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PHYSICAL ACTIVITY BARRIERS IN WHEELCHAIR USERS, AND CARDIOMETABOLIC HEALTH EFFECTS OF UPPER-BODY ROWING EXERCISE IN INDIVIDUALS WITH SPINAL CORD INJURY

BY
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DENMARK

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PHD THESIS

by

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CV

Rasmus Kopp Hansen (RKH), born August 14, 1990, Copenhagen, Denmark. He received his B.Sc. and M.Sc. in Sports Science from Aalborg University, Denmark. In November 2018, he was enrolled as a PhD-student at the doctoral school of the Faculty of Medicine at Aalborg University.

Besides doing research, RKH is an enthusiastic cyclist and winter bather, and he loves traveling together with his family.

In addition to the studies published in relation to the PhD dissertation, RKH has published three other manuscripts during his time as a PhD student, with a fourth in minor revision. RKH has also (co-)supervised four bachelor and master student project groups at the Sports Science education at Aalborg University and has been teaching at both the Sports Science and Occupational Therapy educations.

RKH has completed review assignments for Spinal Cord, and he holds scientific memberships of American College of Sports Medicine and Danish Cardiovascular Academy.

ENGLISH SUMMARY

People using a wheelchair are less physically active than able-bodied because they face tremendous physical, psychological, and socio-environmental barriers for physical activity. Accordingly, wheelchair users, including those with a spinal cord injury (SCI), are at an increased risk of cardiometabolic diseases. Previous exercise studies performed in wheelchair users with SCI have reported limited effects of exercise training on traditional risk factor for cardiometabolic diseases, including lipid profile, glycemic control, and blood pressure. Recently, exercise guidelines for adults with SCI was updated, however few studies have examined the efficacy of these guidelines on traditional cardiometabolic risk factors, as well as measures of vascular function and structure.

Study I, a cross-sectional study, identified physical activity barriers among 181 Danish manual wheelchair users. The most prevalent and severe reported barriers were related to an inaccessible community-built environment, shoulder pain, fatigue, and a lack of accessible exercise equipment. **Study II** investigated associations between wheelchair user sociodemographic characteristics and physical activity barrier perception and found that wheelchair users with body mass index ≥30 kg/m^2; who did not complete high school; or were unemployed rated barriers higher than their non-obese, higher educated and employed counterparts. **Study III** described the protocol for a randomized controlled trial consisting of an exercise intervention designed to mitigate some of the identified barriers from Study I, specifically the 'lack of accessible exercise equipment' and 'shoulder pain' barriers. **Study IV** examined the feasibility, acceptability, and preliminary efficacy of the exercise modality proposed in Study III, ergometer rowing adapted to wheelchair users. This study provided evidence suggesting that upper-body rowing exercise is a feasible and effective exercise modality that provides an available exercise option in community fitness centers and can be performed without exacerbating shoulder pain. **Study V**, a randomized controlled trial, demonstrated that 12-weeks of upper-body rowing exercise complying with current exercise guidelines for adults with SCI improves cardiorespiratory fitness and increases resting brachial artery diameter (determined by high-resolution ultrasound), with limited effects on traditional cardiometabolic risk factors.

The results of this dissertation highlight the need of reducing physical activity barriers among wheelchair users, and/or develop solutions that mitigate the impact of such barriers on physical activity behavior. Work from this dissertation also suggests that ergometer rowing exercise adapted to wheelchair users may provide a useful and pragmatic tool for performing aerobic exercise without exacerbating shoulder pain. Finally, the results indicate that complying with the current exercise guidelines for adults with SCI elicit improvements in cardiorespiratory fitness and structural vascular adaptations.

DANSK RESUME

Personer der sidder i kørestol, har et lavere fysisk aktivitetsniveau end den gående befolkning fordi de oplever markante fysiske, psykologiske, sociale- og miljømæssige barrierer for fysisk aktivitet. Som en konsekvens af dette har personer i kørestol, inklusiv dem med rygmarvsskade, en forhøjet risiko for udvikling af kardiometabolske sygdomme. Tidligere træningsstudier blandt kørestolsbrugere med rygmarvsskade har rapporteret begrænsede effekter af den fysiske træning på traditionelle kardiometabolske risikofaktorer såsom lipidprofil, glykæmisk kontrol, og blodtryk. For nyligt blev de internationale anbefalinger omkring fysisk aktivitetsniveau for voksne personer med rygmarvsskade opdateret. Derfor har kun få studier undersøgt effektiviteten af disse anbefalinger på traditionelle kardiometabolske risikofaktorer, såvel som på vaskulær funktion og struktur.

Studie I, et tværsnitsstudie, identificerede barrierer for fysisk aktivitet blandt 181 danske manuelle kørestolsbrugere. De mest prævalente og største barrierer, der blev rapporteret, relaterede sig til manglende tilgængelighed i bymiljøet, skuldersmerte, følelsen af manglende energi, og en mangel på tilgængeligt træningsudstyr. **Studie II** undersøgte sammenhænge mellem sociodemografiske karakteristika af kørestolsbrugerne og barrierer for fysisk aktivitet, og fandt at kørestolsbrugere med et kropsmasseindeks (dvs. body mass index, BMI) $\geq$30 kg/m^2; som ikke havde færdiggjort en gymnasial uddannelse; eller som stod udenfor arbejdsmarkedet, rapporterede større barrierer end de kørestolsbrugere som ikke var svært overvægtige, som havde højere uddannelsesniveau, og som var i beskæftigelse. **Studie III** beskrev en protokol for et lodtrækningsforsøg bestående af en træningsintervention (ergometerroning tilpasset til kørestolsbrugere) designet med henblik på at afbøde nogle af de identificere barrierer fra Studie I, specifikt barriererne relateret til 'mangel på tilgængeligt træningsudstyr' og 'skuldersmerte', med samtidig afprøvning af de nye træningsanbefalinger. **Studie IV** undersøgte gennemførlighed, acceptabilitet og effektivitet af træningsmodaliteten foreslået i Studie III. I dette studie blev det dokumenteret at overkropsrotræning er en gennemførbar og effektiv træningsmodalitet, der giver kørestolsbrugere en træningsmulighed, som er tilgængelig i fitness og træningscentre, og som kan udføres uden forværring af skuldersmerte. **Studie V** demonstrerede, at 12-ugers overkropsrotræning, udført i overensstemmelse med de nuværende træningsanbefalinger for personer med rygmarvsskade, forbedrer kredsløbskondition og forøger hvilediameter af brachial arterien (bestemt ved ultralyd), dog med begrænsede effekter på traditionelle kardiometabolske risikofaktorer.

Resultater fra denne afhandling understreger vigtigheden af at reducere barrierer for fysisk aktivitet blandt kørestolsbrugere, og/eller udvikle løsninger, der minimerer påvirkningen af sådanne barrierer på fysisk aktivitetsadfærd. Endvidere viser denne afhandling, at ergometerroning tilpasset til kørestolsbrugere kan udgøre et nyttigt og

pragmatisk redskab for afvikling af aerob træning, uden samtidig forværring af skuldersmerter. Slutteligt indikerer resultaterne at fysisk træning, afviklet i overensstemmelse med de nuværende træningsanbefalinger, medfører forbedringer i kredsløbskondition og strukturelle tilpasninger i kredsløbet for voksne personer med rygmarvsskade.

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The studies performed in this dissertation could not have been completed without the support from Wolturnus A/S. I am thankful for the financial support for my stay abroad, and for the support of the necessary equipment for the experimental studies. Also, I would like to thank the Aage and Johanne Louis-Hansen Foundation for the grant that enabled blood sample analyses.
I would like to thank all co-authors contributing to the work presented in this dissertation. To all the participants who took part of the studies, a huge thank you for your commitment, your time, blood, sweat, and enthusiasm for this research. Thanks to the patient organization RYK, especially Birgitte Bjørkman, for bringing content related to the PhD in the RYK magazine, and for supporting transport expenses for your members so they could participate in the exercise study. Additionally, thanks to the three student helpers who assisted with the supervision of the exercise sessions, and to Anna de Wit for your remarkable assistance with data collection while you had your internship in our lab.

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our little family while the demands from this PhD were at their highest. To my parents, Helle and Jan, thank you for providing me with the opportunities to go after my dreams and for your support that has enabled me to get to this stage.

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- Rasmus

March 2022, Aalborg.

LIST OF STUDIES

This thesis is based on the following papers and manuscripts, which from now on will be denoted Study I-V.

Study I

Hansen RK, Larsen RG, Laessoe U, Samani A, Cowan RE. Physical Activity Barriers in Danish Manual Wheelchair Users: A Cross-sectional Study. *Arch Phys Med Rehabil*. 2021; 102:697-693.

Study II

Hansen RK, Samani A, Laessoe U, Larsen RG, Cowan RE. Sociodemographic characteristics associated with physical activity barrier perception among manual wheelchair users. *Disabil Health J*. 2021; 14. 101119.

Study III

Hansen RK, Samani A, Laessoe U, Handberg A, Larsen RG. Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users – Protocol for a randomized controlled trial. *BMJ Open.* 2020; 10:e040727.

Study IV

Hansen RK, de Wit JLJ, Samani A, Laessoe U, Figlewski K, Larsen RG. Wheelchair-modified rowing ergometer exercise in individuals with spinal cord injury: A feasibility, acceptability and preliminary efficacy study. In review: *Spinal Cord Series and Cases*. 2022.

Study V

Hansen RK, Samani A, Laessoe U, Handberg A, Mellergaard, M, Figlewski K, Thijssen DHJ, Gliemann L, Larsen RG. Rowing exercise increases cardiorespiratory fitness and resting brachial artery diameter in spinal cord-injured humans. Expected submission: March/April 2022.

ABBREVIATIONS

AD	Autonomic dysreflexia
ADL	Activities of daily living
AIS	American Spinal Injury Association Impairment Scale
BMI	Body mass index
BPAQ-MI	Barriers to Physical Activity Questionnaire for People with Mobility Impairments
CON	Control group
CVD	Cardiovascular disease
CRP	C-reactive protein
DBP	Diastolic blood pressure
ET-1	Endothelin-1
FES	Functional electrical stimulation
FMD	Flow mediated-dilation
GTX	Graded exercise test to exhaustion
HbA1c	Glycated hemoglobin
HOMA-β	Homeostasis model assessment-pancreatic beta cell function
HOMA-IR	Homeostasis model assessment-insulin resistance
HOMA-S	Homeostasis model assessment-sensitivity
HR_{peak}	Peak heart rate
HRV	Heart rate variability
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
LDL	Low density lipoprotein
LTPA	Leisure-time physical activity
LTPA-SCI	Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury
MET	Metabolic equivalent
NLI	Neurological level of injury
NO	Nitric oxide
PAL	Self-reported physical activity level
PC-WUSPI	Performance-corrected Wheelchair Users Shoulder Pain Index
PO_{peak}	Peak power output
RCT	Randomized controlled trial
RPE	Rating of perceived exertion
SBP	Systolic blood pressure
SCI	Spinal cord injury
sICAM-1	soluble intercellular adhesion molecule-1
sVCAM-1	soluble vascular cell adhesion molecule-1
TG	Triglycerides
TNF-α	Tumor necrosis factor alpha

TSI	Time since injury
T2DM	Type-II diabetes mellitus
UBROW	Upper-body rowing exercise
VAT	Visceral adipose tissue
$\dot{V}O_2$	Oxygen consumption
$\dot{V}O_{2peak}$	Peak oxygen consumption
$\dot{V}CO_2$	Carbon dioxide production
WC	Waist circumference
QoL	Quality of life
QoL-BDS	International Spinal Cord Injury Quality of Life Basic Data Set

PREFACE

The work presented in this PhD dissertation was carried out between November 2018 and March 2022 at the Sport Sciences – Performance and Technology research group at the Department of Health Science and Technology, Aalborg University, and at the Department of Research and Development, University College of Northern Denmark. From August-October 2021 I was on paternity leave with my girl Alba.
The PhD stipend was equally funded by the Department of Health Science and Technology, Aalborg University, and the Department of Research and Development, University College of Northern Denmark.

From September-December 2019, work relating to the thesis was carried out at the Department of Physical Medicine and Rehabilitation at the University of Alabama at Birmingham, Alabama, US, under the mentorship of Assistant Professor Rachel E. Cowan. During my time as a PhD student I also established collaborations with national and international researchers from other institutions, including Professor Aase Handberg, Department of Clinical Biochemistry, Aalborg University Hospital, Associate Professor Lasse Gliemann, Department of Nutrition, Exercise and Sports, University of Copenhagen, and Professor Dick H.J. Thijssen, Radboud Institute for Health Sciences, Department of Physiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands. As part of the collaboration with Professor Thijssen, a master student (Anna de Wit) from Radboud University had a 6-month internship at Aalborg University, where she assisted me in the lab with conducting the 12-week exercise intervention study.

As I was a PhD student during the COVID-19 pandemic, two conference participations were cancelled, but I will present some of the work from this dissertation at the ACSM Annual Meeting and World Congresses in San Diego, CA, in May 2022.

The dissertation is based on the work from four original manuscripts and one study protocol. The study protocol and two of the original manuscripts have been published in international peer-reviewed journals, whereas the two final manuscripts are in review and preparation. In the dissertation, these five manuscripts and/or published papers are referred to as Study I-V.
Study V was funded by a grant I received from the Aage and Johanne Louis-Hansen Foundation, and Wolturnus A/S supported Study IV-V with the provision of laboratory equipment and provided financial support for my research stay abroad.

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CHAPTER 1. INTRODUCTION

Low cardiorespiratory fitness is an independent predictor of all-cause mortality (1) and morbidity (2), and insufficient levels of physical activity is therefore a major public health concern in the general population (3). Despite the importance of physical activity and exercise, a sedentary lifestyle has now become so prevalent that exercise is commonly mentioned as having 'healthy benefits', regardless that the exercise-trained state is the biologically normal condition (4).

Notably, individuals with a mobility disability are even less physically active than able-bodied and they exhibit a higher risk of developing chronic diseases (5,6). Given estimates of more than a billion individuals with disability worldwide (7), there is therefore an urgent need for a better understanding of barriers hindering physical activity and exercise participation in populations with mobility disability.

Among people with a disability, roughly 10% uses a wheelchair for mobility (8). As for other disability groups, physical activity levels are low in wheelchair users (5,6), and compliance and participant retention is an ongoing issue for exercise studies performed in this population (16). These observations suggests that wheelchair users face tremendous barriers for becoming and/or sustaining physically active.

Individuals with a spinal cord injury (SCI) represent a subgroup of wheelchair users. A SCI leads to dramatic physiological alterations that have negative impact on exercise capacity (10) and physical activity levels (6) that expose individuals with SCI to higher risk of developing type 2 diabetes mellitus (T2DM) (11,12) and cardiovascular diseases (CVD) (13,14), collectively referred to as cardiometabolic diseases.

1.1. PHYSICAL ACTIVITY BARRIERS AMONG MANUAL WHEELCHAIR USERS

Several studies and review articles have identified barriers (and facilitators) to physical activity. Some of the identified barriers in wheelchair users are similar to those reported in able-bodied, including lack of energy (15) and lack of time (16). In contrast, others are more specific to wheelchair users, such as lack of transportation (17), inaccessible bathroom facilities (18), lack of accessible curb cuts (19), pavement conditions (20), secondary health complications (e.g. skin breakdown, upper-extremity pain) (21), and low aerobic fitness (10). Previous research have indicated that physical activity levels (22) and barrier perception (23) vary across individuals. Little is known about the factors contributing to this variation, however sociodemographic background characteristics may play a role.

While studies identifying barriers are informative, a list of barriers by itself does not change physical activity behavior. Therefore, researchers aiming at increasing physical activity participation needs to apply such information about barriers into the design, implementation and delivery of specific physical activity enhancing strategies

(21). A successful example on this (i.e. high compliance) was observed in a recent study (24) that addressed the commonly reported barrier 'lack of transportation' in their exercise intervention. Specifically, this study delivered the intervention by using home-based arm-cranking exercise, thereby minimizing potential transport accessibility barriers, which resulted in high compliance (>90%) with the intervention. This finding supports taking barriers into account when designing and delivering an exercise/physical activity promoting intervention, for which compliance and participant retention are crucial for successful outcomes.

Despite the importance of exercise, recreational and exercise facilities commonly lack accessibility for wheelchair users (25,26). People using a manual wheelchair have a limited number of modalities available for performing aerobic exercise. In addition to wheelchair team sports, these typically include wheelchair propulsion/ergometry, arm-cranking or handcycling (27). However, in community fitness centers, such upper-body ergometers are typically not available (28), and a lack of accessible equipment is therefore a prominent barrier (19,29). To support higher levels of physical activity among wheelchair users, increasing the number of available exercise options is therefore needed.

Some barriers do not change quickly, such as those belonging to the community-built environment. Minimizing barriers related to the architecture and construction of the built environment may require interventions acting on a policy-level, which take time (21).

Other prominent physical activity barriers among wheelchair users occur at an individual level and may be modifiable within a relatively short time frame. Shoulder pain represents such a barrier, which may be addressed by use of physiotherapy/exercise interventions (30,31). Shoulder pain is frequently reported in manual wheelchair users, with prevalence estimates varying between 30 and 73% (32), i.e. approximately three times the point prevalence in able-bodied (33). A similar high prevalence was recently confirmed in a large cohort of Danes with SCI, with 63% of participants reporting shoulder pain within the past 3 months (34). Shoulder pain in wheelchair users is a debilitating condition that reduces physical activity levels, physical function, and quality of life (QoL) (30,35). In contrast to able-bodied who experience shoulder pain, manual wheelchair users cannot simply avoid involvement of the shoulders to aid recovery, as they rely on their upper extremities for mobility and activities of daily living (ADL). Therefore, preservation of shoulder function in manual wheelchair users is of outermost importance (36).

The etiology of shoulder pain in wheelchair users is multifactorial, but may relate to the high biomechanical load imposed on the shoulder joint during ADL, such as wheelchair propulsion (37) and transfers (38). Other risk factors suggested to be implicated in the development and progression of shoulder pain are shoulder muscle strength imbalance (39), higher body mass index (BMI) (40), older age (41), and overuse injuries such as rotator cuff impingement (32). Even though exercise can mitigate shoulder pain (30,31), not all interventions are appropriate. For example, exercise using wheelchair ergometry/propulsion may increase the risk of overuse injury and pain, as it involves repeated, high force contractions of chest and shoulder

muscles already heavily engaged during daily mobility (37).
Wheelchair propulsion is a push-dominant movement (42), and muscle strength imbalances has been reported in manual wheelchair users, with relative weakness of the pull musculature (posterior shoulder and scapular retractors) (43). Therefore, there is a need for exercises that preferentially activate and strengthen the less used pull musculature (44). In fact, accumulating evidence suggests that strength training targeting posterior shoulder and scapular retractors muscles combined with anterior shoulder muscle stretching reduces shoulder pain in wheelchair users (31,44–46). As lack of time is a barrier for many people, exercise modalities that integrates several physical fitness components, such as both aerobic exercise and posterior strengthening, are warranted.

1.2. ROWING EXERCISE

Rowing is a strength-endurance, whole-body activity that provides a pronounced challenge to the cardiovascular and respiratory organ systems (47), as illustrated by the extreme maximal oxygen uptakes reported in able-bodied athlete rowers (48,49). The health benefits of rowing is well established in able-bodied (50), including favorable adaptations in vascular function and stiffness (51,52). For example, compared to sedentary controls, young male rowers exhibit increased brachial artery dilation in response to progressive handgrip exercise (52). Moreover, higher compliance of the common carotid artery has been demonstrated in middle-aged and older rowers compared to sedentary age-matched controls, indicating that regularly performed rowing exercise reduces central artery stiffening (51). In addition to the cardiovascular benefits, studies performed in both young and elderly participants have reported rowing exercise to be associated with greater muscle strength (53) and size (53,54).
In the context of shoulder pain, it is noteworthy that rowing, due to the pull motion required for generating the stroke, includes a strength component for several posterior muscle groups. Indeed, activation of scapular stabilizer and posterior shoulder muscles during the rowing stroke have been confirmed by electromyography (55). In wheelchair users, such posterior muscle activation may be important for balancing the muscle strength of the anterior muscles frequently used for propulsion. Therefore, rowing represents an attractive exercise modality for improving cardiovascular function and health, while also preventing or reducing shoulder pain.

1.2.1. ROWING ADAPTED TO WHEELCHAIR USERS

Despite a clear rationale for rowing exercise, arms-only/upper-body rowing has not often been adopted in studies in wheelchair users. Most studies have focused on hybrid functional electrical stimulation (FES) rowing in individuals with SCI, where voluntary upper-body rowing is combined with FES of the legs. In general, these studies have demonstrated that hybrid rowing effectively improves cardiorespiratory fitness (56). Due to the involvement of a larger muscle mass, and contribution from

the skeletal muscle pump (intermittent contraction and relaxation) that aid venous return, FES rowing may be associated with a greater aerobic demand and volume loading of the heart, thereby providing a more effective training stimulus compared to arms-only rowing (57). One disadvantage of FES is, however, that it is not readily available for people with SCI due to the costs and the specialized equipment required (58). Thus, it is relevant to examine to what degree upper-body (i.e. voluntary) rowing can stimulate cardiovascular adaptations.

The few studies adapting upper-body rowing to wheelchair users have primarily made rather unique modifications by turning cycle ergometers into rowing units (59–61). Although pioneering, such ergometers are not commonly available in community fitness centers. An alternative option is to fixate the seat of a commercially available rowing ergometer (62), however this approach is limited in that the user must transfer from their wheelchair to and from the ergometer seat and may require personal assistance with positioning. Accordingly, a rowing modality performed on a commercially available rowing ergometer, while the user remain seated in their wheelchair is warranted.

Recently, Sawatsky demonstrated that an acute bout of exercise performed on a commercially adapted rowing machine (Concept 2) evoked a higher submaximal oxygen consumption ($\dot{V}O_2$) at a given workload, compared to conventional arm-cranking exercise (63). Although this study (63) only investigated the physiological response to a single 5-min exercise bout, these data support the idea that upper-body rowing may induce a relatively large aerobic demand. Given the sparsity of research, the long-term effects of upper-body rowing on cardiorespiratory fitness, shoulder pain, as well as considerations about its feasibility and acceptability in wheelchair users with SCI remain to be determined.

Taken together, adaptive, or wheelchair-modified, upper-body rowing may represent an effective aerobic exercise modality. Further, through the engagement of the functionally important muscles of the posterior shoulder and back, this exercise modality may potentially provide a useful tool to mitigate shoulder pain in wheelchair users. If performed on a commercially available ergometer, adaptive rowing may also help minimizing the barrier of a lack of accessible exercise equipment for wheelchair users, by offering an exercise option available in most community-based fitness centers.

1.3. EXERCISE GUIDELINES FOR INDIVIDUALS WITH SCI

In 2011, exercise guidelines for adults with SCI were formulated (64), suggesting two weekly sessions of 20-min of moderate-to-vigorous intensity aerobic exercise plus muscle strengthening for improvement in cardiorespiratory fitness and muscle strength. In 2018, the exercise guidelines were updated (65), recommending that a larger volume of moderate-to-vigorous intensity aerobic exercise (i.e. at least 30-min three times per week) were required for improvement in cardiometabolic risk factors. However, these recommendations were provided as ‘conditional’ given uncertainty about the exact exercise volume needed for ‘optimal’ cardiometabolic health (65).

Considering the recent launch of the 2018 guidelines, and that few studies have adopted these guidelines, more research is needed to examine the efficacy of the new (2018) exercise guidelines on cardiometabolic health.

1.4. AIMS AND HYPOTHESES

The overall aims of this dissertation were to: 1) identify physical activity barriers among manual wheelchair users; 2) use this knowledge about barriers as a basis for the design, implementation, and delivery of an exercise intervention; and 3) test the effects of the exercise intervention on cardiometabolic disease risk, shoulder pain, and QoL, in wheelchair users with SCI. To accomplish these aims, five studies were conducted. Study I sought to identify the perceived barriers to physical activity among manual wheelchairs users, and the association to self-reported physical activity level (PAL). It was hypothesized that physical activity barriers would be associated with PAL. The aim of Study II was to explore whether the perception of physical activity barriers is associated with wheelchair user sociodemographic characteristics. The aim of Study III was to design a study protocol for an exercise intervention (wheelchair-modified upper-body ergometer rowing) specifically targeting the 'lack of accessible exercise equipment' and 'shoulder pain' barriers. The aim of Study IV was to investigate the feasibility, acceptability, and preliminary efficacy of the upper-body rowing modality in individuals with SCI. Finally, Study V, a randomized controlled trial (RCT), aimed to assess the effects of 12 weeks of wheelchair-modified rowing exercise, complying with current exercise guidelines for adults with SCI, on traditional risk factors and novel biomarkers of cardiometabolic diseases in individuals with SCI. It was hypothesized that upper-body rowing would improve a) cardiorespiratory fitness, and b) biomarkers of cardiometabolic health. Furthermore, it was hypothesized that the rowing exercise would increase c) brachial artery function (flow-mediated dilation, FMD), and d) brachial artery structure (resting lumen diameter) after six and 12 weeks, respectively.

CHAPTER 2. BACKGROUND

In order to describe the target population for the experimental study in this thesis, the following section will address the general impairments resulting from a SCI, and the etiology and epidemiology of the condition. The pathophysiological consequences of a SCI are addressed, as well as the impact of these pathophysiological alterations on cardiovascular and metabolic disease risk, closing the chapter with addressing the potential role of exercise on such disease risk.

2.1. SPINAL CORD INJURY

A SCI is defined as damage to the spinal cord that temporarily or permanently causes changes to its function (66). The spinal cord is located within the spinal column and is the major conduit of nerve fibers that connect the brain and the peripheral nervous system. The spinal cord is organized into neuronal cell bodies (grey matter) and myelinated axons (white matter) surrounding the cell bodies. The grey matter is organized into segments comprising sensory or motor neurons. The white matter can be further divided into descending and ascending tracts that consists of bundles of axons that project to and originate from specific regions in the periphery and brain. Thirty-one spinal nerve roots, or mixed-spinal nerves, emerge from the spinal cord and transmit sensory information to the spinal cord through the dorsal roots and motor information to the periphery through the ventral roots. The cervical spine consists of eight nerve roots; the thoracic spine of 12; the lumbar spine of five; the sacral spine of five; and the coccygeal spine of one nerve root. Each segment in the cord is responsible for conveying sensory (dermatome) and motor (myotome) function from and to a specific part of the body corresponding to that level of the spinal cord. Not only does a SCI result in partial or complete loss of sensorimotor function below the level of injury, it also interrupts normal autonomic nervous system function (67). Injury to the autonomic nervous system results in several autonomic dysfunctions, including altered function of the cardiovascular, respiratory, gastrointestinal, urinary, sexual, and thermoregulatory systems, with the extent of impairment influenced by the injury level (and the degree of autonomic completeness). As preganglionic sympathetic neurons originate between T1 and L2 of the spinal cord, a SCI typically interrupts sympathetic outflow, resulting in a loss of basal vascular tone (among other things) below the level of injury. While parasympathetic outflow to the heart is preserved, a SCI above T6 can disrupt cardiac sympathetic innervation, resulting in bradycardia and low resting blood pressure and orthostatic hypotension (68).

2.1.1. CLASSIFICATION OF SPINAL CORD INJURY

The clinical manifestations of SCI depend on the level of injury and the degree of preserved spinal cord tissue (i.e., completeness of the injury). In general, the higher up the lesion occurs, the more extensive the impairments will be. Cervical SCI

(tetraplegia) causes impairments to sensory and motor function in the arms, as well as the trunk, legs, and pelvic organs (i.e., all four extremities). In contrast, thoracic, lumbar, or sacral SCI (paraplegia) result in spared arm functioning, but depending on the injury level, with sensory and motor impairments in the trunk, legs, and pelvic organs. The established way to classify a SCI of an individual is by neurological examination following the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (69). The standards do not include information about autonomic function, for that another standard is available (70). The ISNCSCI includes a thorough evaluation of remaining sensory function (determined by pin prick and light touch within each of the dermatomes on each side of the body) and motor function (determined by manual muscle testing of key muscles within each of the myotomes on each side of the body). Based on such sensory and motor examination, a SCI is typically characterized by the neurological level of injury (NLI), and the American Spinal Injury Association Impairment Scale (AIS) score, used to describe the completeness of the injury (i.e. absence or presence of sacral sparing) on a scoring system from A-E (69). Individuals with AIS A (motor and sensory complete) and B (motor complete, sensory incomplete) injuries with no innervation of the legs are wheelchair bound, whereas individuals with AIS C and D injuries (both motor incomplete) may achieve some ambulation. AIS E refers to normal motor and sensory function (69).

2.1.2. INCIDENCE AND PREVALENCE

A SCI is a devastating and debilitating condition with wide-reaching physical, psychological, social and vocational consequences for the individual and their families (66,71). Of the 5.8 million people in Denmark, approximately 3,000 are living with a SCI, with an annual incidence of 130-160 cases, with an approximately even distribution between people living with a traumatic or non-traumatic SCI (72). The most common causes of traumatic SCI in Denmark are due to traffic (48%), falls (29%), and sport (11%) accidents (72), which are in broad agreement with international data (71), with the exception of violence, which rarely is the cause in Denmark. The causes of non-traumatic SCI include infectious diseases and tumors to the spinal cord, degenerative conditions of the spinal column, vascular and autoimmune disorders, and congenitally causes such as spina bifida (71,72). Improvements in medical treatment have increased the life expectancy for people with SCI, alongside a reduction in risk of mortality from secondary conditions (71). Despite the improved life expectancy, individuals with SCI are still more likely to die prematurely than individuals without SCI (71). Historically, renal and respiratory diseases have been major causes of death in the SCI population, and they still are (14,71,73). However, more recent data suggests that the principal causes of death are now more similar to the causes for deaths in general population, such as CVD (73,74).

2.1.3. PATHOPHYSIOLOGY OF SPINAL CORD INJURY

Wheelchair users with SCI provide a unique model representing the adaptability of the human body. Extreme inactivity (paralysis) in the lower extremities following a SCI results in extensive alterations in body composition, including a loss of fat free mass (75) and reduction in skeletal muscle quality (76). Paralysis of the lower extremities also result in rapid structural (inward) remodeling of the lower extremity vasculature, as illustrated by a 25% reduction in femoral artery diameter within three weeks after acquiring a SCI, and a 30% reduction in femoral artery diameter in individuals with chronic (>1 yr) SCI (77), a reduction that appears to be closely linked to the reduction in muscle mass (78). The atrophy of lower extremity skeletal muscle and disruption to the sympathetic nervous system lower whole-body energy metabolism at rest (79) and during physical activities (80) that predisposes to positive energy balance and accumulation of adipose tissue, resulting in obesity (81). Indeed, obesity in individuals with SCI is a major concern (81). Greater volumes of both subcutaneous and visceral adipose tissue (VAT) have been reported in SCI. Central obesity, particularly the accumulation of VAT, is more prevalent in individuals with SCI (>50%) compared to able bodied (82). Excess VAT is associated with impaired lipid and carbohydrate metabolism and increased secretion of proinflammatory cytokines (adipokines) that result in insulin resistance, systemic inflammation and induction of a pro-atherogenic environment (81,83). Due to the combination of gain in adipose tissue and loss of lean mass, total body mass may remain stable, highlighting the importance of not simply relying on BMI or body mass assessment following SCI.

The disruption of normal autonomic cardiovascular control mechanisms following SCI has been suggested to increase the risk of CVD (14). The altered autonomic cardiovascular regulation may include loss of control of peripheral vasculature below the injury (84) and a blunted cardiovascular response to exercise that can accelerate fatigue and thereby limit the ability to perform a bout of exercise (85). Moreover, blood pressure fluctuations, characterized by a state of low resting arterial blood pressure and orthostatic hypotension interspersed by periods of abnormally high blood pressure during episodes of autonomic dysreflexia (AD) (68), abnormal heart rate variability (HRV) (86), and arrythmias (87) are also potential consequences of SCI.

Impaired exercise capacity

Acquiring a SCI is also associated with a sedentary lifestyle and impaired exercise capacity (14). The reduced physical function accompanying a SCI and the perception of multiple physical activity barriers profoundly lower physical activity levels (6), thereby further contributing to low daily energy expenditure (79). Low physical activity levels in turn increase morbidity risk, as illustrated by an inverse association between minutes spent in leisure-time physical activity (LTPA) and the presence of risk factors for cardiometabolic diseases (88). The capacity to perform exercise is also impaired in individuals with SCI, with the extent of impairment being influenced by

the degree of preserved motor and autonomic function below the injury (10,89,90). In general, the higher the level of lesion, the greater the impairment of muscle and autonomic nervous system function and therefore the greater the reduction in exercise capacity (90).

As a result of paralysis of the lower extremities, voluntary exercise is typically restricted to the upper-body. In addition to the relative smaller muscle mass of the arms that prevent very high power outputs to be reached (91,92), the reduction in exercise capacity is to a large extent explained by a blunted cardiovascular response to exercise. The normal cardiovascular adjustments to exercise that ensure redistribution of blood flow (and thereby delivery of oxygen and nutrients) to the active muscles (93) is compromised to various extent in individuals with SCI. Loss of sympathetically mediated vasoconstriction in the peripheral vasculature below the level of injury (84), combined with a lack of skeletal muscle pump activity in the lower legs, results in pooling of blood and ensuing increased plasma filtration in the dependent vasculature of the lower extremities. Such blood pooling impairs venous return to the heart that in turn reduces end-diastolic volume and stroke volume through the Frank-Starling mechanism (94,95), i.e. "*the heart cannot do more than send out what it gets"*(96). Accordingly, heart rate is higher during submaximal exercise in order to maintain cardiac output (85).

A particularly blunted cardiovascular response to exercise is observed in individuals with high level injuries (≥T6). In these individuals, reductions in stroke volume cannot always be compensated for by an increase in heart rate due to blunted sympathetic mediated cardio acceleration resulting from the loss of supraspinal control of the sympathetic nervous system (14,97). Therefore, the increase in heart rate in these individuals rely solely on parasympathetic withdrawal. Moreover, as the splanchnic circulation is sympathetically innervated by T5-L2 (70), blood redistribution from this major capacitance bed to the active muscles (and skin) are compromised in individuals with high level lesion (98), thus limiting venous return and exercise capacity even further.

Finally, respiratory dysfunction in individuals with cervical injury, as well as an impaired inability to tolerate exercise-induced increases in heat production due to impaired temperature regulation (99), especially in those with cervical injury (100), may further contribute to diminished capacity to adapt properly to exercise, resulting in premature fatigue, general avoidance of exertion, and deconditioning (14). Unfortunately, such reductions in physical functioning is common among individuals with SCI (101), which may have wide-reaching consequences including a compromised ability to perform ADL to a level that may hinder independent living and impair QoL (102).

Taken together, the unique physiological alterations occurring after a SCI, including reduced energy expenditure and autonomic impairment, result in unfavorable body composition changes, reduced physical activity levels and impaired exercise capacity that together predispose individuals with SCI to cardiometabolic diseases, and impaired physical functioning and QoL.

2.1.4. CARDIOVASCULAR AND METABOLIC DISEASE RISK

CVD has now emerged as the leading cause of mortality in chronic SCI (73,74). Compared with able-bodied, individuals with SCI are at an increased risk of cardiometabolic diseases. For example, compared to age and sex-matched able-bodied controls, a four-fold higher prevalence of T2DM has been observed in adults with SCI (12). More recently, in a study with more than 60.000 individuals (11), results from multivariate analyses suggested that SCI is independently associated with a two-fold heightened risk of T2DM. Based on data from the same cohort (13), it was reported that having a SCI was independently associated with a two and three-fold increased odds of heart disease and stroke, respectively (13).

Traditional cardiometabolic risk factors

The appearance of several, interrelated risk factors of metabolic origin, termed the metabolic syndrome, are associated with an exaggerated risk of cardiometabolic diseases (103,104). The American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) (104) define the metabolic syndrome as the presence of any three of five of the following: hypertriglyceridemia (≥1.7 mmol/L); reduced high-density lipoprotein cholesterol (HDL-C) (<1.03 mmol/L for men, 1.3 for women); hypertension (systolic blood pressure, SBP ≥130 mmHg, or diastolic blood pressure, DBP ≥85mmHg); raised fasting glucose (≥5.6 mmol/L); and central obesity as indicated by elevated waist circumference (WC). For individuals with SCI, appropriate surrogate measures of central obesity has been proposed to be a BMI ≥22 kg/m^2 (105) or WC ≥94 cm (106). Moreover, an individual's risk of atherosclerotic CVD events (i.e. coronary heart disease, cerebrovascular disease, heart failure, and peripheral vascular disease) can be predicted using algorithms such as Framingham Risk Scores that incorporate risk factors traditionally associated with CVD, including age, sex, blood pressure, lipid profile, smoking status, and diabetes (107–109).

Relative to the uninjured population, individuals with SCI exhibit a higher prevalence of traditional risk factors associated with cardiometabolic diseases, such as reduced HDL-C (110), central obesity (82), and impaired glucose tolerance (12).

Notwithstanding the increased cardiometabolic disease risk, interpretation of cardiometabolic disease risk in SCI is not necessarily straightforward. For example, elevated arterial blood pressure, a well-established risk factor in the general population, is not always present in individuals with SCI, especially among those with high thoracic and cervical injuries, as they demonstrate low resting arterial blood pressure and orthostatic hypotension in response to sympathetic nervous system disruption (67). Furthermore, despite the marked disease risk, not all studies show higher prevalence of traditional risk factors such as triglycerides (TG), fasted glucose, and low-density lipoprotein cholesterol (LDL-C) in individuals with SCI, compared to able-bodied (111–113). These findings are supported by a recent study demonstrating that CVD risk, estimated via the Framingham risk score, strongly underestimates true, five-year occurrence of CVD events (114). Taken together, other

risk factors than those traditionally associated with cardiometabolic diseases may therefore contribute to the exaggerated CVD risk observed in individuals with SCI, including, endothelial dysfunction, low cardiorespiratory fitness, and 'novel' biomarkers of cardiovascular risk.

Novel cardiometabolic risk factors and the role of exercise

The vascular endothelium is a single layer of cells that constitutes the barrier between the circulating blood and the surrounding tissue. The endothelium plays a central role in vascular homeostasis by producing and releasing various molecules involved in monocyte and leucocyte adhesion, platelet aggregation, vascular smooth muscle cell migration and proliferation, and the regulation of vascular tone, including the production and release of the important vasodilator nitric oxide (NO) (115). Atherosclerosis is initiated and propagated by damage of the endothelium. Endothelial dysfunction independently predicts future cardiovascular events (116), and is characterized by a reduced endothelium mediated vasodilatory response or abnormal vasoconstriction in response to mechanical (shear stress) or pharmacological (e.g. acetylcholine) stimuli (115). In addition to impaired NO mediated vasodilation, endothelial dysfunction and the progression of atherosclerosis have been associated with increased levels of circulating markers of inflammation like C-reactive protein (CRP) (117) and endothelium adhesive molecules including soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble intercellular adhesion molecule-1 (sICAM-1) (118), and upregulation in vasoconstrictor pathways, such as endothelin-1 (ET-1) (119). Increased levels of these pro-inflammatory and vascular injury biomarkers have been reported in individuals with SCI (113,120), possibly contributing to the increased atherogenic risk in this population.

It is well-established that regular whole-body exercise reduces the risk for atherosclerotic CVD in able-bodied (121), yet only ~60% of the exercise-induced risk reduction can be explained by modification of traditional risk factors (122). Such a risk factor gap (123) may therefore be explained by benefits of exercise on other risk factors, such as improvements in cardiorespiratory fitness and endothelial function (124).

Low cardiorespiratory fitness, which is not a constituent of the metabolic syndrome (104) or the Framingham risk score algorithms (108), independently predicts all-cause mortality in able-bodied (1), suggesting that improved cardiorespiratory fitness may contribute to the cardioprotective effects of exercise. Furthermore, exercise exerts direct effects on the arteries through the repeated exposure of the vascular endothelium to exercise-induced hemodynamic stimuli, such as shear stress (124). Such hemodynamic stimuli evoke anti-atherogenic adaptations in the vasculature, providing another plausible contribution to some of the unexplained CVD risk reduction with exercise (123).

Impact of exercise training on cardiometabolic disease risk

Despite some studies have demonstrated improvements in aspects of cardiometabolic risk, such as elevations in HDL-C (125), reductions in LDL-C (126), fasting insulin (24,127), body mass (128), and indices of insulin resistance (24,128), the weight of the evidence does not support a reduction in cardiometabolic disease risk through improvement of traditional risk factors following upper-body exercise training in individuals with SCI (129).

While most of the existing literature on isolated upper-body exercise have focused on how exercise modifies traditional cardiometabolic risk factors (129,130), few well-designed exercise studies have examined the effects of isolated upper-body exercise training on vascular function (endothelium-dependent and/or independent vasodilation) and structure (e.g. resting diameter or wall thickness). A 16-week exercise intervention following the 2011 exercise guidelines was insufficient for improving vascular function or resting lumen diameter in the peripheral conduit artery (brachial artery) suppling the active upper-limbs of wheelchair users with SCI (131). Recently, Alrashidi (132) reported that 24-weeks of thrice weekly sessions of 30-min of moderate-to-vigorous intensity arm-cranking exercise did not improve arterial stiffness, as indicated by carotid-femoral pulse wave velocity, in individuals with high level (C4-T6) motor-complete SCI. Together, these studies indicate that isolated upper-body exercise training does not improve vascular health in individuals with SCI, however, considering the sparsity of research, further studies are needed within this area. Moreover, whereas a reduction in low-grade inflammation has been reported following arm-cranking exercise training (133), to the author's knowledge, limited knowledge exists about the effects of upper-body exercise on other novel CVD biomarkers, such as endothelium-derived vasoconstrictors and adhesive molecules.

CHAPTER 3. METHODS

The methodology used for this dissertation is summarized in this chapter. For detailed descriptions of the methods, the reader is referred to Study I-V. In addition, some outcomes related to the RCT that are not included in Study V will be presented at the end of this chapter.

Data collection for Study I-II was performed using an online survey over a six-month period in 2019. Data collection for the experimental part of the thesis (Study IV-V) was performed in the laboratory at Aalborg University, for a period of five and a half month in 2021. Finally, a 6-month follow-up assessment was performed at the end of 2021 (data not included in this dissertation).
An overview of the dissertation is presented in Table 1. The work is based upon a logical sequence of steps, which together constitutes Study I-V.

3.1. STUDY DESIGN

The individual studies sought to answer different questions, and therefore different study designs were applied. In Study I-II, a cross sectional design was used to identify perceived physical activity barriers (Study I), and associations between barriers and sociodemographic characteristics (Study II). In Study IV, an exploratory clinical investigation, a pre-post study design was used to test the feasibility, acceptability, and preliminary efficacy of the upper-body ergometer rowing exercise modality. In Study V, a RCT design was used to investigate the longitudinal effects of upper-body rowing exercise on cardiometabolic health, cardiorespiratory fitness, vascular function and structure, and endothelium-derived biomarkers of CVD risk. In that study, the effects of the intervention were assessed after both six (6W) and 12 weeks (12W) (Study V). As part of the effect evaluation, a comprehensive disease risk assessment was performed, in which several, emerging or ’novel’ risk factors were measured in addition to those traditionally associated with cardiometabolic diseases. An overview of these risk factors is presented in Table 2.

Table 1. Dissertation overview.

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Identify PA barriers	X	X			
Design EXR intervention that take identified barriers into account			X		
Identify relevant outcomes (cardiometabolic, CRF, LTPA, shoulder pain, QoL) that can be targeted by EXR intervention			X		
Test implementation of EXR modality, including the feasibility, acceptability, and preliminary efficacy				X	
Deliver the EXR intervention and assess the effects on relevant outcomes (cardiometabolic, CRF, LTPA, shoulder pain, QoL)					X

Abbreviations: PA = physical activity; EXR = exercise; CRF = cardiorespiratory fitness; LTPA = leisure-time physical activity; QoL = quality of life.

3.2. PARTICIPANTS

In Study I-II, 181 participants were included in the analyses. Participants were 48 ± 14 yr old, used a wheelchair for 18 ± 15 yr, had a BMI of 25.8 ± 6.2 kg/m^2, and 52.5% were females. Detailed participant characteristics can be seen in Study I and II (Table 1). Although the participants included in these studies were not limited to specific subpopulations, and thus intended to reflect manual wheelchair users in general, most of the included participants (63%) were individuals with SCI.
Inclusion criteria included ≥18 yr old, use a manual wheelchair for primary mobility, and absence of any intellectual or cognitive disability that could limit the ability to read and understand the survey.

Participants included in Study IV-V all had a SCI. For Study V, 18 participants were included, of which all eight participants in the exercise group also were included in Study IV. Eligible participants had to be 18-70 yr old; with a chronic (≥1 yr post injury), traumatic or non-traumatic SCI (including spina bifida); with preserved arm flexor function to perform upper-body rowing; and using a manual wheelchair for the majority (≥75%) of the waking day.

Details about participant recruitment can be seen in the individual studies, and details about randomization for Study V can be seen in Study III and V.

3.2.1. NEUROLOGICAL ASSESSMENT (STUDY IV-V)

Assessment of participants' SCI followed the ISNCSCI (69). The assessment was performed by a neurologist from the Spinal Cord Injury Centre of Western Denmark, and included AIS classification, neurological level of injury (NLI), time since injury (TSI), and etiology (traumatic vs. non-traumatic SCI).

3.2.2. SAMPLE SIZE CONSIDERATIONS

Study I-II:

Given the exploratory nature of Study I-II, there was no pre-specified sample size that was required to detect a certain effect. In Denmark, there are no records of the total number of individuals with disability, including those who use a manual wheelchair. Without knowing the population size and demographics, it is difficult to predict the number of participants required for having a sample representative of the population from which it was drawn. Hence, a pragmatic approach was chosen by including as many participants as logistically possible.

Study IV-V:

As described in Study III, 30 participants were intended to be included for Study V. This number was derived from a power analysis indicating that a total of n = 20 were required to detect a significant ($\alpha < 0.05$, $\beta = 0.9$) difference in fasting insulin, while also accounting for potential dropouts. The expected change was moderate, based on results from a recent study demonstrating significantly reduced fasting insulin (effect size of d = -0.69) after arm-cranking exercise in individuals with SCI (24). However, as Study IV-V was conducted during COVID-19, the conditions for conducting the studies changed considerably. It was mandatory to reduce the number of participants, as the pre-planned setting (Aalborg Rowing Club) for the exercise training was closed in response to the national lock down. Aalborg Rowing Club had the facilities to accommodate group training (and therefore more participants). However, as this was not possible, all exercise sessions had to be conducted at the university laboratory (which the author obtained extraordinary permission to use as most research studies were paused). Given the size of the laboratory, it was only allowed to exercise 1-2 participants at a time. Therefore, 18 participants were included in Study V of which 15 (CON, n = 7; UBROW, n = 8) completed the study (Study V).

3.3. ONLINE SURVEY

The Barriers to Physical Activity Questionnaire for People with Mobility Impairments (BPAQ-MI) (134) was used in Study I-II to identify perceived barriers among manual wheelchair users. The BPAQ-MI was deployed because of its comprehensiveness, as it includes potential barriers within several domains of influence. Using such an approach, human behavior is viewed as being determined by influences from four major domains (intrapersonal, interpersonal, organizational, and community), implicating that barriers are perceived in the interaction between the individual and his or hers environment (135). The BPAQ-MI consisted of 61 items/potential barriers, distributed over the four domains and eight subdomains (Study I-II). The general structure was to ask the participant whether she/he had experienced a particular barrier hindering the participant from being physically active within the last three months (134). If the participant answered 'no', a score of 0 was given (not a barrier). If the participant responded with a 'yes', the severity of the barrier was rated on a scale from 1 (very small) to 5 (very big) (134). The BPAQ-MI has been validated in individuals with mobility disability, with good test-retest reliability (134), and we have demonstrated acceptable internal consistency of the Danish translated version (Study II).

3.3.1. BPAQ-MI TRANSLATION

The original BPAQ-MI was published in English (134). To avoid potential linguistic difficulties associated with reading and understanding a foreign language questionnaire, the BPAQ-MI was translated and culturally adapted from English to Danish before usage. Cultural adaptation was considered important to ensure not only that the translated questionnaire represented an accurate rendering of the original content, but also that the target population (Danish manual wheelchair users) clearly could comprehend its meaning (136). The translation process followed guidelines for questionnaire translation and cultural adaptation (136,137), and details about this process are provided in Study I, supplementary appendix 1.

3.3.2. BARRIER PREVALENCE, SEVERITY, AND IMPACT SCORE

Physical activity barrier prevalence reflected the absolute number (n) and proportion of participants who reported 'yes' to an item being a barrier (% of yes) (Study I). As barrier prevalence indicates the presence of a barrier, not how large it is, barrier severity (1-5) was also calculated to determine the magnitude of a given barrier (Study I).

Finally, barrier impact provided an integrated measure of prevalence and severity and was scored from 0 (not a barrier) to 5 (very big barrier) (Study I). Barrier impact scores for each item/potential barrier were then summed within each of the four major domains, eight subdomains, and across all domains, and reported as barrier domain

impact score, subdomain impact score, and total impact score, respectively (Study I-II).

3.4. EXERCISE TRAINING INTERVENTION

Consistent with the existing literature, results from Study I indicated a 'lack of accessible exercise equipment' and 'pain', particularly in the shoulder region, as two of the most pronounced, yet modifiable, physical activity barriers among manual wheelchair users. As described in Study III, an exercise intervention was therefore constructed with the intention of addressing these two barriers. The exercise intervention used in Study IV-V consisted of upper-body exercise training performed on a rowing ergometer adapted to wheelchair users (UBROW). Participants randomized to UBROW performed three weekly supervised exercise sessions of 30-min for either six (Study IV) or 12 weeks (Study V). Exercise intensity prescription was based on rating of perceived exertion (RPE), targeting intensities from RPE 12 (moderate) to 17 (vigorous) using the Borg 6-20 RPE scale (138). Participants were instructed to indicate RPE based on a central (cardiorespiratory sensations) and peripheral (working arm-muscles) integration of effort (139), rather than one or the two in isolation (140). Additionally, participants were equipped with a belt (Suunto, iQniter, Aalborg, Denmark) for continuous recording of heart rate. The belt was Bluetooth connected to participants own smartphones, with data saved in the cloud for which the author (RKH) had access to. The belt-smartphone connection allowed participants to review their effort after each session, which they felt motivating. A commercially available rowing ergometer (Concept 2 RowErg D PM5, Morrisville, Vermont, USA) (Figure 1A) was adapted to wheelchair users via an Adapt2row unit (Figure 1B). Specifically, the ergometer was separated into two parts by detaching the seat and track from the front of the ergometer (Figure 1C), followed by attachment of the Adapt2row unit. Importantly, this adaptation, which can be made within seconds, is reversible, allowing both able-bodied and wheelchair users to use the same ergometer. The Adapt2row configuration is central, as it allows the user to remain seated in his or her own wheelchair.

While sitting in their wheelchair, participants then performed upper-body rowing by repeatedly pulling the ergometer handle towards the ribcage (Figure 1D). Considering shoulder pain, careful attention was given towards participants' rowing technique (60,141). In example, participants were encouraged to keep their elbows close to the torso while pulling the handle. This position helps the wrists in a more neutral position, minimizing the risk for repetitive motion overuse (60). Furthermore, having elbows close to the torso reduce shoulder abduction, and strengthen key scapular retractor muscles, such as latissimus dorsi, lower trapezius and the rhomboids (60). To emphasize scapular retraction, participants were instructed to "squeeze the shoulder blades together" while keeping the shoulders down (45). For further details about the rowing technique, and how the exercise was adapted to individuals with varying SCI levels, the reader is referred to Study IV.

Before each exercise session, participants were encouraged to empty their bladder to

reduce the risk of AD (142), and a fan was positioned in front of the ergometer to facilitate convective cooling of the participants during the exercise.

Participants randomized to the control group (CON) in Study V were asked to maintain their usual lifestyle throughout the 12-weeks. After the study, participants in CON were offered three supervised rowing exercise sessions.

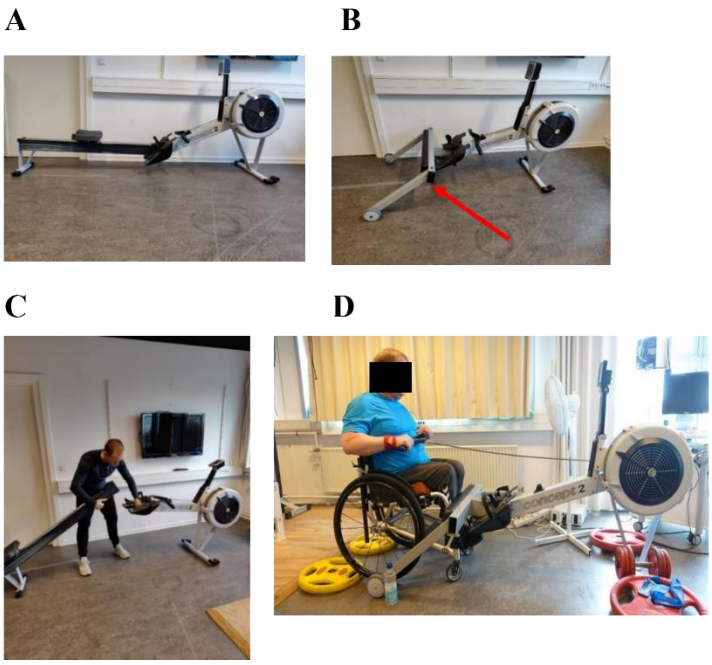

Figure 1. (A) A commercially (Concept 2) rowing ergometer used for able-bodied. (B) The Concept 2 ergometer modified for wheelchair users using the Adapt2row unit. (C) The ergometer can be separated into two parts (reversible) within seconds, allowing both able-bodied and wheelchair users to use the same ergometer. (D) Participant performing upper-body rowing while sitting in his own wheelchair. Adapted from Study IV.

3.5. BLOOD SAMPLES

Blood collection and analyses were performed by trained personnel at the University Hospital in a laboratory that is accredited according to the DS/EN ISO 15189 standard. Details about specific blood sample analyses can be found in Study V. Briefly, after an overnight fast (≥10 hours) participants arrived at the Hospital, where approximately 50 mL was drawn from the antecubital vein for analyses of traditional and 'novel' biomarkers of CVD risk. Strong evidence suggests that the effects on some risk factors (including blood biomarkers) attributed to exercise training may at least partially reflect the result of the latest exercise bout (231). For participants in UBROW, blood sampling was therefore performed between 36 and 60 hours after the

last exercise session at both 6W and 12W to minimize any acute effects from the last exercise session on blood biomarkers.

Total cholesterol, HDL-C, TG, CRP, and glucose were measured on fasting Li-Heparin plasma samples on Cobas 8000 (Roche, Mannheim, Germany), and LDL-C calculated using the Friedewaldt equation. Insulin was measured on fasting serum samples on Cobas 600 e (Roche, Mannheim, Germany), and glycated hemoglobin (HbA1c) was measured on EDTA blood on a Sebia Capillaris 3 (Lissess, France) (Study V). The homeostasis model assessment 2 of insulin resistance (HOMA2-IR), pancreatic β-cell function (HOMA2-β), and insulin sensitivity (HOMA2-S) were computed using the HOMA2 calculator (Study V).
Plasma concentrations of the pro-inflammatory marker tumor necrosis factor alpha (TNF-α) as well as markers of vascular injury, sICAM-1 and sVCAM-1, were measured as described in Study V. Plasma from EDTA blood collection tubes was prepared by centrifugation at 2200xg for 10 minutes at room temperature and samples were frozen at -80°C until analysis.
The vasoconstrictor ET-1 was analyzed using the Quantikine ELISA Endothelin-1 immune-assay (R&D, Abingdon, UK), as described in detail in Study V.

3.6. BLOOD PRESSURE AND ANTHROPOMETRICS

Details about measurements of arterial pressure and anthropometrics can be found in Study III and V. In brief, seated SBP and DBP were measured after at least 10 min of rest using an automated monitoring device (OMRON M3, OMRON Healthcare, Hoofddorp, The Netherlands). Body mass was measured using a platform wheelchair scale (KERN EOB 300K100L, Balingen, Germany) in which body mass of the participants were subtracted the mass of the participant plus the chair. WC, an established surrogate measure of VAT (82), was measured with non-elastic tape immediately below the lowest rib. RKH performed all measurement, blinded to the results obtained at the earlier visits.

3.7. ASSESSMENT OF VASCULAR FUNCTION AND STRUCTURE

FMD is a non-invasive technique to assess conduit artery endothelium-dependent, NO mediated vascular function (143). A strong relationship has been demonstrated between brachial FMD and coronary artery endothelial function, as determined by the vasodilatory response to acetylcholine infusion (144), and FMD independently predicts future CVD events (116,145,146). The physiological concept that underlines the FMD test is that a period of blood flow restriction using suprasystolic cuff inflation (around the forearm when examining the brachial artery) exposes the downstream vasculature to ischemia, with resulting downstream dilation. Upon cuff release, the abrupt increase in blood flow velocity towards the dilated downstream microvasculature augments shear stress to the conduit artery, thereby providing a

stimulus to the endothelial cells to increase NO production, resulting in smooth muscle relaxation and upstream, conduit (brachial) artery vasodilation (147).
In Study V, brachial artery FMD was assessed as recommended (147), with all measurements performed by RKH, who had received guidance and undergone extensive training before conducting the study (148).

Briefly, after a period of supine rest in a quiet, temperature-controlled room brachial artery examination was performed with the participants right arm extended at an angle of ~80° from the torso on an adjustable table (Figure 2). A rapid inflation and deflation pneumatic cuff (E20. Hokanson Inc., Bellevue, WA, USA) was placed on the right forearm immediately distal to the olecranon process. A distal cuff placement (relative to the ultrasound probe) was chosen as dilation of the artery in response to distal cuff occlusion is largely endothelium NO mediated (149). When the artery was identified, the probe (10 MHz multifrequency linear array), that was connected to a high-resolution ultrasound machine (LOGIQ S8 XDclear, GE Healthcare), was held stable and the B-mode image was optimized such that clear vascular borders could be visualized. Red blood cell velocity was simultaneously measured using continuous pulse-wave assessment (Doppler), with a constant insonation angle of ≤60°, and the sample volume encompassing the total width of the artery lumen (intima-to-intima) so that measurements of red cell velocity represented a mean of the entire cross-section of the brachial artery. As the error of the insonation estimation increases exponentially with angles >60° (150), an insonation angle of ≤60° was applied, with the angle correction cursor placed parallel to the direction of flow. All images were recorded for later offline analysis.
Baseline diameter and velocity were recorded for ≥30 s prior to inflation of the pneumatic cuff. The cuff was then inflated for 5 min to ≥200 mmHg. Immediately prior to deflation, diameter and velocity recordings resumed and continued for additional 3 min following cuff deflation.

Brachial artery lumen diameter was analyzed off-line (Figure 3), as described in Study V. FMD were calculated as both the absolute (mm) and relative (%) change in diameter with equation 1 and 2, respectively:

$$(1)\ \text{FMD (mm)} = \text{Peak Diameter} - \text{Baseline Diameter}$$

$$(2)\ \text{FMD (\%)} = \frac{(\text{Peak Diameter} - \text{Baseline Diameter})}{\text{Baseline Diameter}} \times 100$$

To adjust for the potential confounding influence of resting baseline diameter on FMD, an allometrically scaled FMD (corrected FMD%) was also calculated (151). Details about the calculation of the ‘corrected FMD%’ are provided in ‘Statistics’.

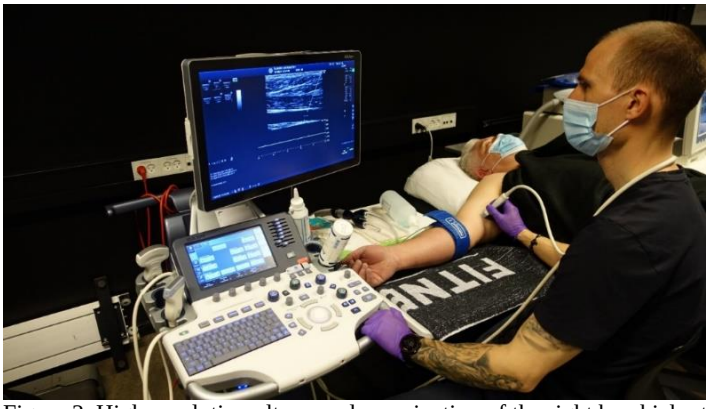

Figure 2. High-resolution ultrasound examination of the right brachial artery in one participant. Ultrasound images were optimized such that clear vascular borders were visible before recording. The pneumatic cuff around the participants' lower arm was inflated/ deflated using a food pedal operated by the author (RKH).

A **B**

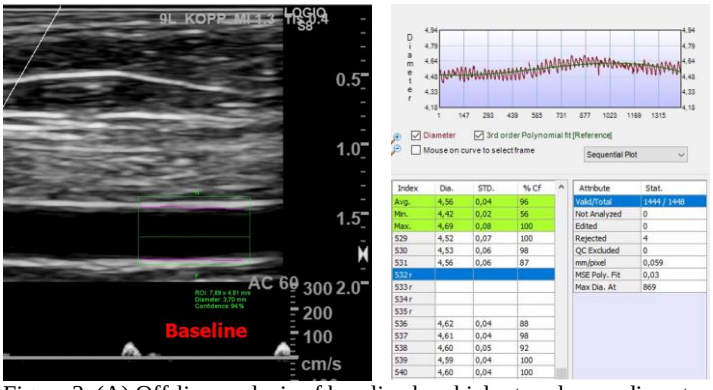

Figure 3. (A) Off-line analysis of baseline brachial artery lumen diameter using semi-automated edge-detecting and wall-tracking software. Green box indicates the region of interest (ROI) with near (N) and far (F) borders indicated. Purple horizontal lines indicate wall-tracking of the intima-medial borders (M-line) used for diameter calculation. (B) Example of output showing frame-by-frame analysis of the change in lumen diameter after cuff deflation.

3.8. CARDIORESPIRATORY FITNESS

Participants in Study IV-V performed a graded exercise test to exhaustion (GTX) on an arm-crank ergometer (Monark 881E, Vansbro, Sweden) for determination of the peak rate of oxygen consumption ($\dot{V}O_{2peak}$), see Study III and V for details. Briefly, the ergometer was fastened to a height-adjustable table and positioned vertically so that the crank axis centre was level with the shoulder joint, and horizontally to allow a slight bent of the elbow joint at the furthest point of the crank cycle. The three

participants with cervical injury all lacked grip strength and were therefore equipped with adaptive gripping aid gloves (The Active Hands Company, Earlswood, Solihull, United Kingdom), serving to support their grip to the ergometer handles (Figure 4). Throughout the test, participants were instructed to maintain a cadence of 70 rpm, with volitional exhaustion defined as an inability to maintain cadence >60 rpm despite verbal encouragement (152).

Heart rate and breath-by-breath $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were measured continuously throughout the test, with RPE noted at the end of each minute. $\dot{V}O_{2peak}$ and peak power output (PO_{peak}) was reported as described in Study III and V).

Figure 4. Participant performing a GTX for determination of $\dot{V}O_{2peak}$. The participant (NLI: C7, AIS: A) did not possess adequate finger flexor strength and was therefore equipped with adaptive gripping aid gloves that supported his grip to the ergometer handle.

3.9. FEASIBILITY AND ACCEPTABILITY

The Feasibility and Acceptability Questionnaire (153) was used in Study IV to obtain indications on the usability and participants' satisfaction with the upper-body ergometer rowing modality. The questionnaire consisted of six questions (see Study IV for details) for which participants rated the feasibility and acceptability on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). To explore if participants attitude towards the exercise modality would change over time, the questionnaire was completed after week 1, 3, and 6. In addition, participants also completed the

questionnaire at the end of week 9 and 12. Results from weeks 9 and 12 will be presented later in this thesis for the first time.

3.10. SHOULDER PAIN

Using the Wheelchair Users Shoulder Pain Index (WUSPI) (154), participant were asked to rate on a visual analog scale (anchored at "no-pain" and "worst pain ever experienced"), the intensity of shoulder pain experienced during 15 different ADL within the past week (Study III and IV). To adjust for any ADL that were not performed, the performance-corrected shoulder pain score (PC-WUSPI) was calculated and used for analysis by dividing the total WUSPI-score by the number of executed activities multiplied by 15 (154). Participants completed the WUSPI as part of Study IV (at baseline and after six weeks), but also at the end of the 12-weeks (12W). These 12W data will be presented later in this thesis.

3.11. QUALITY OF LIFE

As part of the RCT, QoL was assessed at baseline, 6W, and 12W using the International Spinal Cord Injury Quality of Life Basic Data Set (QoL-BDS) (155). The QoL-BDS consist of three items, asking participants to rate from 0 (completely dissatisfied) to 10 (completely satisfied) their (1) 'satisfaction with life in general', (2) 'satisfaction with physical health', and (3) 'satisfaction with psychological health, emotions and mood' during the last four weeks. For analysis, a QoL-BDS score was provided for each of three items and for total QoL (156). Results on these QoL indices will be presented for the first time in this thesis.

3.12. LEISURE-TIME PHYSICAL ACTIVITY

Levels of LTPA were assessed using the Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury (LTPAQ-SCI) (157). The LTPAQ-SCI was administered during a face-to-face interview conducted by RKH. After participants had been presented with a standardized definition of mild, moderate, and heavy intensity LTPA (158), participants were asked to recall over the past 7 days: 1) the number of days that they performed mild intensity LTPA, and 2) on those days, the minutes spent on doing mild-LTPA. These questions were repeated for moderate intensity and heavy intensity. For analyses, the number of minutes per week of LTPA performed at each intensity was determined by multiplying the number of days of activity by the minutes of activity. Total LTPA was calculated as the sum of mild, moderate, and heavy intensity LTPA performed in the past week.
Results from 6W and 12W collected as part of the RCT will be presented in this thesis for the first time.

Table 2. Risk factor overview for Study V

Risk factors traditional associated with cardiometabolic diseases	
Cardiometabolic syndrome	WC
	HDL-cholesterol
	TG
	Fasting glucose
	SBP DBP
Other traditional risk factors [a]	Total cholesterol
	LDL-cholesterol
	Body mass/BMI
	Smoking status
	Diabetes [b]
	Blood pressure treatment
Glycemic control	HbA1c
	Fasting insulin
	HOMA2-IR
	HOMA2-β
	HOMA-S
Novel risk factors	
Vascular health/injury	Endothelial function (FMD)
	Conduit artery structure (LD)
	Vascular adhesive molecules (sICAM-1, sVCAM-1)

	Vasoconstrictors (ET-1)
Cardiorespiratory fitness	$\dot{V}O_{2peak}$
Pro-inflammation	Systemic low grade (CRP)
	TNF-α

[a] Modifiable risk factors (i.e. excluding sex, age).
[b] Already a metabolic disease, but when present, profoundly increases the risk of CVD.
Abbreviations: WC = Waist circumference; HDL = High-density lipoprotein; TG = Triglyceride; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; LDL = Low-density lipoprotein; BMI = Body mass index; FMD = Flow-mediated dilation; LD = Lumen diameter; sICAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = soluble vascular cell adhesion molecule-1; ET-1 = Endothelin-1; $\dot{V}O_{2peak}$ = Peak rate of oxygen consumption; PO_{peak} = Peak power output; CRP = C-reactive protein; TNF-α = Tumor necrosis factor alpha; HbA1c = glycated hemoglobin; HOMA2-IR = Homeostasis model assessment of insulin resistance; HOMA2-β = Homeostasis model assessment of pancreatic β-cell function; HOMA2-S = Homeostasis model assessment of insulin sensitivity.

3.13. STATISTICS

Statistical analyses in Study I-II and IV-V were performed using SPSS (version 25-27; IBM, Armonk, New York, USA). In Study I-II, continuous outcome variables were assessed for normality using the Shapiro-Wilk test. In Study IV, continuous outcomes were presented using non-parametric statistics due to small sample size (n = 8). Statistical significance was accepted at $\alpha < 0.05$ for all studies.

In Study I, barrier prevalence was reported as counts and frequencies. Barrier severity was reported as median and interquartile range (IQR). Spearman rank correlations were performed between barrier impact scores and PAL (1-10 scale), to explore (unadjusted) associations. A multiple linear regression model explored the (adjusted) associations between subdomain impact scores (predictors) and PAL, to determine which (if any) barrier subdomains were independently associated with PAL.

In Study II, the primary aim was to identify whether specific sociodemographic characteristics were associated with physical activity barrier perception among wheelchair users. Candidate variables included age, sex, BMI, years in chair, SCI level (paraplegia or tetraplegia) and completeness (complete or incomplete), resident city size, educational level, and current employment. To examine associations, univariate linear regressions were first performed between each subdomain and total impact score (dependent variable) on one hand, and each of the wheelchair user sociodemographic characteristics (independent variable) on the other hand. The sociodemographic characteristics that showed an unadjusted (univariate) association to the dependent variable were then included in a multiple linear regression model to provide multivariate adjustment for the association between sociodemographic characteristics and barrier impact scores.

The primary objective of Study IV was to provide an exploratory investigation of feasibility, acceptability, and preliminary efficacy of the upper-body ergometer rowing modality, and for this purpose, descriptive (median, IRQ) statistics were used. As secondary objectives, the development over time (baseline to six week) in exercise session data and shoulder pain were explored using Wilcoxon signed-rank tests. Cohen d was calculated to describe the magnitude of change over these six weeks.

In Study V, linear mixed model (LMM) analyses were performed to determine main effects of time (baseline, 6W, and 12W) and time-by-group interactions for outcomes (except 'corrected FMD%'), with 'time', 'group' and the interaction used as fixed factors in the model. Post hoc tests (Bonferonni-corrected) were used for multiple comparisons, where appropriate.
The 'corrected FMD%' was allometrically scaled to resting baseline diameter as recommended (151). First, resting and peak diameters were logarithmically transformed, and then the diameter change expressed on a logged scale was calculated. These logged diameter changes were then entered into a two-way analysis of covariance (ANCOVA) model, with 'group' and 'time' as fixed factors, and the logarithmically transformed baseline diameter as covariate. Covariate (resting diameter) adjusted means for diameter change were then obtained from the model and back transformed by antilog of these means and expressed as 'corrected FMD%' by subtracting 1 and multiplying with 100. SDs was derived from the SEs provided by the model and the square root of the sample size, and then by back transforming (antilog) in the same manner as the adjusted means for diameter change.
To determine the magnitude of effect from baseline to 12W, absolute change scores (Δ12W-baseline) with 95% confidence intervals (CI) were calculated. Standardized effect sizes (Hedges g) for absolute change scores were also calculated to determine the magnitude of differences in responses between groups (Study V), and interpreted as trivial (<0.2), small (>0.2), moderate (>0.5), and large (>0.8) (159).

3.14. PROTOCOL DEVIATIONS

The study protocol (160), herein referred to as Study III, was submitted to enhance transparency of the work. Some issues and considerations arose after the protocol was published, which led to a few deviations from the study protocol that deserve justification.
Number of participants: In the study protocol, we reported to include 30 participants in total (n = 15 allocated to each group). However, as a consequence of the COVID-19 pandemic, it was necessary to limit the number of participants, and we therefore ended up including 18 participants in Study V.
Participant exclusion and inclusion criteria: As described in Study III, we originally aimed only to include individuals who self-reported to engage in less than 90 min/week of moderate-to-vigorous intensity physical activity (i.e. not fulfilling current exercise recommendations for SCI (65). However, as it was not possible to recruit enough participants that met this 90-min threshold, we removed this exclusion

criterion from Study IV-V. Furthermore, the original age range of 18-65 yr was expanded to allow participants up to 70 yr old to be included (n = 1). The Ethics Committee of North Denmark approved these changes to inclusion and exclusion criteria before commencing any data collection.

Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury (LTPAQ-SCI): Participants in CON only completed the LTPAQ-SCI at baseline, 6W and 12W and not once every week. This amendment was done to reduce participation burden for CON and time requirements for RKH.

Exercise prescription: In Study III, each 30-min exercise session was described to be reached through accumulation of 5-min bouts, with a RPE range of 12-15. However, as realized during the intervention, some participants reported the most enjoyment by performing longer bouts or continuous (up to 30 min) exercise. In contrast, others felt 'mentally bored' by rowing on the stationary ergometer for 30 min straight, whereas some participants were not able to row continuously for more than 5-10 min. As participant motivation was highly prioritized, we therefore allowed participants to meet the 30 min of thrice weekly exercise through continuous rowing or via multiple shorter bouts. That we tailored the exercise sessions to the individual, rather than asking each participant to do the same type or amount of work, is indeed considered a strength, as exercise prescription guidelines emphasize the importance of individualizing the exercise stimulus, whenever possible (161,162). Finally, in the SCI literature, there is no clear definition of 'moderate-to-vigorous intensity' exercise (163). Therefore, recommendations for able-bodied were followed, resulting in a RPE range from 12-17, representing the lower and upper borders for moderate (RPE: 12-13) and vigorous (RPE: 14-17) intensity, as guided by the American College of Sports Medicine.

CHAPTER 4. RESULTS

The main results of Study I-II and IV-V are summarized in this section. For a detailed presentation of the results, see the original papers/manuscripts (Study I-II and IV-V) for further details.

4.1. STUDY I

4.1.1. BARRIER PREVALENCE AND SEVERITY

The five most prevalent barriers were all reported by ≥50% of the sample. Two of those related to the intrapersonal subdomain 'health':
I) *you got tired or fatigued* (64%), and II) *you were in pain* (62%), whereas three related to the community subdomain 'community built environment':
III) *uneven or crooked sidewalks* (55%); IV) *lack of accessible curb cuts in community* (50%); and V) *the sidewalks had cracks, gaps, or were under construction* (50%).
The most prevalent pain location reported was 'shoulder' (40%), followed by 'back' (35%), 'neck' (31%), 'arms' (27%), and 'wrist' (25%).

The five most severe reported barriers included one from the organizational subdomain 'fitness center built environment': I) *lack of accessible exercise equipment at fitness center*, 5 (4-5), and four from the community subdomain 'community built environment':
II) *lack of access to public restrooms*, 5 (4-5); III) *lack of accessible curb cuts in community*, 5 (4-5); IV) *sidewalks were not wide enough*, 5 (3.25-5); and V) *lack of adequate street lighting at night*, 5 (3-5).

An exhaustive overview of barrier prevalence and severity for each of the 61 BPAQ-MI (Danish adapted) items are presented in Study I, supplementary appendix 2.

4.1.2. ASSOCIATIONS BETWEEN PAL AND BARRIER IMPACT SCORES

In univariate analyses (Study I, supplementary appendix 3), PAL was inversely associated with the intrapersonal domain ($r = -0.487$, $P < 0.01$), and the two intrapersonal subdomains (health, $r = -0.477$, and beliefs/attitudes towards physical activity, $r = -0.777$) (both $P < 0.01$). There was also an inverse association between PAL and total barrier impact score ($r = -0.241$, $P < 0.01$). However, after multivariate adjustment, only the health subdomain was independently associated with PAL ($P < 0.01$).

4.2. STUDY II

Based on the multivariate regression models, some general themes appeared. First, wheelchair users with a BMI ≥30 kg/m^2 perceived larger barriers across all domains (total barrier score), as well as within the intrapersonal and organizational domains, when compared to wheelchair users with a BMI <30 kg/m^2. Specifically, barriers related to 'health', 'beliefs/attitudes towards physical activity', the 'fitness center-built environment', and 'staff/program/policy' subdomains were all rated higher by wheelchair users who were obese (BMI >30 kg/m^2).
Secondly, wheelchair users who did not complete high school perceived larger intrapersonal ('belief/attitudes towards physical activity') and interpersonal ('friends', family') barriers than wheelchair users with higher levels of education. Thirdly, wheelchair users without current employment perceived larger barriers within all the four major domains, and across all barriers (total barrier score). Specifically, unemployed wheelchair users rated larger barriers associated with 'health', 'friends', 'staff', the 'fitness center-built environment', and the 'community-built environment' compared to wheelchair users in employment. Finally, resident city size was, as the only sociodemographic variable, associated with safety barriers ($P < 0.05$), such that wheelchair users living in larger populated cities reported larger safety concerns for being physically active.

4.3. STUDY IV

4.3.1. FEASIBILITY AND ACCEPTABILITY OF UPPER-BODY ROWING

For week 1, 3 and 6, the median rating of all six items on the feasibility and acceptability questionnaire (1-5, Likert scale) was ≥4.0. These median values were well above the *a priori* used criterion (median ≥3.0) to indicate that the rowing modality would be considered acceptable (Study IV).
During this six-week long study, exercise adherence was 97% (i.e. the number of completed sessions out of total number of sessions). Shoulder pain remained unchanged from week 1 (23 (1.9-45.8)) to week 6 (7.8 (1.5-47.9)) ($d = -0.22$, $P = 0.89$).

4.3.2. PRELIMINARY EFFICACY OF UPPER-BODY ROWING

In terms of efficacy, participants were able to reach moderate-to-vigorous intensity when exercising on the rowing ergometer, as determined by the average RPE and average heart rate (%HR_{peak}) throughout the sessions. Moreover, the relative intensity by which the exercise was performed increased from week 1 to week 6. RPE increased from 15 (14.3-15.6) in week 1 to 16 (15.5-16.7) in week 6 ($d = 0.85$, $P < 0.001$). %HR_{peak} increased from 80% (72.8-84.8) in week 1 to 83% (81-91.5) in week 6 ($d = 0.82$, $P < 0.01$).

4.4. STUDY V

As part of the RCT more data were collected then presented in this dissertation. Specifically, outcome measures related to autonomic cardiovascular function (blood pressure regulation during an orthostatic challenge, HRV, seismocardiography), ventilatory thresholds, carotid artery intima-media thickness, and health-related QoL (Short-Form-36) were all assessed during the RCT, but analyses have not yet been performed. Similarly, due to time constraints, data from the 6-month follow-up have not yet been analyzed and are therefore not presented. Data not included in this dissertation will be analyzed and submitted for publication later.

Out of the 18 participants in Study V, 15 completed the study, with all participants in UBROW completing the intervention (n = 8). Over the 12-weeks, exercise adherence rate was 92 ± 13%. Power output and RPE averaged 42 ± 21 W and 15.8 ± 0.7, respectively, across all sessions. The average heart rate across all sessions reached 130 ± 12 bpm, corresponding to 83 ± 3% of HR_{peak}.

4.4.1. TRADITIONAL CARDIOMETABOLIC RISK FACTORS

At baseline, 80% of the participants who completed Study V had clinically elevated BMI (≥22 kg/m^2); 53% had elevated WC (≥94 cm); 53% had elevated SBP (≥130 mmHg); 47% had elevated DBP (≥85 mmHg); 33% had elevated fasted glucose (≥5.6 mmol/L); 13% had depressed HDL-C (<1.03 mmol/L for men, 1.3 mmol/L) for women); 20% had elevated TG (≥1.7 mmol/L); 40% had elevated total cholesterol (≥5mmol/L); and 47% had elevated LDL-C (>3mmol/L). Despite the relatively high proportion of independently elevated risk factors at baseline, only two participants (both from UBROW) meet the clinical classification for the metabolic syndrome used by AHA/ NHLBI (104), and SCI-specific criteria for central obesity (WC) (106).

Detailed results on the change in traditional risk factors can be seen in Study V (Table 3). In brief, there were no significant time-by-group interactions for the majority of the traditional cardiometabolic blood biomarkers, resting arterial blood pressures, or body mass, with effects sizes ranging from trivial (g = -0.13, TG) to moderate (g = -0.75, HOMA2-IR). However, few exceptions appeared. For HOMA2-β, there was a significant time-by-group interaction (P = 0.04). Post hoc tests showed increases in HOMA2-β from baseline to 6W (P = 0.012) and 12W (Δ22%; 95% CI, -5-50%; g = -1.08; P = 0.017) in CON, with no changes in UBROW. A trend for a time-by-group interaction (P = 0.061) was found for WC, with a large effect size (g = -0.86) suggesting a trend for a reduction in UBROW relative to CON.

Individual blood pressures for UBROW and CON are shown in Figure 5. From baseline to 12W, SBP and DBP increased in the two tetraplegic participants in UBROW (broken lines), whereas there were reductions in SBP and DBP in four out of the five paraplegic participants (Figure 5A, C). In CON, SBP and DBP decreased

from baseline to 12W in the participant with cervical injury, whereas for participants with paraplegia, three out of six demonstrated an increase in SBP and increased or unchanged DBP (Figure 5B, D).

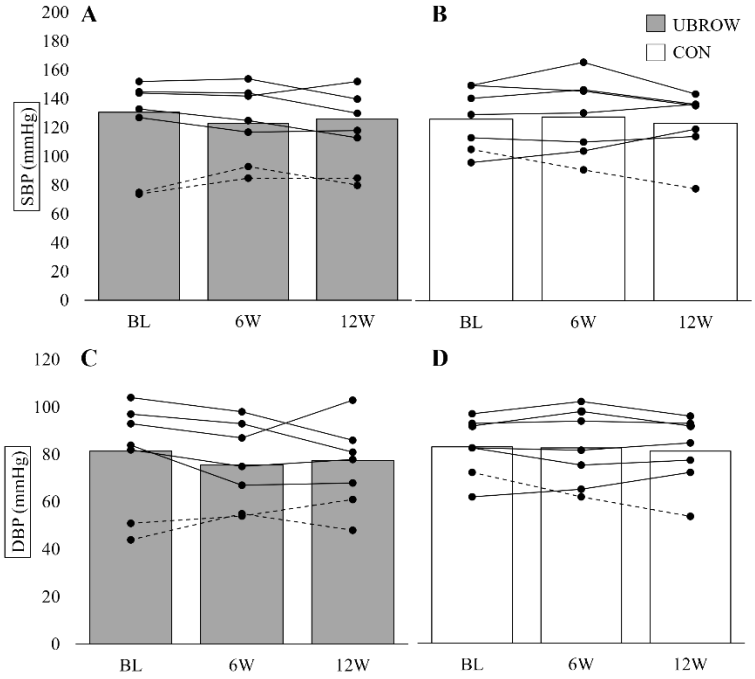

Figure 5. Group mean and individual data on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in UBROW (A, C) and CON (B, D) at baseline (BL) and at 6W and 12W. Broken lines represent participants with cervical injury. Note that n = 7 in UBROW.

4.4.2. NOVEL CARDIOMETABOLIC RISK FACTORS

Detailed results of the change in brachial artery function, aerobic fitness, and inflammatory and endothelium-derived biomarkers are presented in Study V.

There was a significant time-by-group interaction for resting brachial artery lumen diameter ($P = 0.015$). Post hoc tests showed an increase in resting diameter from baseline to 12W ($\Delta 0.28$ mm; 95% CI, 0.05-0.53 mm; $g = 1.34$; $P < 0.01$) in UBROW, with no change at 6W, and no change in CON (Figure 6A). There were no significant time-by-group interactions or main effects of time for either absolute (FMD, mm) or relative (FMD, %) (Figure 6B) brachial artery function, nor when adjusted for baseline diameter (corrected FMD%).

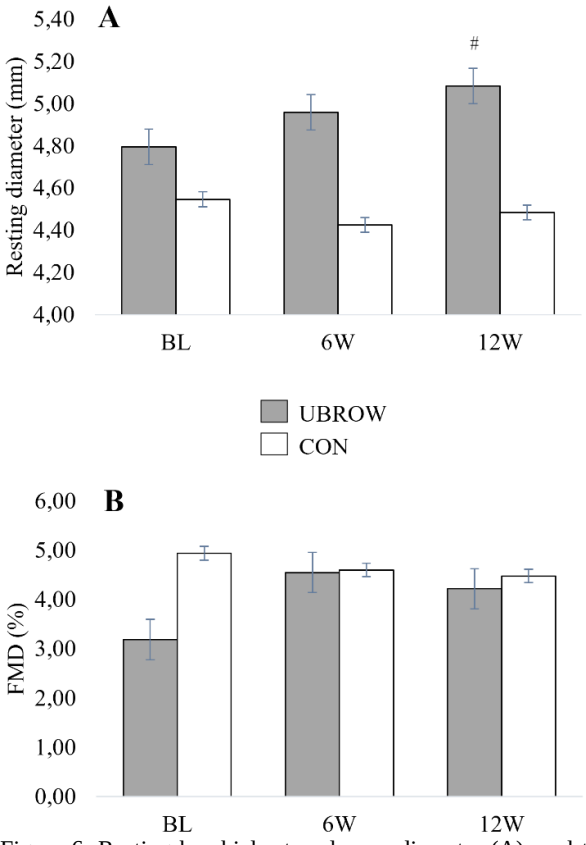

Figure 6. Resting brachial artery lumen diameter (A), and the unadjusted relative change in brachial artery diameter from baseline (FMD%) in response to 5 min ischemia (B), at baseline (BL) and at 6W and 12W. Error bars represent SEM. # Significantly different from baseline ($P < 0.01$). Note that for FMD%, n = 5 in CON and n = 7 in UBROW. Adapted from Study V.

There were significant time-by-group interactions for relative $\dot{V}O_{2peak}$ and absolute $\dot{V}O_{2peak}$ (both, $P < 0.01$). Post hoc tests showed that relative $\dot{V}O_{2peak}$ increased from baseline to 6W ($P < 0.01$) and 12W (Δ2.4 ml/kg/min; 95% CI, 0.9-3.9 ml/kg/min; $g = 2.03$; $P < 0.01$) in UBROW, whereas CON had a significant reduction ($P = 0.041$) from baseline to 6W, but not at 12W. Absolute $\dot{V}O_{2peak}$ increased from baseline to 6W ($P = 0.011$) and 12W (Δ186 ml/min; 95% CI, 79-292 ml/min; $g = 2.04$; $P < 0.01$) in UBROW, with no changes in CON. There was a significant time-by-group interaction for PO_{peak} ($P < 0.01$). Post hoc tests showed that PO_{peak} increased from baseline to 6W ($P < 0.01$) and 12W (Δ17W; 95% CI, 10-24 W; $g = 2.44$; $P < 0.01$) in UBROW, with no change in CON.

Finally, there was a trend for a time-by-group interaction for ET-1 ($P = 0.078$), with a large effect size ($g = -1.36$) suggesting an increase in plasma levels of ET-1 in CON.

4.4.3. ADVERSE EVENTS

There were a few adverse events related to the exercise intervention that warrant attention. When pulling the rowing handle using wrist straps with a hook, one participant with cervical injury (AIS: B, NLI: C6) experienced issues with his tenodesis grasp in week 5. As described in Study IV, a solution was developed that allowed the participant to pull without involvement of his hands, which made it possible to continue the intervention. Towards the end of the intervention, the same participant developed a pressure ulcer, which may have been related to the intervention. This ulcer forced the participant to withdraw from the last two weeks of training, but he was still able to complete the tests at 12W, a few weeks later.

4.4.4. FEASIBILITY AND ACCEPTABILITY: WEEK 7-12

Feasibility and acceptability for week 1-6 was presented in Study IV. For week 9 and 12, the median rating of all six items was ≥4.0, suggesting that acceptability did not deteriorate at the final part of the intervention. For week 9 and 12, respectively, median (IQR) ratings for each of the six items were as follow:

1. *I found the exercise fun to perform*: 4.0 (3.0-5.0) and 5.0 (3.8-5.0).
2. *I was able to perform the exercise without difficulty*: 4.0 (4.0-5.0) and 5.0 (3.8-5.0).
3. *The exercise was worth my time*: 5.0 (5.0-5.0), for both week 9 and 12.
4. *The exercise was easy to perform*: 4.0 (3.0-5.0) and 4.5 (3.8-5.0).
5. *The instructions on how to perform the exercise were clear*: 5.0 (5.0-5.0), for both week 9 and 12.
6. *I received the guidance I needed from the exercise responsible*: 5.0 (5.0-5.0), for both week 9 and 12.

4.4.5. SHOULDER PAIN

There was no significant time-by-group interaction or main effect of time for PC-WUSPI when measured at baseline, 6W and 12W. Individual PC-WUSPI ratings are presented in Figure 7. As can be seen from Figure 7A, seven out of eight participants in UBROW either reduced or had unchanged PC-WUSPI score at 12W. The one participant with an increase in shoulder pain at 12W hurt his shoulder in week 10 during a transfer situation unrelated to the intervention. Despite the shoulder injury, the participant was able to complete the intervention (although with less intensity), but his shoulder pain was intensified during ADL, as indicated on the PC-WUSPI score at 12W. In CON, three participants reported lower, three participants reported higher, and one participant reported unchanged PC-WUSPI scores (Figure 7B).

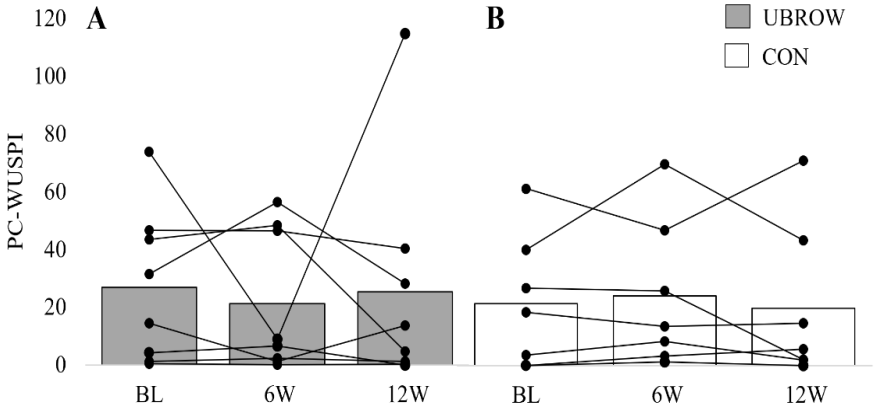

Figure 7. Group mean and individual data on PC-WUSPI in UBROW (A) and CON (B), at baseline (BL) and at 6W and 12W.

4.4.6. QUALITY OF LIFE

Mean (SD) and effect sizes for the individual QoL-BDS items are presented in Table 3. There were no significant time-by-group interactions or main effects of time for any of the QoL indices (Table 3). Individual data on QoL-BDS$_{Total}$ (reflecting the summation of each of the three QoL-BDS items) are presented in Figure 8. Most participants in UBROW increased QoL-BDS$_{Total}$ scores throughout the 12 weeks (Figure 8A). In contrast, QoL-BDS$_{Total}$ remained relatively stable for participants in CON (Figure 8B).

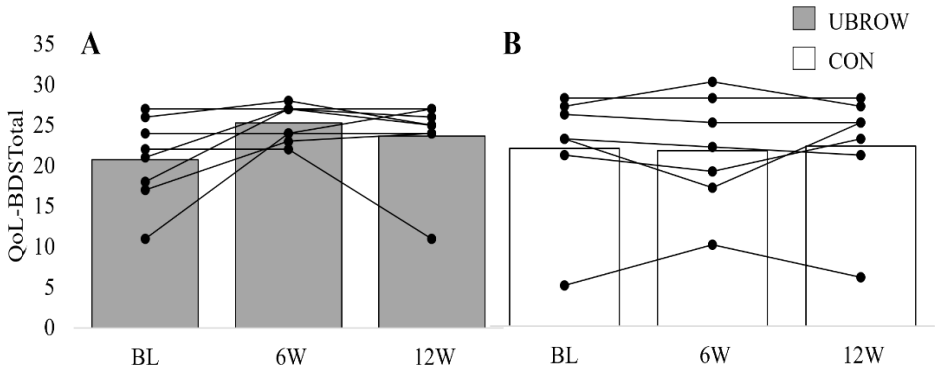

Figure 8. Group mean and individual data on QoL-BDS$_{Total}$ in UBROW (A) and CON (B), at baseline (BL) and at 6W and 12W.

4.4.7. LEISURE-TIME PHYSICAL ACTIVITY

There were no significant time-by-group interactions or main effects of time for any of the LTPA intensities nor total LTPA (Table 3).

Table 3. Quality of life (QoL) and levels of leisure-time physical activity (LTPA) measured at baseline (BL), 6W and 12W.

	CON (n = 7)			**UBROW (n = 8)**				**P-value**	
	BL	6W	12W	BL	6W	12W	Effect size g	Time x group	Time
QoL									
QoL-BDS$_{General}$	7.6± 2.2	7.4± 2.2	7.4± 2.1	6.9± 2.0	8.5± 1.1	7.8± 2.5	0.40	0.205	0.324
QoL-BDS$_{Physical}$	6.9± 2.7	6.0± 3.5	7.3± 2.9	7.0± 1.8	8.0± 0.9	8.3± 1.0	0.50	0.140	0.140
QoL-BDS$_{Psychological}$	7.4± 3.2	8.1± 1.5	7.4± 2.6	6.9± 2.1	8.8± 1.0	7.6± 2.4	0.34	0.545	0.058
LTPA									
Mild LTPA, min/wk	748± 1304	77±60	160± 303	161± 242	233± 323	146± 127	0.54	0.186	0.258
Moderate LTPA min/wk	25±28	49±40	226± 301	76±94	106± 103	111±167	-0.61	0.190	0.076
Heavy LTPA min/wk	21±44	21± 38	116± 219	46±93	54±91	21± 28	-0.68	0.148	0.562
Total LTPA, min/wk	794± 1289	146± 105	501± 757	283± 368	393± 396	278± 172	0.25	0.263	0.506

Data are presented as mean ± SD. Abbreviations: QoL-BDS = International Spinal Cord Injury Quality of Life Basic Data Set; LTPA = Leisure-time physical activity.

CHAPTER 5. DISCUSSION

Findings from the individual studies have been discussed previously (Study I-II and IV-V). In this chapter, a summary of the main findings of the dissertation will be followed by an in-depth discussion of selected aspects that were not included in the individual studies. Next, some general and study-specific methodological considerations will be discussed, followed by some brief perspectives for future work. Lastly, conclusions are made based on the findings from this dissertation.

5.1. SUMMARY OF MAIN FINDINGS

The aims of this dissertation were to a) identify physical activity barriers among wheelchair users (Study I-II); b) develop an exercise intervention, designed to target some of the identified barriers (Study III); c) test the feasibility and implementation of the upper-body rowing exercise modality (Study IV); and d) evaluate the effects of the 12-week exercise intervention, complying with current exercise guidelines for adults with SCI, on cardiometabolic disease risk (Study V), shoulder pain, and QoL, in manual wheelchair users with SCI.

In contrast to previous studies that mainly focused on barriers within a single or few domains (15–17,164–172), Study I-II conducted a comprehensive barrier assessment by investigating physical activity barriers within several domains of influence, as proposed by social ecological models (135). Using such a theoretical framework, health behavior is viewed as being facilitated or inhibited by multiple levels of influence, including factors related to the person itself (intrapersonal), the social (interpersonal), and the physical (institutional and community) environment. As the BPAQ-MI (134) includes items within all of these four domains, this questionnaire was utilized in Study I-II. Notably, the questionnaire was first translated and adapted to a Danish context (19). As such, the main findings of Study I-II were that physical activity barriers are highly prevalent among Danish manual wheelchair users (12 out of 61 potential barriers were reported by >30% of participants); some barriers, especially those related to the built environment (fitness center and community), were perceived as particularly severe; and wheelchair subgroups with BMI $\geq$30 kg/m^2, who did not complete high school, or were unemployed rated physical activity barriers higher than their non-obese, higher educated and employed counterparts.
The two most prevalent barriers reported by manual wheelchair users were of intrapersonal character and related to the ‘feeling of fatigue’ and ‘pain’, both commonly reported barriers in the literature (15,16,173). The causes of the widely reported feeling of fatigue is likely multifactorial, and may include a lack of physical activity (174), poor social functioning (175), blood pressure disturbances in those with SCI (70), and pain (35). In terms of pain, the most frequently reported pain location was the shoulder, which also is in agreement with the existing literature reporting a high prevalence of shoulder pain among wheelchair users (30,34). Not only does

shoulder pain represent a barrier to physical activity, it also negatively affects physical function and QoL (30,35), stressing the priority of interventions that aim to reduce or prevent shoulder pain in wheelchair users.

The finding of 'a lack of accessible exercise equipment at fitness center' as being amongst the most severe and frequently reported barriers is consistent with the existing literature (16,26,176), and highlight the need for fitness centers, and recreational facilities in general, to develop solutions that enable equal participation by individuals using a wheelchair (25). This may be accomplished through construction of universal design of fitness and recreational facilities and exercise equipment (26). An example of such universal design was presented in this dissertation, in which attaching or detaching a single adaptive unit (Adapt2row) to a commercially available rowing ergometer permits both wheelchair users and able-bodied to exercise on the same rowing ergometer.

Results from Study I-II also suggest that the community-built environment is exclusive, rather than inclusive for the non-ambulatory population. This is a concern, as the community environment should be designed such that it stimulates or motivates individuals with mobility disability to become physically active, rather than presenting barriers (170). Lastly, results from Study II revealed that wheelchair users with excess body mass, who are less educated, or without employment have an exaggerated perception of barriers that may hinder them in being physically active. This observation suggests that these individuals may need particular attention and resources to overcome distinct activity barriers. Considering the ecological framework of BPAQ-MI, interventions targeting various levels may be ideal to minimize barrier perception amongst these wheelchair user subgroups.

Despite the abundance of research identifying physical activity barriers in populations with mobility disability, physical activity levels are low in these populations (5), and compliance and participant retention are ongoing issues in exercise studies performed in wheelchair users with SCI (9). These observations suggests that there is a need of more studies focusing directly on applying the knowledge about barriers into the design, implementation and delivery of physical activity enhancing interventions. In this dissertation, the exercise modality utilized sought to mitigate two of the most prevalent and severe reported barriers identified in Study I (a lack of accessible exercise equipment and shoulder pain). At the same time, the modality had to provide a sufficiently large exercise stimuli for improving cardiometabolic health in individuals with SCI. Accordingly, Study IV demonstrated that upper-body ergometer rowing exercise, that includes both an aerobic and strength component, is a feasible and acceptable exercise modality that can be performed without increasing shoulder pain. The latter is particularly important as this suggests that a relatively large volume of moderate-to-vigorous intensity rowing exercise can be tolerated without exacerbating shoulder pain. In fact, seven out of eight participants either reduced (n = 6) or had unchanged (n = 1) shoulder pain after the 12-weeks of rowing, with the only participant reporting larger shoulder pain suffering from a non-study related shoulder injury during a transfer. Moreover, as the rowing modality adapted to wheelchair users

is performed on a commercially available ergometer (Concept 2), it may be possible to implement the exercise modality in community fitness centers. Therefore, wheelchair adapted rowing exercise has the potential to narrow the existing gap in inclusive equipment for wheelchair users.

In Study V, the 12-week exercise intervention was conducted, and a comprehensive assessment of cardiometabolic disease risk was performed both halfway (6W) and post exercise (12W), by measuring traditional cardiometabolic risk factors, and emerging or 'novel' risk factors, including cardiorespiratory fitness, vascular function and structure, as well as endothelium-derived biomarkers. This study provided new evidence that upper-body ergometer rowing exercise improves cardiorespiratory fitness after six and 12-weeks, and induces adaptations in the conduit artery supplying the active upper limbs of wheelchair users with SCI after 12-weeks, as shown by increased lumen diameter of the brachial artery. In contrast, no - or only modest effects of exercise were found on traditional cardiometabolic risk factors. Together, these results support accumulating evidence suggesting that exercise exerts some of its cardioprotective effects beyond modification of traditional risk factors. The observations made from this study are particularly important, as the exercise intervention complied with the recently published exercise guidelines for adults with SCI (65). Hence, findings from this study can help inform multiple stakeholders about the efficacy of these guidelines on traditional and novel biomarkers of cardiometabolic risk. Finally, the 12-week exercise intervention provided some evidence suggesting that upper-body rowing may positively affect QoL in individuals with SCI. However, studies with larger sample sizes and longer intervention periods are needed to adequately address this question.

5.2. GENERAL DISCUSSION POINTS: UPPER-BODY ROWING

5.2.1. LIMITATIONS TO THE ADAPTIVE ROWING MODALITY

A limitation of the upper-body rowing exercise modality is that individuals with high thoracic and cervical lesions usually have insufficient trunk stability to resist the pull-back force of the ergometer handle required for maintaining the seated position. Even though this challenge was successfully counteracted by equipping the participants with a neoprene belt and/or supportive vest secured to a frame, this set-up requires assistance, and therefore the adaptive rowing modality proposed in this dissertation may preferably be adopted by individuals with a low injury. Alternatively, a more elegant way to counteract this gravity challenge for individuals with a high lesion could be by mounting a chest pad on the ergometer, as done by a Canadian research group who, parallel to the completion of this dissertation, published novel data on the usability (29) and physiological load (63) of adaptive rowing.
Another observation, and potential concern, that warrants attention is the risk of pressure ulcers. It is possible that the pressure ulcer developed in one participant (Study V) may have been related to shear forces applied to the skin from micro

motions at the seat. This concern needs further investigation, even though it should be noted that the seven other participants were able to perform 3x30-min of rowing exercise for 12-weeks without any issues.

5.2.2. EFFECTS ON TRADITIONAL CARDIOMETABLIC RISK FACTORS

Individual studies have demonstrated improvements in some aspects of cardiometabolic risk, such as elevations in HDL-C (125), reductions in LDL-C (126), fasting insulin (24,127), body mass (128), and indices of insulin resistance (24,128) following upper-body exercise in individuals with SCI. Nevertheless, the weight of the evidence does not support beneficial effects of isolated upper-body exercise on traditional cardiometabolic risk factors in individuals with SCI (129). For example, consistent with recent randomized controlled studies (24,131), no changes in lipid profile, glycemic control, resting arterial blood pressure, and body mass were observed following the 12-weeks of upper-body rowing in Study V. The lack of effects appeared even though the exercise prescription complied with the current exercise guidelines for SCI (65), recommending at least 30-min of moderate-to-vigorous intensity aerobic exercise three days/week for improvement in cardiometabolic health. Whilst it should be acknowledged that the weekly volume of exercise in Study V only approached the lower border of these recommendations (averaging 2.8 sessions/week), the observations from Study V still raise the question about the 'appropriate' exercise dose in terms of volume and/or intensity required to reduce the aggregation of risk factors in SCI population. Potential explanations for the absent or modest effects of upper-body exercise on risk factor modification will be discussed in the following section.

Individuals with SCI rely on the upper-body for (voluntary) exercise. Accordingly, it is possible that the absolute energy expenditure during exercise with the smaller muscle mass of the arms is insufficient in creating a substantial negative energy balance to significantly impact risk factors such as body mass (177) and lipid profile (178). In able-bodied, it is well described how the ability to produce very high work rates are limited during exercise with the arms, and therefore $\dot{V}O_{2peak}$ values typically only reaches around 70% of the values obtained during lower-body exercise (91,92). Therefore, at an equivalent relative intensity, whole-body metabolic demand and absolute energy expenditure are lower during upper-body exercise compared with leg exercise.

One way to compensate for the lower energy expenditure at the same relative intensity during upper-body exercise could be by raising the intensity (179), for example through high-intensity interval training (HIIT) that is characterized by brief, intermittent bursts of vigorous intensity activities, interspersed by periods of active or passive recovery (180). In able-bodied, HIIT has been proposed to be an effective and time-efficient strategy to induce central and peripheral adaptions that are associated with cardiometabolic health (180). However, as discussed previously, the smaller muscle groups of the upper-body does not evoke the same disturbances to systemic

homeostasis as exercise performed with the legs (92). Indeed, a recent study employing two weekly sessions of handcycling HIIT in individuals with SCI did not observe any improvements in fitness variables after six weeks of exercise (181). Thus, a higher volume of upper-body HIIT would need to be considered, but whether such a higher volume is feasible, acceptable, and safe for wheelchair users with SCI for whom upper extremity pain and fatigue are highly prevalent (Study I) needs to be determined.

Alternatively, interventions of longer duration (>12-weeks) and/or larger weekly volumes of moderate-to-vigorous intensity exercise than presently recommended (65) are required for providing a sufficient stimulus for meaningful changes in traditional risk factors. Notably, the minimum weekly amount of recommended moderate-to-vigorous intensity exercise per week for adults with SCI is well-below the volume recommended by the World Health Organization for able-bodied adults (≥150-300 min of moderate-intensity aerobic physical activity per week, or ≥75-150 min of vigorous-intensity physical activity) (182). As exercise with the smaller active muscle mass of the upper-body likely impact cardiometabolic risk factors to a lesser degree than lower-body exercise, the rationale for promoting a lower volume of moderate-to-vigorous intensity exercise for upper-body exercise can therefore be questioned. Indeed, this has led some researchers to encourage individuals with SCI to meet able-bodied recommendations (183). However, there are notable differences between able-bodied and SCI populations that can complicate individuals with SCI to achieve exercise recommendations for able-bodied. Some SCI-specific issues include potential exercise-related health risks (184), autonomic disturbances (67), physical deconditioning (10), and impactful psychological and socio-environmental physical activity barriers (19,176), as reported in Study I-II. Such nuances are important to consider when prescribing exercise for individuals with SCI.

The lack of effect from upper-body rowing on traditional risk factors may also relate to the relatively healthy cohort participating in this study. As presented in Chapter 4, only two participants met the criteria for the metabolic syndrome at baseline, thereby limiting the ‘window for improvement’.

Differences in injury characteristics among the participants may also have contributed to why exercise did not elicit changes in resting arterial blood pressure at a group level. For example, in four out of five paraplegics in UBROW, SBP and DBP were numerically lower at 12W compared to baseline (Figure 5). In contrast, the two tetraplegics, with low resting blood pressures, showed higher SBP and DBP at 12W relative to baseline. Whilst the higher resting blood pressure in these two individuals may be random (n = 2), the observations are interesting as exercise training usually is associated with increased parasympathetic activity that tends to lower arterial pressure. From a clinical perspective, higher resting blood pressures in tetraplegics may actually render positive implications, as low resting blood pressure is associated with burdens such as exacerbated dizziness, fatigue, and impaired cognitive function (185). This finding warrants further investigation and future studies are required to

investigate the effects of exercise training on blood pressure regulation in a larger group of individuals with cervical injury.

Despite the relatively clear and consistent pattern of no effects of upper-body rowing exercise on traditional risk factors, few potentially clinically relevant observations appeared. For example, the absolute change (Δ -5.7cm) and large effect size (g -0.86) for WC indicate that upper-body rowing evoked a clinically important reduction in VAT (82). This finding is consistent with the existing literature suggesting that upper-body aerobic exercise elicits reductions in WC (129). Several studies have highlighted the predictive ability of WC in identifying adverse cardiometabolic risk in individuals with SCI (106,186). In a cohort of 257 individuals with traumatic SCI, WC showed the strongest association with 10-year CVD risk (186). Considering the magnitude of change in WC (Study V), despite only a modest reduction in body mass (Δ -1.2 kg, g -0.59), suggests that upper-body rowing may have led to changes in body composition through accretion in fat-free mass. In support, studies have shown that both young and elderly rowers have increased muscle size compared to age-matched controls (53,54). Taken together, it is thus possible that participants in UBROW gained upper-body lean mass over the 12-weeks, concomitant with a reduction in VAT.
Other notable observations from Study V relate to indices of insulin resistance, particularly fasting insulin, and HOMA2-IR. Even though fasting insulin and HOMA2-IR were not significantly lower after the 12-weeks of exercise, the changes in these markers could indicate some benefits of upper-body rowing in terms of improving hepatic insulin sensitivity. For example, the absolute change score (Δ) and standardized effect size (g) for fasting insulin (Δ -16.8 pmol/L, g -0.63) was similar in magnitude to recent results demonstrating a significant reduction in fasting insulin after six weeks of arm-crank exercise (Δ -12.7 pmol/L, d -0.69) (24). Notably, as the study by Nightingale et al. (24) included a larger sample (n = 21), it is possible that Study V lacked the statistical power to detect a significant change.

5.2.3. EFFECTS ON NOVEL RISK FACTORS.

Cardiorespiratory fitness

The increase in aerobic fitness, as reflected by enhanced $\dot{V}O_{2peak}$ and PO_{peak}, in UBROW aligns with the current evidence suggesting that upper-body exercise training improves aerobic fitness level in individuals with SCI (27,130). At 12W, $\dot{V}O_{2peak}$ and PO_{peak} were increased relative to baseline in UBROW by 16-17%. Such improvements in aerobic fitness are larger than reported (~10%) by other studies using a similar duration (12-weeks) and weekly volume (90 min) of moderate-to-vigorous intensity arm-cranking exercise (125,133). Possibly, the involvement of a relatively large muscle mass of the upper-body when rowing (60) may have imposed a cardiovascular challenge that stimulated greater adaptations in cardiorespiratory fitness. That upper-body rowing required a considerable effort was reflected in the

average RPE and $\%HR_{peak}$ across the 12 weeks, equaling 15.8 ± 0.7 and 83 ± 3%, respectively, which confirmed that participants exercised with 'vigorous' intensity according to recently published SCI-specific intensity classifications (163).
As stated by the principle of specific adaptations to imposed demands, implying that training adaptations are specific to the muscles or organ systems exercised (187), the improvement in aerobic fitness in UBROW would likely have been even greater if the GTX had been performed on the rowing ergometer. However, the arm-crank ergometer (unspecific exercise modality) was chosen for the GTX to limit any potential learning' or 'familiarization' effect in favor of UBROW (Study V).
While low cardiorespiratory fitness is not traditionally associated with cardiometabolic risk, exemplified by not being a constituent of the metabolic syndrome (104) or Framingham risk scores (107,108), low $\dot{V}O_{2peak}$ is an independent predictor of all-cause mortality in able-bodied (1,188). In example, an improvement of one metabolic equivalent (MET) (3.5 ml/min/kg) in cardiorespiratory fitness has been associated with a 15% and 19% lower risk of all-cause and CVD mortality, respectively (188). As a result of reductions in fat-free mass below the level of injury, resting energy expenditure is lower in individuals with SCI, compared to able-bodied (79). Thus, when applied to individuals with SCI, a more accurate value for 1 MET has been suggested to equal 2.7 ml/min/kg (80). The fact that the improvement in $\dot{V}O_{2peak}$ (Δ 2.4 ml/kg/min) in UBROW approximated 1 MET, suggests a substantial risk reduction.

The robust improvement in aerobic fitness may provide clinical relevance other than directly affecting morbidity and mortality risk. Greater aerobic capacity is associated with enhanced fatigue resistance (189). This may have important implications as fatigue, or the lack of energy, is amongst the most profound physical activity barriers reported by people with a mobility disability (a finding that was confirmed in Study I). In addition, an individual's power output and cardiorespiratory fitness can positively impact her or his functional independence by improving the ability to perform ADL such as performing transfers or propelling one's wheelchair (189).

Vascular health

The cardiovascular system is highly adaptable to changes in physical demand. In example, the conduit arteries undergo an structural inward remodeling process during deconditioning, as illustrated by reductions in resting femoral artery diameter of 13% and 17% after 25 and 52 days of bed rest, respectively (190) and 25% and 30% three weeks after acquiring a SCI (191) and in chronic SCI (77,192), respectively. In contrast, regularly performed exercise is associated with a localized enlargement of the conduit arteries supplying the active limbs in both able-bodied (193,194) and wheelchair athletes (195–197).
Adaptations in conduit artery function and structure in response to exercise training are largely mediated by exercise-induced increases in antegrade blood flow and shear

stress acting on the endothelial cells lining the conduit vessels (198). Despite an accumulating body of literature on peripheral vascular adaptions in individuals with SCI (84), to the authors knowledge, few experimental studies have investigated the effects of upper-body exercise training on brachial artery function and structure in individuals with SCI. Zepetnek et al. (131) reported that two weekly sessions of 20-min of moderate-to-vigorous intensity upper-body aerobic exercise (complying with the 2011 exercise guidelines) was insufficient for increasing brachial artery endothelium-dependent and independent function, as well as resting brachial artery diameter, in individuals with SCI (131). In contrast, work from this dissertation demonstrated that 12-weeks of upper-body rowing exercise, complying with the current exercise guidelines for SCI (i.e. three weekly sessions of 30-min of moderate-to-vigorous intensity aerobic exercise) (65), increased resting brachial artery diameter (Study V). Taken together, these results suggest a critical role of exercise dose for adaptations in the conduit artery supplying the active upper limbs in wheelchair users with SCI. Although some contribution from alterations in vascular tone (i.e. less vasoconstriction) cannot be excluded (see Study V for details), the increase in resting diameter may be interpreted to reflect structural (outward) remodeling of the artery.

In contrast to the increase in resting diameter at 12W, no changes were found in brachial artery function at either 6W or 12W, neither when expressed as unadjusted FMD or when adjusted for the potentially confounding influence of resting diameter (‘corrected FMD’). This may seem surprising, as exercise improves brachial artery NO mediated endothelial function (199), particularly in those with established CVD related risk factors (200). One possible explanation for this result may be that FMD was assessed in the already trained upper-limbs resulting from years of wheelchair propulsion, suggesting that the function of the artery was already enhanced (201). Another plausible explanation is that early increases in FMD may have occurred, but that such increases in endothelial function had returned towards baseline levels at 6W. As originally proposed by Laughlin (202), initial enhancements in vasodilatory function serve to normalize shear stress during bouts of exercise, whereas continuing exercise will cause a more chronic normalization of shear stress. As a result of structural enlargement, early improvement in vascular function returns towards baseline. In support of this hypothesis, observations in able-bodied have suggested a significant increase and ‘peak’ in brachial artery FMD after only two weeks of exercise training (194). Tinken et al. demonstrated that such rapid increase in FMD returned towards baseline levels already after four weeks, and after six weeks the increase in FMD was no longer significant, when structural adaptations started to occur (194).
Even though the change in FMD in UBROW did not reach statistical significance, it should be noted, however, that a 1% increase in FMD is associated with a 13% reduction in the risk of future cardiovascular events (145). Therefore, the mean increase of >1% point observed in UBROW from baseline to 12W in both unadjusted (3.19% to 4.22%) and diameter adjusted FMD% (3.30% to 4.69%) may have resulted in clinically relevant risk reduction.

In response to changes in blood content or flow, the endothelium responds by varying its release of vasoactive substances that modulate vascular tone. Such regulation of vascular tone is determined by the balance between vasodilator and vasoconstrictor pathways (203). In general, vasodilators, in particularly NO, have received the most attention in explaining the mechanisms of vascular adaptations from exercise or inactivity. In Study V, there were no significant time-by-group interaction or changes over time in NO-mediated vasodilation (FMD). However, interestingly, there was a trend for a time-by-group interaction for the vasoconstrictor ET-1. Closer inspection of the data revealed a tendency for ET-1 to increase throughout the 12-weeks in CON, but not in UBROW. ET-1 is mainly produced in the endothelium, and in addition to being a powerful vasoconstrictor, the ET-1 pathway is upregulated in individuals with elevated CVD risk, including essential hypertension and aging (119), and elevated levels of ET-1 have in turn been implicated in the development of atherosclerosis through stimulation of vascular smooth muscle cell proliferation (204). Notably, exercise training decreases plasma levels of ET-1 in healthy able-bodied individuals (205,206), and opposes the age-related elevation in plasma ET-1 and normalizes plasma levels of ET-1 in individuals with essential hypertension (207).
Taken together, attenuation of ET-1 through exercise training may therefore provide a candidate to explain how exercise exerts its cardioprotective effects beyond modification of traditional risk factors in individuals with SCI.

5.2.4. EFFECTS ON QUALITY OF LIFE

QoL has frequently been reported to be lower in individuals with SCI compared to able-bodied (208,209). Previously, increased cardiorespiratory fitness following exercise training has been associated with improved functional ability to perform ADL, which in turn, positively impact health related QoL (210). It may therefore seem surprising that all QoL indices remained unchanged in UBROW over the 12-weeks (Table 3). When looking at the individual data (Figure 8), however, the lack of improvement at group level was primarily explained by one participant in UBROW who rated QoL-BDS_{total} markedly lower at 12W. This reduction in QoL was, according to the participant, caused by the pressure ulcer on his buttocks that occurred during the last part of the intervention. Pressure ulcers are highly prevalent among individuals with SCI, and the physical, psychological and societal burdens associated with pressure ulcers negatively affects QoL (211). Although the participant had a previous history of pressure ulcers and therefore was aware of the importance of preventive actions, this adverse event reinforces the importance of preventive management strategies (212), and also that this must be emphasized for people participating in an exercise intervention. As appreciated from the individual data on Figure 8, most participants in UBROW did increase QoL-BDS_{total} throughout the intervention. In fact, by omitting the participant with pressure ulcer from the LMM analyses, significant time-by-group interactions for QoL-$BDS_{General}$ and QoL-BDS_{Total} appeared, suggesting that UBROW significantly improved QoL indices for the other seven participants. It cannot, however, be justified to omit this participant from the

analyses, and therefore the main conclusion is that UBROW did not improve indices of QoL. Finally, due to its simplicity, the QoL-BDS (155) does not provide an exhaustive assessment of QoL. Therefore, future research may consider including additional indices of QoL, such as health-related QoL (Short-Form-36) (213) in order to accurately evaluate the effects of upper-body rowing exercise.

5.3. METHODOLOGICAL CONSIDERATIONS

Several methodological considerations from this series of studies deserve attention. In the following, such considerations will be discussed with an emphasis on aspects not already addressed in Study I-II and IV-V.

5.3.1. GENERAL CONSIDERATIONS

If only participants with SCI had been included in Study I-II (63% had a SCI), a stronger link to Study III-V would have been established, as all studies then were performed in the same population. However, including only wheelchair users with SCI in Study I-II would have been at the expense of a smaller sample. Moreover, the inclusion of the collective group of manual wheelchair users was based on the assumption that many physical activity barriers are general for individuals who use a wheelchair (such as transportations issues, lack of exercise equipment, upper-extremity pain), irrespective of the underlying etiology for using a wheelchair.

An overarching idea with proposing upper-body rowing as an exercise modality for wheelchair users was that this modality might mitigate several impactful barriers for engaging in physical activities. Therefore, measuring whether upper-body rowing in fact did reduce barrier perception would have been valuable. This could have been achieved by completing the BPAQ-MI before and after the 12-week exercise intervention (Study V), which also would have strengthened the coherence between the individual studies.

The link from Study II to the subsequent experimental studies would have been strengthened if those subgroups who were found to perceive the strongest barriers (identified in Study II) also where those who were included for participation in the RCT. More stringent inclusion criteria could have ensured a more homogenous group of obese, unemployed, and/or lower educated participants. However, this would have negatively affected recruitment and reduced the sample size, as the recruitment basis (i.e. the number of potential participants) was already limited.

5.3.2. STUDY I-II

Agreement between barrier perception and actual behavior

The degree to which barrier ‘perception’ reflects actual ‘behavior’ deserves consideration. In Study I, participants were asked to self-report physical activity levels (PAL), thereby enabling an investigation of the relationship between barrier

perception (BPAQ-MI) and physical activity behavior. This approach has several limitations. First, self-reported PAL increases the risk of recall bias, typically with overestimation of activity levels (214). Secondly, consistent with previous studies (16,23,176), a simple self-report item (1-10 scale) was used to attain information about levels of physical activity. In contrast to other self-report measures, the 1-10 scale has not been validated for use in the wheelchair user population (or other populations as far as known), and the scale does not capture physical activities performed with different intensities. Alternatively to self-report, objective measures of physical activity levels, such as wrist-worn accelerometers (215) could have been used. However, wearable devices typically underestimate the intensity of activities when wheeling upwards and on uneven surfaces (216), requiring accelerometers to be used with the addition of a heart rate belt, or integrated in a multi sensor device, which requires individual calibration for accurate assessment (217).

Barrier impact score

Calculation of barrier impact score in Study I-II was performed by summation of impact scores (0-5, with 0 = not a barrier, 5 = very big barrier) for each barrier item within each subdomain and domain. Accordingly, barrier impact scores may have been biased towards those domains and subdomains with most items. To correct for the different number of items in each domain (and subdomain), the summed barrier score could have been divided by the number of items, thereby providing a "corrected barrier impact score".

5.3.3. STUDY IV-V

Sample size

The relatively small, heterogenous sample may have increased the risk of type II errors. Even though there were significant changes in $\dot{V}O_{2peak}$, PO_{peak}, and resting brachial artery diameter (Study V), it is possible that the study was underpowered to detect changes in outcomes with smaller magnitude of change. However, only trivial to moderate effect sizes were evident between groups for the majority of cardiometabolic blood biomarkers (Study V), suggesting that the conclusion likely would not be different with inclusion of additional participants. Despite the relatively small sample size, the inclusion of the control group is a considerable strength, as this allowed discriminating a 'true effect' of the intervention from any inherent variability in outcome measures and natural time course changes over 12 weeks in this population. Regarding the latter, this may have been important, as the COVID-19 lockdown may have altered the usual exercise and physical activity habits among the participants due to closing of sport and exercise facilities.
While the lack of homogeneity may impact the generalization of the findings, the SCI population is, by virtue of the many combinations of lesion level and severity, characterized as a heterogeneous population.

Finally, it should be stressed that conducting a 12-week exercise intervention in individuals with SCI is complex. Adding further to this complexity, the current intervention was conducted during the COVID-19 pandemic resulting in several challenges to the completion. In example, opposed to the original plan of having student helpers independently supervising the exercise sessions, RKH had to be physically present during each session, resulting in an extensive number of hours in the lab.

Behavioral compensation

The possibility exists that behavioral compensation (either through reductions in energy expenditure or increases in energy intake) may explain why weight loss was not as large as what could be anticipated based on 12-weeks of exercise training in Study V. It is possible that the increased energy expenditure from the prescribed exercise intervention may simply have replaced energy expenditure from habitual physical activity, thereby leading to a small or negligible energy deficit, a concept referred to as 'substitution' (218). However, such a substitution was not supported by the LTPA data presented in this thesis, as there were no time-by-group interactions or main effects of time for either of the LTPA intensities, nor for total LTPA. There were, however, moderate effect sizes in favor of CON for moderate and heavy LTPA, possibly reflecting the extra time these participants may have had for leisure-time activities, as they did not engage in supervised exercise three times per week. An important consideration in that respect is the extent to which LTPA data obtained from the LTPAQ-SCI reflected actual LTPA behavior. The LTPAQ-SCI has good test-retest reliability, and has shown to correlate significantly with the criterion measure 'Physical Activity Recall Assessment for People with SCI' (PARA-SCI) (157). Recently, the construct validity of the LTPAQ-SCI was supported by a study showing significant correlations between minutes of moderate, heavy and total LTPA, and $\dot{V}O_{2peak}$ (219). Despite these promising properties, the LTPAQ-SCI still relies on participant recall, which particularly for mild-intensity LTPA, may reduce the reliability, as these activities are usually done spontaneously and therefore are difficult to recall (157). As the LTPAQ-SCI assesses LTPA performed over the past seven days, there is also a risk that these seven days are not representative of 'usual' living. For one participant in CON, this was the case for mild-intensity LTPA performed the week prior to baseline assessment.

Evidence indicates a role for dietary compensation in response to exercise training (i.e. an increase in energy intake to balance the increase in energy expenditure) (220). It is therefore possible that the modest weight loss (Δ -1.2 kg) in UBROW is attributed to increased energy intake in response to the increased energy expenditure from the exercise (220). Although participants were asked not to change their current eating habits throughout the study, there was no control of participants' diet. Whilst participants could have been asked to register and self-report their energy intake (as they did for LTPA), this approach is time consuming and individuals tend to underreport their energy intake (221), especially those who are obese (222).

Doppler ultrasound assessment of vascular function

At the time of analyses, the software required for analyzing the flow velocity (red blood cell velocity) signal for the calculation of shear rate was unavailable. The lack of shear rate calculation in Study V presents a limitation, as shear rate (or shear stress) represents the stimulus for post-deflation vasodilation (223). Whilst some studies have suggested normalizing the FMD response to the shear rate stimulus (224), this approach is disputed (225). Indeed, some studies have reported either a week (226) or non-existing (227) relation between the shear rate stimulus and FMD.
A caveat of FMD assessment is that the exact shear stimulus cannot be controlled (228). To minimize the extent that such uncontrolled stimuli could vary between visits, meticulous standardization and between-visit replication of the conditions for FMD assessment were performed, as recommended (147). This included cuff placement and inflation pressure, and duration of ischemia. Although FMD is largely endothelium NO-dependent, especially when the cuff is placed distally to the ultrasound probe (149), the contribution from endothelial-independent vasodilation to the FMD response cannot be delineated from the results. Thus, future studies are needed to examine the role of endothelium-dependent and endothelium-independent vasodilation in response to moderate-to-vigorous intensity upper-body rowing exercise in individuals with SCI.

Fasted vs. postprandial blood samples

In accordance with the current evidence (129), there was no effect of UBROW on lipid profile in Study V. While dyslipidemia, inferred from fasted blood samples, is recognized as an important risk factor for cardiometabolic diseases (104,108), elevated postprandial lipids have also been suggested to be implicated in the progression of atherosclerosis (183). Compared to able-bodied controls, exaggerated postprandial lipids have been reported among paraplegics with normal fasting TG (229). Accordingly, it cannot be excluded that measuring lipids in the postprandial rather than fasted state would have revealed important information about potential improvements in lipid metabolism following 12-weeks of upper-body rowing. The same discussion can be raised for blood glucose assessment, for which fasting glucose and postprandial glucose concentrations may reveal different information about the primary site of insulin sensitivity/resistance, with impaired fasting glucose in isolation typically reflecting hepatic insulin resistance, and impaired glucose tolerance (postprandial assessment) being characterized by muscle insulin resistance (230).

5.4. FUTURE PERSPECTIVES

The adapted rowing modality presented in this dissertation provides some perspectives beyond the laboratory. As the rowing exercise can be performed on a commercially available ergometer (Concept 2), in combination with a single adaptive

unit (Adapt2row), it is possible to implement rowing exercise in community fitness centers, thereby offering an extra exercise option to wheelchair users who currently are extremely limited by the availability of exercise equipment.

A common challenge for exercise studies conducted in individuals with SCI, as well as other populations, is the relatively short intervention period, typically limited to 6-16 weeks. Although this period may be sufficient for demonstrating improvement in outcomes immediately post intervention, the residual/long-term effects are typically unresolved.

Along these lines, to the author's knowledge, very few exercise studies conducted in the SCI population have included a follow-up assessment after a period of free-living. As described in Study III, a follow-up assessment was conducted 6-months after completion of the RCT. Results from this follow-up (data not presented in this dissertation) may provide insight into the residual effects of the exercise intervention, and whether the rate of decay of some outcomes (e.g. lumen diameter) may differ from others (e.g. cardiorespiratory fitness).

Finally, as the data presented in this dissertation suggests beneficial effects of upper-body rowing exercise on the cardiovascular system, the additional cardiovascular-related outcomes (e.g. HRV and orthostatic blood pressure regulation) collected during the experimental work may reveal further insights about the effects of exercise on autonomic cardiovascular regulation in individuals with SCI.

5.5. CONCLUSIONS

Study I identified that manual wheelchair users perceive multiple highly prevalent and severe barriers for engaging in physical activities. Amongst the most pronounced barriers reported were those related to an inaccessible community-built environment, fatigue, pain (particularly in the shoulder region), and a lack of accessible exercise equipment. Study II demonstrated that among wheelchair users, subgroups with BMI $\geq$30 kg/m^2; who did not complete high school; or were unemployed rated physical activity barriers significantly higher than their non-obese, higher educated and employed counterparts. Study III set the scene for the RCT by describing the study protocol for an exercise intervention (upper-body rowing adapted to wheelchair users) designed to mitigate some of the identified barriers from Study I. Study IV demonstrated that the exercise modality proposed in Study III (upper-body rowing exercise) is a feasible and acceptable exercise modality that can evoke moderate-to-vigorous intensity exercise without exacerbating shoulder pain in wheelchair users with SCI. Finally, Study V demonstrated that 12-weeks of upper-body rowing exercise, complying with current exercise guidelines for adults with SCI, elicited adaptations in the cardiovascular system, as indicated by significant increases in $\dot{V}O_{2peak}$ and resting brachial artery lumen diameter. In contrast, no - or only modest effects were found on traditional cardiometabolic risk factors, and the results from this study therefore support accumulating evidence suggesting that exercise exerts some of its cardioprotective effects beyond modification of traditional risk factors. Finally, data presented in this thesis provide some evidence indicating that upper-body

rowing may positively affect QoL in individuals with SCI, however more studies with larger sample sizes and longer intervention periods are needed for adequately addressing this question.

Collectively, the results of this dissertation highlight the need of reducing physical activity barriers among wheelchair users, and/or develop solutions that mitigate the impact of such barriers on physical activity behavior. Work from this dissertation also suggests that ergometer rowing exercise adapted to wheelchair users may provide a useful tool for performing aerobic exercise without exacerbating shoulder pain. Finally, the results indicate that complying with the current exercise guidelines for adults with SCI elicit improvements in cardiorespiratory fitness and structural vascular adaptations.

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APPENDICES

Appendix 1. Study I

Appendix 2. Study II

Appendix 3. Study III

Appendix 4. Study IV

Appendix 5. Study V

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