2008;15(5):211-8.

243. Csuka M, McCarty DJ. Simple method for measurement of lower extremity muscle strenght. Am J Med. 1985;78(1):77-81.

244. Newcomer KL, Krug HE, Mahowald ML. Validity and reliability of the timed-stands test for patients with rheumatoid arthritis and other chronic diseases. J Rheumatol. 1993 Jan;20(1):21-7.

245. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the nine hole peg test of finger dexterity. Occup Ther J Res. 1985;5(1):24-38.

246. Chen HM, Chen CC, Hsueh IP, Huang SL, Hsieh CL. Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. Neurorehabil Neural Repair. 2009 Jun;23(5):435-40.

247. Svensson E, Hager-Ross C. Hand function in Charcot Marie Tooth: test retest reliability of some measurements. Clin Rehabil. 2006 Oct;20(10):896-908.

248. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-8.

249. Bohannon RW. Reference values for the timed up and go test: a descriptive meta-analysis. J Geriatr Phys Ther. 2006;29(2):64-8.

250. Nilsagard Y, Lundholm C, Gunnarsson L, Denison E. Clinical relevance using timed walk tests and 'timed up and go' testing in persons with multiple sclerosis. Physiother Res Int. 2007;12(2):105-14.

251. Flansbjer U-B, Holmbäck A-M, Downham D, Patten C, Lexell J. Reliability of gait performance tests in men and women with hemiparesis after stroke. J Rehabil Med. 2005;37(2):75-82.

252. Steffen T, Seney M. Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-Item Short-Form Health Survey, and the Unified Parkinson Disease Rating Scale in people with parkinsonism [corrected] [published erratum appears in PHYS THER 2010 Mar;90(3):462]. Phys Ther. 2008;88(6):733-46.

253. Tyson S, Connell L. The psychometric properties and clinical utility of measures of walking and mobility in neurological conditions: a systematic review. Clin Rehabil. 2009 Nov;23(11):1018-33.

254. Gyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc 1985 Apr 15;132(8):919-23.

255. Finch E, Brooks D, Stratford PW, Mayo NE. Physical rehabilitation outcome measures: a guide to enhanced clinical decision making. Second ed. Baltimore: Lippincott Williams & Wilkins; 2002, p 248-51.

256. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7.

257. Borg G. Borg´s perceived exertion and pain scales. Human Kinetics. 1998.

258. Borg G, Hassmen P. Upplevd ansträngning som hjälp att styra motionsintensiteten [Perceived exertion as a help to control physical activity intensity]. Physical Activity in the prevention and treatment of disease. Stockholm: Statens folkhälsoinstitut; 2003. p. 53-64.

259. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. Eur Respir J. 1999;14(2):270-4.

260. Paltamaa J, West H, Sarasoja T, Wikström J, Mälkiä E. Reliability of physical functioning measures in ambulatory subjects with MS. Physiother Res Int. 2005;10(2):93-109.

261. Andersson C, Asztalos L, Mattsson E. Six-minute walk test in adults with cerebral palsy. A study of reliability. Clin Rehabil. 2006 Jun;20(6):488-95.

262. Collen FM, Wade DT, Robb GF, Bradshaw CM. The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. Int Disabil Stud. 1991 Apr-Jun;13(2):50-4.

263. Sackley C, Richardson P, McDonnell K, Ratib S, Dewey M, Hill HJ. The reliability of balance, mobility and self-care measures in a population of adults with a learning disability known to a physiotherapy service. Clin Rehabil. 2005 Mar;19(2):216-23.

264. Forlander DA, Bohannon RW. Rivermead Mobility Index: a brief review of research to date. Clin Rehabil. 1999 Apr;13(2):97-100.

265. Green J, Forster A, Young J. A test-retest reliability study of the Barthel Index, the Rivermead Mobility Index, the Nottingham Extended Activities of Daily Living Scale and the Frenchay Activities Index in stroke patients. Disabil Rehabil. 2001 Oct 15;23(15):670-6.

266. Sonn U, Hulter Åsberg K. Assessment of activities of daily living in the elderly. A study of a population of 76-year-olds in Gothenburg, Sweden. Scand J Rehabil Med. 1991;23(4):193-202.

267. Hulter Åsberg K, Sonn U. The cumulative structure of personal and instrumental ADL. A study of elderly people in a health service district. Scand J Rehabil Med. 1989;21(4):171-7.

268. Sonn U, Grimby G, Svanborg A. Activities of daily living studied longitudinally between 70 and 76 years of age. Disabil Rehabil. 1996 Feb;18(2):91-100.

269. Sonn U. Longitudinal studies of dependence in daily life activities among elderly persons. Scand J Rehabil Med Suppl. 1996;34:1-35.

270. Holbrook M, Skilbeck CE. An activities index for use with stroke patients. Age Ageing. 1983 May;12(2):166-70.

271. Wade DT, Legh-Smith J, Langton Hewer R. Social activities after stroke: measurement and natural history using the Frenchay Activities Index. Int Rehabil Med. 1985;7(4):171-81.

272. Turnbull JC, Kersten P, Habib M, McLellan L, Mullee MA, George S. Validation of the Frenchay Activities Index in a general population aged 16 years and older. Arch Phys Med Rehabil. 2000 Aug;81(8):1034-8.

273. Hsieh CL, Jang Y, Yu TY, Wang WC, Sheu CF, Wang YH. A Rasch analysis of the Frenchay Activities Index in patients with spinal cord injury. Spine (Phila Pa 1976). 2007 Feb 15;32(4):437-42.

274. Hsueh IP, Wang WC, Sheu CF, Hsieh CL. Rasch analysis of combining two indices to assess comprehensive ADL function in stroke patients. Stroke. 2004 Mar;35(3):721-6.

275. Mendell JR, Florence J. Manual muscle testing. Muscle Nerve. 1990;13(suppl):S16-S20.

276. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization; 2000.

277. Grimby G. Physical activity and muscle training in elderly. Acta Med Scand Suppl. 1986;711:233-7.

278. Mattiasson-Nilo I, Sonn U, Johannesson K, Gosman-Hedström G, Persson GB, Grimby G. Domestic activities and walking in the elderly: evaluation from 30-hour heart rate recording. Aging. 1990;2(2):191-8.

279. Frändin K, Grimby G. Assessment of physical activity, fitness and performance in 76-years olds. Scand J Med Sci Sports. 1994;4(1):41-6.

280. Johansson E, Lindberg P. Low back pain patients in primary care: subgroups based on the multidimensional pain inventory. Int J Behav Med. 2000;7(4):340-52.

281. Yordy GA, Lent RW. Predicting aerobic exercise participation: social cognitive, reasoned action, and planned behavior models. J Sport Exerc Psychol. 1993 Dec;15(4):363-74.

282. Dzewaltowski DA. Toward a model of exercise motivation. J Sport Exerc Psychol. 1989;11(3):251-69.

283. Boyer F, Morrone I, Laffont I, Dizien O, Etienne JC, Novella JL. Health related quality of life in people with hereditary neuromuscular diseases: an investigation of test-retest agreement with comparison between two generic questionnaires, the Nottingham health profile and the short form-36 items. Neuromuscul Disord. 2006 Feb;16(2):99-106.

284. Dallmeijer AJ, de Groot V, Roorda LD, Schepers VP, Lindeman E, van den Berg LH, et al. Cross-diagnostic validity of the SF-36 physical functioning scale in patients with stroke, multiple sclerosis and amyotrophic lateral sclerosis: a study using Rasch analysis. J Rehabil Med. 2007 Mar;39(2):163-9.

285. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr. 2007 May;96(5):644-7.

286. Kirkwood BR, Sterne JAC. Essential medical statistics. 2nd ed. Oxford: Blackwell Publishing Ltd; 2003.

287. Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. Psychol Bull. 1979;86(2):420-8.

288. Hicks CM. Research for physiotherapists: project design and analysis. second ed. Edinburgh: Churchill Livingstone; 1995.

289. Ahlstrom G, Gunnarsson LG, Kihlgren A, Arvill A, Sjoden PO. Respiratory function, electrocardiography and quality of life in individuals with muscular dystrophy. Chest. 1994 Jul;106(1):173-9.

290. Boström K, Ahlström G. Living with a deteriorating disease: the trajectory with muscular dystrophy over ten years. Disabil Rehabil. 2004;26(23):1388-98.

291. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med. 1999 Jun;48(11):1507-15.

292. Schwartz CE. Applications of response shift theory and methods to participation measurement: a brief history of a young field. Arch Phys Med Rehabil. 2010 Sep;91(9 Suppl):S38-43.

293. Schneidert M, Hurst R, Miller J, Ustun B. The role of environment in the International Classification of Functioning, Disability and Health (ICF). Disabil Rehabil. 2003;25(11-12):588-95.

294. Michelsen SI, Flachs EM, Uldall P, Eriksen EL, McManus V, Parkes J, et al. Frequency of participation of 8-12-year-old children with cerebral palsy: a multi-centre cross-sectional European study. Eur J Paediatr Neurol. 2009 Mar;13(2):165-77.

295. Ostensjo S, Carlberg EB, Vollestad NK. The use and impact of assistive devices and other environmental modifications on everyday activities and care in young children with cerebral palsy. Disabil Rehabil. 2005 Jul 22;27(14):849-61.

296. Eek MN, Beckung E. Walking ability is related to muscle strength in children with cerebral palsy. Gait Posture. 2008 Oct;28(3):366-71.

297. Erdmann PG, Teunissen LL, van Genderen FR, Notermans NC, Lindeman E, Helders PJ, et al. Functioning of patients with chronic idiopathic axonal polyneuropathy (CIAP). J Neurol. 2007 Sep;254(9):1204-11.

298. Nitz JC, Burns YR, Jackson RV. Sit-to-stand and walking ability in patients with neuromuscular conditions. Physiotherapy. 1997;83(5):223-7.

299. Horlings CG, Kung UM, van Engelen BG, Voermans NC, Hengstman GJ, van der Kooi AJ, et al. Balance control in patients with distal versus proximal muscle weakness. Neuroscience. 2009 Dec 29;164(4):1876-86.

300. Pieterse AJ, Luttikhold TB, de Laat K, Bloem BR, van Engelen BG, Munneke M. Falls in patients with neuromuscular disorders. J Neurol Sci. 2006 Dec 21;251(1-2):87-90.

301. Eek MN, Tranberg R, Zugner R, Alkema K, Beckung E. Muscle strength training to improve gait function in children with cerebral palsy. Dev Med Child Neurol. 2008 Oct;50(10):759-64.

302. Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology. 2009 Nov 3;73(18):1478-84.

303. Flansbjer UB, Miller M, Downham D, Lexell J. Progressive resistance training after stroke: effects on muscle strength, muscle tone, gait performance and perceived participation. J Rehabil Med. 2008 Jan;40(1):42-8.

304. Kroksmark AK, Ekstrom AB, Bjorck E, Tulinius M. Myotonic dystrophy: muscle involvement in relation to disease type and size of expanded CTG-repeat sequence. Dev Med Child Neurol. 2005 Jul;47(7):478-85.

305. Milner-Brown HS, Miller RG. Muscle strenghtening through high-resistance weight training in patients with neuromuscular disorders. Arch Phys Med Rehabil. 1988 Jan;69(1):14-9.

306. Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. Sleep Med Rev. 2006 Feb;10(1):63-76.

307. Phillips MF, Steer HM, Soldan JR, Wiles CM, Harper PS. Daytime somnolence in myotonic dystrophy. J Neurol. 1999;246(4):275-82.

308. Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BG, Bleijenberg G. The development of a model of fatigue in neuromuscular disorders: a longitudinal study. J Psychosom Res. 2007 May;62(5):571-9.

309. Chasens ER, Sereika SM, Weaver TE, Umlauf MG. Daytime sleepiness, exercise, and physical function in older adults. J Sleep Res. 2007 Mar;16(1):60-5.

310. Basta M, Lin HM, Pejovic S, Sarrigiannidis A, Bixler E, Vgontzas AN. Lack of regular exercise, depression, and degree of apnea are predictors of excessive daytime sleepiness in patients with sleep apnea: sex differences. J Clin Sleep Med. 2008 Feb 15;4(1):19-25.

311. Nitz J, Burke B. A study of the facilitation of respiration in myotonic dystrophy. Physiother Res Int. 2002;7(4):228-38.

312. Ugalde V, Breslin EH, Walsh SA, Bonekat HW, Abresch RT, Carter GT. Pursed lips breathing improves ventilation in myotonic muscular dystrophy. Arch Phys Med Rehabil. 2000 Apr;81(4):472-8.

313. Haas CF, Loik PS, Gay SE. Airway clearance applications in the elderly and in patients with neurologic or neuromuscular compromise. Respir Care. 2007 Oct;52(10):1362-81; discussion 81.

314. Hoffman AJ, Jensen MP, Abresch RT, Carter GT. Chronic pain in persons with neuromuscular disease. Phys Med Rehabil Clin N Am. 2005 Nov;16(4):1099-112, xii.

315. Wu G, Sanderson B, Bittner V. The 6-minute walk test: How important is the learning effect? Am Heart J. 2003 Jul;146(1):129-33.

316. Jordan JL, Holden MA, Mason EE, Foster NE. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2010(1):CD005956.

317. Belanger AY, Noel G. Compliance to and effects of a home strengthening exercise program for adult dystrophic patients: a pilot study. Physiother Can. 1991 Jan-Feb;43(1):24-30.

318. Nätterlund B, Ahlström G. Experience of social support in rehabilitation: a phenomenological study. J Adv Nurs. 1999;30(6):1332-40.

319. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev. 1977 Mar;84(2):191-215.

320. Mulligan H. Promotion of physical activity for individuals with neurological disability. Dunedin: University of Otago; 2010.

321. Bandura A. Health promotion from the perspective of social cognitive theory. Psychol Health. 1998;13(4):623-49.

322. McAuley E, Blissmer B. Self-efficacy determinants and consequences of physical activity. Exerc Sport Sci Rev. 2000 Apr;28(2):85-8.

323. Trost SG, Owen N, Bauman AE, Sallis JF, Brown W. Correlates of adults' participation in physical activity: review and update. Med Sci Sports Exerc. 2002 Dec;34(12):1996-2001.

324. Ayotte BJ, Margrett JA, Hicks-Patrick J. Physical activity in middle-aged and young-old adults: the roles of self-efficacy, barriers, outcome expectancies, self-regulatory behaviors and social support. J Health Psychol. 2010 Mar;15(2):173-85.

325. Physical activity programs and behavior counseling in older adult populations. Med Sci Sports Exerc. 2004 Nov;36(11):1997-2003.

326. ACSM. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness and flexibility in healthy adults. Med Sci Sports Exerc. 1998;30(6):975-91.

327. O'Keefe DJ. Post hoc power, observed power, a priori power, retrospective power, prospective power, achieved power: sorting out appropriate uses of statistical power analyses. Commun Methods Meas. 2007;1(4):291-9.

328. Rimmer JH, Chen MD, McCubbin JA, Drum C, Peterson J. Exercise intervention research on persons with disabilities: what we know and where we need to go. Am J Phys Med Rehabil. 2010 Mar;89(3):249-63.

329. Estellat C, Torgerson DJ, Ravaud P. How to perform a critical analysis of a randomised controlled trial. Best Pract Res Clin Rheumatol. 2009 Apr;23(2):291-303.

330. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, Group ftC. Extending the CONSORT Statement to Randomized Trials of Nonpharmacologic Treatment: Explanation and Elaboration. Annals of Internal Medicine. 2008 February 19, 2008;148(4):295-309.

331. Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34-42.

332. Bohannon RW, Shove ME, Barreca SR, Masters LM, Sigouin CS. Five-repetition sit-to-stand test performance by community-dwelling adults: a preliminary investigation of times, determinants, and relationship with self-reported physical performance. Isokinetics & Exercise Science. 2007;15(2):77-81.

333. Bohannon RW. Reference values for the five-repetition sit-to-stand test: a descriptive meta-analysis of data from elders. Percept Mot Skills. 2006 Aug;103(1):215-22.

334. Buatois S, Miljkovic D, Manckoundia P, Gueguen R, Miget P, Vancon G, et al. Five times sit to stand test is a predictor of recurrent falls in healthy community-living subjects aged 65 and older. J Am Geriatr Soc. 2008 Aug;56(8):1575-7.

335. Talbot K, Stradling J, Crosby J, Hilton-Jones D. Reduction in excess daytime sleepiness by modafinil in patients with myotonic dystrophy. Neuromuscul Disord. 2003;13(5):357-64.

336. Whittaker RG, Ferenczi E, Hilton-Jones D. Myotonic dystrophy: practical issues relating to assessment of strength. J Neurol Neurosurg Psychiatry. 2006 Nov;77(11):1282-3.

337. Wynia K, Middel B, Van Dijk JP, De Ruiter H, Lok W, Ha De Keyser J, et al. Broadening the scope on health problems among the chronically neurologically ill with the International Classification of Functioning (ICF). Disabil Rehabil. 2006;28(23):1445-54.

338. Cieza A, Geyh S, Chatterji S, Kostanjsek N, Ustun B, Stucki G. ICF linking rules: an update based on lessons learned. J Rehabil Med. 2005;37(4):212-8.

Appendix

The modified ICF checklist

* Categories added to the ICF checklist by the authors.

List of 29 Body Functions

b1.	**Mental functions**
b110	Consciousness (Daytime sleepiness)
b114	Orientation
b130	Energy and drive functions
b134	Sleep
b140	Attention
b144	Memory
b164	Higher-level cognitive functions
b2.	**Sensory functions and pain**
b210	Seeing
b215*	Functions of structures adjoining the eye (ptosis)
b230	Hearing
b280	Pain
b3.	**Voice and speech functions**
b310	Voice
b320*	Articulation functions
b4.	**Functions of the cardiovascular, haematological, immunological, and respiratory systems**
b410	Heart
b435	Immunological (allergies, hypersensitivity)
b440	Respiration (breathing)
b445*	Respiratory muscle functions
b450*	Additional respiratory functions (coughing, blowing)
b5.	**Functions of the digestive, metabolic and endocrine systems**
b510*	Ingestion functions (chewing, swallowing)
b515	Digestive
b525	Defecation
b540*	General metabolic functions (diabetes, insulin resistance)
b555	Endocrine glands (hormonal changes)
b6.	**Genitourinary and reproductive functions**
b620	Urination functions
b7.	**Neuromusculoskeletal and movement-related functions**
b710	Mobility of joint
b730	Muscle power
b765	Involuntary movements (myotonia)
b770*	Gait pattern functions
b8.	**Functions of the skin and related structures**
b850*	Functions of hair (baldness)

List of 52 Activities and Participation

d1.	**Learning and applying knowledge**
d166*	Reading
d170*	Writing
d172*	Calculating
d175	Solving problems
d2.	**General tasks and demands**
d210	Undertaking a single task
d220	Undertaking multiple tasks
d230*	Carrying out daily routine
d3.	**Communication**
d310-329	Communicating – receiving
d330-349	Communicating – producing
d4.	**Mobility**
d410*	Changing basic body position
d415*	Maintaining a body position
d430	Lifting and carrying objects, light objects
d430	Lifting and carrying objects, heavy objects
d440	Fine hand use (picking up, grasping)
d445*	Hand and arm use
d4500*	Walking short distances
d4501*	Walking long distances
d4502*	Walking on different surfaces
d4503*	Walking around obstacles
d4551*	Climbing
d4552*	Running
d4600*	Moving around within the home
d4601*	Moving around within buildings other than home
d4602*	Moving around outside the home and other buildings
d465	Moving around using equipment (wheelchair, walker etc.)
d470	Using transportation (car, bus, train, plane)
d475	Driving (riding bicycle and motorbike, driving car, etc.)

d5.	**Self-care**
d5100*	Washing body parts
d5101*	Washing whole body
d5102*	Drying oneself
d5201*	Caring for teeth
d5202*	Caring for hair
d5203-d5204*	Caring for finger and toenails
d530	Toileting
d5400*	Putting on clothes
d5401*	Taking off clothes
d5402*	Putting on footwear
d5403*	Taking off footwear
d550	Eating
d560	Drinking
d6.	**Domestic life**
d620	Acquisition of goods and services (shopping)
d630	Preparation of meals (cooking etc.)
d640	Doing housework (cleaning house, washing dishes, laundry, ironing, etc.)
d650*	Caring for household objects
d7.	**Interpersonal interactions and relationships**
d710	Basic interpersonal interactions
d720	Complex interpersonal interactions
d8.	**Major life areas**
d820	School education
d830	Higher education
d850	Remunerative employment
d860	Basic economic transactions
d870	Economic self-sufficiency
d9.	**Community, social and civic life**
d910	Community life
d920	Recreation and leisure

List of 23 Environmental factors

e1.	**Products and technology**
e110	For personal consumption (food, medicines)
e115	For personal use in daily living
e120	For personal indoor and outdoor mobility and transportation
e125	Products for communication
e155	Design, construction and building products and technology of buildings for private use
e3.	**Support and relationships**
e310	Immediate family
e320	Friends
e325	Acquaintances, peers, colleagues, neighbours and community members
e340	Personal care providers and personal assistants
e350*	Domesticated animals
e355	Health professionals
e4.	**Attitudes**
e410	Individual attitudes of immediate family members
e420	Individual attitudes of friends
e425*	Individual attitudes of acquaintances, peers, colleagues, neighbours and community members
e440	Individual attitudes of personal care providers and personal assistants
e450	Individual attitudes of health professionals
e460	Societal attitudes
e5.	**Services, systems and policies**
e525	Housing services, systems and policies
e540	Transportation services, systems and policies
e570	Social security, services, systems and policies
e575	General social support services, systems and policies
e580	Health services, systems and policies
e590	Labour and employment services, systems and policies