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Health-enhancing participation in girls and women with Rett syndrome - a balancing act

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Health-enhancing participation in girls and women with Rett syndrome

– A balancing act

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Key words:Rett syndrome, multiple disabilities, outcome measures, physical behavior, physical activity, sedentary behavior, facilitators, barriers, participation, 'uptime' activities

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Don't walk behind me; I may not lead.
Don't walk in front of me; I may not follow.
Just walk beside me and be my friend.

Albert Camus

Contents

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Abstract

Rett syndrome (RTT) is a rare neurodevelopmental disorder usually affecting females. It is associated with multiple disabilities including intellectual disability leading to a high level of dependency in all aspects of daily living including participation in physical activities.

The overall aim of this thesis was to investigate physical activity behaviors by developing measures of walking, describing patterns of physical behavior and influencing factors, and evaluating the effects of an intervention that focuses on participation in standing and walking activities (i.e. 'uptime' activities) in Danish girls and women with RTT.

This thesis comprises four studies. In study I, measurement properties of a modified two-minute walk test (2MWT) and a modified RTT-specific functional mobility scale (FMS-RS) were determined. Forty-two girls and women with RTT aged 2.4–60.9 years were included. Comparison measures were the Clinical Severity Score (CSS), Rett Syndrome Gross Motor Scale (RSGMS) and the mobility domain in the Pediatric Evaluation of Disability Inventory (PEDI-m). In study II, patterns of sedentary behavior and physical activity were described in a population-based sample including 48 girls and women with RTT aged 5.5–60.5 years. Participants wore the activPAL and StepWatch Activity Monitor (SAM) for at least four days. In study III, facilitators and barriers to participation in 'up-time' were explored from the perspectives of parents and professionals using focus groups. Data was analyzed using thematic analysis. In study IV, the feasibility and effectiveness of an individualized 12-wk 'uptime' participation intervention (U-PART) were evaluated in 14 girls and women with RTT aged 5.6-48.3 years. Each individual program focused on participation in enjoyable activities to promote 'uptime' in home, school/day center and community settings. Feasibility was assessed using a study-specific questionnaire. Primary outcomes were sedentary time (activPAL) and daily steps (SAM). Secondary outcomes were gross motor skills (RSGMS), walking capacity (2MWT), quality of life (Quality of Life Inventory-Disability, QI-Disability) and participation-level goals (Goal Attainment Scaling, GAS). Outcomes were evaluated on four occasions: at baseline and after a 6-week interval, immediately following the 12-week intervention program and 12 weeks after the intervention program.

Results showed low-moderate and moderate-high correlations between comparison measures and the 2MWT and FMS-RS, respectively. Intraclass correlation coefficients (ICC) were high for both the 2MWT (ICC=0.86-0.98) and FMS-RS (ICC=0.94-0.99) test values. In the 2MWT standard error of measurement (SEM) was 13.8m and minimal detectable difference (MDD) was calculated to be 38m (study I). On average 83.3% (SD 13.9%) of waking hours were spent in sedentary behaviors (n=48) and the median (IQR) daily step count was 5128 (2829–7704) (n=28). Advancing age and poorer walking skills were associated with higher levels of sedentary time (study II). Several facilitators and barriers of 'uptime' activities were identified within five subthemes relating to the individual girl/woman and her physical, organizational, social and attitudinal environment. The resources within each of the five areas needed to be balanced to enable optimal participation in 'uptime' activities (study III). Stakeholders perceived the U-PART intervention as feasible and significant positive effects were seen after the intervention in sedentary time (-4.1%), daily steps (+708 steps), 2MWT (+18.9m), QI-Disability (+2.8) and for individually determined goals. At follow-up, effects on sedentary time (-3.4%) and 2MWT (+12.4m) were maintained (study IV).

In conclusion both walking measures showed good concurrent validity and test-retest reliability and have the potential to be used in both clinical practice and research (study I). High levels of sedentary time and low daily step counts were demonstrated in RTT (study II). Parents and professionals described how opportunity for participation in 'uptime' activities depended on a balance of facilitators and barriers within the individual with RTT and the environment (study III). Knowledge from study I-III enabled the planning and implementing of a health-promoting intervention. The U-PART intervention was considered feasible with regards to acceptability and practicality, and positive effects were seen in the outcomes of sedentary time, daily step count, walking capacity, quality of life and participation-level goals, some maintained after a further 12 weeks (study IV).

This thesis contributes important knowledge to disability research in Denmark and internationally by focusing on the availability of valid outcome measures and health-promoting strategies in girls and women with RTT.

Summary in Danish

Rett syndrom (RTT) er en sjælden medfødt neurologisk udviklingsdefekt, der primært rammer piger. Personer med RTT har multiple funktionsevnenedsættelser, hvilket betyder, at de er afhængige af hjælp til at udføre alle dagligdags aktiviteter deriblandt til at deltage i fysiske aktiviteter. Det overordnede mål med denne afhandling har været at udvikle måleredskaber til at vurdere gangfunktion samt at beskrive mønstre i den stillesiddende tid og fysiske aktivitet og hvilke faktorer, der har indflydelse på dette hos piger og kvinder med RTT. Med denne viden blev en intervention udviklet og de sundhedsrelaterede effekter vurderet. Interventionen fokuserede på deltagelse i 'uptime' aktiviteter, dvs. stående og gående aktiviteter.

Selve afhandlingen består af fire delstudier. Som et første skridt mod at udvikle en intervention til piger og kvinder med RTT fokuserede delstudie I på at modificere og validere relevante måleredskaber til at vurdere gangkapacitet og gangformåen – en modificeret 2-minutters gangtest (2MWT) og en RTT-specifik udgave af Functional Mobility Scale (FMS-RS). I alt 42 piger og kvinder med RTT i alderen 2-60 år deltog i studiet. For at vurdere den samstemmende validitet blev 2MWT og FMS-RS sammenlignet med to RTT-specifikke og et generisk måleredskab. For at vurdere test-retest reliabiliteten blev 2MWT og FMS-RS gennemført to gange med en uges mellemrum. Både 2MWT og FMS-RS havde god samstemmende validitet og test-retest reliabilitet. Resultatet viste endvidere at en person med RTT skal forbedre sin gangkapacitet med minimum 38m på 2 minutter for at være 95 % sikker på, at der ikke er tale om måleusikkerhed.

For det andet har det været vigtigt at opnå viden omkring mønstre i den stillesiddende tid og fysiske aktivitet i en hel population af piger og kvinder med RTT. I delstudie II deltog 48 piger og kvinder med RTT i alderen 5-60 år. Deltagerne skulle anvende to accelerometre i minimum fire dage (activPAL og StepWatch Activity Monitor). Studiet viste, at deltagerne i de vågne timer var stillesiddende 83,3 % af tiden, og det daglige antal skridt var 5128 i gennemsnit hos de gående deltagere. Stigende alder og lavere niveau af gangfunktion var forbundet med mere stillesiddende tid.

I delstudie III blev der udført fokusgruppe interviews med forældre og fagpersoner for at få deres perspektiver på hvilke faktorer, der henholdsvis fremmer og hindrer

deltagelse i 'uptime' aktiviteter. Mange forskellige facilitatorer og barrierer blev identificeret og inddelt i fem områder i forhold til den enkelte pige/kvinde med RTT og de fysiske, organisatoriske, sociale og holdningsmæssige omgivelser. Ressourcerne indenfor disse områder skulle balanceres for at opnå optimale muligheder for deltagelse i 'uptime' aktiviteter.

I delstudie IV blev gennemførbarheden og effekten af en 12-ugers intervention undersøgt hos 14 piger og kvinder med RTT i alderen 5-48 år. Interventionen kaldes U-PART – 'Uptime' Participation. Hvert enkelt individualiserede program fokuserede på deltagelse i sjove og motiverende aktiviteter for at fremme 'uptime' i hjemmet, skolen/dagscentret og nærområdet. Gennemførbarheden blev undersøgt med et studie-specifikt spørgeskema. De primære effektmål var stillesiddende tid og daglige antal skridt. De sekundære effektmål var grovmotorik, gangkapacitet, livskvalitet og deltagelses-specifikke mål. Effektmålene blev vurderet i alt fire gange – to gange med et 6-ugers interval ved baseline og to gange med 12-ugers intervaller efter interventionen og en opfølgningsperiode. Forældre og fagpersoner vurderede, at interventionen var anvendelig og praktisk at gennemføre. Ved interventionens ophør sås positive effekter i forhold til stillesiddende tid (reduceret med 4,1 %), antal daglige skridt (øget med 708 skridt), gangkapacitet (øget med 18,9m på 2 minutter), livskvalitet (øget med 2,8 point) og deltagelses-specifikke mål (54 ud af 56 mål opfyldt helt eller delvist). Efter opfølgningsperioden var de positive effekter bevaret i forhold til stillesiddende tid (reduceret med 3,4 %) og gangkapacitet (øget med 12,4m på 2 minutter).

Med denne afhandling er to måleredskaber blevet modificeret og valideret, hvilke potentielt kan anvendes i klinisk praksis og forskning til at vurdere forskellige aspekter af gangfunktionen. Danske piger og kvinder med RTT udviste høje niveauer af stillesiddende tid og et lavt antal daglige skridt. Forældre og fagpersoner pegede på vigtigheden af at balancere pigens/kvindens og omgivelsernes ressourcer for at sikre deltagelse i 'uptime' aktiviteter. Den genererede viden fra delstudie I-III understøttede udviklingen og udførslen af en sundhedsfremmende intervention. U-PART interventionen blev opfattet som gennemførbar og førte til positive effekter i forhold til stillesiddende tid, antal daglige skridt, gangkapacitet og livskvalitet, hvoraf nogle af effekterne blev bibeholdt efter en kort opfølgningsperiode.

Sundhedsfremmende indsatser i mindre og sårbare grupper såsom personer med RTT understøtter udviklingen og bevarelsen af den størst mulige selvstændighed, inklusion, deltagelse og livskvalitet gennem hele livet. Denne afhandling bidrager med ny og vigtig viden både i Danmark og internationalt ved at sikre tilgængeligheden af valide og reliable måleredskaber og ved at fokusere på sundhedsfremmende strategier til piger og kvinder med RTT.

Abbreviations

ANOVA	Analysis Of Variance
ARSD	Australian Rett Syndrome Database
ASD	Autism Spectrum Disorder
CI	Confidence Interval
CP	Cerebral Palsy
CRS	Center for Rett Syndrome in Denmark
CSS	Clinical Severity Score
DIMS	Disorders of initiating and maintaining sleep subscale
DS	Down Syndrome
FMS-RS	Functional Mobility Scale – Rett Syndrome
GAS	Goal Attainment Scaling
HAS	Hoffer Ambulation Scale
HEPA	Health-Enhancing Physical Activity
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Functioning, Disability and Health
ID	Intellectual Disability
InterRett	International Rett Syndrome Database
IQR	Interquartile Range
MDD	Minimal Detectable Difference
MECP2	Methyl-CpG-binding protein 2
MCID	Minimal Clinically Important Difference
MRC	Medical Research Council
PA	Physical Activity
PEDI-m	Pediatric Evaluation of Disability Inventory – mobility subscale
QI-Disability	Quality of Life Inventory - Disability
RSBQ	Rett Syndrome Behavior Questionnaire
RSGMS	Rett Syndrome Gross Motor Scale
RTT	Rett Syndrome
SAM	StepWatch Activity Monitor
SD	Standard Deviation
SEM	Standard Error of Measurement
2MWT	Two Minute Walk Test
U-PART	'Uptime' Participation intervention
VAS	Visual Analogue Scale
WHO	World Health Organisation

Original papers

This thesis for the doctoral degree is based on the following papers referred to in the text by their Roman numerals:

I   Stahlhut M, Downs J, Leonard H, Bisgaard AM, Nordmark E. Building the repertoire of measures of walking in Rett syndrome. Disability and Rehabilitation. 2017 Sep;39(19):1926-1931.
https://doi.org/10.1080/09638288.2016.1212280

II   Stahlhut M, Downs J, Aadahl M, Leonard H, Bisgaard AM, Nordmark E. Patterns of sedentary time and ambulatory physical activity in a Danish population of girls and women with Rett syndrome. Disability and Rehabilitation. 2017 Oct 2: 1-9.
https://doi.org/10.1080/09638288.2017.1381181

III   Stahlhut M, Esbensen BA, Larsen JL, Bisgaard AM, Downs J, Nordmark E. Facilitators and barriers of participation in 'uptime' activities in girls and women with Rett syndrome – perspectives from parents and professionals. *Submitted for publication, minor revisions required.*

IV   Stahlhut M, Downs J, Wong K, Bisgaard AM, Nordmark E. Feasibility and effectiveness of an individualized 12-wk 'uptime' participation intervention (U-PART) in girls and women with Rett syndrome. *In manuscript*.

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Thesis at a glance

Study	Aims	Methods	Results
I	To modify two existing measures of walking capacity (2MWT) and performance (FMS) to enable their use in RTT To examine concurrent validity and test-retest reliability of the modified measures	N=42 girls/women aged 2.4-60.9 years with RTT (n=27 participated in 2MWT assessments) Comparative measures: CSS, RSGMS, PEDI-m Spearman Rank Correlation, ICC and MDD	Concurrent validity: Moderate correlations between 2MWT and comparative measures, moderate to strong correlations between FMS-RS and comparative measures. Test-retest reliability: Good in 2MWT (ICC=0.86-0.98) and FMS-RS (ICC=0.94-0.99). MDD in 2MWT = 38m.
II	To describe patterns of sedentary time and daily steps in girls/women with RTT To identify the associations between individual and environmental characteristics with sedentary time	N=48 girls/women aged 5.5-60.5 years with RTT ActivPAL (n=48) and SAM (n=28) worn ≥4 days Descriptive statistics, sedentary time and step count plotted by time, linear regression	Sedentary time: 83.3% (SD=13.9%) of waking hours. Daily step count: median 5128 (IQR=2829-7704). Majority of standing and walking activities took place during morning hours with sedentary time accumulating later in the day. Advancing age and lower walking skills were associated with higher sedentary time. High maternal PA and presence of PA policy were associated with reduced sedentary time in univariate analyses.
III	To explore the facilitators and barriers of participation in 'uptime' activities in girls/women with RTT from the perspectives of parents and professionals working with this group	N=25 parents and professionals (n=9 parents, n=4 care assistants, n=7 professionals from schools, n=5 professionals from day centers) 4 focus groups analysed using thematic analysis	One central theme: A constant balance to do the best thing for the girl/woman. Five subthemes of facilitators and barriers: 1) The girl/woman engaging in activity, 2) Using aids and the indoor and outdoor environ-ment, 3) Creating possibilities within organizational structures, 4) Together we provide the best possible daily life, 5) Our knowledge, motivation, attitude and beliefs have an impact.
IV	To evaluate the feasibility and health-related effects of an individualized 12-week 'Uptime' Participation (U-PART) intervention in girls/women with RTT	N=14 girls/women aged 5.6-48.3 years with RTT, 1-group pretest-posttest design N=30 parents and professionals assessed feasibility; ActivPAL, SAM (n=9), RSGMS, 2MWT (n=9), QI-Disability and GAS Descriptive statistics, linear mixed-effect models, Wilcoxon Signed Rank test	The U-PART intervention was very feasible with regards to acceptability and practicality. Positive effects in sedentary time (-4%), daily step count (+708), walking capacity (+18.9m), quality of life (+2.8points) and participation-level goals after intervention. Maintained effects on sedentary time and walking capacity at short-term follow-up.

Introduction

Rett syndrome (RTT) is one of the up to 8000 rare diseases that affect 6-8% of the population in Europe (~30 million people). In Europe a disease is rare when it affects less than 1 in 2000 citizens (1). Rare diseases typically begin in childhood, continue throughout life and are disabling. An individual with a rare disease presents with complex medical needs and as such heavy impacts are seen on the individual, the family, health services and the society (2). Across the lifespan economic costs often relate to special education services, reduced parental productivity and residential care (3). Individuals with RTT may suffer from comorbidities such as epilepsy, breathing abnormalities, feeding difficulties, constipation, scoliosis and osteoporosis which often require acute or planned hospitalizations. Each year, a girl with RTT attends on average nine medical appointments and approximately one third require hospital admission (4). Medical conditions such as lower respiratory tract infections could be mitigated through an active lifestyle and daily physical activity (5). Physical activity and recreation is a human right. The World Health Organization (WHO) state that:

> "Persons with disability should be provided with enough opportunities and support to perform sport and physical activities adapted to their physical conditions. The aim is to help persons with disability improve their muscle strength, their psychological well-being and quality of life by increasing the ability to perform daily living activities" (6)

According to Articles 25 and 26 in the United Nation's Convention on the Rights of Persons with Disabilities individuals have the right to enjoy the highest attainable standard of health and to receive habilitation services to attain and maintain maximum independence and participation in all aspects of life (7). Small and vulnerable groups of individuals with a disability such as RTT require special attention in this regard. The message to health professionals is to work towards the development and maintenance of gross motor skills, an active lifestyle and participation in everyday and recreational activities in individuals with RTT, using evidence-based strategies. This health-enhancing approach necessitates a balance of resources within the individual with RTT and her environment.

This introduction will start by giving a theoretical overview of important conceptual frameworks within disability research and the key concepts within this thesis. A thorough description of the clinical picture seen in RTT will then follow.

Conceptual frameworks

International Classification of Functioning, Disability and Health

Health is a state of complete physical, mental and social well-being and not merely the absence of disease (8). The International Classification of Functioning, Disability and Health (ICF) is a multidimensional framework involving the concepts of health, functioning and disability at individual and population level (9). It constitutes a biopsychosocial model integrating the dimensions of functioning and disability with contextual factors. Functioning and disability (part 1) includes two components of health: 1) body functions and structure and 2) activities and participation. Contextual factors (part 2) include environmental and personal factors which influence each of the components of health. The ICF model is presented in figure 1 with examples relevant to an individual with multiple disabilities.
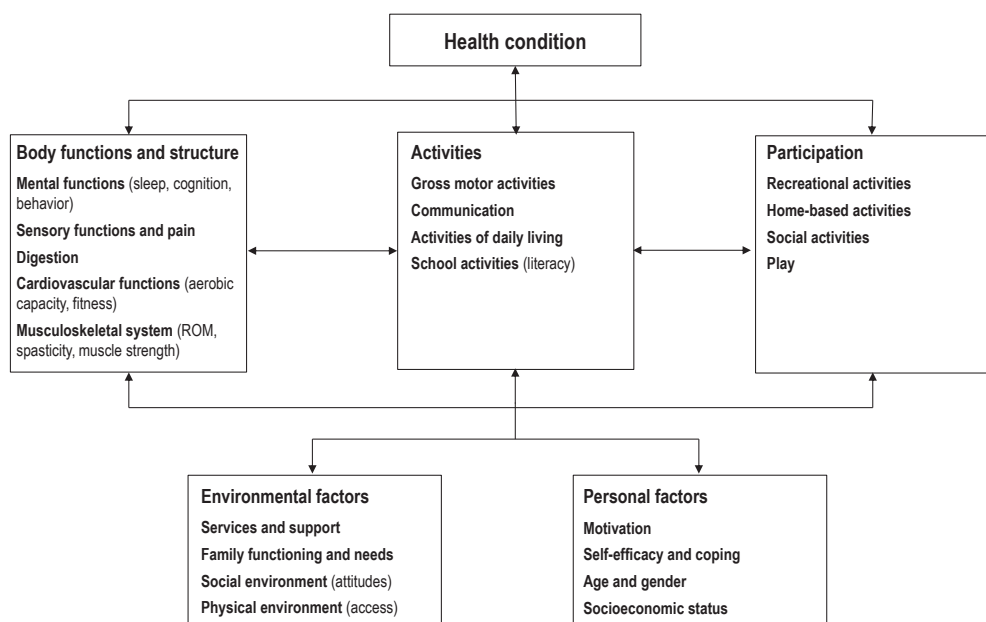
Figure 1. The ICF model with examples of content in each domain (9)

Impairments relate to problems in body functions and structure such as inadequate motor planning skills, reduced physical endurance and musculoskeletal deformity. Difficulties in performing age-appropriate tasks or actions denote activity limitations. Participation restrictions include difficulties in involvement in

different life situations. Participation in everyday activities such as physical, recreational, school/day center and household activities has positive impacts on the quality of life in children with neurodevelopmental disabilities (10). In adults with intellectual disability (ID) participation in physical activities also positively affects quality of life (11). In the ICF model, health can be considered in terms of the health status (e.g. elevated blood pressure, increased Cobb angle) of an individual (body functions and structure), what the individual can and does do (activities and participation) and the extent to which the health condition affects the life of the individual (9).

Within the field of intellectual and developmental disabilities individual quality of life has been defined as:

> 'A multidimensional phenomenon composed of core domains that constitute personal well-being. These domains are influenced by personal characteristics and environmental factors' (12)

The core domains are: physical well-being, material well-being, emotional well-being, interpersonal relations, self-determination, personal development, community participation and rights. The individual's quality of life can be favourably impacted by maximizing personal involvement, providing individualized supports and facilitating opportunities for personal growth (12).

The ICF model does not include the dimension of quality of life. McDougall el al have proposed a modified ICF model where quality of life and potential for development in an individual are incorporated as emergent and changing phenomena within all aspects of functioning that may be impacted by the individual's health condition and contextual factors (13).

Model of optimal participation

The conceptual model of optimal participation is informed by the ICF (see figure 2). This model proposes the notion that optimal participation in recreational activities involves an interaction and balance between multiple dimensions and determinants of participation (14). The three dimensions of participation are: 1) Physical engagement – doing the activity. Being actively involved underlies participation and has positive impacts on fitness and physical health; 2) Social engagement – interactions and feeling included. A sense of belonging defines successful and meaningful participation; 3) Self-engagement – enjoyment and choice-making. Enjoyment is paramount to engagement in activities and through choice people can identify preferred activities.

The three determinants of participation are: 1) Child-related attributes – combination of body function and personal factors, 2) Family-related attributes – socioeconomic status and family functioning, and 3) Environmental attributes – supportive physical, social, attitudinal and service environments. It is proposed that optimal participation results in better quality of life, a healthier lifestyle and emotional and psychosocial well-being.
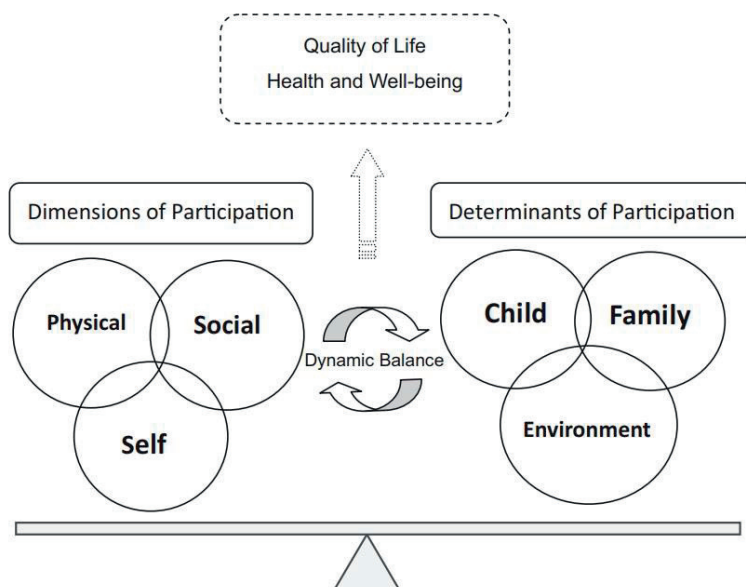
Figure 2. Model of optimal participation (14), reprinted with permission from Disability and Rehabilitation, www.tandfonline.com

In children living with their parents, the family provides the home environment and when they become adults and live in a residential setting, this then becomes their home environment. Even though this model is proposed for children with physical disabilities it could be valuable in adults also. Cohesion between residents and staff, resources and supports remain important determinants of participation in adults who live in residential settings. The dynamic balance of dimensions and determinants of participation changes across the lifespan. Kang et al suggest that during childhood playing with siblings may be an important activity with family support and home environment being key determinants. In adolescence and adulthood activities with peers and accessibility to community resources may be more relevant.

In individuals with multiple disabilities such as RTT, this dynamic balance of dimensions and determinants to enable adequate participation might be challenging to achieve. The limitations in physical and communicative functions (child-related attributes) could challenge active participation and choice-making (physical- and self-engagement) despite the desire for social engagement being very evident. Additionally, individuals with multiple disabilities experience a high need for assistance in all daily activities and therefore rely heavily on the resources and support within the family/residence and the physical, social, attitudinal and services environment.

Physical behavior

Physical behavior is defined as body movements, body postures and/or daily activities of a person in his/her own environment (15). In this thesis the umbrella term physical behavior will be used to encompass both physical activity and sedentary behavior. Physical activity, exercise and physical fitness are related but distinct terms. Fundamentally, physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is defined as repeated bodily movements that are planned and structured to improve or maintain physical fitness. Physical fitness refers to a set of attributes (e.g. health-related attributes such as cardiorespiratory endurance, muscle strength and flexibility) that relates to the ability to perform physical activity (16). Sedentary behavior is defined as any waking behavior characterized by an energy expenditure ≤ 1.5 metabolic equivalents while in a sitting or reclining posture (17).

Physical activity can be seen as a continuum from rest to high intensity activity. The continuum categorizes physical activity in different intensity zones such as "sedentary" (sitting, reclining), "light" (slow walking), "moderate" (walking,

cycling) and "vigorous" (fast walking, jogging, cycling uphill) (18). In children with cerebral palsy, standing is also seen as a light physical activity (19). In this thesis light physical activities such as standing and walking will be referred to as 'uptime' activities (20).
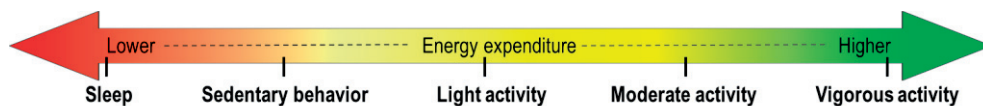
Figure 3. The physical activity continuum (modified from (21))

Health-enhancing physical activity

Health-enhancing physical activity (HEPA) is defined as any form of physical activity that benefits health and functional capacity. Examples of health-enhancing physical activities include walking, cycling, swimming, skiing, hiking, gardening, recreational sport, and dancing (22). In this thesis the term health-enhancing participation is used to describe the physical-, social- and self-engagement when the individual participate in motivating physical activities such as standing and walking, or 'uptime' activities.

Physical activity recommendations

Regular physical activity is an essential health behavior with benefits for physical fitness, bone density, muscle and joint function and well-being in all individuals including those with a disability (11, 23-25). Furthermore, the pattern of sedentary behaviors is important with shorter sedentary bouts and frequent breaks providing bursts of physical activity having beneficial effects on metabolic health (26). Low levels of physical activity are often seen in individuals with disabilities which could lead to a downward spiral of deconditioning, physical deterioration and further reduction in physical activity. An inactive lifestyle has negative impacts on health such as reduced cardiorespiratory fitness, osteoporosis and greater dependence upon others for daily living (24).

The current physical activity recommendations in children and adults are moderate intensity physical activity for 60 minutes per day and 30 minutes per day, respectively. Vigorous intensity activities should be incorporated three times a

week for children and twice a week for adults (27). Step output from pedometer or accelerometers has been suggested as a reasonable approximation of daily physical activity with $\geq$ 11,500 steps/day recommended in children and $\geq$ 10,000 steps/day recommended in adults (28, 29). Based on limited evidence a general recommendation for individuals with a disability is 6,500-8,500 steps/day (30).

Recommendations to reduce the amount of sedentary time have not been developed to the same extent. It has been suggested that there should be a 5-minute break for every 60 minutes of sitting and some countries recommend that children should limit their screen-time to $\leq$ 2 hours/day (31, 32).

Recently, physical activity guidelines for people with cerebral palsy (CP) include participation in moderate-vigorous physical activity for 60 minutes $\geq$ 5 days/week. Sedentary time should be minimized on all days with $<$ 2 hours of non-occupational sedentary time per day or by breaking up periods of sitting for 2 minutes every 30-60 minutes (33). The authors acknowledge that promotion of physical activity in people with CP and especially in those with greater mobility limitations is challenging. However, it is plausible that a dose-response relationship could be evident in people with CP, suggesting that small increases in activity (moving from sedentary to light physical activities) could still have health benefits (23, 33, 34).

Factors influencing physical activity

Several studies have examined the factors that in particular influence physical activity and participation in recreation and sports in children and adults with physical and mild-moderate ID. Less is known in relation to individuals with multiple disabilities (35) and the potential role of light physical activities in this group. In cross-sectional studies the factors associated with physical activity have been assessed (36-42). Qualitative studies including both children and adults with disabilities, parents and professionals have suggested facilitators and barriers to physical activity (35, 43-47). Below a short list of some of the influencing factors found in the above mentioned literature is presented (table 1). From the table it is seen that the combination of quantitative and qualitative studies provides a broad and complex description of factors influencing physical activity. All domains of the ICF are covered in this body of studies. The quantitative studies provide evidence of significant associations within the domains of body functions and structure and activity/participation in particular whereas the qualitative studies of facilitators and barriers deepen our understanding especially within the environment.

Table 1. Factors influencing physical activity in individuals with physical and intellectual disabilities in different ICF domains

	Associated factors	Facilitators	Barriers
Body functions and structure	*Health issues (e.g. obesity, mental illness) *Level of mobility impairment *Fitness level (e.g. aerobic capacity, muscle strength) *Level of intellectual disability	*Walking ability *Good communication level	*Health issues *Severe physical limitations *Pain *Fatigue *Aging *Cognitive/communication impairments
Activities and participation	*TV-viewing with siblings/friends *Participation in home and community activities *Sport club participation	*Opportunities of social interaction	
Personal factors	*Age *Gender *Preferences	*Meaningful activities *Positive attitude	*Lack of enjoyment/ motivation *Frustration
Physical environment	*Weather *Costs *Transportation	*Optimum mobility aids *Use existing facilities *Establishing routines	*Weather *Costs *Lack of: equipment, programs, trained staff *Accessibility *Limited health promotion focus *Limited time
Social environment	*Support *Socioeconomic status * Father physical activity level	*Support from health professionals *Proactive parents/ family involvement *Positive attitudes/role-models *Communication between trainers	*Lack of support people/ health professionals *Balance family needs *Parental exhaustion *Negative attitudes *Lack of knowledge/ interest/acceptance *Limited partnerships between schools/activity providers/disability groups

Intervention approaches

Health promotion is the process of enabling people to increase their health and includes a range of social and environmental interventions designed to benefit the health and quality of life of people (48). It is generally recognized that promotion of physical activity needs to be a priority for individuals with disabilities and that evidence-based information is needed to provide guidelines of physical activity across the lifespan (37, 49).

In a review, Heller et al suggested that health promotion interventions for people with intellectual and developmental disabilities could be adapted from the health promotion research in aging populations (50). Strong research designs including randomized controlled trials with long-term follow-up are necessary to determine the evidence base. Important features of the intervention could include the use of natural settings and peer leaders or volunteers for meaning and motivation, structured using of behavior change theories such as the Trans-Theoretical Model. This model is a motivational theory for behavior change including Stages of Change as one dimension. The five stages of Stages of Change include: Precontemplation, contemplation, preparation, action and maintenance. An individual can be classified in one of the stages according to their behavior or intention towards physical activity (51).

Participation-based approach

The participation-based approach for interventions is based on the model of optimal participation and has implications for physical and occupational therapy practice and research (52). The expected output of a participation-based approach would be achievement of identified goals for home and community participation and as such it complements a health promotion intervention. Therefore, interventions should be goal-oriented (meaningful and client-selected goals), family/client-centred (promoting self-determination and decision making), collaborative (building partnership between professionals and caregivers), strength-based (building on participant and caregiver's strengths), ecological (based on natural environment and real-life experiences) and self-determined. Building upon the theory of self-determined learning changes are supposed to occur when the participant and caregivers believe the intervention is beneficial, are engaged, feel in control of decisions and that goals and strategies are coherent (52). Self-Determination Theory is a motivational theory that describes three basic needs associated with motivation: Autonomy (initiate and regulate actions), competence (self-efficacy) and relatedness (be connected to others). When these needs are met individuals should be more prone to pursue a healthy behavior (53).

The participation-based intervention should follow a five-step process including development of a collaborative relationship, assessment of strengths of the participant and the environment, determination of goals, implementation of individualized intervention plan and evaluation of processes and outcomes with caregivers. In this process the physical therapist should act as a consultant and collaborate with the caregivers to share knowledge, identify necessary adaptations

and provide support and instructions to build capacity within the participant and caregivers (52).

Rett syndrome

Rett syndrome (RTT) is a neurodevelopmental disorder which mainly affects females and results in multiple disabilities. The incidence is approximately 1 per 9000 females (54) and is considered to be one of the most common genetic causes of severe intellectual disability in females (55). The syndrome was first described by an Austrian neurologist Andreas Rett (56) and later Bengt Hagberg and colleagues brought international attention to the disorder (57). In the textbox below the revised clinical criteria are described (58).

Clinical criteria (58)
Period of regression followed by stabilisation
4 main criteria:
1. Loss of hand skills
2. Loss of communication skills
3. Gait abnormalities (dyspraxic or absent)
4. Hand stereotypies

11 supportive criteria:
1. Breathing abnormalities when awake
2. Bruxism when awake
3. Sleep dysfunction
4. Abnormal muscle tone
5. Vasomotor disturbances
6. Scoliosis/kyphosis
7. Poor growth
8. Small cold hands and feet
9. Inappropriate laughing/screaming
10. Diminished response to pain
11. Intense eye communication

Typical RTT is characterized by regression of purposeful hand use and spoken language, development of abnormal gait and hand stereotypies. In atypical RTT individuals present with many but not necessarily all of the clinical features (58). In 1999, Amir and colleagues identified mutations in the gene encoding Methyl-CpG-binding protein 2 (*MECP2*) as the main cause of RTT (59). Mutations in *MECP2* are found in 95-97% of cases with typical RTT and in 50-70% of cases with atypical RTT (60, 61). More than 200 distinct *MECP2* mutations have been documented with 8 mutations being the most common (62). The clinical presentation of RTT varies significantly and thus multiple genotype-phenotype correlation studies have been performed (60, 62-65). These studies have found that p.Arg133Cys, p.Arg294*, p.Arg306Cys and C-terminal mutations are associated with less severe clinical severity whereas p.Arg168*, p.Arg255*, p.Arg270* and large deletions are associated with greater clinical severity. For most mutations clinical severity also increases with age (62). Knowledge of genotype-phenotype associations could serve as a prognostic tool for both health care professionals and families (62).

During the first 6-18 months of life the development in females with RTT is largely normal. Then development is arrested and the girl loses many of her acquired skills (57). Some retrospective studies have, however, found subtle signs such as low muscle tone, feeding difficulties, autistic traits and problems initiating movements during early development (66, 67). Furthermore, Einspieler et al found abnormal fidgety movements in 22 cases during the first 6 months of life and Marschik et al have found deviations in the development of speech-language in 15 cases in the first two years of their lives (68, 69). The period of regression most often occurs when the child is between 1 and 4 years. Additionally, the girl can experience extreme screaming/crying episodes, autistic-like behaviors, gait abnormalities and the hallmark characteristic of stereotypic hand movements becomes apparent. Subsequently, a period of stabilisation occurs which lasts from preschool ages to adulthood for the majority. Often the girl becomes more aware of her surroundings and she is able to make some progress in skill development. Later in life deterioration might occur where the woman experiences reduced mobility with development of foot and hand deformities (70, 71). However, some studies show that girls/women with RTT can regain walking and preserve gross motor abilities indicating that this motor deterioration could be avoided in some cases (72-75).

Clinical characteristics and co-morbidities

Hand stereotypies

Hand stereotypies are a necessary criterion for diagnosis in typical RTT (58). In 2009, an Australian study analyzed video recordings of 144 individuals with RTT and found that hand stereotypies were present in 94.4% (76). Midline symmetric washing or wringing movements were the most common stereotypies but clapping, tapping and mouthing or clasping of one hand were also very frequent (76, 77).

Breathing abnormalities

Breathing abnormalities are present in more than 80% and occur during wakefulness (78, 79). In an international cohort of 413 girls and women with RTT aged 2-57 years abnormal breathing patterns were reported in 74% with 46.4% hyperventilating and 68.8% breath-holding (80). Breathing irregularities include apnea, hyperventilation, breath holding, deep breathing, and valsalva breathing and are caused by an immature brain stem which modulates the respiratory rhythm (81, 82).

Sleep dysfunction

In a longitudinal study using data from the Australian Rett Syndrome Database (ARSD) sleep problems occurred in more than 80% and the prevalence decreased with age (83). A cross-sectional study using data from International Rett Syndrome Database (InterRett) showed that night waking (75.4%), difficulties falling asleep (60.4%) and night laughing (58%) were the most prevalent sleep problems. Initiating and maintaining sleep was most disturbed in younger children (84).

Epilepsy

Epilepsy is a common comorbidity in RTT. Cross-sectional studies using the Rett Networked Database and InterRett have shown that epilepsy was present in 68.1% and 61%, respectively (85, 86). Findings from the longitudinal Rett syndrome Natural History Study show that point prevalence of active seizures ranged from 30-44% whereas the cumulative lifetime prevalence approached 90% (87). Studies have reported stabilisation or improvement in epilepsy in older women (88). In a large cross-sectional study of adult health approximately 45% of women aged ≥18 years experienced seizures and almost two-thirds continued to use anti-epileptic drugs (89). All seizure types can be present in RTT with generalized tonic-clonic, complex partial, tonic and myoclonic seizures being the most common. However,

non-epileptic events are also common (90). Frequency of seizures is associated with physical behaviors. It has been shown that girls/women with weekly or daily seizures were less physically active and more sedentary than those with monthly or no seizures (91).

Neurological impairments

Dyspraxia makes it difficult to plan movement and is very pronounced in RTT. Sensory and motor pathways seem intact, yet, central processing of sensory and motor input seems to be problematic (92). For example, spontaneous movements like scratching ears or brushing away hair from the face are well preserved in RTT (93). Individuals with RTT also experience altered muscle tone. Most children with RTT have low muscle tone but later in life, increased muscle tone, dystonia and parkinsonian rigidity may be observed (92, 94).

Musculoskeletal impairments

Individuals with RTT often develop orthopedic problems such as scoliosis, hip instability, and feet deformities. Neuromuscular scoliosis is the most frequent complication which affects posture, movement, digestion, respiration and quality of life (95). In a population-based study from Australia including 394 females scoliosis occurred in more than half (66.2%) and the median age of scoliosis onset was 11 years. Age of onset and scoliosis progression were influenced by genotype with more severe mutations associated with earlier onset and greater progression. Furthermore, those who never learned to walk and those with later loss of walking showed marked progression of scoliosis compared to those who could walk independently or with assistance (96). The risk of osteoporosis and fractures is also high in RTT as bone mass is significantly reduced compared to healthy controls (97, 98).

Growth, nutrition and gastrointestional disorders

During the first two years of life, growth often decelerates and height and/or weight for height may fall 2SD below average (71). In 123 women with RTT 52.8% were underweight and 46.3% were within normal weight (89) but these data could be influenced by survival bias. Most individuals with RTT enjoy eating, however, many experience feeding difficulties (99). The difficulties include spitting, poor oromotor control affecting chewing and swallowing and reflux. Mild to moderate malnutrition is not uncommon and dietary supplementation might be needed. If low weight persists and excessive time is spent feeding a percutaneous gastrostromy tube (PEG) might be considered (100, 101). Gastroesophageal reflux

disease (GERD) and constipation are common problems in RTT. In a US survey families reported that 39% suffered from GERD and 80% suffered from constipation (102). Reflux was reported in 15.3% and constipation in 82.8% of women ≥18 years in an Australian study (89).

Gross motor skills

Crawling and walking is often delayed in RTT. Most of the children will not learn to crawl in a reciprocal pattern (103) but a high proportion of individuals with RTT are able to sit independently (99, 104). Retrospective reports from the 1990's have shown that between 65-80% of individuals with RTT learn to walk, yet, 30-60% might lose this ability later in life (74, 105). In a UK cross-sectional study of 87 participants Cass et al found that 51.8% were able to walk independently or with light support (99). Similarly, in an Australian study of 99 participants Downs et al found that 45.8% were able to walk 10 steps independently or with minimal support (104). In 27 Danish women older than 30 years, Schönewolf-Greulich found that 66% were able to walk 10 steps independently or with minimal support (72), possibly affected by survival bias. For those individuals with RTT who can walk, gait is characterized by ataxia and dyspraxia. Two gait patterns have been described: A stiff-legged gait with constant heel contact during the stance phase, significant lateral trunk movement and wide base of support and toe-walking with no heel contact (106, 107).

In general, the gross motor repertoire is limited in RTT, but some children have been able to jump, ski or use rollerblades (108). Furthermore, Downs et al have shown that many individuals with RTT experience difficulties with transitions (sit-to-stand from chair/floor) which could be explained by dyspraxia, altered muscle tone and poor balance (104). Only a minority (13.5–24.2%) could perform complex daily mobility activities such as stepping over an obstacle, walking on a slope or bending down to pick something up independently in a sample of 99 individuals (104). An Australian longitudinal study analyzed change in gross motor skills over a 3-4 year period. Overall, skills were maintained or slightly better in 40% and decreased in 60% of the participants. The greatest stability was seen in women with the ability to walk. This study shows that skills can be maintained and even acquired in girls and women with RTT over this time period (109).

Physical behavior

Knowledge of both gross motor skills and physical activity levels in RTT provide useful information about what they can do and what they actually do (110). In an Australian study using a StepWatch Activity Monitor (SAM) to assess activity in 64 girls and women with RTT aged 3½-38 years, the median daily step count was 5,093 steps and on average 62% of the waking hours were spent sedentary. Adults or those who needed assistance to walk took fewer steps and had more sedentary

time suggesting that advancing age and walking ability are predictors of physical behavior in RTT (91). The Australian sample was limited to those who could walk independently or with assistance and their definition of sedentary time as zero steps recorded on a SAM was a conservative estimate of sedentary behavior in the absence of a known step cut-point. Previously it had been suggested that many girls and women with RTT have the capacity to be more physically active (110). More data on physical activity patterns, comprising both sedentary behavior and physical activity and their influencing factors in both ambulant and non-ambulant individuals with RTT is needed to inform the development of health-promoting interventions to reduce sedentary time and increase light physical activity ('uptime' activities) in this group.

Fine motor and self-care skills

The loss of purposeful hand use is characteristic in RTT. Downs el al found that in 144 cases with RTT 30% were unable to grasp an object, 17% were capable of holding an object placed in their hand, 12% were able to grasp and hold a large object whereas the remaining had finer grasping skills (pick up small object like a raisin) (111). When grasping is poor the girl/woman might be able to press a switch to operate a toy (112). In a large genotype-phenotype correlation study the authors found that hand function was influenced by genotype. The poorest hand function was seen in p.R168X, p.R270X and large deletions and better hand function was seen in p.R133C, p.R306C and p.R294X (62). Hand function seems to be relatively stable over time (113, 114). Some reports show that girls and women with RTT are capable of learning self-feeding skills and they perform better when they are highly motivated (115, 116). In a study of 87 girls and women with RTT Cass et al found that approximately half were able to self-feed with fingers independently or assisted, about 55% cooperated or even assisted in dressing, and 28% were partially toilet trained (99). However, complete dependence for dressing, bathing/grooming and toileting functioning were observed for all 27 women ≥30 years in a Danish cohort (72).

Communication and cognition

Only approximately 7% of individuals with RTT are able to produce words with meaning (99). In 27 Danish women ≥30 years, high dependency in both comprehensive and expressive communication skills were observed, although, the majority could point to things of interest with their hands or eyes and they sought

social eye contact (72). Nevertheless, communication efforts can be difficult to interpret. Many individuals with RTT have intense eye contact and use eye-pointing, distinctive in RTT compared to individuals with an autism spectrum disorder (ASD). Individuals with RTT are able to make choices but they need more time due to latency in producing a response (71, 93, 99, 117, 118). Parents have described that their daughters are capable of expressing discomfort and pleasure and can make choices using vocalizations, body movements and eye gaze. Features of successful communication include the communication partners establishing eye contact, observing and responding to the individual's communicative attempts and allowing adequate time for the communication interactions (119).

ID is evident to a variable extent in RTT, yet it is not possible to perform intelligence tests which require well-developed hand function and/or communication skills which the individual with RTT does not possess (71). One study examined nonverbal cognitive social abilities in RTT with eye-tracking technology and found that 46 of 49 girls with RTT demonstrated a preference for socially weighted stimuli (they looked at people, and into people's eyes) (120). Recently, eye-tracking technology has been used to assess receptive vocabulary in 17 girls with RTT aged 3-12 years. The verbal comprehension abilities ranged from low-average to mild cognitive impairment in 32% and moderate to severe cognitive impairment in 68% (121).

Participation and quality of life

Knowledge about participation in activities at home or in the community in girls and women with RTT is now emerging. One study explored community participation in 214 girls and women with RTT aged 3-34 years (122). Participation was restricted and the frequency was influenced by walking ability, community support and the level of maternal education. A qualitative study involving six parent-carers of young women with RTT found that they wanted their daughters to have friends and participate in activities in the community, but that this was limited by their daughter's restricted communication skills and parental lack of time. Often the presence of siblings and families doing things together were associated with higher levels of social participation (123).

In 23 Danish girls aged 3-19 years living with their parents, family social activities (e.g. having tea/dinner together), indoor activities (e.g. watching TV and listening to music) occurred very often and showed high levels of participation and engagement. Outdoor activities such as using a swing and bicycling occurred

occasionally despite high levels of engagement (124). Similarly in a Swedish study from the Swedish National Rett Center, bathing/swimming, being outdoors/walking, listening to music, watching TV and being with family and friends were the most enjoyed activities among girls/women with RTT over time (125).

In a qualitative study 21 parents of daughters with RTT aged 7-18 years were interviewed about the aspects of life that were important for the happiness of their daughters. The importance of movement was highlighted with ambulant girls experiencing pleasure in walking and non-ambulant girls being satisfied with having their body position changed. Additionally, being included and social interactions were satisfying experiences (126). This suggests that offering motor opportunities has the potential to enhance quality of life in girls with RTT. However, less is known about the facilitators and barriers of participation in the activities that they seem to enjoy.

Mood and interest/pleasure was investigated in 91 girls and women with RTT aged 4-47 years and children consistently had better mood and more interests than the adolescents and adults with the possibility that well-being declines with age in RTT (127). Quality of life is an important outcome of services and interventions. However, available quality of life measures have not been directly validated in RTT. Recently, a new quality of life measure (QI-Disability) has been validated in 253 caregivers of children with RTT, Down syndrome (DS), CP and ASD. Compared to DS, children with RTT had lower 'social interaction', 'physical health', 'leisure and outdoors' and 'independence' subscale scores reflecting the differences in severity and impairments and their influences on quality of life in the two disorders (128).

Aging

In general improved longevity is seen in people with ID (129). Due to improved clinical management since RTT was first recognized, an increase in survival in RTT might be expected and thus careful planning of the long-term care becomes essential (130). A longitudinal study from Australia showed that survival was 77.6% at 20 years and 59.8% at 37 years (89). One 5-year longitudinal study of aging in RTT has been performed in 2012 in a group of 37 adult women with RTT aged 16-53 years. The overall profile showed a slow gross motor deterioration, preserved communication, less autonomic and epileptic features and a good general health (88). Further longitudinal studies are warranted to learn more about the aging process in RTT and to develop guidelines for life-long care management.

Outcome measures

In clinical practice valid outcome measures are needed to understand the effects of rehabilitation and interventions. Clinicians need to consider which ICF domains are relevant to the intervention and to the goals of the individual and family. Within certain populations such as CP, toolboxes or core sets of outcome measures have been developed to allow clinicians to choose the most useful tools (131, 132). Ideally, the same toolbox should be used internationally to create a cohesive approach and common language to outcome measurement (133). Concurrently with emerging clinical trials researchers recognize the need for robust outcome measures in RTT (134, 135). A large number of scales and outcome measures have been used in research but there is no international consensus regarding a core set to be used in RTT and a suite of disease-specific and psychometrically sound outcome measures is lacking. Table 2 shows a list of outcome measures commonly used in RTT classified according to the relevant ICF domains. The list is not exhaustive but includes measures from currently registered clinical trials, intervention studies within the last 5 years and measures that have been validated in RTT from the year 2000 and onwards. At the beginning of this PhD project measures of functional walking capacity and walking performance in different environments had not been used and are therefore not included in the table. Building the repertoire of walking measures is very important to understand how walking abilities are affected in RTT.

Table 2. Outcome measures used in RTT

ICF domain	Measures	Target population	Psychometric testing	Format
Body functions and structures				
Severity[a]	Clinical Severity Score (CSS) (60)	RTT (all ages)	Not available	13-item rating scale (clinicians)
	Clinical Global Impression Scale (severity and improvement) (135)	RTT (all ages)	Ongoing psychometric testing	Key anchors related to CSS on 7-point Likert scale (clinicians)
Cardiorespiratory (hyperventilation, apnea, heart rate)	BioRadio Wireless Physiology monitor (136)	Individuals with health conditions	Validity (n=17 24-35y, healthy controls, patients with acute lung injury and anaesthetised patients) (137)	Continuous chest respiratory inductance plethysmography and three lead ECG signals data collected (90-180 minutes)
Sleep	Disorders of initiating and maintaining sleep subscale (DIMS) (138)	School-aged children with/without sleep disorders	Internal consistency, Test-retest reliability (n=1157 controls, n=147 with sleep disorder, 6-15y)	7-item rating scale (caregivers)

Mental status	Anxiety, Depression and Mood Scale (ADAMS) (139)	Individuals with mental retardation	Convergent and discriminant validity (construct), internal consistency, test retest and interrater reliability (n=74 RTT 2-11y) (140)	28-item questionnaire (caregivers)
	Mood, Interest and Pleasure Questionnaire (MIPQ) (141)	Severe/profound ID (all ages)	Internal consistency, inter-rater and test-retest reliability (n=53 severe/profound ID 22-58y)	25-item questionnaire (caregivers)
Behavior	Rett Syndrome Behavior Questionnaire (RSBQ) (142)	RTT (all ages)	Face and content analysis, internal consistency, test-retest reliability (n=143 RTT, n=85 severe retardation, <19y) (142) and further validated in n=74 RTT 2-11y (140)	45-item questionnaire (caregivers)
	Aberrant Behavior Checklist (143)	Individuals with mental retardation >5y	Convergent and discriminant validity (construct), internal consistency (n=47 RTT 2-11y) (140)	58-item questionnaire (caregivers)
Physical behavior	Stepwatch Activity Monitor (SAM) (134)	Individuals with health conditions	Construct validity (accuracy), test-retest reliability (n=26 RTT, mean age 18y)	Objectively measured step count and cadence
	ActivPAL (144)	Sedentary populations	Construct validity (accuracy) (n=26 RTT, 9-20y)	Objectively measured time in lying/sitting
	Bouchard Activity Record (BAR) (20)	Children and adults	Concurrent validity (modified BAR, n=43 RTT, mean age 21y)	Self-report diary (caregivers)
Activity and participation				
Gross motor skills	Rett Syndrome Gross Motor Scale (RSGMS) (145)	RTT (all ages)	Factor analysis and comparison of known groups (n=255 RTT 2-37y), test-retest and absolute reliability (n=38 RTT 3-60y)	15-item standardized observational instrument (clinicians)
Communication	Inventory of Potential Communicative Acts (IPCA) (146)	Individuals with developmental disabilities and severe communication impairments	Inter-informant agreement in n=30 children with developmental disabilities and severe communication impairments	Descriptive tool with observation of 10 communication functions

	Communication and Symbolic Behavior Scales Developmental Profile (CSBS-DP) (147)	Young children with developmental delays (6mo-6y)	Concurrent and predictive validity, test-retest reliability (n=603 children from a non-randomized cohort 6-24mo)	Parent-report checklist, caregiver questionnaire and observation
Hand function	Level of hand function (adapted from Hand Apraxia Scale) (111)	RTT/(individuals with mental retardation)	Face and concurrent validity in n=239 adults with mental retardation	Classification scale 1-8
Functional abilities (fine and gross motor skills, social skills, language, cognitive skills, self-care)	Motor Behavioral Assessment (MBA) (148)	RTT (all ages)	No systematic validation	37-item observation (clinicians)
	Adapted Mullen Scales of Early Learning (MSEL-A) (149)	RTT (children), original version birth-5y8mo	Convergent and discriminant validity (construct), interrater reliability (n=47 RTT, 1y10mo–10y11mo)	144-item observation (clinicians)
	Functional Independence Measure for children (WeeFIM) (150)	Children with disabilities 6mo-7y	Content and concurrent validity, test-retest and inter-rater reliability	18-item rating scale (interview or observation)
	Vineland-II Adaptive Behavior Scales (VABS) (151)	Individuals with developmental delay or deficits in adaptive behavior (Birth-90y)	Factor analysis, content/ concurrent/ discriminant validity, internal consistency, test-retest and interrater reliability	383 items, interview or self-report format
Environmental factors				
Caregiver burden	RTT Caregiver Inventory Assessment (RTT-CIA) (152)	RTT (all ages)	Face and construct validity, internal consistency, test-retest reliability (n=70 RTT, mean age 12y)	26-item questionnaire (caregivers)
Quality of life				
Multidomain	Child Health Questionnaire (CHQ) (153)	Children 5-18y	Concurrent and discriminative validity, internal consistency, test-retest reliability (n=353 non-disabled children 5-13y)	50-item questionnaire (caregivers)
	Quality of Life Inventory – Disability (QI-Disability) (128)	Children with ID including RTT (5-18y)	Factor analysis, convergent and divergent validity (construct) (n=253, RTT, DS, CP, ASD, 5-18y)	32-item questionnaire (caregivers)

[a]Several other severity scores exist such as Kerr scale (154) and Pineda scale (155).

Interventions

There have been few intervention studies aiming to develop gross motor skills and promote an active lifestyle in RTT. A conductive education approach in 3 pre-school girls with RTT had positive effects on gross motor skills after a 18 months intervention period (156). Using a step wedge randomized controlled trial design, Downs et al evaluated the effect of an environmental enrichment intervention in 12 preschool girls with RTT (157). The intervention was consistent with motor learning theory and provided an enriched environment with motor, visual, and somatosensory stimulation for 2-3h six times a week during a 6 month period. Significant increases in gross motor skills and levels of Brain Derived Neurotrophic Factor (BDNF) in the blood were seen. BDNF is a neurotrophic factor necessary for neuronal development and brain function. This study suggests that environmental enrichment influences functioning and therefore clinical trials using new drugs or gene therapies that are also aiming to improve functioning could possibly benefit from adjusting for adjunctive enriched environment programs to properly estimate effects (157).

In a case study of four girls with RTT, Lotan et al used a daily treadmill intervention for 2 months and found significant improvements in gross motor function and physical fitness (158). In CP fitness interventions (e.g. cardiorespiratory and muscle strengthening exercise) result in short-term improvements. The lack of maintenance at long-term follow-up could be explained by mobility and time constraints and psychological burdens (159).

Health promotion research including lifestyle interventions in children and adults with intellectual and physical disabilities have not provided clear evidence of effectiveness (160-162). Fragmentation of sedentary time has been proposed as a potential target in health promoting interventions especially in those individuals with more severe mobility limitations (159). Reducing sedentary time and enhancing 'uptime' activities could be an important intervention focus to address long-term health and quality of life in RTT. However, feasible methods to employ an intervention focusing on participation in 'uptime' activities have not yet been described.

Rationale

From the current literature on RTT we know that:

- Girls and women with RTT have a high dependency on caregivers in all areas of daily life.

- Girls and women with RTT have limited gross motor skills and are at risk of high levels of sedentary time and low levels of physical activity.

- Girls and women are restricted in their participation in everyday and community activities but they enjoy physical and social activities.

- Women live into older age and are at risk of decline in gross motor skills and physical activity levels.

- Validated and reliable outcome measures in RTT are few in number.

- Interventions to promote health throughout the lifespan in girls and women with RTT are lacking.

Thus this thesis will build upon the current evidence-base in girls and women with RTT by focusing on walking measures, physical behavior, participation in 'uptime' activities and improvement of health and quality of life.

Aims

The overall aim of this thesis was to develop measures of walking and describe patterns of physical behavior and influencing factors, in order to develop and evaluate the physical and psychological effects of an intervention that focuses on participation in 'uptime' activities in Danish girls and women with RTT.

The specific aims in each study were:

- Study I: To modify two existing measures of walking capacity (2MWT) and performance (FMS) to enable their use in RTT and to examine their concurrent validity and test-retest reliability.

- Study II: To describe daily patterns of sedentary time and steps in girls/women with RTT and to identify the associations between individual and environmental characteristics with sedentary time.

- Study III: To explore the facilitators and barriers to participation in 'uptime' activities in girls/women with RTT from the perspectives of parents and professionals working with individuals with RTT.

- Study IV: To evaluate the feasibility and health-related effects of an individualized 12-week 'Uptime' Participation (U-PART) intervention in girls/women with RTT.

Methods

Table 3 presents an overview of the methods used in the four studies. The individual designs, study populations and data collection/analyses are then described.

Table 3. Methodologies of the four studies

Study	I	II	III	IV
Design	Methodological	Cross-sectional	Qualitative	One-group pretest posttest
Study population	N=42 girls/women aged 2.4-60.9 years (Walking subgroup: HAS level I-II, n=27)	N=48 girls/women aged 5.5-60.5 years (Walking subgroup: HAS level I-II, n=28)	N=25 parents and professionals (n=9 parents, n=4 care assistants, n=7 professionals from schools, n=5 professionals from day centers)	N=14 girls/women aged 5.6-48.3 years (Walking subgroup: HAS level I-II, n=9)
Sampling method	Consecutive	Population-based	Purposive	Quota sampling
Inclusion criteria	RTT and *MECP2*, walking subgroup should reside in Capital Region, Region Zealand	RTT and *MECP2*, >5 years	Parents: Daughter with RTT living at home, HAS level I-IV; Professionals: Working in Capital Region	RTT and *MECP2*, >5 years , HAS level I-IV, live in Capital Region and Region Zealand
Exclusion criteria	Orthopedic surgery in LE ≤6mo ago, spinal fusion ≤12mo ago	Orthopedic surgery in LE ≤6mo ago, spinal fusion ≤12mo ago		Orthopedic surgery in LE ≤6mo ago, spinal fusion ≤12mo ago
Data collection	May – Jun 2014, May – Jul 2015 Study group characteristics 2MWT, FMS-RS, CSS, RSGMS, PEDI-m	Dec 2014 – May 2015 Study group characteristics, activPAL, SAM, CSS, RSGMS	Sep – Nov 2016 4 focus groups	Feb – Dec 2017 Study group characteristics, activPAL, SAM, RSGMS, 2MWT, QI-Disability, GAS
Data analyses	Descriptive statistics, Spearman Rank Correlation, ICC, MDD	Descriptive statistics, sedentary time and steps plotted by time, linear regression	Thematic analysis	Descriptive statistics, linear mixed-effect models, Wilcoxon Signed Rank test

HAS: Hoffer Ambulation Scale; LE: Lower Extremities; 2MWT: Two-Minute Walk Test; FMS-RS: Functional Mobility Scale – Rett Syndrome; CSS: Clinical Severity Score; RSGMS: Rett Syndrome Gross Motor Scale; PEDI-m: Pediatric Evaluation of Disability Inventory – Mobility; SAM: StepWatch Activity Monitor; QI-Disability: Quality of Life Inventory – Disability; GAS: Goal Attainment Scaling; ICC:I ntraclass Correlation Coefficient; MDD: Minimal Detectable Difference

Design

The intervention developed within this thesis can be regarded as a complex intervention, because it contained several interacting components, such as targeting individual goals across different daily settings assessed with a variety of outcomes (163). The thesis followed the Medical Research Council (MRC) guidelines for developing and evaluating complex interventions and as a pilot study, primarily focused on the development, feasibility and exploration of potential effects (163). A systematic phased approach for developing a complex intervention is recommended using the best available evidence and appropriate theory. The feasibility of the intervention should be tested before commencing with exploratory and full scale evaluation. The results should be disseminated through an implementation process which also includes long term follow-up.

Figure 4 illustrates the relationships between the MRC framework and the four studies of this thesis. In the development phase two outcome measures were modified and validated in a methodological study (study I) and physical behavior in RTT was quantified in a population-based cross-sectional study (study II). When assessing feasibility, a mixture of methods is often necessary. Thus, the feasibility phase consisted of two parts: Firstly, a qualitative study of the facilitators and barriers to engage the target group in 'uptime' participation from the perspectives of parents and professionals (study III) and secondly a quantitative study of the acceptability and practicability of the intervention in combination with an explorative evaluation of its effectiveness using a 1-group pretest-posttest design (study IV).
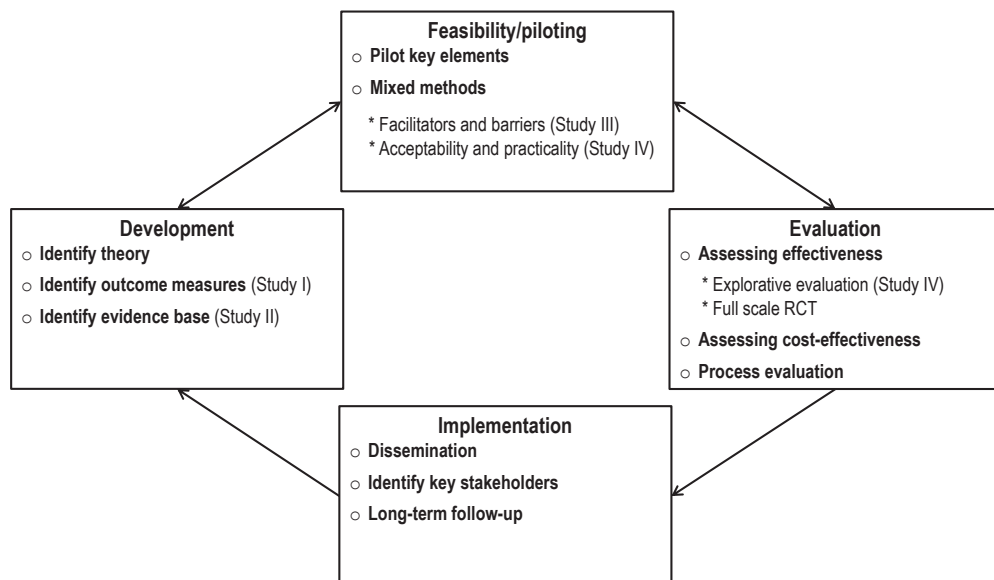
Figure 4. The MRC framework for developing and evaluating complex interventions (163) and the categories of the studies from this thesis

Context of the studies

The Danish Center for Rett syndrome (CRS) was established in 2007 and offers counselling and annual follow-up throughout the lifespan of all individuals diagnosed with RTT. Currently (February 2018), we have knowledge of 107 confirmed individuals (aged 4-63 years) with RTT in Denmark of whom 100 (n=99 females, n=1 male) have a *MECP2* mutation. At the CRS, the multidisciplinary team consists of a neuropediatrician, physical therapist, educational psychologist, social worker, nurse and nutritionist who each contribute knowledge, research and counselling aimed at the individual with RTT and their families and other caregivers. Additionally, the physical therapist and educational psychologist offer local visits to preschools, schools, day centers and residential homes throughout the whole country to teach professionals about the clinical characteristics of RTT in general and to provide specific recommendations about the daily management in the individual with RTT with whom they work.

The CRS is located in Copenhagen in the Capital Region of Denmark, however, the majority of assessments and meetings in all four studies were conducted in the local settings of the participants. To perform the assessments in a well-known

environment was chosen to make the participants feel safe and comfortable. Additionally, this strategy puts less strain on families and professionals.
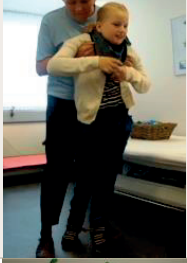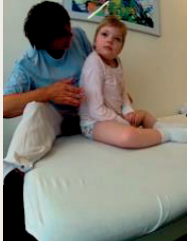
Study populations

In this thesis it was chosen to have a population that most represented RTT and therefore included females with RTT and a *MECP2* mutation. There is only one male with RTT in Denmark and the majority of individuals with a clinical diagnoses of RTT also have a *MECP2* mutation. Clinical assessments and the intervention involved standing and walking and thus participants were excluded if they had undergone orthopaedic surgery in the lower extremities during the last 6 months or spinal fusion during the last 12 months.

The Hoffer Ambulation Scale (HAS) has been used to characterize the participants in this thesis by ambulation status assisted sampling strategies in study I, III and IV. HAS was originally used in individuals with spina bifida (164) and modified by Vogel et al in individuals with spinal cord injuries (165). In table 4 the definitions of the five ambulation levels as proposed by Vogel et al are shown. The HAS has not been validated in RTT, however, the inter-rater reliability between two physical therapists at CRS has been established (ICC=0.98, [95%CI 0.967, 0.988]) (166). In 2015 the CRS described the ambulation level in the Danish population of girls and women with RTT and a *MECP2* mutation using HAS (166). The distribution of ambulation levels in the total population of n=95 Danish girls/women with RTT and a *MECP2* mutation aged 3-60 years was:

I) Community ambulators: 47.4% (n=45)
II) Household ambulators: 10.5% (n=10)
III) Therapeutic ambulators: 13.7% (n=13)
IV) Non-ambulant/Standers: 15.8% (n=15)
V) Non-ambulant: 12.6% (n=12)

Table 4. Definitions of Hoffer Ambulation Scale levels (165)

Level		Definition	
I	**Community ambulator**	The person is capable of walking indoors and outdoors for most of his/her activities on a daily basis with or without physical assistance/walking aids. A wheelchair might be needed for longer trips within the community.	
II	**Household ambulator**	The person is capable of walking indoors in the home or at school/day center on a daily basis with or without physical assistance/walking aids. A wheelchair might be needed for some indoor activities and for all activities within the community.	
III	**Therapeutic ambulator**	The person walks with therapists or parents in the home or at school/day center. The gait is not functional as observed for levels I and II.	
IV	**Non-ambulant/Stander**	The person needs a wheelchair for all daily mobility activities but is able to stand. The person is capable of standing on the floor with or without physical assistance or in a standing frame.	
V	**Non-ambulant**	The person needs a wheelchair for all daily mobility and is unable to stand.	

In table 5 characteristics of the participating girls and women with RTT in study I, II and IV are presented. Table 6 shows the characteristics of the participating parents and professionals in study III.

Table 5. Characteristics of girls and women with RTT in studies I, II and IV

	Study I (n=42)	Study II (n=48)	Study IV (n=14)
Age median (IQR)	18.4 (7.2, 35.5)	22.0 (14.3, 36.5)	18.7 (9.2, 36.1)
CSS mean (SD)	19.7 (6.3)	22.9 (7.2)	22.3 (4.3)
RSGMS mean (SD)	27.5 (12.3)	21.6 (11.9)	21.6 (8.6)
Residence			
Parental home	23 (54.8)	24 (50.0)	6 (42.9)
Residential home	19 (45.2)	24 (50.0)	8 (57.1)
HAS			
I. Community ambulator	28 (66.7)	21 (43.8)	6 (42.9)
II. Household ambulator	3 (7.1)	6 (12.5)	3 (21.4)
III. Therapeutic ambulator	4 (9.5)	7 (14.6)	3 (21.4)
IV. Non-ambulant/Stander	6 (14.3)	8 (16.6)	2 (14.3)
V. Non-ambulant	1 (2.4)	6 (12.5)	-
Mutation			
C-terminal	5 (11.9)	5 (10.4)	0
Early truncating	2 (4.8)	5 (10.4)	0
Large deletion	4 (9.5)	7 (14.6)	3 (21.4)
p.Arg106Trp	1 (2.4)	2 (4.2)	0
p.Arg133Cys	1 (2.4)	1 (2.1)	1 (7.1)
p.Arg168*	3 (7.1)	6 (12.5)	0
p.Arg255*	1 (2.4)	3 (6.2)	1 (7.1)
p.Arg270*	1 (2.4)	1 (2.1)	1 (7.1)
p.Arg294*	5 (11.9)	6 (12.5)	0
p.Arg306Cys	2 (4.8)	1 (2.1)	1 (7.1)
p.Thr158Met	12 (28.5)	7 (14.6)	5 (35.7)
Other	5 (11.9)	4 (8.3)	2 (14.3)

Data expressed in n (%) unless otherwise stated.
CSS: Clinical Severity Score; RSGMS: Rett Syndrome Gross Motor Scale; HAS: Hoffer Ambulation Scale

Table 6. Characteristics of parents and professionals in study III

Study III (n=25)	
Parents (n=9)	
Gender (female/male)	8/1
Age [median (range)]	43 (41-44)
Care assistants (n=4)	
Gender (female/male)	4/0
Age [median (range)]	48.5 (34-53)
Professionals at schools (n=7)	
Gender (female/male)	7/0
Age [median (range)]	45 (27-59)
Profession	
Teacher	3
Pedagogue	2
Physical therapist	2
Professionals at day centers (n=5)	
Gender (female/male)	4/1
Age [median (range)]	39 (27-59)
Profession	
Pedagogue	3
Physical therapist	2

Study I
Participants with RTT of all ages and HAS levels were recruited consecutively in relation to their visit at CRS during two periods of data collection. The goal was to include 30 participants at HAS levels I-II (functional walking ability) in order to have sufficient data to assess validity and reliability of the 2MWT. Parents and legal guardians received written information about the study prior to the visit and then received oral information at the visit. A total of 42 girls/women aged 2.4-60.9 years were included in the study with 27 girls/women at HAS level I-II. As this study focused on walking performance and walking capacity the majority of the included participants had relatively high RSGMS scores because of their ability to walk. All of the common mutation types were represented (62).

Study II
Participants with RTT who were older than 5 years of age and at all HAS levels were recruited using the available population-based sample. The lower age limit of 5 years was chosen because the validity and reliability of accelerometry in preschool children was limited (167), although, by the time of the data collection, the SAM had been validated in girls with RTT as young as 3 years (134). In the preschool years, girls with RTT may still be learning to walk whereas by age five years, most who will learn to walk will have acquired this skill (personal correspondence with Jenny Downs) and thus the age limit for this study seemed appropriate. At the time of recruitment 88 girls/women with RTT met the inclusion criteria. Parents and legal guardians received written information about the study and oral information was given approximately 1 week later by phone. The recruitment process is shown in figure 5. In 48 girls/women aged 5.5-60.5 years, sufficient data was provided to be included in the study. Half of the participants lived with their parents and the other half in residential homes. The distribution of HAS levels was comparable to that found in the total Danish RTT population in 2015 and all common mutation types were represented.
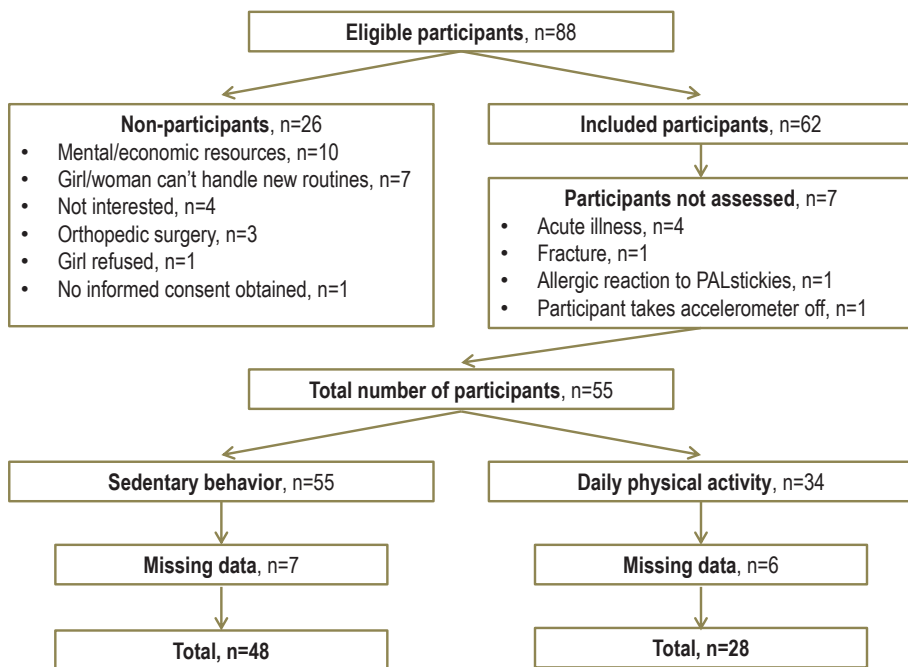
Figure 5. Flowchart of recruitment process in study II

Study III

Purposive sampling was used to recruit participants for four focus groups: 1) parents, 2) care assistants, 3) professionals at schools, 4) professionals at day centers. The aim was to achieve maximal variation in the experiences of parents and professionals according to the age and ambulation level (HAS I-IV) of the girls and women with RTT with whom they were involved. Six to 10 participants are recommended to create sufficient interaction to allow comparison and contrast of the participants' views in focus groups. However, researchers are advised to over-recruit as those who have agreed to participate may not then participate (168). We contacted 10 potential participants for each focus group by phone and those interested received written information about the study. The recruitment process is shown in figure 6. Nine parents, four care assistants, seven professionals from schools and five professionals from day centers participated in the focus groups. The majority of participants were females (92%). The parents' daughters with RTT were 6-18 years old and included both ambulant (HAS level I-II, n=7) and therapeutic ambulators and non-ambulant (HAS level III-IV, n=2) girls. According to their workplace, professionals worked with girls and women at various ambulation levels and ages (schools: 5-21 years, day centers: 23-47 years, residential homes: 25-47 years).
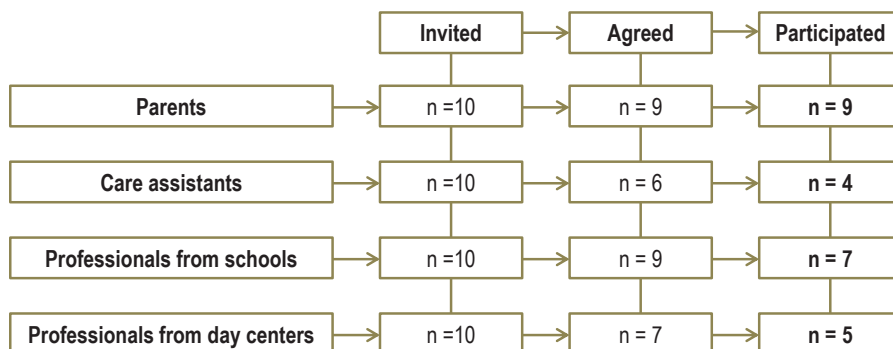
Figure 6. Recruitment process in study III

Study IV

Participants with RTT above 5 years of age and with HAS levels I-IV were recruited using quota sampling. To perform 'uptime' activities, participants needed to have some ability to walk and/or stand (HAS levels I-IV). Walking ability in those at HAS level III is not functional and in this study, participants at HAS level III and IV were both classified as non-ambulators. Due to time constraints only girls and women living in the capital Region and Region of Zealand were included leaving 50 eligible participants. These participants were divided into four subgroups based on their residence (parental home/residential setting) and ambulation level (ambulant/non-ambulant) (figure 7). A total of 16 eligible participants were selected to include equal proportions of participants living in a parental home (n=8) or residential setting (n=8) and approximately two thirds being ambulant (n=10) to reflect the Danish population of females with RTT. Fourteen girls/women aged 5.6-48.3 years with RTT completed the intervention study and their clinical characteristics were comparable to the population-based sample in study II (see table 5). Six of the common mutation types were represented.
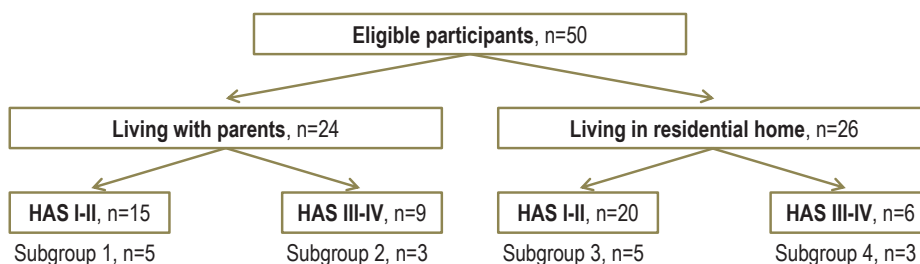
Figure 7. Recruitment process in study IV

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Data collection and procedures

An overview of the characteristics of participants and measures used throughout the studies is given in table 7. The measures will be further described below.

Table 7. Overview of characteristics and measures in study I-IV

	Study I	Study II	Study III	Study IV
Clinical characteristics of girls/women with RTT				
Age	X	X	X	X
Mutation	X	X		X
HAS/ambulation level	X	X	X	X
Characteristics of parents/family				
Age			X	
Number of siblings		X		
Education		X	X	
Income (not reported)		X		
PA level		X		
Characteristics of residential home				
Number of residents		X		
PA practices		X		
Characteristics of professionals				
Age			X	
Profession			X	X
Work experience			X	
Measures				
2MWT	X			X
FMS-RS	X			
CSS	X	X		X
RSGMS	X	X		X
PEDI-m	X			
ActivPAL		X		X
SAM		X		X
QI-Disability				X
RSBQ				X
DIMS				X
GAS				X
Feasibility				X

HAS: Hoffer Ambulation Scale; PA level: Physical Activity level; PA practices: Physical Activity practices; 2MWT: Two Minute Walk Test; FMS-RS: Functional Mobility Scale – Rett Syndrome; CSS: Clinical Severity Score; RSGMS: Rett Syndrome Gross Motor Scale; PEDI-m: Pediatric Evaluation of Disability Inventory – Mobility; SAM: StepWatch Activity Monitor; QI-Disability: Quality of Life Inventory – Disability; RSBQ: Rett Syndrome Behavior Questionnaire; DIMS: Disorders of initiating and maintaining sleep subscale; GAS: Goal Attainment Scaling

Modified two-minute walk test (2MWT)
In the 2MWT (169) the test person walks back and forth between two cones on a 20 meter track for two minutes and the distance covered is noted. Several modifications of the 2MWT were made to enhance comprehension, motivation

and maximal effort of the girls and women with RTT (see Appendix I). The 2MWT requires two assessors and one walk assistant. Assessor 1 walks next to the test person and is timing the test, counting rounds and giving instructions and encouragement. Standardized phrases of encouragement are given every 30 seconds. If needed, assessor 2 uses strategic motivators and walks 5 meters ahead of the test person. The walk assistant is a person who knows the girl/woman well (e.g. parent, caregiver, therapist) and provides the necessary physical support for the girl/woman to keep her balance and to maintain the highest possible gait speed.

The Functional Mobility Scale – Rett Syndrome (FMS-RS)
FMS-RS was modified from the FMS (170) with permission from the Hugh Williamson Gait Laboratory, The Royal Children's Hospital, Melbourne, Australia. FMS-RS assesses walking performance on level ground at home, in the day center (pre-school, school, activity center) and within the community (see Appendix II). The walking performance was assessed over three distances: 5 meters, 50 meters, and 500 meters corresponding to home ambulation, day center ambulation, and community ambulation, respectively. The scoring system in the FMS-RS refers to the level of assistance needed to walk the given distance. A score of 0-4 is given at each distance with 0 defined as "unable" and 4 as "independent". The FMS-RS is completed by asking the parents/caregivers how much assistance the person with RTT needs to walk short distances in the house, around in and between classes/rooms in the school/day center, and for longer distances such as at the shopping center, the local grocery store or to the nearest bus/train station.

Clinical Severity Score (CSS)
The CSS is a 13-item RTT-specific scale describing early development and current clinical characteristics including comorbidities with a maximum score of 58 indicating greater severity (60).

Rett syndrome gross motor scale (RSGMS)
The RSGMS is a RTT-specific outcome measure of gross motor skills including fifteen items that are rated on a four-point scale. A maximum score of 45 indicates better gross motor skills (145).

Pediatric Evaluation of Disability Inventory (PEDI)
The PEDI describes functional skills in children with a disability and their needs for caregiver assistance in the domains of self-care, mobility and social function (171). A Danish version has been validated (172, 173). For the purposes of study I, the Mobility-Caregiver assistance subscale (PEDI-m) was used with higher scores indicating greater independence.

ActivPAL
The activPAL is a small (53x35x7mm, 20g) uni-axial accelerometer which is worn on the upper third of the thigh (174). It is attached to the skin with adhesive pads called PALstickies. An inclinometer determines the position of the thigh to estimate the time spent in a lying/sitting or standing position in 15s epochs. Validation of the activPAL has been completed in 26 girls/women with RTT (144). ActivPAL data was compared to video observation and showed that activPAL accurately measured duration of sedentary time with a mean difference of -0.98 minutes. Regarding other postures, activPAL overestimated time spent standing and underestimated time spent walking. A valid day of ActivPAL data was defined as >480 min of recording during daytime hours.

Stepwatch Activity Monitor (SAM)
The SAM is a small (70x50x20mm, 38g) accelerometer that records the number of steps taken every minute (175). It is attached to the ankle using an elastic Velcro strap. SAM has showed superior accuracy (-1 step/min) and repeatability (ICC = 0.92) of step counts when compared to ActiGraph and activPAL and therefore has the capacity to accurately measure daily physical activity in RTT (134). A valid day of SAM data was defined as >480 min of recorded wear time.

Quality of Life Inventory – Disability (QI-Disability)
QI-Disability is a 32-item questionnaire developed for children 5-18 years of age with ID (including RTT). Responses are used to calculate an overall score and six subscale scores (social interaction, positive emotions, physical health, negative emotions, leisure/outdoors and independence), each scored on a 0-100 scale with higher scores representing better quality of life (128).

Rett syndrome behavior questionnaire (RSBQ)
RSBQ is a 45-item questionnaire used to assess different aspects of behavior in RTT such as mood, fear and anxiety, and hand behaviors. Items are rated on a 0-2 scale with 2 representing more behavior problems (142).

Disorders of initiating and maintaining sleep (DIMS)
DIMS is a subscale of the Sleep Disturbance Scale for Children (138). DIMS consists of 7 items that are rated on a five-point Likert scale. Higher scores represent greater sleeping difficulties.

Goal Attainment Scaling (GAS)
GAS is a validated method for evaluating achievement of individual goals. A five-point rating scale ranging from -2 to +2 was used to assess the extent to which the individual goals were achieved. Baseline was set at -2, the expected level after the intervention at zero and the most favourable outcome at +2 (176). In study IV the goals were graded in relation to frequency or duration of an activity (see example in table 8 below).

Table 8. Example of school-based Goal Attainment Scaling goal: The girl participates in class chores while walking

Score	Goal
-2 (baseline)	The girl does not perform any class chores (e.g. picking up the daily note from the printer in the school library, distributing lunch boxes to classmates)
-1 (less than expected)	The girl participates in class chores once a week while walking; she chooses between two tasks
0 (expected level)	The girl participates in class chores twice a week while walking; she chooses between two tasks
+1 (better than expected)	The girl participates in class chores three times a week while walking; she chooses between two tasks
+2 (much better than expected)	The girl participates in class chores four times a week while walking; she chooses between two tasks

Feasibility
A study-specific feasibility questionnaire assessed each part of the intervention in study IV on a 1-10 visual analogue scale (VAS) with 1 representing "very difficult/poor/low extent" and 10 "extremely easy/good/high extent". The questionnaire comprised 22 items assessing the acceptability, practicality, overall satisfaction and appropriateness of the intervention.

Study I

To establish concurrent validity the modified measures FMS-RS and 2MWT were compared to the CSS, RSGMS and PEDI-m. The CSS and the PEDI were completed using observation and interview data. The RSGMS was scored through direct observation. The FMS-RS was assessed during a short interview with parents or other care providers and to assess the test-retest reliability, the interview was conducted twice approximately within 7 days. The first assessment took place at the day of the visit at CRS and the second assessment was done by telephone interview. A subgroup of the participants was assessed with the 2MWT on a separate occasion; in the pre-school, school, day-time activity center or in the home of the participants according to the preferences of the parents/caregivers. The 2MWT was assessed twice on the same day with a short break between trials to assess test-retest reliability and this testing procedure was repeated approximately within 7 days.

Study II

All participants wore the activPAL for 7 consecutive days. Participants who were functional ambulators (HAS I-II) also wore the SAM for 7 consecutive days (see picture 1). Parents and/or care assistants were carefully instructed in the use and correct placement of the activPAL and SAM. A written guideline was also provided. Parents and/or care assistants were instructed to keep the activPAL attached for 24h a day, whereas the SAM should be worn when the participant woke up in the morning and removed at bedtime. Neither accelerometer should be worn during water-based activities. During the data collection period parents or care assistants were asked to fill in a diary about sleep (including naps during the day), non-wear time and planned activities like swimming, bicycling and horse riding. The diary information documented wear time and enabled 'cleaning' of the activPAL data to only include sedentary activities during waking hours. Furthermore, the SAM was calibrated for the height and gait pattern of each participant. The settings were tested during the first 40 steps taken by the participant. In the majority of participants (n=26, 93%), a geriatric or severely affected gait pattern was used (gentle and slow speed which rarely varied in pace) and a normal gait pattern was used for the remaining participants.

Prior to the accelerometer data collection, participants were assessed with the RSGMS and CSS. To secure a high participant rate, assessments took place at the most convenient location including the CRS, Odense University Hospital, two residential homes and at three schools in Jutland, according to the preferences of the parents or care assistants.

Picture 1. Participant wearing the ActivPAL (on thigh) and SAM (around ankle)

Study III

One week prior to the focus group participants received a short information letter about the purpose of the focus group. The focus group with parents took place at the yearly RTT venue in Denmark. One focus group was held at a school and the last two focus groups were held at CRS.

Following definition of the key concepts of physical activity, sedentary time and 'uptime', semi-structured and open-ended questions were used to provide the participants with the opportunity to share their personal perspectives in their own words. An experienced moderator conducted all focus groups with the assistance of an observer. In the introductory stage of the focus group participants were invited to introduce themselves and their daughter/workplace to ensure that all participants had contributed with something from the beginning of the discussion (168). After group introduction, the moderator asked a general question to introduce the topic of interest and establish a rapport with the participants. Secondly, participants were asked about their experiences of participation in sedentary and 'uptime' activities in relation to the girl/woman with RTT and the factors that either enabled or hindered this participation. The focus groups each lasted approximately 1½ hour.

Study IV

Primary outcomes were sedentary time and daily physical activity as measured by the activPAL and SAM, respectively. Secondary outcomes were gross motor skills (RSGMS), walking capacity (2MWT), quality of life (QI-Disability), behavior (RSBQ), sleep (DIMS) and participation-level goals (GAS). Outcomes were evaluated with a comprehensive assessment protocol 4 times at a 6-week interval at baseline (T0, T1) and 12-week intervals after the intervention (T2) and at follow-up (T3) (See figure 8).

Baseline 6 weeks	Intervention 12 weeks	Follow-up 12 weeks

T0   T1   T2   T3

Accelerometry
ActivPAL
SAM

Other measures
RSGMS
2MWT
QI-Disability
RSBQ
DIMS

Accelerometry
ActivPAL
SAM

Other measures
RSGMS
2MWT
QI-Disability
RSBQ
DIMS
GAS

Accelerometry
ActivPAL
SAM

Other measures
RSGMS
2MWT
QI-Disability
RSBQ
DIMS
GAS

Feasibility questionnaire

Accelerometry
ActivPAL
SAM

Other measures
RSGMS
2MWT
QI-Disability
RSBQ
DIMS

Preparation period
Interdisciplinary observation
Interview with parents/care assistants and teachers/pedagogous

Intervention period
Individualized intervention program
Joint meeting with involved stakeholders
PT supervision bi-weekly

Follow-up period
No supervision
If the participant used special equipment during the intervention it remained with her throughout the follow-up

Figure 8. Schematic presentation of the workflow of study IV (PT = Physical therapist)

The intervention was designed for each individual and was consistent with the model for participation-based interventions (52). The intervention comprised three steps:

Step 1) Preparation period

An interdisciplinary team from CRS observed each participant from 9am until bedtime to identify the opportunities and challenges within the individual and the environment. All relevant caregivers were interviewed to clarify activities that the girl/woman enjoyed in different settings. Data from the observation, interview and

accelerometry assessments were used in the development of an individualized intervention program.

Step 2) Intervention period

Each program focused on participation in enjoyable activities which could reduce sedentary time and encourage 'uptime' in home, school/day center and community settings, aiming to increase the number of sedentary breaks/number of steps taken or decreasing the length of sedentary bouts. Realistic participation goals were selected by caregivers. Caregivers were asked to fill in a diary with information about 'uptime' activities and the participant's enjoyment (see figure 9). During the intervention period a physical therapist supervised the caregivers. Relevant equipment and aids to encourage 'uptime' (e.g. Switch-adapted toys, Standers, Walkers) were rented during the intervention period.

Date:
'Uptime' activities

What?	How much did she enjoy the activity?	Comments
	😀 🙂 😐 ☹️ 😮	
	😀 🙂 😐 ☹️ 😮	
	😀 🙂 😐 ☹️ 😮	

Figure 9. Example of how enjoyment of an activity was recorded in the 'uptime' activity diary

Step 3) Follow-up period

All special equipment remained with the participants during the follow-up. No supervision was provided during this period.

Data analyses

Descriptive statistics were used to present characteristics of the participants and summary scores for each of the independent and outcome variables. Statistical analyses were conducted using SPSS (version 19.0 and 22.0) and STATA (version 14). Statistical significance was defined as $p < 0.05$. Transcribed focus groups were uploaded into and analysed using NVivo (version 11).

Study I

Concurrent validity: Spearman rank correlation (non-parametric correlation coefficient) was used to determine the relationships between the FMS-RS and 2MWT and the clinical measures (CSS, RSGMS, PEDI-m).

Test-retest reliability: Intraclass correlation coefficients (ICC) were calculated in FMS-RS and 2MWT to determine test-retest reliability.

Measurement error: To identify differences in distances walked on the 2MWT by occasion (Day 1: test 1, test 2; Day 2: test 3, test 4) repeated measures analysis of variance (ANOVA) was used. To detect a possible learning effect on the same day and between assessment days *a priori* planned contrast tests were performed which is the preferred method over t-tests (test 1 vs test 2, test 2 vs test 3, test 2 vs test 4, test 3 vs test 4). Absolute agreement for the 2MWT (test 2 and test 4) were calculated using the standard error of measurement (SEM) and the minimal detectable difference (MDD).

Variance in 2MWT: Multivariate linear regression was used to test whether age and gross motor skills predicted distance walked measured with the 2MWT.

Study II

Representativeness of sample: Differences between participants and non-participants were compared using independent t-test for numeric data and X^2 test for comparison of proportions.

Pattern of physical behavior: Sedentary time and step counts were plotted by time using MATLAB to observe hour-by-hour patterns of activity. Physical behavior on weekdays and weekends were compared using a within-subject t-test for sedentary time and Wilcoxon Signed Rank test for daily step count.

Variance in sedentary time: Linear regression was used to examine the relationships between sedentary time (dependent variable) and individual characteristics: age (<16½years/16½-33½years/>33½years), CSS (above/below mean), RSGMS (above/below mean), walking ability (independent/assisted/ unable) and residence (parental home/residential). Environmental characteristics were examined for those living with their parents and those living in a residential

home. The linear regression models included maternal physical behavior (high/moderate) for those living in their parental home and presence of a physical activity policy (yes/no) for those living in a residential home. Both univariate and multivariate models were fitted.

Study III

Data were analyzed using thematic analysis. The analysis was situated within an essentialist framework reporting experiences, meanings and the reality of the participants (177). Accordingly, the analysis consisted of 6 phases: 1) To familiarize with the data the entire transcripts were read several times by the research team; 2) Initial codes were produced with each focus group analyzed separately to ensure equal consideration. Consensus on the initial coding was reached in the research team; 3) All codes were then sorted into potential themes and an initial thematic map was made; 4) Theme/subthemes were reviewed and refined to consider whether they constituted a coherent pattern. A candidate thematic map was made; 5) To identify the essence of each theme/subtheme they were further defined and refined and 6) Final compelling data-extracts were chosen.

Study IV

Feasibility: Descriptive statistics (median, interquartile range) were used to assess the feasibility of the intervention.

Stability of baseline period: To estimate the within-subject agreement in outcome variables between T0 and T1 (baseline period) intra-class correlation coefficients (ICC) were calculated.

Effects on primary and secondary outcomes: Effects of the intervention on primary and secondary outcomes were analysed using linear mixed-effects models with random intercepts. This method takes the within-subject correlated nature of repeated measures into account and is preferred over ANOVA as it acknowledges individual patterns and differences in change, handles missing data and allows flexible time periods for longitudinal data (178). The random-effects variable was the unique participant ID and fixed-effects variables were intervention (baseline/T2/T3), age at assessment (centred around the overall median value of 19 years), residence (parental home/residential setting) and ambulation level (non-ambulant/ ambulant). Both univariate and multivariate models were fitted.

Effects on participation-level goals: Wilcoxon Signed Ranks test was used for GAS to determine the differences between medians at T1 and T2 (using medians of each participant's GAS scores). Subgroup effects were also analyzed with regards to residence and ambulation level. A positive difference of at least 2 points between the T1 median and T2 median was considered to be clinically relevant.

Ethical considerations

All studies were registered at the Danish Protection Agency (ID-03202). Studies requiring ethical permission were approved by the Capital Region Ethics Committee in Denmark: H-6–2014-074 (Study I and II) and H-16030785 (Study IV). In Denmark qualitative studies do not require approval from a Human Research Ethics Committee. The ethical principles of the Declaration of Helsinki were followed in all studies (179). Participation in all studies was optional, the confidentiality of the participants was ensured and informed consent was provided by the parents or legal guardians depending on the age of the girl/woman with RTT. Parents and legal guardians received written and oral information about the studies prior to their consent.

Children and adults with multiple disabilities comprise a vulnerable population and thus all ethical issues must be carefully considered before involving them in research. In medical research four ethical principles have been described (180): Autonomy, beneficence, non-maleficence and justice and the four studies adhered to these principles.

Autonomy

All participants have the right to receive information and to make their own decisions. Informed consent and confidentiality are part of respecting the autonomy of participants (180). Individuals with RTT face physical and cognitive challenges and are not capable of providing and signing an informed consent. However, in study I, II and IV information leaflets in plain language were made to allow parents and legal guardians to talk to the girl/woman with RTT about the study and to assist them to indicate their attitude towards the study.

Beneficence and non-maleficence

The benefits for the participants in research studies as well as the target population should outweigh the potential risks and inconveniences (180). Assessments were scheduled in the local settings to decrease the stress level in participants and the burden on families and pre-schools/schools/day centers and residential homes. Objective measurements of sedentary time using the activPAL could cause some minor physical discomfort (e.g. skin rash). The risk of adverse events was expected to be minimal as the girls/women did not engage in vigorous and high-intensity activities. The amount of assessments, diaries, questionnaires and interviews could burden and inconvenience the parents and professionals throughout the studies. However, participation was voluntary and these studies

could generate new knowledge about physical behavior and participation in 'uptime' activities and contribute to the development of health promotion interventions for individuals with RTT in the wider community.

Justice

Justice involves the allocation of health resources and equality in who receives what intervention (180). In the studies the eligible participants were not discriminated or excluded because of ethnicity or socioeconomic factors. The results and experiences gained from the studies will benefit the Danish population of individuals with RTT as it will be incorporated into the counselling at CRS.

Results

The results will be presented in accordance with the overall aim of this thesis: To develop measures of walking (study I), describe patterns of physical behavior (study II) and influencing factors (study II and III) and to develop and evaluate the physical and psychological effects of an 'uptime' intervention (study IV) in Danish girls and women with RTT.

Walking measures in RTT

2MWT (study I)

A subgroup of 27 girls and women aged 3.8–60.9 years participated in 2MWT assessments. Participants needed supervision (n=3), minimal assistance (n=12) or moderate assistance (n=12) to walk continuously along the track without losing balance. Four of the participants required strategic motivators to complete the assessments (e.g. favourite music or snack). Moderate correlations were seen between 2MWT and clinical severity (r=-0.48), gross motor skills (r=0.51) and mobility (r=43) providing initial support for concurrent validity of 2MWT.

Summary scores of the 2MWT are shown in table 9. A significant learning effect was seen between test 1 and test 2 (p=0.03) with participants walking 8 meters longer on average during test 2. On the second test day, the mean distance walked was also shorter at the first assessment (test 3) than the second assessment although not significantly shorter. ICC values between tests on the same day (ICC=0.95-0.98) and between days (ICC=0.86-0.88) were high supporting the test-retest reliability of 2MWT. Test 2 and 4 were used to calculate SEM (13.8m) and MDD (38m) values taking the learning effect and week-to-week variation into account. Gross motor skills (coefficient =2.03, t=3.41, p=0.002, [95%CI 0.79, 3.26]) but not age (coefficient=-0.067, t=-0.25, p=0.801, [95%CI -0.61, 0.48]) was a strong predictor of the distance walked on the 2MWT.

Table 9. Mean (SD) of the 2MWT (meters) on the four test occasions

Day 1		Day 2	
Test 1	Test 2	Test 3	Test 4
75.97 (30.16)	83.07 (27.57)	83.67 (24.23)	87.13 (25.75)

FMS-RS (study I)

FMS-RS was administered in 42 girls and women with RTT aged 2.4-60.9 years. Results revealed that even though 66.7% of the participants were classified as community ambulators at HAS level I (walking indoors/outdoors for most daily activities) only approximately 50% walked 500m independently or with minimal-moderate support when assessed with the FMS-RS. Moderate to strong correlations were seen between FMS-RS and clinical severity (r=-0.60– -0.66), gross motor skills (r=0.71-0.93) and mobility (r=0.74-0.94) supporting the concurrent validity of FMS-RS. ICC values between the two FMS-RS ratings were high (ICC=0.94-0.99) supporting the test-retest reliability of the FMS-RS.

Patterns of physical behavior

Amount of sedentary time and daily step counts (study II)

A total of 48 girls and women with RTT aged 5.5-60.5 years provided sufficient data for analysis of sedentary time. A subgroup of 28 participants also provided sufficient step count data to analyse daily physical activity. The sample was representative of the Danish population of girls/women with RTT as no significant differences were found in age (p=0.69), residence (p=0.94), and ambulation level (p=0.99) when comparing the 48 participants with those not known to the CRS and who did not provide data (n=26).

Mean daily sedentary time was 10.11 (SD 1.92) hours corresponding to 83.3% (SD 13.9%) of waking hours and the median daily steps was 5128 (IQR 2829;7704) (see table 10). Sedentary bouts of 1 hour or more were seen ~20% of the time in those walking with assistance and ~30% of the time in those unable to walk. Those with the ability to walk mostly walked at very slow cadences.

Table 10. Summary of daily sedentary behavior and physical activity

Sedentary behavior (n=48)		Physical activity (n=28)	
Daily sedentary time (mean, SD)	83.3% (13.9%)	**Daily step count** (median, IQR)	5128 (2829;7704)
Sedentary bouts ≥ 1 hour		**Cadences of <20 steps/min**	
Walking independently (n=18)	7.9%	Walking independently (n=18)	53.4%
Walking with assistance (n=14)	20.9%	Walking with assistance (n=10)	75.5%
Unable to walk (n=16)	29.7%		

Physical behavior patterns on weekdays and weekends (study II)

No significant difference was found in sedentary time between weekdays and weekends (p=0.97), however, significantly more steps were taken during weekdays compared to weekends (p=0.001).

During weekdays most sedentary time accumulated from noon/early afternoon and after dinner in those unable to walk. Similar trends were observed in those participants needing assistance to walk. In those who walked independently a greater variation of minutes spent sitting each hour was seen. During weekends all groups showed a similar pattern throughout the day. However, the weekend pattern differed from weekdays by demonstrating higher amounts of sedentary time in the morning, greater fluctuations each hour and with a peak later in the afternoon (see figure 10).

During both weekdays and weekends participants who could walk independently took more steps each hour, however, the stepping pattern over the course of the day was quite similar to those walking with assistance. Most steps accumulated in the morning hours and then gradually declined, with the greatest peak around 10am on weekdays and 11am on weekends and a smaller peak around 3pm. The steps per hour on weekends were lower on weekends especially in those walking with assistance (see figure 11).

In those who needed assistance walk, a decrease in sedentary time was accompanied with an increase in steps within any given time frame and vice versa during both weekdays and weekends. However in those who walked independently, both the sedentary time increased and the number of steps increased in the morning hours (most evident on weekdays). This could indicate that these participants engage in short but brisk walking activities in the morning hours. Late in the afternoon on weekdays a decrease in sedentary minutes was seen in the independent walkers but this was not followed by an increased number of steps. An explanation could be that the participants engage in standing activities rather than walking activities during these hours.
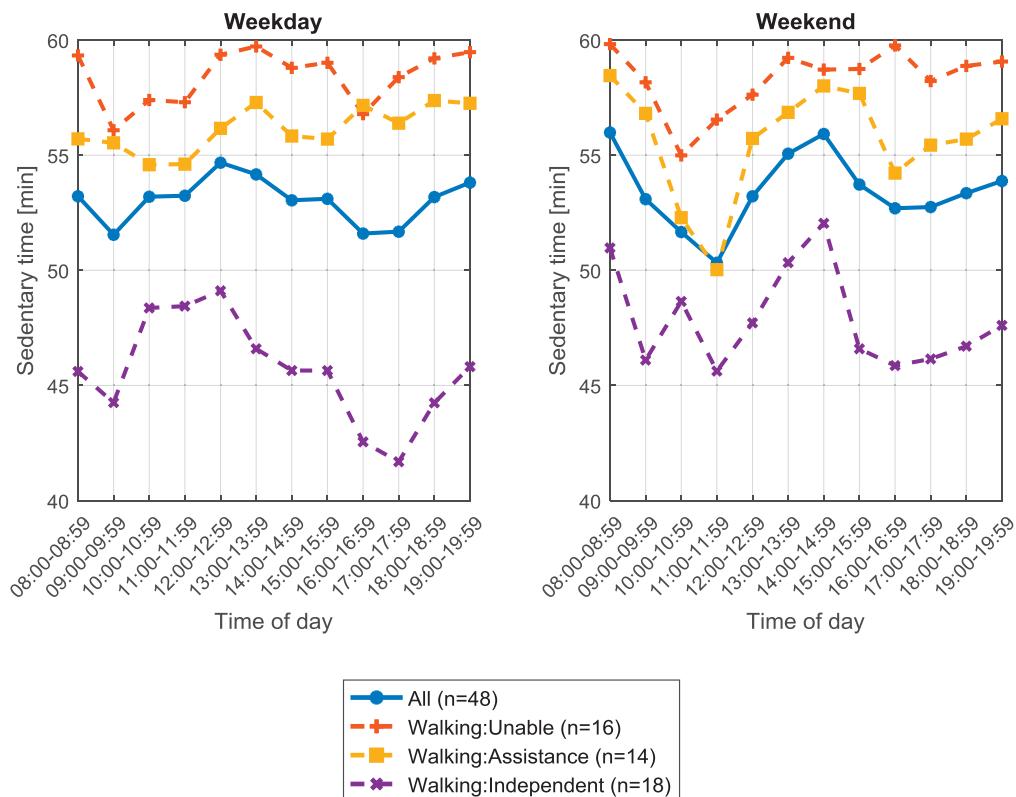
Figure 10. Average minutes spend sitting/reclining each hour between 8am and 8pm on weekdays and weekends
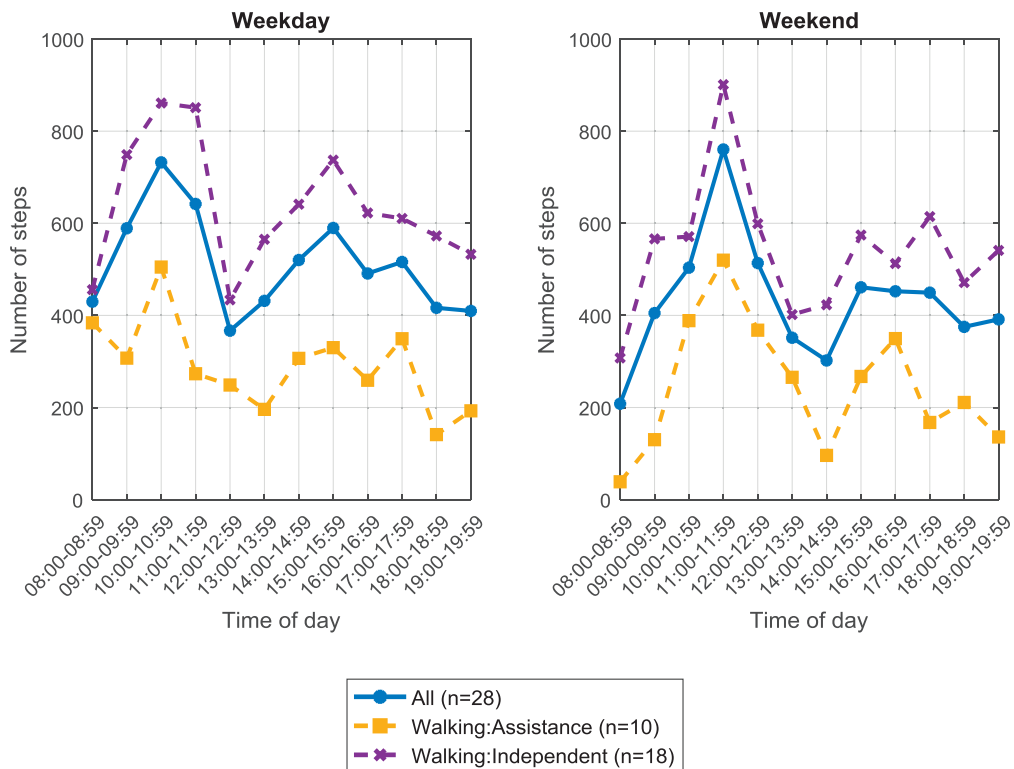
Figure 11. Average steps taken each hour between 8am and 8pm on weekdays and weekends

Associated factors, facilitators and barriers of physical behavior

Findings from Danish girls/women with RTT (study II)

In the population-based study of Danish girls/women with RTT, factors associated with sedentary time were investigated.

In the univariate linear regression models the following individual and environmental factors predicted amount of sedentary time:

- Increasing clinical severity was associated with more sedentary time (coefficient 16.69 [95%CI 9.5,23.88], $R^2=0.36$).
- Decreasing gross motor skills was associated with more sedentary time (coefficient 18.64 [95%CI 12.6,24.7], $R^2=0.46$).
- Inability to walk was associated with more sedentary time (coefficient 23.84 [95%CI 17.61,30.6], $R^2=0.60$).
- Low maternal physical activity level in those living with their parents was associated with more sedentary time (coefficient 13.76 [95%CI 1.42,26.10], $R^2=0.21$).
- Absence of a physical activity policy in the residential home was associated with more sedentary time (coefficient 12.2 [95%CI 1.55,22.85], $R^2=0.21$).

In the multivariate linear regression models age and clinical severity, age and gross motor skills and age and walking ability explained 39%, 54% and 70% of the variance of sedentary time, respectively. Taking age into account, participants who walked with assistance and those unable to walk had more sedentary time than those who walked independently (assisted: coefficient 6.75, [95%CI 0.69,12.83] and unable: coefficient 25.7 [95%CI 20.05,31.35]). Taking walking ability into account, participants older than 33½ years of age were more sedentary than those younger than 16½ years (coefficient 10.03 [95%CI 4.16, 15.9]). The effects of modifiable environmental factors (maternal physical activity level, physical activity policy) were not sustained when considering covariates.

Perspectives from parents and professionals (study III)

Facilitators and barriers to participation in 'uptime' activities were explored from the perspectives of parents and professionals in four focus groups. One central theme emerged: "A constant balance to do the best thing for the girl/woman". Parents and professionals always attempted to make the girl/woman with RTT feel comfortable and well and when providing her with 'uptime' activities they needed to balance what to do within the current situation and resources. Any imbalances in a resource area could compromise participation in 'uptime' activities. To optimize the opportunities for participation other resource areas could compensate to create a balance. Five subthemes emerged within the central theme: 1) The girl/woman engaging in activity, 2) Using aids and characteristics of the indoor and outdoor environment, 3) Creating possibilities with the support of organizational structures, 4) Together we provide the best possible daily life, and 5) Our knowledge, motivation, attitude and beliefs have an impact. In each subtheme, several facilitators and barriers were identified (see figure 12). Findings suggest that optimal participation in 'uptime' activities can be facilitated by balancing:

- The girl/woman's active, social and preferred engagement in relation to her functional and mental resources.
- The optimum use of aids/equipment within a flexible and accessible environment.
- The schedules of active daily routines in relation to staffing resources.
- The collaborative attributes across and within settings acknowledging and utilizing each other's strengths.
- The inner motivation and positive attitude against having an open-minded approach to our knowledge base and beliefs.

Facilitators		Barriers

A constant balance to do the best thing for the girl/woman	The girl/woman engaging in activity	*Walking independently *Social interaction and engagement *Finding the right and meaningful motivators *Positive reactions to 'uptime' activities *Opportunity and capability to communicate what she wants	*Need of physical assistance *Presence of co-morbidities and other symptoms *Limited physical/psychological resources *Lack of enjoyment and boredom *Limited communication skills
	Using aids and the indoor and outdoor environment	*Standing/mobility aids *Flexible indoor environment *Easy access to equipment	*Need of wheelchair when ambulant *Difficulties getting aids granted *Not knowing the range of possible aids *Weather
	Creating possibilities within organizational structures	*'Uptime' part of everyday life and daily routines *Active and creative individual strategies *Established daily program with good instructions and room for spontaneity *Having enough "hands"	*Time constraints *Constantly prioritizing activities *Few trained professionals *No clear focus on PA from management *Limited staffing
	Together we provide the best possible daily life	*Presence of a physical therapist *Interdisciplinary collaboration *Collaboration between parents and professionals	*Limited access to a physical therapist *Different priorities between stakeholders *Physical condition of parents/professionals *Lack of surplus energy in parents/ professionals *Need of being a family
	Our knowledge, motivation, attitude and beliefs have an impact	*Awareness and focus on 'uptime' *Knowledge about RTT and needs of the individual girl/woman *Motivation in parents and professionals *Positive and active attitude and approach to PA	*Insecurity and lack of knowledge *Tendency to help too much *Concerns about violating the personal rights and physical capability of the individual

Figure 12. Facilitators and barriers in each subtheme (PA = Physical activity)

The 'Uptime' Participation (U-PART) intervention

Feasibility (study IV)

Thirty caregivers comprised of six families and 24 professionals (including 10 teachers/ pedagogues and physical therapists from schools, six pedagogues from day centers and eight care assistants from residential homes) filled in a study-specific feasibility questionnaire. The 24 professionals working with the study participants were the facilitators of the intervention in their specific setting. The acceptability and general evaluation of the U-PART intervention was high with a median score ≥8 out of 10. One caregiver commented that the intervention period was probably too short to see substantial reduction in sedentary time. The expectations for the intervention were fulfilled to a high extent (median=8, IQR =7,9) and caregivers felt persuaded to focus on 'uptime' activities in the future (median=9, IQR=8,10). No negative effects were reported for the girl/woman and only two caregivers expressed a negative effect on themselves due to their own time limitations. Positive effects were perceived for both the girl/woman (spending more time in 'uptime' activities) and the caregiver (knowledge about RTT and physical activity). The use of accelerometers and diaries were generally assessed as good (median=7.5, IQR=5-9) even though it could be time consuming. In residential settings, it was sometimes difficult to ensure consistent information to all staff members, although the minimum requirement of 4 valid days of accelerometer data was met at all time points. The usefulness and satisfaction with all elements in the preparation period and the instructions and supervision during the intervention period were very high with a score of ≥9. The selected 'uptime' activities were perceived as appropriate (median=8, IQR=6,10) and caregivers reported a moderate to high engagement of the girl/woman during activities (median=8, IQR=6,9). Only 14 of the caregivers reported on the use of self-chosen activities with variable satisfaction with this aspect (median=6, IQR=3.3,10). For example, caregivers generally felt it was too difficult to allow choice-making either due to time constraints or correct interpretation of the choice. The intervention was perceived as somewhat time consuming (median=6, IQR=4,7) but mostly did not require extra resources (median=3.5, IQR=1,6). During the intervention, all participants had access to one or more special equipment (e.g. switch-adapted aids) and 6 participants used a large aid (e.g. Stander, Walker) (see table 11) and these aids were perceived as helpful in most cases to facilitate 'uptime' (median=8, IQR=4.25,9).

Work and travel hours for the multidisciplinary team at CRS who implemented the intervention are shown in table 11. On average the multidisciplinary team spent 35.5 (SD 3.39) work hours and 8.72 (SD 3.99) travel hours on each participant during the study period.

Table 11. Time use and cost of special equipment and aids

Time use (mean, SD)	
Observations (including assessment T0)	
Work hours	24.93 (3.23)
Travel hours	3.22 (2)
Individual program design	
Work hours	3 (0)
Joint meetings (including assessment T1)	
Work hours	2.14 (0.35)
Travel hours	2.25 (1.11)
Assessments at T2 and T3	
Work hours	2.25 (0.37)
Travel hours	2.05 (1.16)
Supervision	
Work hours	3.18 (1.36)
Travel hours	1.2 (0.4)
Total time used	
Work hours	35.5 (3.39)
Travel hours	8.72 (3.99)
Special equipment and aids	
Special equipment (e.g. Powerlink, switch-adapted aids)	
Number	21
Median cost in USD (range)	125 (13 – 560)
Large aids (e.g. Stander, Walker)	
Number	6
Median cost in USD (range)	3150 (3,135 – 10,595)

Health-related effects – physical (study IV)

Primary outcomes

Sedentary time as measured by activPAL and step counts as measured by SAM were the primary physical outcomes. Summary scores are shown in table 12. Compared to baseline and when adjusting for age, ambulation level and residence, sedentary time was reduced by 4.09% ([95%CI -5.87,-2.32], $p<0.001$) after the intervention (T2) and 3.36% ([95%CI -5.15,-1.58], $p<0.001$) at follow-up (T3). In participants who were ambulant increased step count was observed at T2 (+708 steps/day, [95%CI 126,1290], $p<0.019$) but this effect was not maintained at T3.

Table 12. Summary scores of sedentary time and step counts at the four time points

	T0	T1	T2	T3
Daily sedentary time, n=14				
Relative to waking h (%)	83.5 (10.7)	84.8 (10.5)	80.1 (10.2)*	80.9 (9.6)*
Daily physical activity, n=9				
Step count	4291 (2650)	4522 (2642)	5096 (2546)*	4700 (2665)

*Denotes significant changes in outcomes

For sedentary time, exploratory subgroup analyses were performed to compare children (n=8, 5-19 years) and adults (n=6, >19 years) as well as ambulant (n=9) and non-ambulant (n=5) participants.

When adjusting for covariates the following changes in sedentary time were seen in children and adults:
- Children
    - After intervention (T2): -3.48% ([95%CI -6.14,-0.81], p=0.013)
    - At follow-up (T3): -3.76% ([95%CI -6.44,-1.07], p=0.008)
- Adults
    - After intervention (T2): -5.21% ([95%CI -7.44,-2.99], p<0.001)
    - At follow-up (T3): -3.37% ([95%CI -5.6,-1.13], p=0.005)

When adjusting for covariates the following changes in sedentary time were seen in ambulant and non-ambulant participants:
- Ambulant
    - After intervention (T2): -4.3% ([95%CI -6.78,-1.82], p=0.001)
    - At follow-up (T3): -2.28% ([95%CI -4.77,0.21], p=0.071)
- Non-ambulant
    - After intervention (T2): -3.71% ([95%CI -5.65,-1.76], p=0.001)
    - At follow-up (T3): -5.28% ([95%CI -7.23,-3.34], p<0.001)

Secondary outcomes

Secondary physical outcomes included gross motor skills (RSGMS), walking capacity (2MWT) and the initiation and maintenance of sleep (DIMS). Summary scores are shown in table 13. Gross motor skills and sleep remained unchanged whereas walking capacity increased at T2 (18.94m [95%CI 7.45,30.42], p=0.002) and T3 (12.4m [95%CI 0.87,23.29], p=0.036) when taking age and residence into account.

Table 13. Summary scores of RSGMS, 2MWT and DIMS at the four time points

	T0	T1	T2	T3
RSGMS (/45)	21.6 (8.6)	21.3 (8.4)	21.5 (8.3)	21.1 (8.3)
2MWT (meters), n=9	81.9 (35.4)	93.6 (35.3)	106.5 (33.7)*	99.9 (34)*
DIMS (/35)	12.4 (3.8)	11.9 (3.3)	11.8 (3.7)	11.5 (3.5)

*Denotes significant changes in outcomes
RSGMS: Rett Syndrome Gross Motor Scale; 2MWT: Two Minute Walk Test; DIMS: Disorders of initiating and maintaining sleep subscale from the Sleep Disturbance Scale for Children

Health-related effects – psychological (study IV)

Secondary outcomes

Secondary psychological outcomes were behavior (RSBQ) and quality of life (QI-Disability). Summary scores are shown in table 14. Behavior did not change throughout the study period. When taking age, ambulation level and residence into account, the total quality of life score improved at T2 (2.81 [95%CI 0.5,5.11], p=0.018). Positive adjusted effects were seen at T2 in two of the subscales: Social Interaction (5.06 [95%CI 1.18,8.94], p=0.012) and Leisure/Outdoors (5.71 [95%CI 1.6,9.81], p=0.008).

Table 14. Summary scores of RSBQ and QI-Disability at the four time points

	T0	T1	T2	T3
RSBQ (/90)	40.8 (16.8)	41.4 (15)	42.1 (12.5)	42.8 (11.6)
QI-Disability (/100)	78.3 (7.9)	78.6 (7.8)	81.4 (8.8)*	79.8 (10.6)
Social Interaction subscale (/100)	80.4 (10.9)	80.1 (11)	85.3 (11.2)*	81 (14.7)
Positive Emotions subscale (/100)	82.3 (13.6)	83 (14.5)	81.3 (15.8)	83.3 (17.6)
Physical Health subscale (/100)	79.5 (10.7)	78.6 (9.1)	82.1 (10.5)	78.6 (12.6)
Negative Emotions subscale (/100)	75 (14.6)	75 (13.7)	77.7 (10.5)	78.1 (10)
Leisure/Outdoors subscale (/100)	74.3 (11.5)	76.1 (9.1)	80.7 (12.2)*	77.9 (15.1)
Independence subscale (/100)	49 (10.8)	48.4 (12.3)	48.3 (10.7)	49.4 (12.2)

*Denotes significant changes in outcomes.

RSBQ: Rett Syndrome Behavior Questionnaire; QI-Disability: Quality of Life Inventory – Disability

Participation-level effects (study IV)

Secondary outcome

GAS was used to assess individual participation-level goals. A total of 56 goals were assessed after the intervention (T2) with a median of 4 goals (range 2-6 goals) for each participant. For 58.9% (n=33) goals the expected positive changes was reached (GAS score of ≥0). Minor improvements (GAS score of -1) were seen in 37.5% (n=21) of goals. At participant level and in the residence and ambulation subgroups significant improvements were seen (see table 15). The median GAS scores did not reach a clinically relevant level (+2 points) in those who lived in a residential home and those who were non-ambulant.

Table 15. GAS scores at T1 and T2

| | Median | | *p*-value |
	T1	T2	
GAS scores			
Total (n=14)	-2	0	0.001
Residence			
Parental home (n=6)	-2	0	0.026
Residential home (n=8)	-2	-0.75	0.011
Ambulation level			
Ambulant (n=9)	-2	0	0.007
Non-ambulant (n=5)	-2	-0.5	0.043

GAS: Goal Attainment Scaling

Discussion

Methodological considerations

Research involving individuals with multiple disabilities requires careful and thorough considerations. Following the MRC framework of complex interventions the results regarding valid walking measures (study I), patterns of physical behavior (study II) and facilitators and barriers of 'uptime' activities (study III) each aided the development and piloting of an 'uptime' intervention (study IV). As such the studies in this thesis constitute the development, feasibility/piloting and initial evaluation stages of the MRC framework (163). A combination of both quantitative and qualitative methods was employed in this thesis and the generalizability and quality of the studies will be discussed below.

Design and sample sizes

In the methodological study (study I) a consecutive sampling strategy was chosen to reach a minimum of 30 functional ambulators (HAS I-II). Variable sample sizes for reliability and validity studies in the field of neurology have been proposed ranging from n≥20 to n≥80, respectively, to obtain robust estimates. However, in validity analyses n≥40 correlation estimates remained relatively stable (181). The sample sizes of n=42 (all) including n=27 with HAS levels I-II in study I were relatively small but could be sufficient given these sample size recommendations. Preferably, validity estimates of the 2MWT (n=27) should include a larger sample.

In the population-based cross-sectional study (study II) the sample (n=48) included 54.5% of the eligible participants in Denmark and comparison with non-participants suggested that the two groups were similar. However, the sample size remained relatively small and compromised the multivariate linear regression models. A general rule of thumb is that the number of subjects per variable should be 10 which limited the number of variables in each of the models in study II (182). Furthermore, the findings of this cross-sectional design could be influenced by survival bias since more severely affected individuals could have died at an earlier point (89).

Using a qualitative approach in study III, it was possible to get a deeper understanding of the perceived influences on participation in 'uptime' activities. Data was collected using focus groups rather than individual interviews because focus groups are very useful in cases of complex patterns of behavior as they encourage a range of responses that provide substantial insights into the perspectives of the participants (168). Parents and professionals from school, day center and residential settings were chosen as informants. Due to cognitive and communicative challenges it was not possible to include the girls/women with RTT as informants. In focus groups 6-10 participants are recommended (168) and an over-recruiting strategy was used to ensure adequate participants per focus group. However, the number of professionals from day centers and residential homes did not reach this recommendation for focus groups size. Time constraints and limited staffing were evident in those professionals working with adults which has also been described elsewhere (183).

No specific recommendations on sample size exist for feasibility studies. A review of 39 feasibility trials in the UK showed that the sample sizes ranged from 10-300 participants (184). Study IV was a feasibility study and involved 16 participants (corresponding to one third of the eligible participants in Denmark according to the inclusion criteria) in a pretest-posttest design which was suitable to the explorative nature of the study. Randomized designs in small heterogeneous populations such as RTT can be limited by the lack of available participants and lack of resources to recruit an adequate sample size to ensure equal characteristics in the intervention and control arms of the study (185). Non-randomized designs such as the pretest-posttest design lack control of extraneous factors and have limited generalizability because the individualized intervention is difficult to replicate (186) although within subject comparisons reduce some variability. A sample size calculation for a full-scale evaluation study requires information about the population-based mean and the expected reduction of sedentary time. The mean sedentary time in girls/women with RTT was 83.3% (SD 13.9%). The two baseline assessments in 14 participants in study IV could serve as an initial indicator of the SEM=2.26% and MDD=6.26% in sedentary time. Using a two-sided test with a significance level of 0.05 and power of 80%, the estimated sample size would be 156 – 78 in the intervention group and 78 in the control group. Recruiting 156 participants would require an international sample and substantial funding resources.

Research validity

Research validity concerns the extent to which the conclusions of a research study are believable and useful. The quality of a research study relates to internal, construct and external validity although controlling one type of validity often leads to problems in another. For instance when researchers wish to achieve high internal validity by standardizing the intervention it compromises the external validity because results can only be applied in that controlled setting (186).

Internal validity relates to whether the intervention caused the effects seen – that is whether the independent variables provide a plausible explanation of group differences in the dependent variable. Factors like history (events unrelated to intervention), maturation (changes in participant with time) and testing (familiarization with testing procedure) could threaten the internal validity of a study. These factors can be controlled with random assignment and the use of a control group (186). Several strategies were implemented to increase the internal validity of the studies in this thesis. Regarding the effects of learning on 2MWT results, data were collected following a test trial. The SAM was individually calibrated before each assessment period. In the intervention study (study IV) two baseline assessments were performed to observe stability of the variables and for participants to act as their own controls. However, clinical assessments were not blinded and some outcomes were based on proxy-report.

Construct validity relates to the meaning attached to the variables and concepts used within the study (186). For instance, accelerometer-type devices such as the SAM are used to measure daily physical activity, but is the daily step count a true indicator of physical activity? Neither activPAL nor SAM can describe the full range of physical behavior because they cannot be used in water-based activities. In this thesis it is recognized that SAM only provided information on ambulatory physical activity. However, walking is the most common physical and participation-based activity in adults with ID (187) and thus daily steps likely provide a good estimate of physical activity level. To increase construct validity of the studies, measures that were validated and reliable for RTT were chosen.

External validity relates to the generalizability of results which can be threatened by sample selection and the setting. Participants who are willing to participate in research studies may differ from the general population. Researchers should choose the setting to which they hope to generalize their results (186). In study I the sample had an overrepresentation of functional walkers (HAS I-II), however the purpose was to modify and validate walking measures and the subgroup sample will likely be representative of girls/women with RTT with the ability to walk. The standardized procedure for the 2MWT was applied within many settings

which is pragmatic and could enhance the generalizability of findings. In study II the sample was representative of the Danish population of girls/women with RTT. In study IV the sample reflected the Danish population of girls/women with RTT with regards to ambulation level and living arrangements. In all studies the generalizability to countries other than Denmark could be compromised due to differences in living arrangements, services and organizational structure. However, similar daily step counts were found in an Australian sample which supports the generalizability of the results in study II (91).

Measurement reliability and validity

Measurement reliability relates to the extent to which test scores are free from errors, i.e. how stable test scores remain over time and when measured by different raters. The main types of reliability are test-retest reliability, interrater and intrarater reliability, and internal consistency (188).

Test-retest reliability relates to the consistency of the assessment/test score over time. *Interrater and intrarater reliability* refers to the agreement between different and same raters, respectively. *Internal consistency* is the degree to which all test items measure the same construct. An outcome measure should always have adequate test-retest reliability because the stability over time allows the measure to pick up true changes in function (188). Thus, the test-retest reliability was chosen in study I to initially support the reliability of the 2MWT and FMS-RS.

Both relative and absolute reliability are important for interpretation of the accuracy of a measure. *Relative reliability* indicates the relationship between repeated measurements using a correlation coefficient (e.g. ICC and weighted kappa values) and *absolute reliability* indicates the variability on repeated measurements using the SEM and MDD (186, 189, 190). In this thesis, SEM was defined as the square root of the mean square within-subjects error using repeated measures ANOVA and MDD as SEM*$\sqrt{2}$*1.96 (190). Whilst correlations between measures could be high, the SEM/MDD could suggest that large changes are needed to be sure that a participant has truly changed beyond within subject measurement error. De Vet et al have argued that the minimal clinically important difference (MCID) provides additional important information when interpreting change in scores. SEM/MDD is seen as a distribution-based approach based on sample characteristics and doesn't provide an indication of the importance and clinical relevance of the observed change. In anchor-based methods an external criterion is used to operationalize an important change (191). Further research is needed to determine the MCID for these measures.

Measurement validity relates to the meaningfulness and utility of a measure and provides evidence of the measure as an indicator of what it was designed to measure. During development of a measure, content, construct and criterion-related validation are often performed in several processes. Criterion-related validity studies are often performed at the end of development (188).

Content validity refers to whether the measure assesses what it is supposed to based on the appropriateness of its content. *Construct validity* refers to whether the measure assesses the underlying theoretical construct. *Criterion-related validity* refers to the practical validity of a measure which is about the effectiveness of a measure in predicting the individual's performance. Criterion-related validity can be determined using predictive and/or concurrent measures. *Predictive validity* relates to whether the scores predict any criterion performance or some future event. *Concurrent validity* (or congruent/convergent validity) refers to whether the test result agrees with other established measures of the same content or construct (188). The 2MWT and FMS were existing measures that were modified to be used in individuals with RTT in study I. As such the study focused on concurrent validity.

Trustworthiness

The quality and rigour of the analysis and findings in qualitative studies relates to the trustworthiness of the study. Concepts of trustworthiness are credibility, dependability, transferability and confirmability. In study III the guidelines on data collection and analysis described by Lincoln and Guba were followed to ensure trustworthiness (192).

Credibility refers to confidence in the truth of the data and that the data and analysis represent the intended research focus. Important aspects of credibility include the selection of participants and approach to gathering and analysing data. In study III participants were chosen from various settings to shed light on the research question from a range of perspectives. Thematic analysis was chosen over content analysis since rich thematic descriptions emphasizing the context is a useful method when investigating an understudied area (177). In contrast, the focus of content analysis is to describe the characteristics of the content in the data whereas thematic analysis aims to identify patterns across an entire data set (193). An essentialist theoretical framework was used to substantiate the data analysis. Data represent essential meanings of the lives of the participants and the essentialist framework offers valuable means to understand the individual in a social context (194). To ensure rigour the analysis process followed the six steps

procedure recommended by Braun and Clarke and using an inductive approach the themes were strongly linked to the data themselves (177). Two researchers independently coded and interpreted the data and discussions provided a more complete understanding. Through a reflective approach, the moderator and assistant debriefed after each focus group and documented their own reflections. Triangulation was used to limit systematic bias by involving research team members with various professional backgrounds. Members of the research team were asked to audit the decisions and interpretation of data throughout the process to make sure that no relevant data was excluded or irrelevant data included (195). Decisions were illustrated with data representative quotes. Quotations also clarified the differences between themes.

Dependability refers to the extent to which data, data collection or analysis change over time. In study III dependability was enhanced through the choice of methodological framework and a consistency throughout the data collection with continuous open dialogue within the research team. The same opening question was used in all focus groups and the interview guide was followed to cover all areas.

Transferability refers to the extent to which the findings can be transferred to other settings or groups. By providing a description of the selection and characteristics of participants, the data collection and analysis in study III, the transferability was supported. Members from the research team who worked at the CRS had met most of the participants on the annual visits of the girl/woman with RTT prior to the study. Thus, a third researcher provided a more independent perspective throughout the analysis. The relatively small sample size may not be representative of all parents and professionals working with RTT although purposive sampling was used to seek variability in participant experiences. Rich and thick descriptions of the findings and representative quotations were chosen to further strengthen the transferability.

Confirmability refers to the objectivity of the data and the interpretations made. Philosophically, researchers in qualitative studies have their own pre-understandings and cannot be completely objective. To reduce the risk of researcher bias the research team consisted of members with different educational backgrounds and the thorough methodological descriptions enabled examination of the research findings. Data source (wide range of informants) and site triangulation (informants from different settings) further supported the confirmability. Quotations from informants in all settings were used to confirm results.

General discussion of results

The results in this thesis highlight that girls and women with RTT have high levels of sedentary time. However, with the additional knowledge of valid outcome measures and facilitators and barriers of 'uptime' an 'Uptime' Participation (U-PART) intervention has the potential to reduce time spent sedentary with positive impacts on health and quality of life. The main results regarding walking measures in RTT (study I), patterns of physical behavior and influencing factors (study II-III) and the U-PART intervention (study IV) will be discussed below.

Walking measures in RTT

The 2MWT and FMS-RS measures were modified to accommodate the specific challenges associated with RTT. Severe dyspraxia, poor balance and reduced hand use limits the execution and self-initiation of movements and increases the dependence and need of physical assistance. When assessing walking capacity in comparable groups (e.g. CP, ID) visual goals, pacers and frequent encouragement have also been used (196, 197). All modifications to the 2MWT and FMS-RS should be applied in a standardized and consistent manner but it remained feasible to perform the 2MWT in the natural settings of the participants. High ICC's indicated good test-retest reliability in both measures. Low-moderate and moderate-high correlations with the comparative measures were found in the 2MWT and FMS-RS which supported their concurrent validity. Both RSGMS and CSS are RTT-specific measures for gross motor skills and severity, respectively. PEDI-m is generic and focuses on daily mobility tasks such as bed transfers, indoor ambulation and walking up/down stairs. The low-moderate correlations found with the 2MWT could be explained by the fact that it represents a somewhat different domain than the comparative measures. The 2MWT could not be validated against variables such as perceived exertion or a maximal exercise criterion due to the cognitive, communicative, neuromuscular and musculoskeletal impairments seen in individuals with multiple disabilities (198). Results from the 2MWT showed the need of a practice trial in girls and women with RTT indicating how the measure should be administered. A MDD of 38m was found for the 2MWT. However, a change of less than 38m could reflect a clinical important difference for some individuals (191). As an outcome measure, the 2MWT might be useful in interventions targeting gross motor skills and physical activity. The FMS-RS could be used to describe recovery following orthopedic surgeries and provide detailed longitudinal information on daily ambulation for clinical monitoring and to guide the planning of activities that support participation and quality of life.

Patterns of physical behavior

The level of sedentary behavior found in this Danish population of females with RTT aged 5-60 years was comparable to objectively measured levels found in older adults (>60 years) without disabilities (199) and in disorders such as Parkinson's disease (200) and CP (201). In 64 younger (3-38 years) and ambulant females with RTT a lower level of sedentary time (62%) was found using SAM data (91). Using the activPAL to estimate sedentary time (as done in this thesis) is likely more accurate. The average daily step count found in study II similar to the 5,093 steps/day reported in Australian females with RTT (91) and comparable to step counts in children with CP at GMFCS level III and adults with mild-moderate ID (38, 49). The hourly patterns of sedentary time and step count provided new knowledge about daily physical behavior in RTT. Those walking with assistance were almost as sedentary as those unable to walk and in both these groups sedentary time accumulating especially later in the day. In those walking independently and with assistance steps accumulated during the morning hours and gradually declined throughout the day but with peaks occurring slightly later during the afternoon on weekends compared to weekdays. In those who could walk independently a decline in steps was not always followed by an increase in sedentary time and vice versa which could be due to brisker walking episodes in the morning hours and standing activities in the afternoon. However, this explanation needs to be confirmed.

Associated factors, facilitators and barriers of physical behavior

Multivariate regression models showed effects of age and walking ability on sedentary time, with later adulthood (33.5-60 years), walking with assistance and inability to walk increasing sedentary time. In another study of females with RTT an age effect on physical behavior was already evident in teenage girls (91). Living arrangements did not influence sedentary time in study II. However, lower levels of physical activity have been found in adults with mild-moderate ID living in congregate care (202). Other environmental factors could potentially influence physical behavior as individuals with RTT experience high dependency on others in all daily activities. In the univariate analysis, higher maternal physical activity levels and the presence of a physical activity policy in the residence were associated with a significant reduction in sedentary time in the participants. The effects of these variables were not maintained in the multivariate analyses possibly due to the small subgroup sizes.

The perceived facilitators and barriers to participation in 'uptime' activities shared some similarities and differences to previous studies in individuals with CP and

ID. Within the individual facilitators such as social and active engagement, motivation and enjoyment and barriers such as lack of physical resources have also been found in previous studies (35, 44, 45, 47, 203). Providing the girl/woman with choices for activities was not mentioned as a facilitator in study III, even though self-engagement by choosing activities of interest has been described as an important dimension of optimal participation (14) and identified as a facilitator in a physical activity program in other disability studies (203). Within the physical environment facilitators such as versatile mobility aids and accessible interior designs and barriers such as the weather have also been described previously (43, 44, 47, 203). The facilitators within the organizational environment (e.g. establishing daily routines, structured programs and creative strategies) from study III were comparable to the findings in children and adults with DS (204, 205). Organizational barriers such as restricted time, staffing issues, less priority given to physical activity and limited focus on health promotion were identified across settings and also align with previous studies (35, 203, 204, 206). Within the social environment, facilitators such as collaboration across and within the daily settings together with the combined resources of parents and professionals were unique findings in study III. Involvement of parents but not the supporting role of professionals and this specific collaboration have been described (35, 43, 45-47). Health professionals such as physical therapists are necessary to facilitate and promote physical activity (43, 47, 183, 206). Barriers like caregiver resources and family needs have also been identified previously (44, 45, 123). Our findings also accentuated the negative consequences of lack of resources in professionals. Within the attitudinal environment important facilitators were positive attitudes, inner motivation and role-modelling approach whereas barriers included ethical beliefs and concerns about autonomy versus healthy care. These facilitators and barriers are consistent with previous studies (35, 45-47, 203, 206, 207). The ethical dilemma of 'freedom of choice' faced by professionals may not always be achievable given the comprehension level of the individual and the knowledge professionals have about healthy behavior (208, 209).

The 'Uptime' Participation (U-PART) intervention

Caregivers assessed the overall feasibility of the intervention as good with high levels of fulfilled expectations, satisfaction and perceived appropriateness. Particular strengths included the observational assessments, joint meetings and supervision which were perceived as useful, highly motivating and educational. The selected 'uptime' activities were appropriate and the participants showed moderate to high engagement in these activities. Self-selected physical activities and individual support from a physical therapist supporting children with CP were

also perceived as feasible in a previous study (210). In participation-based interventions, the physical therapist supervises and collaborates with the caregivers to share knowledge, identify necessary adaptations and provide support and instructions to build capacity within the individual and caregivers (52). Environmental changes such as organizing transportation of mobility aids between home and school and engaging volunteer 'Walk Buddies' in residential settings were supported by the physical therapist in the U-PART intervention.

Alternatively, challenges related to time, choice-making and availability of aids. Time constraints and heavy workloads have previously been described as barriers to implementing health promotion interventions in adults with ID (183). Providing the participants with choices within the 'uptime' activities proved difficult and time consuming for some caregivers. To optimize participation in 'uptime' activities nine participants required the use of standers and walkers but in three participants the aids could not be rented and were not granted by the municipality during the study period. This barrier was already described by parents and professionals in study III and in another feasibility study (210).

The primary outcomes of sedentary time and the daily step count were objectively measured. Sedentary time was reduced by 4% (~36min/day) after the intervention and the reduction was sustained at follow-up. Even though the clinical relevance of this reduction is unknown, it seems plausible that this reduction could be clinically meaningful given the high baseline level of sedentary time. In older non-disabled adults a smaller reduction of sedentary time of ~22min/day was seen following an intervention (211). Subgroup analyses in the current study showed that children maintained their reduction of sedentary time after the intervention and at the follow-up assessment (~3.5%). In contrast, adults showed a larger reduction in sedentary time at the end of the intervention (5.2%) and then a smaller reduction at the follow-up assessment (3.4%). At the day centers and residential homes pedagogous and care assistants stated that they redistributed their work patterns during the intervention period to focus on the particular participant which might explain the reduction in sedentary behaviors in adults. In individuals who could walk, the reduction in sedentary time decreased at the follow-up assessment (4.3% vs 2.3%). In participants who walked independently, the daily step count was above average (i.e. >5,000 steps/day) and thus caregivers may not have considered the additional strategies for reducing sedentary time to the same extent. In non-ambulant participants, the sedentary reduction was greater at follow-up (3.7% vs 5.2%). This group required aids to promote 'uptime' and full implementation of these strategies may have extended beyond the 12 week intervention period in daily schedules. Post-intervention an increase of 708 steps/day was seen in ambulant participants but this effect was not maintained at follow-up. Other lifestyle interventions have shown different effects on physical

activity in which adults with ID increased their step count with 1608 steps/day and no changes were seen in children and young adults with CP (212-214).

RSGMS scores were stable across the entire study period, likely because the U-PART intervention did not target the learning of new gross motor skills. Sleep disturbances as measured with DIMS also remained unchanged. Sleep was also unaffected in this regard following an early enriched environmental intervention in girls with RTT who were younger than six years (157). Walking capacity was not a direct goal of the U-PART intervention but positive gains were seen in ambulant participants where the distance walked in two minutes increased significantly. This change was smaller than the minimal detectable difference (MDD) of 38m but nevertheless, girls and women with RTT showed potential to improve their walking capacity.

Behavior as measured by RSBQ did not change which is also consistent with the findings following enriched environmental RTT intervention (157). In study IV, a quality of life questionnaire (QI-Disability) validated in RTT was used (128). A significant increase in total quality of life scores was found immediately after the U-PART intervention with even greater increases in subscale scores for social interaction and leisure and the outdoors. These subscales reflect the focus areas of the U-PART intervention. Previous lifestyle interventions have not shown changes in quality of life (215) and the U-PART intervention is promising in this regard.

Participation level goals as measured with GAS showed improvements in the majority of goals with 60% reaching the expected level of improvement. Optimal improvements might require a longer intervention period especially in those who are non-ambulant and need maximal support to participate in standing activities and those who live in a residential setting where staffing issues and time constraints are evident.

In sum, the U-PART was found to be feasible and was associated with multiple positive effects on activity levels, walking capacity and quality of life. However, the positive health-related effects were only partially sustained or lost at follow-up and the intervention period may have been too short to expect sustainable changes in physical lifestyle behaviors. In girls/women with RTT changing physical activity routines depend heavily on the caregivers and the support by professionals such as physical therapists. Extending the intervention period and including supervision from physical therapists could be important strategies to consider in future studies.

Conclusion

In conclusion, this thesis has shown that in Danish girls and women with RTT:

- The concurrent and test-retest reliability were established in the modified 2MWT and FMS-RS measures. Building the repertoire of walking measures is valuable for researchers and practitioners for clinical monitoring and evaluation studies. The 2MWT and FMS-RS together with measures of gross motor skills and physical activity offer a comprehensive understanding of capacity and everyday function in relation to mobility in girls and women with RTT.

- The level of sedentary time was high during awake hours and in those who were ambulant, the daily step count was low. Advancing age and poorer walking skills were strongly associated with greater sedentary time. Detailed patterns of physical behavior were established with most 'uptime' activities taking place during the morning. This knowledge can aid health care professionals in promoting active lifestyles and developing interventions to reduce sedentary time and increase 'uptime' activities.

- Optimal participation in 'uptime' activities was achieved when balancing facilitators and barriers within the individual (engagement ↔ resources) and her physical environment (aids/equipment ↔ accessibility), organizational environment (routines ↔ time burden), social environment (collaboration ↔ acknowledgement) and attitudinal environment (motivation ↔ beliefs). Interventions promoting 'uptime' activities should take these identified facilitators and barriers into account to optimize participation across settings throughout day-time activities.

- The 12-week U-PART intervention was considered feasible by parents and professionals with regards to both acceptability and practicality. Post-intervention positive health-related effects were seen in the outcomes of sedentary time, daily step count, walking capacity, quality of life and participation-level goals. At short-term follow-up positive effects were maintained in sedentary time and walking capacity.

Clinical implications and future research

Health-promoting efforts in small and vulnerable populations like RTT will enable the optimal amount of independence, inclusion, participation and quality of life throughout the lifespan. The new knowledge gained from this thesis has important implications in Denmark and internationally, to ensure that valid and reliable outcome measures are available and to develop health-promoting strategies for girls and women with RTT.

Within this thesis several steps have been taken in the development and evaluation of a complex intervention aiming at enhancing participation in 'uptime' activities in Danish girls and women with RTT. In the development phase, available outcome measures (study I) and the evidence base (study II) were broadened. In the feasibility phase a qualitative approach contributed valuable knowledge of the everyday lives of girls/women with RTT (study III) that informed the development of the U-PART intervention and ensured its acceptability (study IV). Finally, in the evaluation phase an explorative evaluation provided initial support of the health-related effects (study IV). Further steps within the development, feasibility and evaluation phases are warranted to adjust and refine the intervention.

The identified theories that formed the foundation for this thesis are based on conceptual frameworks developed for children with disabilities although their applicability has yet to be determined in adults with disabilities. The assumption is that due to the severity, complexity and high dependency throughout life in individuals with RTT many concepts will apply in adults as well. A critical component to change health behaviors is to target the environment in which individuals live their lives (216). In other health-promoting research involving adults with mild-moderate ID the use of the Trans-Theoretical Model and stages of change have been proposed to determine staff readiness and tailor training and materials accordingly (203). The application of stages of change has also been recommended to understand family readiness in physical activity interventions in children with CP (217). Since girls/women with RTT rely heavily on the supports in their environment the incorporation of stages of change determining family and/or staff readiness should be explored further.

With regards to the modified outcome measures, their clinical utility remains to be determined. Studies are needed to clarify whether the MDD of 38m on the 2MWT is achievable following an intervention or if smaller changes would be considered a clinically important change (MCID). With larger sample sizes, it may even be possible to determine the MDD and MCID in subgroups (e.g. independent walkers and assisted walkers). In children with CP, gross motor function subgroups have been used with several outcome measures to establish MCID (218). Future studies should also address the applicability of the FMS-RS as an outcome measure and the limitations associated with the ordinal nature of the scale. In addition, more research is needed to determine clinically meaningful and sustainable reductions in sedentary time in individuals with multiple disabilities including subgroups (219). With clinical trials and intervention studies emerging within RTT, there has never been a greater need for a toolbox of outcome measures with strong psychometric properties which have been validated in individuals with RTT to avoid the risk of floor effects and irrelevant items.

Larger sample sizes are needed to better understand factors influencing physical behavior in severe disabilities, supplemented with longitudinal studies and clear identification of modifiable environmental factors. Involving the managers to explore their perspectives on the facilitators and barriers to participation in 'uptime' activities would deepen our understanding and enable 'buy in' from a top-down approach (216). With growing use of eye-gaze technologies, it may be possible to collect the perspectives of the girls/women with RTT as well by assisting them to indicate liked and disliked activities and to indicate their level of enjoyment when performing an activity.

In the feasibility study (study IV) caregivers found the U-PART intervention acceptable and applicable to the individuals with RTT for whom they provided care. The U-PART intervention provided a systematic framework for the promotion of 'uptime' within the participant's natural environment that could be embedded within existing support systems for economic efficiency. A future full-scale evaluation should include a longer intervention period (215), a facilitating physical therapist (183) to advocate 'uptime' in each setting and assessment of additional health-related outcomes such as bone and lung health and nutritional status over the longer term. One research group has argued that promotion of health should include management of sleep and nutrition (220), a trio of issues that are commonly experienced in individuals with RTT (83, 100). A future focus on physical activity, sleep and nutrition will enhance our understanding of this triad and hopefully contribute to the well-being of individuals with RTT.

The U-PART intervention was delivered in the home (parental/residential) and day-time (school/day-center) settings targeting individually determined goals.

Future studies could target a whole class/day-center group, to determine whether U-PART would reinforce the 'uptime' mind-set and routines using a whole of school or whole of day-center approach and targeting organizational and policy level changes. Supporting the organizational capacity such as work routines and staffing resources as well as developing policies to ensure a mandatory commitment to health promotion have been underlined in previous research in adults with ID (183, 216). Weekly sport participation within the community setting could also be promoted with the use of switch-adapted aids such as a bowling ramp and ball machine where the ball is released with a touch of the switch.

Many steps are necessary in the development of an optimal health-promoting intervention for girls/women with RTT. Health-enhancing participation in RTT requires careful considerations and balancing of potential health benefits and available resources in the individual, family, staff, the specific setting, the community and society. The complexities of this task are yet to be fully understood. Other groups of children and adults with multiple disabilities might also benefit from this kind of intervention but effectiveness in larger scale studies and cost-effectiveness must be established before any long-term implementation phases are commenced.

Nevertheless, this thesis has provided novel findings within RTT with a particular focus on light physical activities which will add to the growing knowledge base of lifestyle interventions in individuals with multiple disabilities.

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