HIGH-LOAD RESISTANCE TRAINING FOR AT-RISK OLDER ADULTS

HIGH-INTENSITY RESISTANCE TRAINING FOR AT-RISK OLDER ADULTS

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Lay Abstract

As people get older, the amount of muscle they have and their strength start to decrease. When too much strength is lost, individuals can begin to have difficulties completing tasks around their home or can be at risk for developing health issues such as disability and frailty. Strength training has been one way proposed to increase strength and physical function for those at risk for mobility disability and those at risk for frailty (prefrailty). This strength training is often of low intensity despite guidelines advocating for higher-intensity exercise. This thesis evaluates the benefit of strength training, specifically using high-load, for those with mobility disability and the safety and feasibility of high-intensity resistance training for those with prefrailty and those at risk for or with established mobility disability.

Abstract

With our global aging population, low muscular strength and function significantly impact an older adult's capacity to remain independent. Older adults experience gradual declines in physical function and mobility leading to difficulty completing activities of daily living. These difficulties are conceptualized as an expression of mobility disability or through diagnoses of clinical geriatric syndromes such as frailty. Aging physiology in the musculoskeletal system clinically translates into declines in physical function due to losses in muscular strength. Preventative interventions may be appropriate as failing to intervene until critical thresholds are reached will increase healthcare expenditure.

Resistance training is a highly beneficial, cost-effective, conservative strategy for community-dwelling older adults to optimize physical resiliency through increasing muscular strength and function lost due to aging, sedentary behaviour and/or physical inactivity. Resistance training needs to be dosed appropriately for function to improve, but clinicians rarely prescribe high-load resistance training with older adults, especially those at risk for mobility decline and frailty.

The overarching goal of this thesis was to evaluate the role of resistance training in managing mobility disability and prefrailty. This thesis is comprised of three studies to address this goal:

(1) The role of resistance training to improve or prevent mobility disability in community-dwelling older adults: a systematic review and meta-analysis.

(2) The use of High- Intensity Enhanced Resistance Training (HEaRT) to optimize independence and quality of life in older adults with or at-risk of mobility disability: a pilot randomized controlled trial.

(3) An Ounce of Prevention: a substudy of pre-frail older adults from the HEaRT pilot randomized controlled trial

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To my incredible committee members, I thank you. Drs Phillips and Richardson, you both were so understanding of the demands of being a working mom and part-time student while also keeping me accountable to my timelines and, along with Dr. Tang, kept me making progress on my dissertation.

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Finally, I want to thank my parents. When I completed my physiotherapy degree, my dad told me he could see me in research and teaching. He laughs now as he sees me building into

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They say it takes a village and this dissertation is no different. There were so many people that made this degree possible. Thank you

-Christina Prevett

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List of Abbreviations

6MWT	Six-Minute Walk Test
ABC Scale	Activity-specific Balance Confidence Scale
ADL	Activity of Daily Living
BBS	Berg Balance Scale
HEaRT	High-intensity EnhAnced Resistance Training
Mini-BEST	Mini Balance Evaluations Systems Test
MD	mean difference
MOD-RT	Moderate-intensity Resistance Training
PCD	Preclinical Disability
pQCT	Peripheral Quantitative Computed Tomography
RAPA	Rapid Assessment of Physical Activity
RT	Resistance Training
SD	Standard Deviation
SMD	Standardized Mean Difference
SF-36	Short Form 36
TUG	Timed Up and Go

Declaration of Academic Achievements

This is to declare that Christina Prevett was involved in all stages of the research process for each chapter of this thesis.

In Chapter 2, Prevett developed the systematic review protocol, performed the search, and completed title, abstract and full-text screening. She completed the risk of bias assessment. Prevett completed data extraction and synthesis. She was the primary author of the manuscript. Moncion participated in the title, abstract and full-text review, risk of bias assessment, and manuscript review. Phillips and Richardson advised on study conception and development and manuscript review. As senior author, Tang provided oversight for all aspects of the research, including idea generation, analysis, manuscript review, and mentorship to Prevett.

In Chapters 3 and 4, Prevett was involved in protocol creation, training of assessors and exercise professionals, participant recruitment, execution of assessments and study protocols, data analysis and manuscript generation. Phillips and Richardson advised on study conception and development, and manuscript review.

In Chapter 4, Gordon, Adachi, and Feng were contributing investigators to the Ounce of Prevention project and were involved in protocol creation and project direction. Gordon was involved in consulting and training on pQCT data acquisition. Adachi consulted on ways to conceptualize frailty and study design. Feng was also involved in a separate substudy of the project investigating healthcare utilization after a preventative exercise intervention.

CHAPTER 1: Introduction and Literature Review

The Global Aging Population

Our global population is aging, with persons over 65 representing the largest growing cohort across all age demographics.[1] Higher physical function, as marked by independence in daily tasks, enables individuals to live independently and reduce caregiving needs which are increasingly more relevant as individuals age and become at higher risk for loss of independence.[2] The concept of aging in place refers to older adults' capacity to stay in their homes as long as their health allows. [3] A recent national survey of 4,507 adults in Canada (age 18-85) found that 78% wish to age in their current home but only 26% over 65 believed they would be able to do so, with many ending up in institutionalized settings.[4]

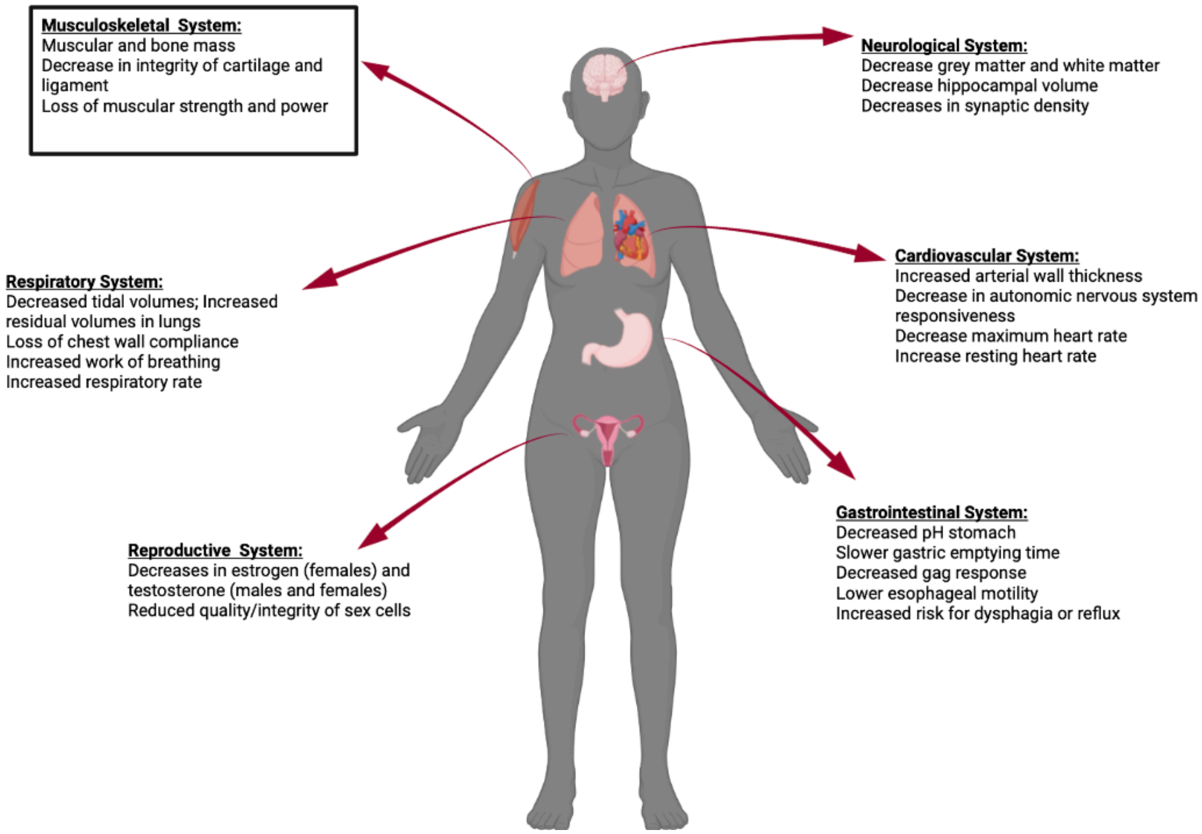
The need for institutionalization occurs due to various risk factors, including loss of physical function, but also advancing age, cognitive decline, multimorbidity, and muscular weakness. [5–7] A person's capacity to complete activities of daily living is associated with their ability to live independently.[6] Activities of daily living refers to basic tasks that individuals participate in daily.[8] Instrumental activities of daily living are tasks involved in day-to-day life that require more complex planning.[8] Preserving physical function enables individuals to withstand external stress, such as acute illness or injury and pertains to the ability to return to an individual's previous level of function following an adverse health event while maintaining or returning to independence. This is a construct known as ***physical resiliency***. [9,10] The time required to return to baseline characterizes physical resiliency along a spectrum from high to low resiliency.[9] The capability to respond to stressors and thus the characterization of physical resiliency is conceptualized through defining the health of the person (system), the physical function (state) and the magnitude and context of the stressor applied.[11] Individuals with low physical resiliency are thus more likely to require institutionalized care or have prolonged recovery times.[12]

Fortunately, many risk factors relating to low physical resiliency, such as muscular weakness and impairments in functional mobility, that are modifiable through physical activity.[13–15] Of concern, however, is that older adults are the most physically inactive and sedentary age cohort.[16] Physiological systems have some embedded reserve as a "safety net" from stress and to prevent breakdowns in function.[17] While the safety net also reduces with age, the degree to which it does is highly variable and is influenced by physical inactivity, sedentary behavior[18] and the accumulation of physiological changes.[19] Thus, there is a need for interventions focusing on increasing physical activity to optimize physical resiliency and improve physical function.

1.2 An Overview of Aging Musculoskeletal Physiology

To establish interventions to optimize a person's physical resiliency to illness, it is important to first recognize which physiological attributes are amenable to change and to differentiate these from fixed attributes that occur in the natural history of aging.
Physical inactivity and sedentary behaviour both accelerate losses in muscular strength, power and joint range of motion seen with musculoskeletal aging.[20,21] However, age-related changes occur across all body systems independent of physical inactivity but at a slower rate.[9,22–24] Therefore, age-related physiological changes can be complicated to distinguish from accumulating chronic diseases (i.e. multimorbidity) and physical inactivity.[25,26] Figure 1.1 briefly outlines some of the physiological changes in other systems due to advancing age. This thesis will focus on age-related changes and clinical expressions in the musculoskeletal system to explore novel interventions to mitigate the rate of these changes.

FIGURE 1.1. Summary of physiological changes that occur with age. A box is placed around the musculoskeletal system, as this is the focus of this thesis.



Aging and the Musculoskeletal System

The musculoskeletal system is comprised of the muscles, tendons, connective tissue, cartilage, ligaments and bones that provide structure and allow us to move and explore our environment.[27]

Older adults also lose muscular mass at a rate of 1-2%/year starting at age 50, [28] which can reduce muscular performance and thus create difficulties completing day-to-day tasks. [27,29] There is a loss of the absolute number of muscle cells due to muscle cell apoptosis and reduced muscular cell repair, translating into a loss of muscular reserve.[27] Of the two main types of myofibers that make up skeletal muscle, there is a preferential loss of type II (fast twitch) fibres with advancing age.[30] Activation of type II muscular fibres is required at higher external loads or when activities are performed at higher speeds relating to rates of force development.[30] Rate of force development slows with advancing age due to reductions in the excitatory drive to spinal motor neurons and reductions in motor neuron discharge rates.[28] These changes can be blunted but not completely mitigated with preventative interventions.[31]

As individuals age, there is a net loss of bone, as bone cell breakdown exceeds regeneration leading to a microarchitecture of porous bone,[32] decreased tensile strength,[33] and increased risk for fracture.[27] In females, estrogen deficiency during the menopausal transition accelerates these changes leading to a heightened risk for low bone mineral density [34] that can lead to a subsequent diagnosis of osteopenia or osteoporosis.[33]

There appears to be a bidirectional relationship between impairment in bone formation and impairments in muscular function.[35] Individuals with clinically relevant amounts of muscular weakness are diagnosed with sarcopenia.[29] Sarcopenia describes a clinical geriatric syndrome where muscular weakness threatens independence with activities of daily living.[29] Much overlap exists between osteoporosis and sarcopenia and indeed can co-exist as osteosarcopenia.[35]

Sex-related differences exist in the aging musculoskeletal system. Estrogen has a protective effect on the muscles and bones. The reduction in estrogen levels during the menopause transition is associated with higher rates of osteoporosis.[36] Estrogen deficiency increases reactive oxygen species and increases rates of bone resorption contributing to higher rates of porous bone.[37] Lower estrogen also causes a satellite cell proliferation leading to the decrease in muscular mass and strength seen in postmenopausal females, and an increase in visceral adiposity.[38]

Age-related changes within the musculoskeletal system, and the rate at which they progress, can be slowed through appropriately-dosed physical activity, particularly resistance training.[39] This slower decline of musculoskeletal strength provides greater reserve in the muscular system for longer to preserve independence with activities of daily living.[39,40]

1.3 Mobility Disability, Frailty, Sarcopenia and Multimorbidity as Constructs Related to Physical Function

To improve aspects of physical function for those with a low physical resiliency state, research must first identify constructs that appropriately describe these states for older adults. In doing so, optimal strategies based on individuals' current levels of mobility can be investigated.

Critically, there may be an opportune time window for intervention to promote physical function and thus increase physical resiliency. We propose that identifying those with clinically relevant changes in physical function such as *mobility disability*, *frailty*, *sarcopenia* and disease burden from *multimorbidity* [18] is an important first step towards creating an effective care pathway. These constructs are described and operationally defined herein for this thesis:

Mobility disability describes a state in which persons experience difficulty completing activities of daily living such as transfers and toileting.[41,42] While mobility disability is often conceptualized and measured in the physical domain, it is important to recognize that there are several interacting dimensions that can contribute to its presentation.[43,44] Mobility disability pertains specifically to tasks that individuals experience difficulty in performing and can be the result of a functional impairment at the level of body structure or organ system.[45] Mobility disability is a product of decreased strength and endurance that contribute to struggles in meeting the demands of daily tasks.[46,47] Mobility disability is defined either by self-reported difficulty completing tasks such as climbing stairs or walking a city block,[48] or using established thresholds in objective outcome measures, such as the Short Physical Performance Battery.[49] a 2020 report from the Annual Disability Statistics Compendium, 31% of community-dwelling older adults reported mobility disabilities related to self-care from census data.[50] Mobility disability has been correlated to decreased quality of life, greater risk of falls, and transitions to institutionalized care.[46,51,52] It is important to acknowledge however that the intersection of physical and social environments is also relevant as it interacts with a person's physical capacity and mobility ability. [43,44] While constructs such as life-space mobility[53] refs are proposed to bridge these constructs and encourage a multi-dimensional approach to mobility, this thesis focuses on the physical function dimension of mobility disability.

Frailty is described as a decrease in a person's physical reserve and resistance to stressors.[17] Frailty is associated with physical resiliency[9,11] but can be differentiated as it is more commonly referred to as a general state of being and exists along a spectrum from robust, to a subclinical state of prefrailty, to frailty.[17,54] Physical resiliency is often conceptualized after an acute insult, such as the amount of time it takes to return to baseline when discharged from hospital.[9] Frailty Classification of individuals along the frailty spectrum is most commonly completed using the Physical Phenotype of Frailty, which describes frailty in five domains: physical inactivity, muscular weakness, slow gait speed, fatigue or lethargy, and unexplained weight loss.[17] These domains of frailty describe the functional changes in those with low physical resiliency, and both low physical resiliency and frailty demonstrate blunted recovery from illness, injury or disease exacerbation. [55,56] Frailty has been linked to a wide range of adverse health outcomes, including increased risk of all-cause mortality, institutionalization, increased length of hospital stay, and falls.[57–61]

Sarcopenia, as mentioned above, is a clinical geriatric syndrome[62] whose definition requires two criteria: loss of muscular size and a loss of muscular performance.[29,62] Sarcopenia is intrinsic to the definition of frailty,[63] as muscular weakness is a component of the frailty definition, and therefore those with sarcopenia are either pre-frail or frail.[63] While sarcopenia and frailty are correlated, they have been independently studied and have unique properties.[63] Sarcopenia has been linked to falls, fractures, increased healthcare utilization, and the development of chronic diseases such as cardiovascular disease.[62]

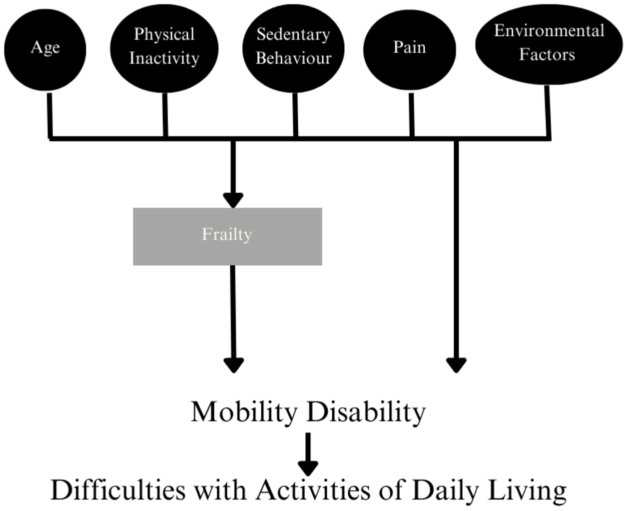
Multimorbidity refers to the accumulation of chronic disease that more commonly occurs in older age, and is defined when a person has been diagnosed with two or more chronic conditions.[26] It is estimated that 90% of persons over the age of 75 have at least one chronic disease.[26] As the burden of chronic disease increases, subsequent challenges in physical mobility occur[5] whereby individuals with multimorbidity are almost twice as likely to report limitations in physical function.[64]

The constructs of mobility disability, frailty, sarcopenia, and multi-morbidity are independently associated with physical function, but research has also demonstrated overlap between constructs.[25,65,66] Baseline frailty status appears predictive of the development of future mobility disability and difficulties with activities of daily living.[67] Impairments in physical function are integral to the definitions of both frailty and mobility disability.[17,29,57] While there are established criteria to define the presence or absence of these conditions, it is important to acknowledge that frailty and mobility disability are not binary concepts but rather exist along a spectrum. Individuals also more commonly progress along the continua towards states of worsened function rather than being able to reverse course to revert towards robust independent function.[4,30,33,51]

Moreover, frailty and mobility disability often co-exist.[25] Individuals presenting with physical attributes of frailty may also demonstrate mobility disability through functional impairment.[57] In a cohort of almost 4000 older adults, 16% demonstrated mobility disability and multi-morbidity, and almost 40% reported both multi-morbidity and frailty.[25] These findings underscore the need to target mobility disability and frailty to optimize physical function and resiliency in older adults.

The constructs of ***mobility disability*** and ***frailty*** will be explored in greater detail in the following sections. Figure 1.2 outlines interactions between mobility disability, frailty and its associated risk factors.

FIGURE 1.2. Contributing factors and conceptualization of mobility disability in relation to frailty.



1.4 Mobility Disability

1.4.1 The Spectrum of Mobility Disability & Risk of Adverse Health Outcomes

Although mobility disability can happen suddenly (injurious or catastrophic disability), it is more common that mobility gradually worsens over time (progressive) before an eventual diagnosis of mobility disability is made.[68–70] Those with overt difficulty completing tasks or those unable to complete household tasks around the home are described as having *mobility disability*.[68,71] Individuals with no issues with activities of daily living or community ambulation are considered *robust*.[42] An intermediary, preclinical state of mobility, or *preclinical disability*, exists where persons would describe themselves as independent but have begun modifying the frequency (how often) or method of task completion (e.g. how often, how quickly) or use of a compensatory aid (e.g. handrails or mobility devices). [52,72]

Preclinical disability is predictive of worsening mobility status as well as predicting incident mobility disability following an acute health event in prospective studies.[51,73] Preclinical disability is also a risk factor for falls,[52] which is highly relevant, as falls and fall-related injuries are a significant burden to our healthcare system,[74] often results in hospitalization and further declines in mobility status.[52]

Mobility status is dynamic in nature. One can experience transitions in mobility status in either direction based on injury onset and recovery, environment, age, or the natural history and management of chronic disease.[46] Transitions to worsening states are much more common.[42] A 5-year prospective cohort of individuals over the age of 80 years old demonstrated that transitions from no disability to intermittent (impairment lasting 0-6 months) or disability lasting greater than 6 months were common (17-34%), but transitions from intermittent or continuous disability to no disability were rare (1.3-1.6%).[42] Worsening mobility disability is a risk factor for transition into long-term care,[7,75] with those reporting difficulties completing activities of daily being twice as likely to transition to institutionalized care compared to those with no difficulty.[75]

As preclinical disability is the intermediary state preceding overt mobility disability, it may be an ideal time to intervene to improve physical function.[73] Indeed, the LIFE-P study of over 1600 participants with preclinical disability demonstrated that with an intervention consisting of low-intensity physical activity, transitions to mobility disability could be slowed.[76]

To date, no intervention studies have been conducted in those with preclinical disability using a high-intensity physical activity program.

1.4.2 Conceptualizing Mobility Disability through Outcome Measures

Mobility disability is identified through physical outcome measures or self-reported mobility status,[41,52,77,78] such as the Preclinical Disability and Mobility Scale developed by Manty et al.,[48] and the Mobility Assessment Tool-short form.[79]

Performance-based measures used to characterize mobility disability include the Short Physical Performance Battery (SPPB),[49] 5-times Sit to Stand,[80] usual gait speed,[80] and aerobic capacity.[47,78] A recent systematic review identified several cut-off scores for preclinical disability utilizing outcome measures, including usual gait speed and 5-times Sit to Stand.[72] There remain discrepancies between studies in these cut-off scores, with some values for mobility disability identical to or even higher than those for preclinical disability. For example, an SPPB score <10 has been identified as a marker of preclinical disability[72] and mobility disability.[49]

For this thesis, we selected the Manty Preclinical Disability and Mobility Scale as it was developed specifically to differentiate between preclinical disability and mobility disability.[48]

1.5 Frailty

1.5.1 The Spectrum of Frailty & Risk of Adverse Health Outcomes

Similar to mobility disability, frailty is also a dynamic state where individuals can move towards or away from progressive levels of frailty,[81] and similar to mobility disability, transitions to worse states are more common than reversing towards more robust states. To date, multiple systematic reviews and meta-analyses have evaluated transitions in frailty status.[81,82] A meta-analysis that included 42,775 community-dwelling older adults followed for an average of 3.9 years found that only 14% of older adults improved their frailty status while 29% worsened the degree of frailty and 56% maintained their current frailty level.[81] Persons are also more likely to transition from a state of robustness to pre-frailty than they are to transition to full frailty.[82] Although the incidence of worsening frailty is more frequently reported, it is important to note that older persons can show improvements in frailty status.[83] Another meta-analysis of 23,869 older adults with prefrailty found that 23% transitioned to robust over three years without intervention, and of 4,180 frail individuals, 35% transitioned to pre-frail.[84]

Also similar to mobility disability, where there is an intermediary state of preclinical disability, *prefrailty* is an intermediary state preceding frailty that has also been associated with increased risk for negative adverse outcomes,[85–87] [88] including higher risk of falls and functional decline in activities of daily living,[61] all-cause mortality, transitions to institutionalized care and hospitalizations.[87]

Healthcare utilization and accrued healthcare costs are higher in those with prefrailty compared to robust, though less than those who are frail.[59] Individuals with frailty admitted to hospital are more likely to pass away, have a longer stay, stay longer than 28 days, and develop pressure ulcers, delirium or accelerated functional decline during their stay.[60] For those living in the community, frailty has been linked to increased falls and falls-related injuries, transition to institutionalized care and all-cause mortality.[56,58] This leads to increased healthcare utilization due to increased demands on the healthcare system, including higher rates of hospital readmission (OR 1.41 [95% CI 0.97-2.06] among frail vs. robust women) and higher odds for temporary or permanent need for placement in a skilled nursing facility (OR 2.24 [95% CI 1.16-4.34] among those who are prefrail vs. robust women.[59,88]

1.5.2 Conceptualizing Frailty through Outcome Measures

While frailty status is a robust metric for stratifying risk for adverse health events and prognosis, much variability exists in the literature in how frailty is conceptualized.[89] Several scales and classification systems have been developed to characterize frailty status in older adults, including the Physical Phenotype of Frailty,[17] the Frailty Index,[19] the Study of Osteoporotic Fracture,[90] the Clinical Frailty Scale,[91] the Edmonton Frail Scale,[92] and the FRAIL scale.[93] Each of these outcome measures is valid and reliable for predicting frailty status in older adults across various settings.[94,95] There is currently no gold standard criterion for the classification of frailty status.[94,95] Outcome measures with an established cut-off score for pre-frailty are highlighted in Table 1.1 and described briefly below.

TABLE 1.1. Outcome measures for the classification of frailty status in older adults with established cut-off scores for prefrailty

Outcome Measure	**Criteria**	**Cut-Off Score for Prefrailty**
Physical Phenotype of Frailty[17]	5 Physical attributes: slow gait speed, physical inactivity, muscular weakness, fatigue/lethargy, unexplained weight loss	1-2/5 physical attributes
Frailty Index[19,96]	Composite index of roughly 40 independent items ranging from issues with activities of daily living to diagnosis of chronic health conditions	0.13-0.25
Study of Osteoporotic Fracture	3 Attributes: weight loss>5% in last 2-3 years, inability to complete 5 chair stands without use of hands, reduced energy level	1/3 attributes
Clinical Frailty Scale[91]	Subjective clinician reporting tool ranging from 1 (very fit) to 9 (terminally ill)	4-5/ 9 on scale
Edmonton Frail Scale[92]	2 performance measures (Clock Drawing Test and Timed Up and Go); 8 self-report measures (general health status [/4], functional independence [/2], social support [/2], medications [/2], fatigue/lethargy [/1], incontinence [/1], nutrition [/1]).	6-11/17 score
FRAIL Scale	5 self-report questions pertaining to fatigue, difficulty walking stairs, walking a couple blocks with no aid, loss of weight in last 12 months, number of chronic conditions >5	1-2/5 questions

Part of the variability in the characterization of frailty stems from advancements in our understanding of the multiple domains of frailty. Historically, frailty has largely been contextualized in the physical domain, characterized by lower capacity in mobility and muscular weakness.[17] However, it is being recognized that vulnerability may exist outside the physical domain with a growing body of literature supporting a broader spectrum of frailty, including cognitive frailty [97] and social frailty.[98] The resultant challenge is identifying frail among the myriad of outcome measures that encapsulate these different domains. Nonetheless, the physical constructs of frailty have shown to be correlated with metrics of cognitive and social frailty[99] and remain the most commonly referenced in the literature.

The Physical Phenotype of Frailty postulates that frailty manifests in five physical attributes: physical inactivity, muscular weakness, fatigue or lethargy, unexplained weight loss and slow gait speed.[17] Persons with none of these five attributes are considered robust, those with one to two attributes are considered pre-frail, and those with three or more are deemed frail.[17] Each attribute has defined thresholds that are used to evaluate frailty status, although there is a high degree of heterogeneity in thresholds used in research. The criteria outlined in the original study of the criteria outlined in the original Physical Phenotype of Frailty are outlined in Table 1.2.[17] However, a systematic review of 264 studies reported that there have since been 262 different permutations of the same five criteria reported in the literature.[89]

TABLE 1.2. Description of the five physical phenotypes of frailty as originally described by Fried.[17]

Phenotype	**Criterion (Cardiovascular Health Study)** [17]
Physical Inactivity	Minnesota Leisure Time Activity Questionnaire kcals/week: males <383 kcals/week females: <270 kcals/week
Muscular Weakness	Grip Strength in Dominant Hand (3 trials) using a JAMAR hand-held dynamometer. Male: <24-29 kg depending on BMI Female: <17-21 kg depending on BMI
Slow Gait Speed	Usual pace walking time/15 feet: Male: >0.76 m/s if >173 cm in height Women: >0.76 m/s if >159 cm in height
Fatigue or Lethargy	"Exhaustion" via self-report using the Centres for Epidemiological Studies Depression Scale
Unexplained Weight Loss	>10 lbs lost unintentionally in the past year

The Frailty Index is a composite index developed by Rockwood and Mitnitski founded on the hypothesis that frailty exists across a spectrum and is worsened by an accumulation of deficits over several domains.[19,96] The index was created to be used easily with electronic medical records and in longitudinal data sets where individual health histories are collected.[96] There are no pre-established questions; instead, items used to produce the composite score must include elements from various domains such as mobility, chronic disease, continence and cognition.[96] Questions are then transformed into binary (yes=1, no=0) or ternary (always=1, sometimes=0.5, never=0) variables and the total number of positive attributes is divided over a total number of items to generate a composite index.[96] A score >0.25 is indicative of frailty, although prefrailty cut-off scores are variable with lower anchors ranging from 0.13 to 0.20 and upper limits more consistently designated as 0.249.[96]

The Clinical Frailty Scale is a subjective, clinician judgment-based tool that assesses frailty based on clinician-patient interaction (most commonly by a physician).[100] It was originally designed as a 7-point scale but updated to a 9-point measure.[91] From 1 (very fit) to 9 (terminally ill), where scores >5 are considered frail, and 4 (very mild frailty) or 5 (mild frailty) are considered prefrail.[91,95,101]

The Study of Osteoporotic Fracture assessment was created in response to the need to reduce the time needed to complete frailty evaluation. It consists of three components: weight loss >5% body weight in the last 2-3 years, inability to rise from a chair five times without the use of their hands, and "no" response to the question "Do you feel full of energy?".[102] Individuals meeting two or7 three criteria are considered frail, meeting one criterion prefrail, and exhibiting none of the criteria are robust or non-frail.

The Edmonton Frail Scale targets multiple dimensions of frailty including physical, cognitive and social domains.[103] The Edmonton Frail Scale is a 10-item scale. It consists of two performance measures (Clock Drawing, Timed Up and Go) and eight self-reported domains (general health status (two questions), functional independence (one question), need for social support (one question), medication usage and management (two questions), mood (one question), and issues with incontinence (one question)).[103] Higher scores infer higher degrees of frailty (non-frailty ≤5, vulnerable or prefrail 6-11, frail ≥12).[95,103] The maximum score is 17. This scale has moderate predictive validity for 2-year mortality risk (AUC = 0.70 (95% CI 0.67-0.72)).[104,105]

The FRAIL (Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight) Scale is a self-report measure based on five questions: fatigue in the past four weeks, ability to walk up 10 steps, ability to walk a couple of blocks, number of diagnosed illnesses, and weight loss experienced in the last year.[106] Individuals are considered robust if no concerns are reported, prefrail if 1-2 concerns are reported, and frail when 3 or more are present.[95,106]

As these outcome measures all have cut-off scores for frailty and prefrailty, all can be utilized to screen individuals for eligibility into preventative exercise programs or programs of care aimed at improving frailty levels in community-dwelling older adults. For this dissertation, I will be focusing on the Physical Phenotype of Frailty as it is the most utilized in the literature space and uses common outcome measures in the field of rehabilitation. The Physical Phenotype of Frailty has been shown to have strong predictive validity for all-cause mortality (hazard ratio 2.24 at 3 years [confidence interval 1.51-3.33, $p<0.001$]), hospitalization (hazard ratio 1.29 at 3 years [confidence interval 1.09-1.54]), and worsening mobility status (hazard ratio 2.68 at 3 years [confidence interval 2.26-3.18]).[17] It has shown strong construct validity (kappa 0.84) with clinician evaluation.[107]

1.6 The need for programs to prevent transitions in frailty and mobility disability

Given the higher likelihood of transitioning towards worse states of frailty and mobility disability, it is important to establish strategies to help prevent these transitions to maintain or improve physical function in our community-dwelling older adults. Interventions that aim to prevent, improve or reverse frailty and mobility disability have shown some success in changing functional status and improving physical function.[76,108,109] Preventative studies have focused on modifiable risk factors such as movement-focused interventions (exergaming,[110,111] resistance training, multi-component programs (different exercise types or exercise + supplementation[112–114]) and nutritional interventions (protein and/or vitamin supplementation[115,116]). Exercise-based interventions appear to be superior for improving or reversing frailty status, mobility status, and physical function and preventing transitions to worsening frailty and disability.[14,109,117,118] Of the different types of exercise, resistance training (RT) has been highlighted as an effective modality to increase muscular strength needed for activities of daily living,[109,112,119,120] but the optimal dosage of RT has yet to be established, and high-load RT schemas have not been previously investigated.

1.7 Resistance Training for the Community-Dwelling Older Adult

A strong body of evidence has established the efficacy of RT in the general population of community-dwelling individuals. Among older adults, RT has been shown to be safe and effective at optimizing physical function and reducing musculoskeletal deterioration that results from advancing age when an appropriately progressed and dosed exercise program is applied.[121] RT has consistently shown benefits to health-related quality of life.[121] Improvement in muscular strength and decreasing risk of musculoskeletal pain associated with RT has important implications for maintaining independence, falls recovery/getting up from a fall and mobility, reducing healthcare expenditures and optimizing physical resilience in older adults.[39,121,122]

Given the benefits of RT among older adults, the Canadian 24-hour Movement Guidelines for Adults 65 Years and Older recommends RT of major muscle groups two times per week, although specific recommendations for dosage and repetition schemas are not provided.[123] The National Strength and Conditioning Association position statement on RT for older adults provided dosage recommendations of 2-3 sets of 1-2 multi-joint exercises per major muscle group at the intensity of 70-85% of one repetition maximum (1RM, the maximum load a person can lift for one repetition for a specific exercise).[124] The statement also emphasized the importance of taking a progressive approach to RT through linear progression or similar loading schemas, monitoring rate of perceived exertion to ensure appropriate intensities are maintained and periodic re-testing of 1RM.[121]

Exercise guidelines from the International Conference for Frailty & Sarcopenia Research have also been released for older adults in general[124] and specifically for those with frailty which align with the recommendations from the National Strength and Conditioning Association[124] in highlighting RT as a core component of exercise.[125] For the general population of older adults, International Conference for Frailty & Sarcopenia Research recommended RT at 2-3 sets of 8-10 repetitions, progressing up to 70-80% 1RM[121] and prioritizing multi-joint exercises and those that mimic and support the clients' personal goals (for example, if they report difficulty standing up from a chair without using their hands, the program may prioritize squats).[124] For individuals with frailty, progressive overload in RT interventions was recommended, although specific dosage was not discussed.[125]

1.8 Resistance Training for Optimizing Function for Community-Dwelling Older Adults with Mobility Disability and Pre-Frailty

By first identifying those with subclinical to clinical amounts of mobility impairment such as those with preclinical disability or prefrailty, preventative interventions can be then pursued. Interventions such as RT may be well-suited to build muscular strength, optimize muscular reserve and thus preserve physical resiliency and independence with activities of daily living.[39]

1.8.1 RT in Mobility Disability

RT has been highlighted as a potential intervention for individuals with mobility disability and studies have examined various methods including low to moderate intensity strength training, power-based training,[126] and low-intensity training with resistance bands.[127,128] Currently, only one systematic review has focused on the effects of RT in older adults with mobility disability and found notable improvements in Timed up and Go, functional reach and static balance.[120] To date, no studies have evaluated higher-intensity RT using a high-load training schema in individuals with preclinical disability or mobility disability.

1.8.2 RT in Pre-frailty

Muscular weakness is the most common criterion of frailty and prefrailty seen in older adults[129] and RT interventions across a range of intensities are safe and effective for those with frailty. RT programs at low intensity included chair-based programs with institutionalized prefrail older adults[130] or elastic band exercise programs,[131] or weights at 30-59% 1RM and rate of perceived exertion <5/10. Low-intensity programs were completed 3x/week, utilizing 2-3 sets of 6-15 repetitions for all exercises, with programs lasting 8[131]-14[130] weeks. Low-intensity programs may offer the minimally effective dose to drive positive adaptations in musculoskeletal health and capacity in prefrail older adults as long as progressive overload is maintained.[124] Low-intensity RT studies have demonstrated improvements in gait speed[131] and frailty status,[130] although data on grip strength is inconsistent.[124,131] Any RT exercise may provide a stimulus sufficient to drive adaptation in muscular function in those with greater deconditioning.[13,30,132]

While there are benefits to low-intensity training, introducing higher intensities to promote progressive overload may be possible and arguably more beneficial for prefrail older adults. Moderate intensity is characterized as utilizing a rate of perceived exertion between 5-6/10 or 60-74% 1RM, and high-intensity resistance at >75% 1RM.[121,125] Systematic reviews differ regarding their recommendations for optimal dosing and prescription for prefrailty. Low- and moderate-intensity exercise at 1-3 sets of 6-15 repetitions at 30-70% 1RM per session have shown to be beneficial in those with prefrailty.[133] There is a noted gap, however, in feasibility and effectiveness data for RT parameters exploring high-load dosage schemas.

To date, only one small quasi-experimental pilot study (n=16) found that a high-intensity RT intervention using complex movements and progressive overload was safe and feasible and more effective in improving frailty status, knee extensor strength, and grip strength than a no-intervention control.[112] However, this study, while higher in intensity based on rate of the perceived exertion and being able to hit the upper limit of the prescribed repetition range , utilized a 6-12 repetition schema.[112] No studies have utilized repetition schemas less than 6, which appears to lend itself to the highest recruitment of muscular fibres (particularly Type II fast twitch) and may therefore optimize strength acquisition for older adults.[30,134]

1.9 A Novel Paradigm in Older Adults: High-Load, Low-Volume Resistance Training

1.9.1 Justification

Physical therapists implementing exercise interventions with at-risk older adults can be worried or unsure about introducing high-load RT interventions in older adults [135] and are at risk of underdosing.[136] Underdosing is the utilization of suboptimal loads during RT that do not reach a threshold to drive neuromuscular adaptation, which can limit the ability to achieve meaningful changes in physical function.[137] Older adults living in the community are known to be working at high percentages of their estimated 1RM to perform activities of daily living: 88% 1RM lower extremity strength to descend stairs, 78% 1RM to ascend stairs and 80% 1RM to stand up from a chair.[138] It is thus necessary for RT to be prescribed at loads that exceed the demands of daily living activities. For physical therapists to feel empowered and justified to move towards heavier loading for older adults with frailty and mobility disability, research must demonstrate that persons with declining physical function can safely participate in high-load exercise program. Justification for evaluating high-load repetition schemas requires knowledge of the mechanisms driving strength adaptations in older adults.

1.9.2 Theoretical Hypotheses on the Effectiveness of High-Load, Low-Volume Resistance Training

RT principles of *specificity*, *progressive overload*, *repetitions*, *load*, and *intensity* drive neuromuscular adaptations and strength development.[121]

Specificity is the principle where exercise selection mimics activities individuals aim to strengthen or, in the context of physical function loss, activities in which persons are experiencing difficulties.[121] For example, people may select a deadlift or hip hinge motion if individuals express challenges picking objects up off the floor. Reinforcing and strengthening movement patterns where individuals have difficulty aims to build self-efficacy and confidence in completing these activities of daily living.[139]

Progressive overload is then needed to continue challenging the musculoskeletal system, which is achieved through an increase or change in the difficulty of an exercise to continue applying a progressive stimulus and prevent adaptation that may stall strength gain. Progressive overload thresholds are determined in clinical trials and exercise programs through periodic testing of 1RM or increasing repetitions or load when intensity is less than the intended threshold.[121,140,141] This is important irrespective of the prescribed load or repetition schema utilized.

Repetition and *load* are inversely related and together dictate the *intensity* of RT intervention. As load increases, the number of repetitions that can be successfully performed will decrease, but a higher number of muscular fibres and motor units are recruited,[30] in particular, an increased activation of Type II fibres.[30] Greater activation of Type II muscle fibres is particularly important given their role in force development but is preferentially lost with advancing age.[142] Most programs for older adults use a repetition range schema between 8-15 repetitions, and therefore load is lower, and activation of Type II fibres is decreased.[30,134,143]

To date, few studies have evaluated high-load RT programs among older adults, and none have utilized lower repetitions schemas <6 repetitions in those with prefrailty or mobility disability. This may be due to apprehension from rehabilitation and exercise providers and the bias towards prescribing lower intensity "senior friendly" exercises for older adults.[144] It is important to examine the safety and feasibility of high-load, low repetition paradigms for older adults, particularly those at greater risk for falls, injuries, and declines in functional status, to determine effectiveness on health and functional outcomes. The first large-scale randomized controlled trials to evaluate the use of high-intensity RT in older adults were the LIFTMOR trials. These studies implemented 5 sets of 5 repetitions schema at >85% of 1RM with 49 older females[145] and 34 older males[146] with moderate to severe osteoporosis. These trials were the first to demonstrate that high-load, low-volume RT was safe feasible, and effective in improving strength, function, and bone mineral density in individuals at risk for bone fracture and generally advised to avoid forward flexion and heavy lifting tasks.[145,146] Another quasi-experimental study implemented moderate-to-high intensity, high-volume training as part of a multi-component program with 20 older adults with pre-frailty and also reported no adverse events related to RT.[112]

To date, no studies have been conducted using high-load, low-volume RT in mobility disability or those with prefrailty.

1.10 Overall Thesis Aims and Study Objectives

The overarching aim of this thesis was to investigate the utility of RT training programs in older adults with preclinical disability, mobility disability and prefrailty. This thesis is comprised of three studies.

Study 1: The role of resistance training in mitigating risk for mobility disability in community-dwelling older adults: a systematic review and meta-analysis.

The primary objective of this systematic review was to synthesize the evidence related to the effectiveness of RT interventions on outcomes of physical function (gait speed, walking endurance, muscle strength, muscle power) among adults >60 years of age with or at risk for mobility disability. Secondary objectives were to examine the effects of RT on transitions in mobility status and investigate possible adverse events related to RT for those with or at risk for mobility disability.

Study 2: High- Intensity Enhanced Resistance Training (HEaRT) to optimize independence and quality of life in older adults with or at-risk of mobility disability: a pilot randomized controlled trial.

The objectives of this pilot randomized controlled trial were 1) to evaluate the safety (occurrence of intervention-related serious adverse events) and feasibility (attendance, attrition) of a high-intensity RT program in community-dwelling older adults with PCD or mobility disability utilizing high-load and low-volume, and 2) to estimate the effects of high-intensity RT relative to moderate-intensity RT on mobility status, walking endurance, strength, physical function, and balance. We hypothesized that: 1) there would be no adverse events among participants with PCD or mobility disability related to a High-intensity EnhAnced Resistance Training (HEaRT) intervention and that participants will attend at least 80% of sessions and attrition will be <20%; and 2) that high-intensity RT would yield greater improvements in mobility status, walking endurance, strength, physical function, and balance compared to moderate-intensity.

Study 3: An Ounce of Prevention: a substudy of pre-frail older adults from the HEaRT pilot randomized controlled trial

The objectives of this substudy were: 1) to evaluate the safety (occurrence of adverse events) and feasibility (attendance and attrition) of HEaRT in community-dwelling older adults with pre-frailty, 2) to estimate effects of HEaRT on functional outcome measures (walking endurance, knee extensor strength, balance and health-related quality of life) and physiological outcomes (muscular mass and area) immediately post-intervention and at 8-week follow-up as compared to a moderate-intensity RT program (MOD-RT). We hypothesized that: 1) there would be no adverse events among participants with prefrailty related to a High-intensity EnhAnced Resistance Training (HEaRT) intervention and that participants will attend at least 80% of sessions and attrition will be <20%; and 2) that high-intensity RT would yield greater improvements in mobility status, walking endurance, strength, physical function, and balance compared to moderate-intensity and those results would be sustained over an 8-week follow up period.

CHAPTER 2: The role of resistance training in mitigating risk for mobility disability in community-dwelling older adults: a systematic review and meta-analysis

Trial Registration Number: International Prospective Registrar for Systematic Reviews

(CRD42019120854)

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2.1 Abstract

Objective: To examine the effects of community-based resistance training (RT) on physical function for older adults with mobility disability.

Data Sources: Four databases (PEDro, MedLine, Ovid, CINAHL and Web of Science) were searched from inception to February 2, 2021.

Study Selection: Randomized controlled trials that examined community-based RT for improving physical function in community-dwelling older adults were included.

Data Extraction: Two reviewers independently conducted title and abstract screening, full-text evaluation, data extraction, and risk of bias quality assessment.

Data Synthesis: Twenty-four studies (3,656 participants, age range 63-83 years) were included. RT programs ranged from 10 weeks to 18 months in duration. RT was more effective than control in improving 6MWT distance (n=638; mean difference (MD) 16.1 meters; 95% CI 12.27-19.94, $p<0.0001$), lower extremity strength (n=785; standard MD 2.01; 95% CI 1.27-2.75, $p<0.0001$) and usual gait speed (n= 2,106; MD 0.05 meters/second, 95% CI 0.03-0.07, $p<0.001$). In sensitivity analyses, benefits were maintained when studies with a high risk of bias were excluded. There was no effect of RT on fast gait speed or Short Physical Performance Battery score compared to control.

Conclusions: RT improves walking distance, lower extremity strength, and usual gait speed in older adults with mobility disability. Improvements in physical function could increase independence in activities of daily living for this at-risk population.

Keywords: Mobility limitation, resistance training, preclinical disability

2.2 Introduction

Preserving mobility, or the ability to move around one's home and community, is critical for maintaining independence into older age.[18] When mobility is compromised, limitations can exist along a spectrum from *preclinical disability*,[73,147] a subclinical state where compensatory strategies are used to complete daily tasks, to *mobility disability* which can threaten independent living.[18] Mobility disability and its precursor preclinical mobility disability are associated with adverse health outcomes, including increased risk for falls, hospitalization and institutionalization.[148] Mobility disability is a physical manifestation often seen in clinical geriatric syndromes such as frailty and sarcopenia.[57]

The onset of mobility disability can be multi-factorial in its cause.[149] The presence of chronic diseases such as obesity and diabetes, sedentary behaviors, or age-related physiological changes such as loss of muscular strength and power may contribute to mobility disability.[46-150] Mobility disability is not a static state but a dynamic one that can improve with intervention or worsen with changes in health status or chronic disease.[18] Older adults with mobility disabilities work much closer to their physical capacity to perform many daily activities. For example, older adults work at ~88% of maximal lower extremity strength to descend stairs, ~78% to ascend stairs and ~80% to stand up from a chair,[138] which is fatiguing and unsustainable. Identifying interventions that can reduce mobility disability in community-dwelling older adults is critical since such interventions would allow older persons to complete activities of daily living.

Exercise is a key strategy for mitigating changes in mobility status. In particular, resistance training (RT) may effectively attenuate declines in muscular strength associated with age and inactivity,[120] thus preventing transitions towards major mobility disability by improving or reversing preclinical disability and allowing older adults to remain independent.[120] Cut-off scores for clinical outcome measures evaluating physical function have been identified that may predict an incident or worsening mobility disability. For example, a Short Physical Performance Battery (SPPB) scores <9,[49] time to complete 5-time Sit to Stand (an indicator of lower extremity strength) >13.6 seconds, usual gait speed <1.2 m/s, or inability to walk 400 m in 15 minutes (an indicator of aerobic capacity)[47] have been linked to a higher risk of mobility disability. Improving physical function through RT would reduce the risk for mobility disability or the worsening of current mobility impairment.

Systematic review evidence supports the benefits of various exercise paradigms to improve physical function for those with mobility disability, including aerobic training,[151] and yoga.[152] To date, only one systematic review has focused on the effects of RT in older adults with activity limitation, but this review did not define the population using the criterion for mobility disability and focused on balance measures.[120] There have been no previous reviews to examine the effectiveness of RT to improve or prevent mobility disability in older adults.

The primary objective of this systematic review was to synthesize the evidence related to the effectiveness of RT interventions on outcomes of physical function (gait speed, walking endurance, muscle strength, muscle power) among adults >60 years of age with or at risk for mobility disability. Secondary objectives were to examine the effects of RT on transitions in mobility status and investigate possible adverse events related to RT for those with or at-risk for mobility disability.

2.3 Methods:

This review follows guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[153] This review was registered with the International Prospective Registrar for Systematic Reviews (CRD42019120854).

2.3.1 Study Selection and Inclusion Criteria

We systematically searched PubMed, MedLine, OVID, CINAHL and Web of Science from onset until January 2, 2019. The search was updated again on August 4, 2020 and February 2, 2021. The search strategy included terms: [“mobility limitation” OR “mobility disability” OR “preclinical disability” OR “mobility difficulty”] AND [“older adult” OR “senior” OR “elder”] AND (exercise) OR resistance training) AND English. Citation lists of included articles were hand-searched to identify further studies for inclusion.

Studies were included if they: a) enrolled community-dwelling adults >60 years of age at risk for, or with established, mobility limitation as measured by self-report or physical performance outcome measures with appropriate cut-off scores,[15-17] b) provided a community-based RT program (completed in a clinic, gym or other non-institutionalized setting) as a component or sole intervention, c) included a control group (different intervention which may include lower-load power training, lower-intensity RT, balance, walking or flexibility-based exercises) or no intervention/waitlist), d) included physical performance-based outcome measures that have shown good content validity and reliability for use with community-dwelling older adults (e.g. gait speed, Six-Minute Walk Test (6MWT), SPPB, muscular strength)[47,49,72,154] or self-reported mobility limitation as measures of physical function.[48] Exclusion criteria included: a) non-randomized controlled trials, b) participants with mobility disability due to neurological conditions (e.g. stroke, multiple sclerosis) or other degenerative pathologies (e.g. metastatic cancer, chronic obstructive pulmonary disease, chronic kidney disease) that would be the sole reason for mobility impairment, c) exercise interventions that focused on other aspects of fitness (aerobic, balance, yoga, virtual interventions) where no RT stimulus was applied.

Two independent reviewers (C.P and K.M) conducted titles and abstracts screening and full-text evaluation. Disagreements were resolved through discussion or by a third reviewer (A.T).

2.3.2 Data Extraction

Two authors (C.P and K.M) extracted the data from included studies using a spreadsheet with predetermined content fields. Information extracted included: lead author, year of publication, participant age and sex, exercise parameters for RT-focused experimental and control interventions (frequency, intensity, time, type), time points for assessments, adverse events if reported, and means and standard deviations of relevant mobility disability outcomes for each group. In the event of non-reported data in the manuscript, the corresponding author was contacted for raw data or clarification.

Quality Assessment

Methodological quality of included studies was evaluated independently by two authors (C.P and K.M) using the Cochrane Risk of Bias Tool 2.[155] The overall risk of bias of each study was characterized as low risk, some concerns or high risk of bias.[155]

Quantitative Analysis

Where possible, meta-analysis was performed to determine mean difference (MD) or standardized mean difference (SMD). SMDs were calculated using Hedge's g. A small effect size was identified as 0.2, a medium effect size was 0.5 and a large effect size was >0.8.[156] A random-effects model was utilized as exercise intervention varied across studies and heterogeneity existed across participant populations.[157] Heterogeneity was assessed using the I^2 statistic. We conducted sensitivity analyses with studies of high risk of bias removed, and with studies involving RT as the sole intervention only (multi-component programs removed). Meta-analysis and forest plots were generated using the Review Manager software, Version 5.4.1, The Cochrane Collaboration, 2020.

2.4 Results

The flow of studies through the review is presented in Figure 2.1. From the initial search conducted in January 2019, 3,175 titles were identified; an additional 548 titles were identified in August 2020 and 135 in February 2021, totaling 3,858 articles. After title and abstract screening and full-text assessment, 24 papers from 21 unique studies were included in the final review were included in the final review. Study characteristics are presented in Table 2.1.

FIGURE 2.1. Flow chart of included studies

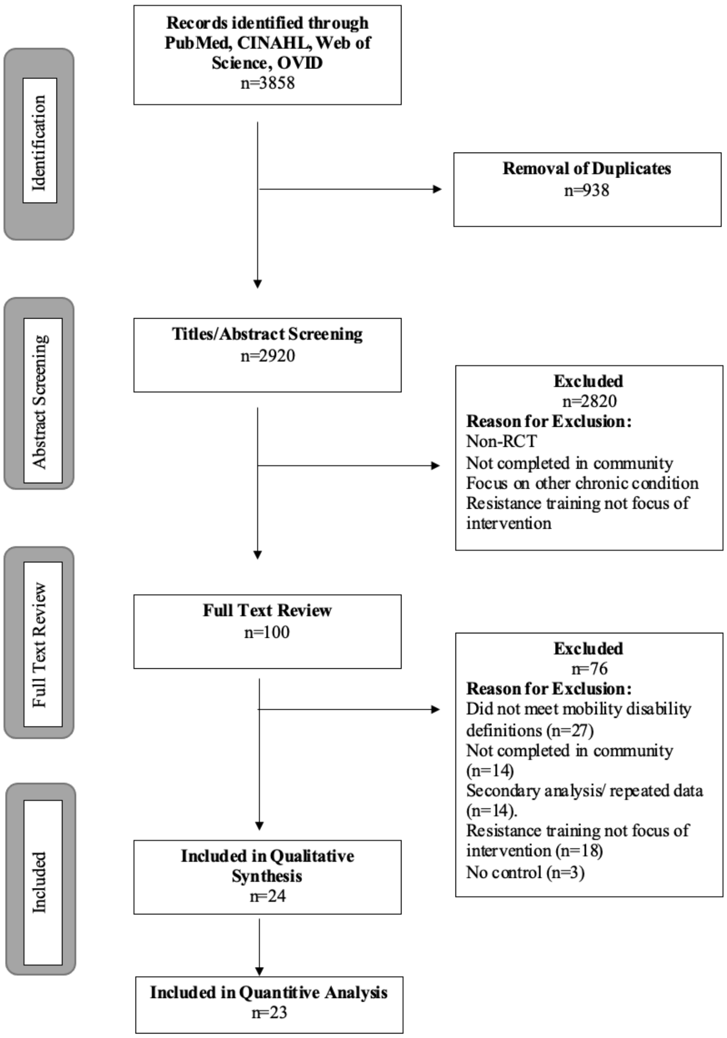


TABLE 2.1. Baseline characteristics of studies included in qualitative synthesis

Study	**Participant Characteristics**	**Assessment Time Points**	**Resistance Training**	**Control Intervention**	**Physical Outcome Measures**
Aas 2020	Total n=22 Control (n=11): Age 82.6 +/- 4.5 years Female (%): 27% RT (n=11): Age 86.6 +/- 6.0 years Female (%): 36%	Pre- (0 weeks) and post-intervention (10 weeks)	F: 3x/week for 10 weeks I: 3-4 sets at 6 RM; 2 minute rest periods T: Approximately 30 minutes T: Leg press, knee extension, adapted one-leg squat	No intervention	Knee extensor strength
Alqahtani 2019	Total n= 131 Control (n=77): Age 81.7 +/- 6.4 years Female (%): 76% RT (n=54): Age 78.1 +/- 8.0 years Female (%): 89% Standard RT: Age 81.2 +/- 7.9 years Female (%): 88%	Pre- (0 weeks) and post-intervention (12 weeks)	F: 2x/week for 12 weeks I: Not specified T: 1 hour T: Exercises in standing (RT) Exercises primarily in sitting (standard RT) eg chair stands, standing/seated abductions	Waitlist	SPPB balance subscale Knee extensor strength

Balachandran 2014	Total n= 21 Control (n=11): Age 71.6 +/- 7.8 years RT (n=10): Age 71 +/- 8.2 years Sex	Pre- (0 weeks) and post-intervention (15 weeks)	F: 2x/week for 15 weeks I: 3 sets x 10-12 repetitions at 70% 1 RM T: 40-45 minutes T: Leg press, hamstring curls, shoulder press, calf raise	F: 2x/week for 15 weeks I: 3 sets x 10-12 repetitions at 50% 1 RM as fast as possible T: 40-45 minutes T: Leg press, hamstring curls, shoulder press, calf raise	SPPB Grip strength
Bean 2009	Total n=138 Control (n=68): Age 76.1 +/- 6.9 years Female (%): 68% RT (n=72): Age 74.7 +/- 6.8 years Female (%): 69%	Pre- (0 weeks) and post-intervention (16 weeks)	F: 3x/week for 16 weeks I: 2 sets at RPE 15/29 T: 45-60 minutes T: Upper and lower body exercises with weighted vest	F: 3x/week for 16 weeks I: 2 sets x 10 repetitions T: 45-60 minutes T: NIA program - 11 exercises for upper and lower body	SPPB Knee extensor strength
Binder 2002	Total n=119 Control (n=50): Age 83 +/- 4 years Female (%): 52% RT (n=69): Age 83 +/- 4 years Female (%): 53%	Pre- (0 weeks), mid-point (3 months), post-intervention (6 months), follow up (9 months)	F: 3x/week for 6 months I: 2 -3 sets x 6-12 repetitions at 85-100% 12 RM (last 3 months aerobic training) T: 65 minutes T: Sit to stand and free-weight exercises to strengthen hips and knees	F: 2-3x/week for 9 months I: Not specified T: 65 minutes T: Home exercise program with 9 of 22 core exercises	Knee extensor strength

Brach 2017	Total n=424 Control (n=223): Age 80.5 +/- 8.1 years Female (%): 82% RT (n=201): Age 79.6 +/- 8.2 years Female (%): 86%	Pre- (0 weeks) and post-interventions (24 weeks)	F: 5 days/ week for 24 weeks I: Progressed when exercise completed 80% of the time T: 50 minutes T:Lower extremity exercises performed in standing	F: 5 days/ week for 24 weeks I: Not specified T: 50 minutes T: Usual care "exercise class" including stretching and balance program	6MWT Gait Speed
Brown 2000	Total n=87 Control (n=39): Age 83 +/- 4 years Female (%): Not specified RT (n=48): Age 83 +/- 4 years Female (%): Not specified	Pre- (0 weeks) and post-intervention (after 36 sessions)	F: 2x/week for 36 sessions I: Not specified T: Not specified T: 22 resistance training exercises including sit to stand and free-weight exercises to strengthen hips and knees	F: 2x/week for 36 sessions I: Not specified T: Not specified T: Home exercise program with 9 of 22 core exercises	Knee extensor strength Usual gait speed Fast gait speed
Cecchi 2009	Total: n =50 Control (n=25): Age 72.1 +/- 5.4 years Female (%): 60% RT (n=25): Age 73.2 +/- 6.0 years Female (%): 68%	Pre- (0 weeks), post-interventions (12 weeks) and follow-up (6 months and 9 months)	F: 2x/week for 12 weeks I: Low-moderate intensity T: 60 minutes T: Lower extremity exercises;	F: 2x/week I: Continuous self-paced T: 1 hour T: Walking Group for 12 weeks	Knee extensor strength

Cook 2017	Total: n=36 (Blood flow restriction group excluded from analysis) Control (n=12): Age 74.8 (69.6-79.9) years Female (%): 58% RT (n=12): Age 76.7 (95% CI Range 71.3-82.0) years Female (%): 58%	Pre- (0 weeks) and post-intervention (12 weeks)	F: 2x/week for 12 weeks I: 3 sets to volitional failure with 70% 1 RM T: Not specifid T: Leg extensions and leg curls	F: 2x/week for 12 weeks I: 3 sets x 10 repetitions T: Not specified T: Stretching and upper body strengthening with light dumbbells (<2.27 kg)	Knee extensor strength SPPB Fast gait speed
Englund 2019	Total n=70 Control (n=35): Age 80.3 +/- 6.3 years Female (%): 60% RT (n=35): Age 77.4 +/- 4.4 years Female (%): 60%	Pre- (0 weeks) and post-intervention (12 weeks)	F: 3x/week for 12 weeks I: 2-3 sets x 10-12 repetitions at 80% 1 RM T: To completion of program, 2-3 minute rest period between sets T: Leg press, seated row, leg extension, chest press, leg curl	F: 3x/week for 12 weeks I: 1 set x 30 seconds T: Not specified T: Flexibility program hamstring, quadriceps, chest, upper back.	Knee extensor strength
Fahlman 2011	Total n=100 Control (n=50): Age 76 +/- 2 years Female (%): Not specified RT (n=50): Age 75 +/- 1	Pre- (0 weeks), mid-interventions (9 weeks) and post-intervention (17 weeks)	F: 3x/week (1x in group at University; 2x at home) for 16 weeks I: "Mild" fatigue T: Not specified T: 13 exercise eg. Chair stand, hip	No intervention	Fast gait speed

	years Female (%): Not specified		flexion/extension/ abduction		
Gill 2016	Total n=1657 Control (n=817): Age 79.1 +.- 5.2 years Female (%): 67.4% RT (n=818):Age 78.7 +/- 5.2 years Female (%): 66.9%	Pre- (0 weeks), mid-(6 months), post-intervention (12 months), and follow-ups (18, 24 months)	F: 3x/week (2 in centre, 3-4x/week at home) I: RPE 15-16/20 T: Accumulate 150 minutes T: Walking, strength, flexibility, balance training	F: Weekly I: Not applicable T: Not specified T: Successful Aging intervention of weekly workshops for 26 weeks, monthly after	Transitions in mobility status
Hvid 2016	Total n=37 Control (n=21): Age 81.6 +/- 1.1years Female (%): 67% RT (n=16): Age 82.3 +/- 1.3 years Female (%): 56%	Pre- (0 weeks) and post-interventions (12 weeks)	F: 2x/week for 12 weeks I: 3 sets x 8-12 repetitions at 70-80% 1 RM T: Not specified T: Upper body, lower body and balance exercises specifically leg press/ plantarflexion.	No intervention	Knee extensor strength Fast gait speed
King 2002	Total n=155 Control (n=75): Age 77.9 +/- 4.4 years Female (%): 80%	Pre- (0 weeks) and post-intervention (18 months)	F: 3x/week, 6 months in senior centre, 6 months 1x in centre, 2x at home, 6 months at home I: RPE 12-14/20	F: 3x/week I: Moderate exercise T: Accumulate 150 minutes/week T: Home	Usual gait speed Fast gait speed 6MWT

	RT (n=80): Age 77 +/- 4.6 years Female (%): 77.5%		T: 60 minutes T: Ankle/wrist weights and weighted vests exercises for upper and lower body exercises	exercise program	
Manini 2007	Total n=49 Total cohort female (%) : 90% Control (n=27): 78.9 +/- 6.7 years RT (n=11): Age 74.4 +/- 10.6 years Functional RT (n=11): Age 74.4 +/- 7.4 years	Pre- (0 weeks) and post-interventions (10 weeks)	F: 2x/week, 2 sets x 10+ repetitions I: Not specified T: 30-45 minutes T: Three lower body exercises (leg press, leg extension, leg curl); three upper body (tricep extension, arm curls, shoulder press) & Functional training of daily activities. Functional + RT: 1 day functional, 1 day RT for 10 weeks	F: 2x/week for 10 weeks I: Not specified T: 30-45 minutes T: Functional Training eg. Vacuum cleaning, kneeling.	Knee extensor strength Usual gait speed Fast gait speed
Manini 2014	Total n=27 Control (n=13): Age: 64.0 +/- 7.3 years Female (%): 100% RT (n=14): Age: 63.6 +/- 4.7 years	Pre- (0 weeks) and post-intervention (24 weeks)	F: 2x/week for 24 weeks I: RPE 15-16/20 + dietary restriction T: T: 2 sets lower extremity focused	F: Monthly for 6 months I: Not applicable T: Not specified T: Education lectures	Knee extensor strength Usual gait speed

	Female (%): 100%				
Ng 2015	Total n= 246 (nutritional and cognitive interventions excluded from analysis) Control (n=50): Age 70.1 +/- 5.02 years Female (%): 66% RT (n=48): Age 70.3 +/- 5.25 years Female (%): 66.2%	Pre- (0 weeks), post-interventions (6 months) and follow-up (12 months)	F: 2x/week for 6 months I: 1 set x 8-15 repetitions at 60-80% 10RM T: 90 minutes T: 8-10 major muscle groups incorporating functional tasks	Usual Care (one standard care visit from health and aged care services)	Knee extensor strength Fast gait speed
Pahor 2014	Total n=1635 Control (n=817): Age 79.1 +/- 5.2 years Female (%): 67.4% RT (n=818): Age 78.7 +/- 5.2 years Female (%): 66.9%	Pre- (0 weeks), mid-(6 months), post-intervention (12 months), and follow-ups (18, 24 months)	F: 3x/week (2 in centre, 3-4x/week at home) I: RPE 15-16/20 T: Accumulate 150 minutes T: Walking, strength, flexibility, balance training	F: Weekly I: Not applicable T: Not specified T: Successful Aging intervention of weekly workshops for 26 weeks, monthly after	Adverse events

Reid 2008	Total n= 57 Control (n=12): Age 79.7±9 years Female: Not specified RT (n=22): Age 73.1 +/- 6 years Female (%): Not specified Power (n=23): Age 72.3 +/- 6 years Female (%): Not specified	Pre- (0 weeks) and post-intervention (12 weeks)	F: 3x/week for 12 weeks I: RT: 3 sets x 8 repetitions at 70% 1 RM; Power: 3 sets x 8 repetitions at 70% 1 RM with speed T: Not specified T: Focus on leg press and knee extension	F: 2x/week for 12 weeks I: Not specified T: Not specified T: Range of motion and flexibility training	Knee extensor strength SPPB
Reid 2015	Total n=52 Control (n=25): Age: 78.3 +/0 5 years Female (%): Not specified RT (n=27): Age: 77.6 +/- 4 years Female (%): Not specified	Pre- (0 weeks) and post-intervention (16 weeks)	F: 2x/week for 16 weeks I: 3 sets x 10 repetitions at 70% 1 RM T: T: Leg press and knee extension	F: 2x/week for 16 weeks I: 3 sets x 10 repetitions at 40% 1 RM T: T: Leg press and knee extension	Knee extensor strength
Santasto 2017	Total n=1635 Control (n=817): Age 79.1 +/- 5.2 years Female (%): 67.4% RT (n=818): Age 78.7 +/- 5.2 years	Pre- (0 weeks), mid-(6 months), post-intervention (12 months), and follow-ups (18, 24 months)	F: 3x/week (2 in centre, 3-4x/week at home) I: RPE 15-16/20 T: Accumulate 150 minutes T: Walking, strength, flexibility, balance training	F: Weekly I: Not applicable T: Not specified T: Successful Aging intervention of weekly workshops for 26 weeks, monthly after	SPPB balance subscale Usual gait speed

	Female (%): 66.9%				
Sunde 2020	Total n=89 Control (n=44): Age 77.9 +/- 5.2 years Female (%): 59% RT (n=45): Age 78.6 +/- 5.7 years Female (%): 39%	Pre- (0 weeks) and post-intervention (5 months)	F: 2-4x/week for 5 months I: 2 sets x 8-12 repetitiions at 8-12 RM T: 53 minutes T: Multi-component program with RT and balance training. RT exercises: forward lunges and sit to stands	Usual Care (Written guidelines on the activity recommendations for older adults)	SPPB 6MWT
Tarazona-Santabalbina 2016	Total: n=100 Control (n=49): Age 80.3 +/- 3.7years Female (%): Not specified RT (n=51): Age 79.7 +/- 3.6 years Female (%): Not specified	Pre- (0 weeks) and post-interventions (24 weeks)	F: 5x/week for 24 weeks I: 25-75% 1 RM 1 set progressing to 3 sets, 8-30 repetitions T: 65 minutes T: Multicomponent program with strength, balance and endurance component. RT using resistance bands	No intervention	SPPB

Timonen 2002	Total n=68 Control (n=34): Age 82.6 +/- 3.7 years Female (%): 100% RT (n=34):Age 83.5 +/- 4.1 years Female (%): 100%	Pre- (0 weeks), post-intervention (11 weeks) and follow-up (22 weeks and 11.5 months)	F: 2x/week for 10 weeks I:1 set x20-30 repetitions progressed to 2x8-10 T: 30 minutes T: Lower body exercises for knee flexion, knee extension, squats, calf raises	F: 2-3x/week for 10 weeks I: 2-3 sets x 10-15 repetitions T: Not specified T: Home exercise program of functiona exercises	Knee extensor strength Fast gait speed

Note: SPPB= Short Physical Performance Battery; 6MWT = Six-minute walk test

Population

Across all 21 studies, 3,656 participants were included, with sample sizes ranging from 21[158] to 1635[76] participants. Mean age ranged from 63[159] to 83[160] years. Nineteen studies included participants with established mobility disability,[115,118,126,127,158–171,45] and five papers from three unique studies focused on those at risk for mobility disability.[14,76,172–174] All participants were living independently in the community. Of the 18 studies that disaggregated data based on sex, females made up 27%[115] to 100%[159,171] of the samples.

Interventions

Resistance training interventions ranged from 10 weeks[171,174] to 18 months[166] in duration, with sessions lasting 50- to 90-minutes, two to three times per week. RT focused on lower extremity exercises in 15 studies[14,76,115,119,159,161–163,167–173] and a combination of upper and lower extremity weighted exercises in nine studies. [17,20,22,23,36,37,38-40]

RT was used as a sole intervention in 18 studies[14,76,115,118,119,126,127,158,163–169,171–173,174(p20)] and as a component of a multicomponent program in six studies. Multi-component programs included dietary interventions,[159] balance and flexibility,[160,170] or endurance components.[161,162,170]

Interventions were entirely group-based in 18 studies[115,119,126,127,158–163,165–171,174], a combination of group- and home-based exercise in five studies,[23,32,35,,42,43] and format of training was not specified in one study.[172] Group-based exercise was led by exercise physiologists or exercise professionals in 11 studies,[22,23,25,28,29,32,33,35,42–44] physical therapists in five studies[163,166,169–171] and researchers in two studies.[159,168] Profession of group instructor was not described in six studies.[115,119,161,162,167,172].

Resistance loads ranged from "low-intensity" or body weight[127,163] to higher intensities at 80-90% of one-repetition maximum.[115] Resistance training was done as a power program (concentric phase as quickly as possible) in four studies.[158,165,167,168] Power training intensity was completed at 70-80% of one repetition maximum in all studies.[158,165,167,168] Exercise progression was described in 12 studies, of which eight studies[115,126,162,166–168,170,172] provided specific details (ability to complete three sets of target repetition,[28,30,34,41] fixed progression table,[115,170] or fixed time intervals[167,168]). The remaining four studies[158,162,169,171] described progression based on movement quality or subjective interpretation of difficulty by the instructor.

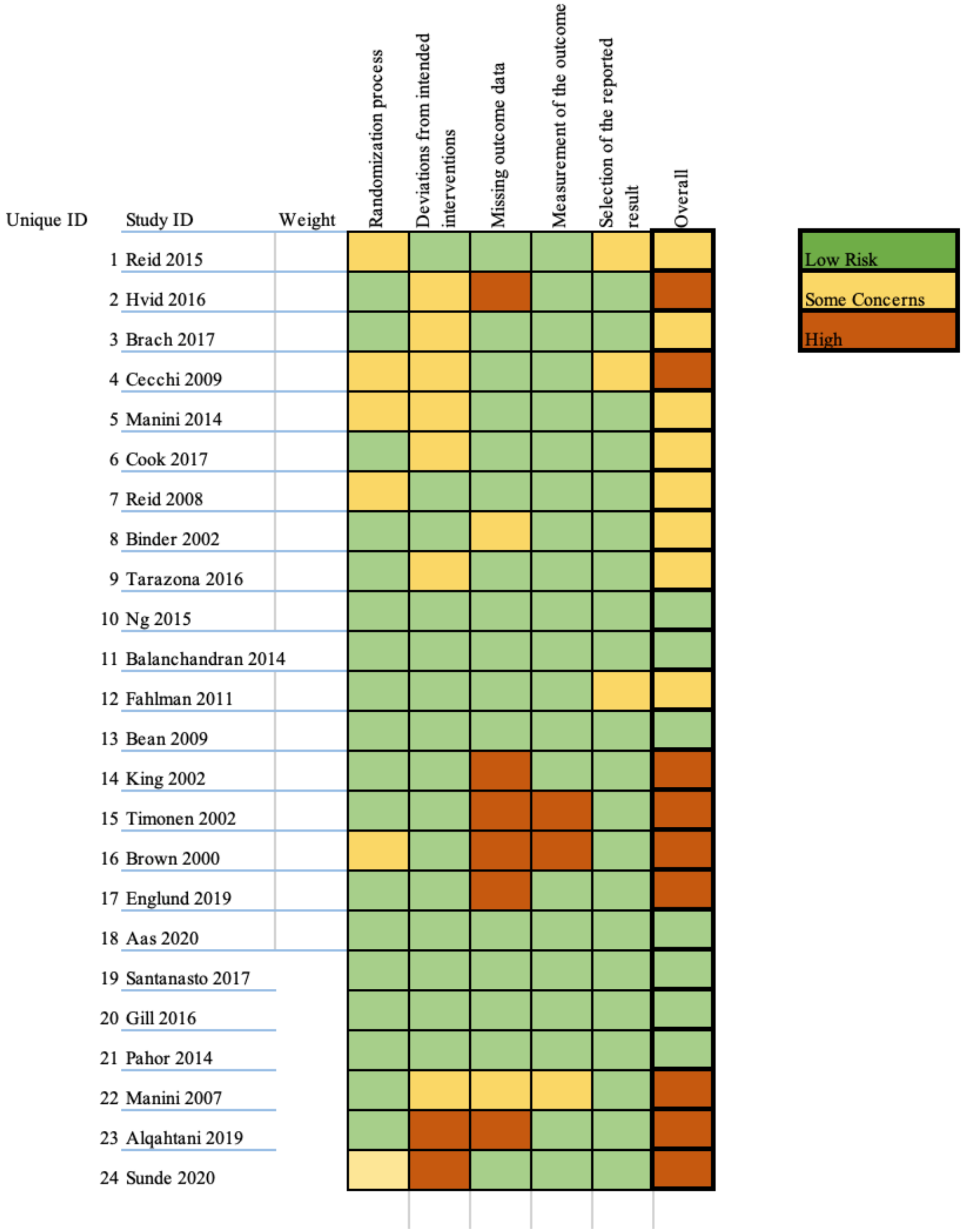
Comparison

Eleven studies compared RT to usual care (no intervention or follow-up as required),[29,32,34,37,38,40,41] monthly education,[14,159] or waitlist control.[161,174] A comparison was made to a home exercise program (including balance, flexibility and stretching movements) in ten studies.[23,24-26,28,29,30,32,35,42] Lower-intensity RT program was utilized in three studies,[126,158,167] including one study that compared RT to low-load power training.[158]

Study Quality

Quality assessment is presented in Figure 2.2. Low risk of bias was found in seven studies.[14,76,115,118,126,158,173] Of the studies showing some concern for risk of bias, issues were most often related to incomplete reporting of outcomes and insufficient reporting of statistical methods. High risk of bias was reported in nine studies,[119,127,161,163,165,166,169,171,174] most commonly as a result of not accounting for missing data (n=6 studies). [119,127,161,165,166,171]

FIGURE 2.2: Quality assessment of studies included in systematic review using the Cochrane Risk of Bias Tool 2.



Unique ID	Study ID	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
1	Reid 2015		🟨	🟩	🟩	🟩	🟨	🟨
2	Hvid 2016		🟩	🟨	🟧	🟩	🟩	🟧
3	Brach 2017		🟩	🟨	🟩	🟩	🟩	🟨
4	Cecchi 2009		🟨	🟨	🟩	🟩	🟨	🟧
5	Manini 2014		🟨	🟨	🟩	🟩	🟩	🟨
6	Cook 2017		🟩	🟨	🟩	🟩	🟩	🟨
7	Reid 2008		🟨	🟩	🟩	🟩	🟩	🟨
8	Binder 2002		🟩	🟩	🟨	🟩	🟩	🟨
9	Tarazona 2016		🟩	🟨	🟩	🟩	🟩	🟨
10	Ng 2015		🟩	🟩	🟩	🟩	🟩	🟩
11	Balanchandran 2014		🟩	🟩	🟩	🟩	🟩	🟩
12	Fahlman 2011		🟩	🟩	🟩	🟩	🟨	🟨
13	Bean 2009		🟩	🟩	🟩	🟩	🟩	🟩
14	King 2002		🟩	🟩	🟧	🟩	🟩	🟧
15	Timonen 2002		🟩	🟩	🟧	🟧	🟩	🟧
16	Brown 2000		🟨	🟩	🟧	🟧	🟩	🟧
17	Englund 2019		🟩	🟩	🟧	🟩	🟩	🟧
18	Aas 2020		🟩	🟩	🟩	🟩	🟩	🟩
19	Santanasto 2017		🟩	🟩	🟩	🟩	🟩	🟩
20	Gill 2016		🟩	🟩	🟩	🟩	🟩	🟩
21	Pahor 2014		🟩	🟩	🟩	🟩	🟩	🟩
22	Manini 2007		🟩	🟨	🟨	🟨	🟩	🟧
23	Alqahtani 2019		🟩	🟧	🟧	🟩	🟩	🟧
24	Sunde 2020		🟨	🟧	🟩	🟩	🟩	🟧

🟩 Low Risk
🟨 Some Concerns
🟧 High

Outcomes

SPPB was reported in nine studies[21,23,26,27,35,37,38,40,42] with intervention duration ranging from 12 weeks[172] to one year,[14] of which five studies utilized RT as a sole intervention. [17,24,27,38,41]

Usual gait speed was reported in five studies.[19,24,29-31] All studies compared RT to a control group. Intervention duration varied between 12 weeks[162] to one year.[14]

Fast gait speed was reported in eight studies[118,127,164–166,171,172,174] that used RT as the sole intervention. Intervention duration ranged from 10 weeks[174] to 18 months.[166]

Lower extremity strength was examined in 15 studies,[20–22,24,26-28,29,31,32,34,36,38-40] using a broad range of outcomes. Ten studies evaluated isometric knee extensor strength using dynamometry,[119,127,159,160,163,165,167,171,172,174] two studies used pneumatic equipment for isokinetic knee extensor strength .[126,167] The remaining studies used a uni-axial load cell,[161] a strap and gauge method [118] and a lower extremity one repetition maximum.[115] Intervention duration ranged from 12 weeks[172] to 18 months.[166] RT protocols were used as a solo intervention in 13 of 15 studies.[21,22,24,26,27,29,31,32,34,36,38–40]

6MWT was included in three studies[162,166,169]; all used RT as the sole intervention ranging from 12 weeks[162] to 18 months[166] in duration.

Only one study[76] examined transitions in mobility status and reported a 25% reduction in risk for transitioning to major mobility disability among participants in a multicomponent exercise program compared to a health education intervention (risk ratio =25%, 95% CI = 10-37%, p=0.002).[22]

Adverse Events

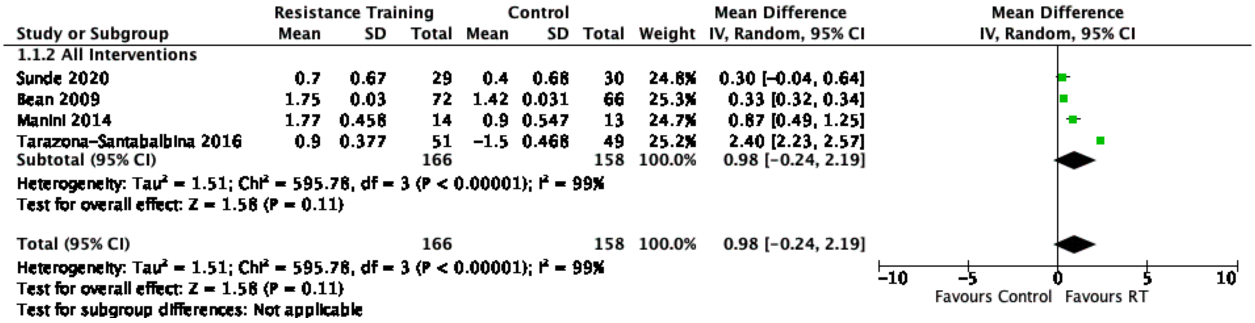
Seven studies reported adverse events related to study interventions.[20,27, 29-30,32,35,36] None reported serious adverse events; rather, most events pertained to muscular strains or exacerbations of pre-existing musculoskeletal pain.[119,160,162,166] Two studies reported no adverse events related to RT.[163,164] Only one study compared adverse events between intervention groups, where no difference was found.[76]

Quantitative Analysis

A meta-analysis of four studies[126,159,169,170] was completed for SPPB, as two studies did not have full data reported,[167,172] two studies reported individual subscale scores but not total score,[14,161] and one study performed a modified version of the SPPB.[158] There was no difference between RT interventions on SPPB scores compared to control (n=324; MD 0.98, 95% confidence interval (CI) [-0.24, 2.19], p=0.11; Figure 2.3a). Results were maintained in sensitivity analysis with studies with high risk of bias removed (3 studies, n= 265 participants; MD 1.2, 95% CI [-0.33, 2.73] p=0.12). However, in sensitivity analysis with multi-component programs removed, programs with RT as the sole intervention were more effective in improving SPPB compared to control (n=3 studies, n=226 participants; MD= 0.46, 95% CI [0.17,0.75]; Figure 2.4).

FIGURE 2.3. Meta-analysis evaluating the role of resistance training compared to control on differing functional outcome measures related to mobility disability. A) Short Physical Performance Battery, B) Usual Gait Speed, C) Fast Gait Speed, D) Lower extremity strength, E) 6-Minute Walk test Distance

A) Short Physical Performance Battery

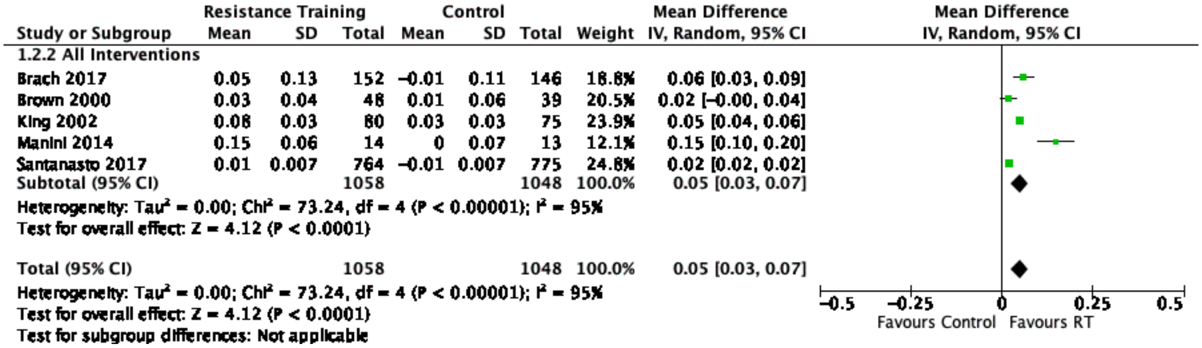


	Resistance Training			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.1.2 All Interventions								
Sunde 2020	0.7	0.67	29	0.4	0.68	30	24.8%	0.30 [−0.04, 0.64]
Bean 2009	1.75	0.03	72	1.42	0.031	66	25.3%	0.33 [0.32, 0.34]
Manini 2014	1.77	0.458	14	0.9	0.547	13	24.7%	0.87 [0.49, 1.25]
Tarazona–Santabalbina 2016	0.9	0.377	51	−1.5	0.468	49	25.2%	2.40 [2.23, 2.57]
Subtotal (95% CI)			166			158	100.0%	0.98 [−0.24, 2.19]
Total (95% CI)			166			158	100.0%	0.98 [−0.24, 2.19]

Subtotal: Heterogeneity: $Tau^2 = 1.51$; $Chi^2 = 595.78$, $df = 3$ ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 1.58$ ($P = 0.11$)

Total: Heterogeneity: $Tau^2 = 1.51$; $Chi^2 = 595.78$, $df = 3$ ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 1.58$ ($P = 0.11$)
Test for subgroup differences: Not applicable

B) Usual Gait Speed

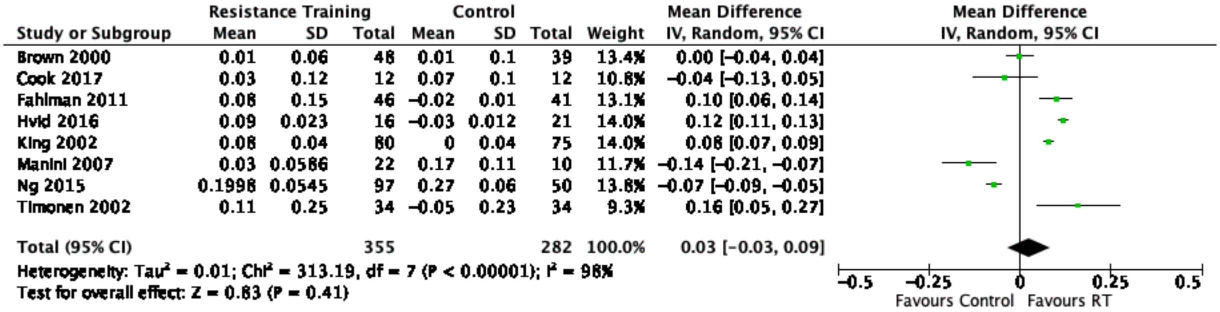


	Resistance Training			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.2.2 All Interventions								
Brach 2017	0.05	0.13	152	−0.01	0.11	146	18.8%	0.06 [0.03, 0.09]
Brown 2000	0.03	0.04	48	0.01	0.06	39	20.5%	0.02 [−0.00, 0.04]
King 2002	0.08	0.03	80	0.03	0.03	75	23.9%	0.05 [0.04, 0.06]
Manini 2014	0.15	0.06	14	0	0.07	13	12.1%	0.15 [0.10, 0.20]
Santanasto 2017	0.01	0.007	764	−0.01	0.007	775	24.8%	0.02 [0.02, 0.02]
Subtotal (95% CI)			1058			1048	100.0%	0.05 [0.03, 0.07]
Total (95% CI)			1058			1048	100.0%	0.05 [0.03, 0.07]

Subtotal: Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 73.24$, $df = 4$ ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 4.12$ ($P < 0.0001$)

Total: Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 73.24$, $df = 4$ ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 4.12$ ($P < 0.0001$)
Test for subgroup differences: Not applicable

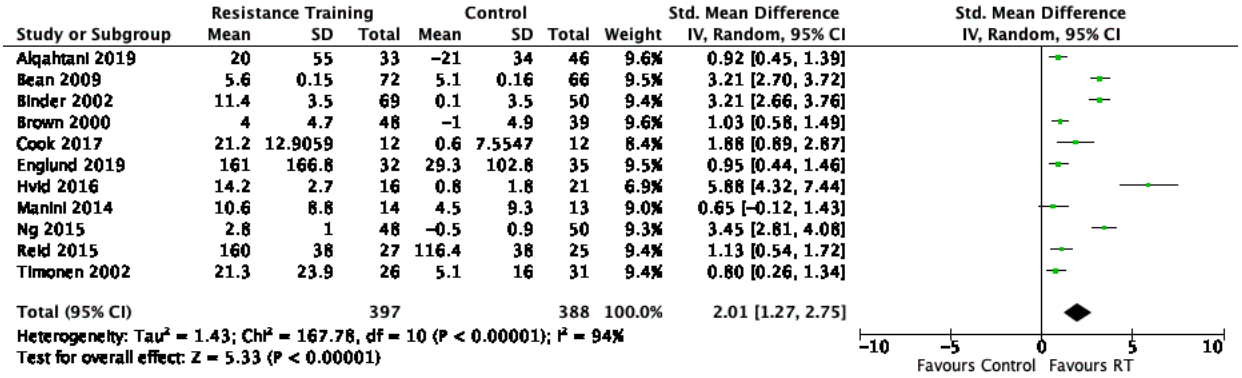
C) Fast Gait Speed



	Resistance Training			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Brown 2000	0.01	0.06	48	0.01	0.1	39	13.4%	0.00 [−0.04, 0.04]
Cook 2017	0.03	0.12	12	0.07	0.1	12	10.8%	−0.04 [−0.13, 0.05]
Fahlman 2011	0.08	0.15	46	−0.02	0.01	41	13.1%	0.10 [0.06, 0.14]
Hvid 2016	0.09	0.023	16	−0.03	0.012	21	14.0%	0.12 [0.11, 0.13]
King 2002	0.08	0.04	80	0	0.04	75	14.0%	0.08 [0.07, 0.09]
Manini 2007	0.03	0.0586	22	0.17	0.11	10	11.7%	−0.14 [−0.21, −0.07]
Ng 2015	0.1998	0.0545	97	0.27	0.06	50	13.8%	−0.07 [−0.09, −0.05]
Timonen 2002	0.11	0.25	34	−0.05	0.23	34	9.3%	0.16 [0.05, 0.27]
Total (95% CI)			355			282	100.0%	0.03 [−0.03, 0.09]

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 313.19$, $df = 7$ ($P < 0.00001$); $I^2 = 98\%$
Test for overall effect: $Z = 0.83$ ($P = 0.41$)

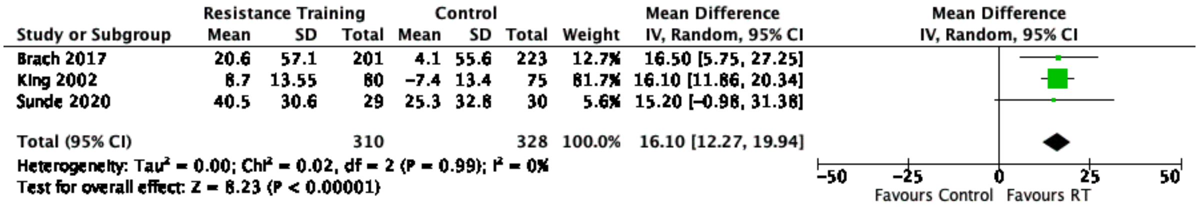
D) Lower Extremity Strength



Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alqahtani 2019	20	55	33	−21	34	46	9.6%	0.92 [0.45, 1.39]
Bean 2009	5.6	0.15	72	5.1	0.16	66	9.5%	3.21 [2.70, 3.72]
Binder 2002	11.4	3.5	69	0.1	3.5	50	9.4%	3.21 [2.66, 3.76]
Brown 2000	4	4.7	48	−1	4.9	39	9.6%	1.03 [0.58, 1.49]
Cook 2017	21.2	12.9059	12	0.6	7.5547	12	8.4%	1.88 [0.89, 2.87]
Englund 2019	161	166.8	32	29.3	102.8	35	9.5%	0.95 [0.44, 1.46]
Hvid 2016	14.2	2.7	16	0.8	1.8	21	6.9%	5.88 [4.32, 7.44]
Manini 2014	10.6	8.8	14	4.5	9.3	13	9.0%	0.65 [−0.12, 1.43]
Ng 2015	2.8	1	48	−0.5	0.9	50	9.3%	3.45 [2.81, 4.08]
Reid 2015	160	38	27	116.4	38	25	9.4%	1.13 [0.54, 1.72]
Timonen 2002	21.3	23.9	26	5.1	16	31	9.4%	0.80 [0.26, 1.34]
Total (95% CI)			397			388	100.0%	2.01 [1.27, 2.75]

Heterogeneity: Tau² = 1.43; Chi² = 167.78, df = 10 (P < 0.00001); I² = 94%
Test for overall effect: Z = 5.33 (P < 0.00001)

E) Six- Minute Walk Test



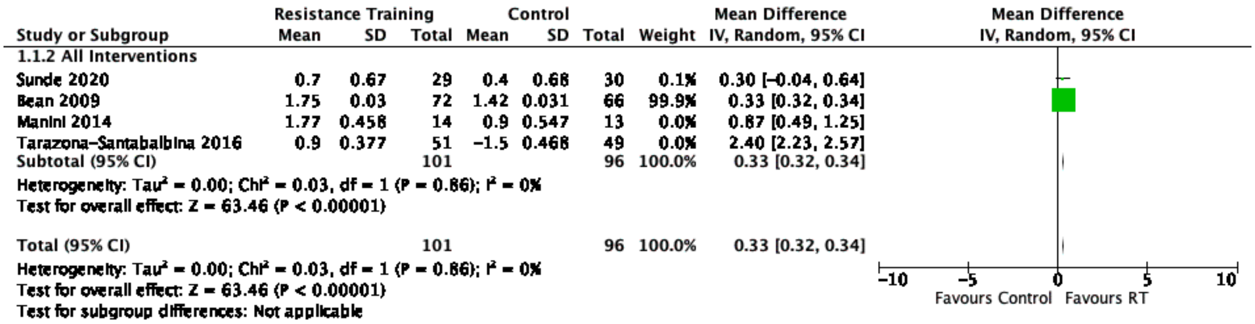
Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Brach 2017	20.6	57.1	201	4.1	55.6	223	12.7%	16.50 [5.75, 27.25]
King 2002	8.7	13.55	80	−7.4	13.4	75	81.7%	16.10 [11.86, 20.34]
Sunde 2020	40.5	30.6	29	25.3	32.8	30	5.6%	15.20 [−0.98, 31.38]
Total (95% CI)			310			328	100.0%	16.10 [12.27, 19.94]

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 8.23 (P < 0.00001)

RT was more effective than control on improving usual gait speed (5 studies, n = 2106, MD 0.05 m/s, 95% CI [0.03-0.07], p<0.0001; Figure 2.3B)[14,127,159,162,166] but not fast gait speed (8 studies, n= 637, MD 0.03 m/s, 95% CI [-0.03, 0.09], p=0.41; Figure 2.3C).[118,127,164–166,171,172,174] Results were preserved in sensitivity analyses with high risk of bias studies removed (usual gait speed 3 studies, n=1,864; MD 0.07 m/s 95% CI [0.01,0.13] p=0.02; fast gait speed 3 studies, n=258, MD -0.03 m/s 95% CI [-0.13, 0.12], p=0.97) and for RT only interventions (usual gait speed 3 studies, n=1,781 participants; MD 0.03; 95% CI [0.01,0.05]) (Figure 2.4).

FIGURE 2.4: Sensitivity analysis for resistance training only interventions (multicomponent programs removed) A) Short Physical Performance Battery, B) Usual Gait Speed, C) Fast Gait Speed, D) Lower extremity strength, E) 6-Minute Walk test Distance

A) Short Physical Performance Battery



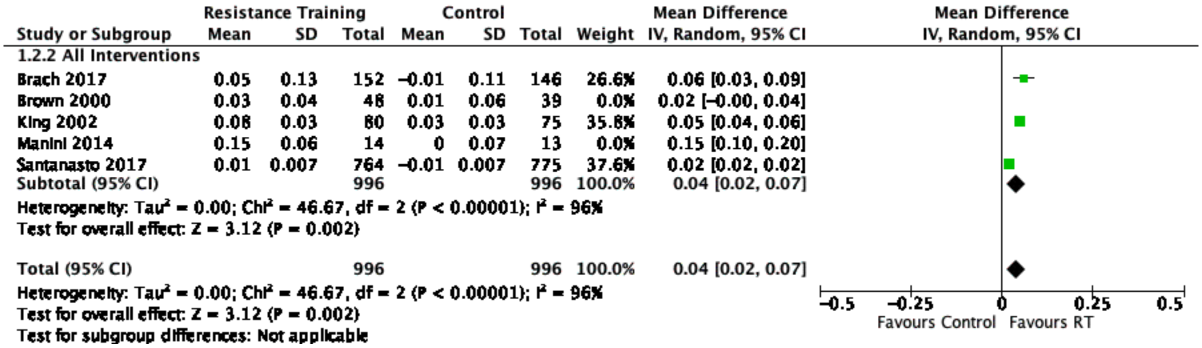
Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.2 All Interventions								
Sunde 2020	0.7	0.67	29	0.4	0.68	30	0.1%	0.30 [−0.04, 0.64]
Bean 2009	1.75	0.03	72	1.42	0.031	66	99.9%	0.33 [0.32, 0.34]
Manini 2014	1.77	0.458	14	0.9	0.547	13	0.0%	0.87 [0.49, 1.25]
Tarazona−Santabalbina 2016	0.9	0.377	51	−1.5	0.468	49	0.0%	2.40 [2.23, 2.57]
Subtotal (95% CI)			101			96	100.0%	0.33 [0.32, 0.34]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 ($P = 0.86$); $I^2 = 0\%$
Test for overall effect: $Z = 63.46$ ($P < 0.00001$)

Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Total (95% CI)			101			96	100.0%	0.33 [0.32, 0.34]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 ($P = 0.86$); $I^2 = 0\%$
Test for overall effect: $Z = 63.46$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

B) Usual Gait Speed



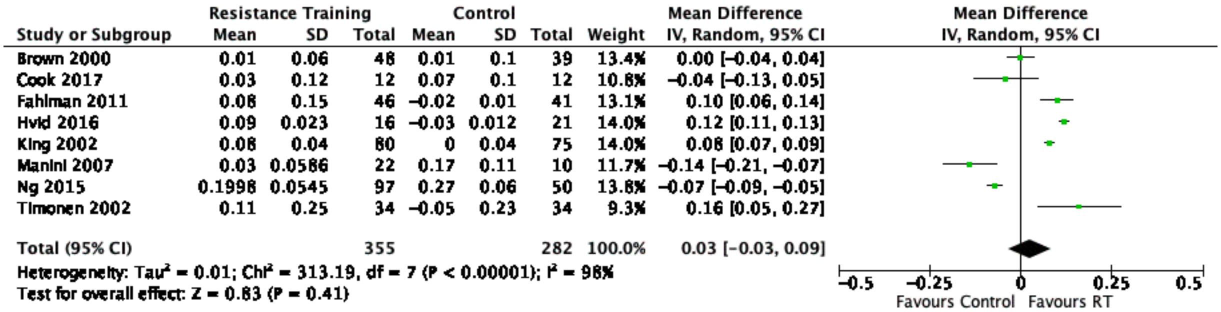
Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.2 All Interventions								
Brach 2017	0.05	0.13	152	−0.01	0.11	146	26.6%	0.06 [0.03, 0.09]
Brown 2000	0.03	0.04	48	0.01	0.06	39	0.0%	0.02 [−0.00, 0.04]
King 2002	0.08	0.03	80	0.03	0.03	75	35.8%	0.05 [0.04, 0.06]
Manini 2014	0.15	0.06	14	0	0.07	13	0.0%	0.15 [0.10, 0.20]
Santanasto 2017	0.01	0.007	764	−0.01	0.007	775	37.6%	0.02 [0.02, 0.02]
Subtotal (95% CI)			996			996	100.0%	0.04 [0.02, 0.07]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 46.67$, df = 2 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 3.12$ ($P = 0.002$)

Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Total (95% CI)			996			996	100.0%	0.04 [0.02, 0.07]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 46.67$, df = 2 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 3.12$ ($P = 0.002$)
Test for subgroup differences: Not applicable

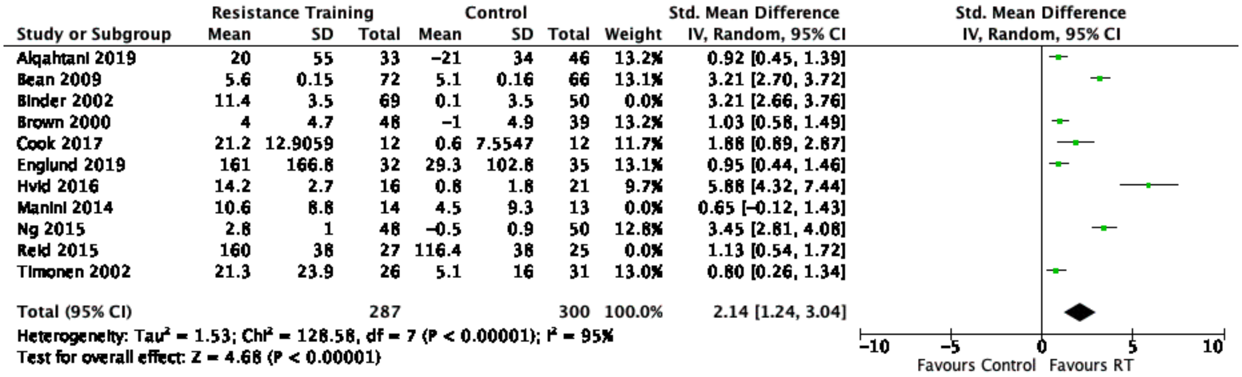
C) Fast Gait Speed



Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Brown 2000	0.01	0.06	48	0.01	0.1	39	13.4%	0.00 [−0.04, 0.04]
Cook 2017	0.03	0.12	12	0.07	0.1	12	10.8%	−0.04 [−0.13, 0.05]
Fahlman 2011	0.08	0.15	46	−0.02	0.01	41	13.1%	0.10 [0.06, 0.14]
Hvid 2016	0.09	0.023	16	−0.03	0.012	21	14.0%	0.12 [0.11, 0.13]
King 2002	0.08	0.04	80	0	0.04	75	14.0%	0.08 [0.07, 0.09]
Manini 2007	0.03	0.0586	22	0.17	0.11	10	11.7%	−0.14 [−0.21, −0.07]
Ng 2015	0.1998	0.0545	97	0.27	0.06	50	13.8%	−0.07 [−0.09, −0.05]
Timonen 2002	0.11	0.25	34	−0.05	0.23	34	9.3%	0.16 [0.05, 0.27]
Total (95% CI)			355			282	100.0%	0.03 [−0.03, 0.09]

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 313.19$, df = 7 ($P < 0.00001$); $I^2 = 98\%$
Test for overall effect: $Z = 0.83$ ($P = 0.41$)

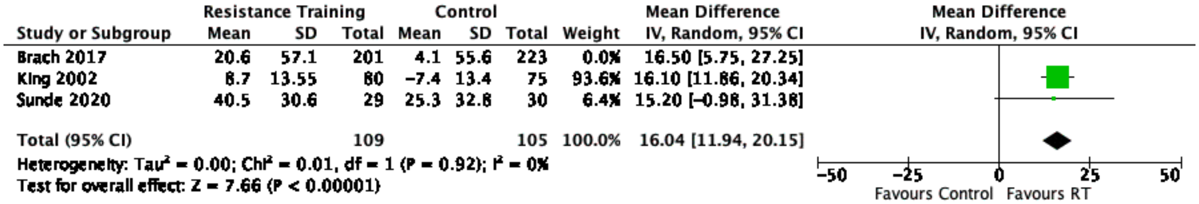
D) Lower Extremity Strength



	Resistance Training			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Alqahtani 2019	20	55	33	−21	34	46	13.2%	0.92 [0.45, 1.39]
Bean 2009	5.6	0.15	72	5.1	0.16	66	13.1%	3.21 [2.70, 3.72]
Binder 2002	11.4	3.5	69	0.1	3.5	50	0.0%	3.21 [2.66, 3.76]
Brown 2000	4	4.7	48	−1	4.9	39	13.2%	1.03 [0.58, 1.49]
Cook 2017	21.2	12.9059	12	0.6	7.5547	12	11.7%	1.88 [0.89, 2.87]
Englund 2019	161	166.8	32	29.3	102.8	35	13.1%	0.95 [0.44, 1.46]
Hvid 2016	14.2	2.7	16	0.8	1.8	21	9.7%	5.88 [4.32, 7.44]
Manini 2014	10.6	8.8	14	4.5	9.3	13	0.0%	0.65 [−0.12, 1.43]
Ng 2015	2.8	1	48	−0.5	0.9	50	12.8%	3.45 [2.81, 4.08]
Reid 2015	160	38	27	116.4	38	25	0.0%	1.13 [0.54, 1.72]
Timonen 2002	21.3	23.9	26	5.1	16	31	13.0%	0.80 [0.26, 1.34]
Total (95% CI)			287			300	100.0%	2.14 [1.24, 3.04]

Heterogeneity: $Tau^2 = 1.53$; $Chi^2 = 128.58$, df = 7 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: Z = 4.68 ($P < 0.00001$)

E) Six-Minute Walk Test



	Resistance Training			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Brach 2017	20.6	57.1	201	4.1	55.6	223	0.0%	16.50 [5.75, 27.25]
King 2002	8.7	13.55	80	−7.4	13.4	75	93.6%	16.10 [11.86, 20.34]
Sunde 2020	40.5	30.6	29	25.3	32.8	30	6.4%	15.20 [−0.98, 31.38]
Total (95% CI)			109			105	100.0%	16.04 [11.94, 20.15]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 ($P = 0.92$); $I^2 = 0\%$
Test for overall effect: Z = 7.66 ($P < 0.00001$)

Eleven studies[19–21,24,27,31,32,36,38-40] were included in meta-analysis for lower-extremity strength where RT was superior to control (n=785; SMD = 2.01, 95% CI [1.27, 2.75], p<0.001; see Figure 2.3D). Results were unaltered in sensitivity analysis with studies with high risk of bias removed (6 studies, n=458 participants; SMD = 2.28, 95% CF [1.32, 3.23], p<0.001) and for RT only interventions (8 studies, n=560 participants, SMD 2.17; 95% CF [1.27, 3.07].

For 6MWT, RT was more effective than control in increasing distance walked (3 studies, n=638; MD 16.1 m, 95% CI [12.27,19.94], p<0.001).[162,166,169] Results were also maintained for sensitivity analysis when high risk of bias studies was removed (one study, n=424 participants; MD 16.5 m 95% CI [5.75, 27.25], p=0.003) and with RT only interventions (2 studies, n=214 participants; MD 16.0 m; 95% CI [11.9, 20.1]).

2.5 Discussion

We found that RT, whether provided as a sole intervention or part of a multicomponent program, was effective for improving lower extremity strength, distance walked on 6MWT and usual gait speed in community-dwelling older adults with mobility disability. Our meta-analysis demonstrated that RT interventions resulted in significant and clinically relevant increases in lower extremity strength. For many older adults, strength is a limiting factor for completing daily tasks[10] where activities such as climbing stairs often require effort above 80% of their overall strength capacity.[138] Muscular weakness is limiting for many older adults in several activities of daily living. Weakness is a key variable in the development of mobility disability and in the presentation of many other common clinical geriatric syndromes such as sarcopenia and frailty.[57] By improving strength to optimize physical function and mobility, RT interventions may also reduce the risk of developing other conditions that occur more commonly with older age. Increasing lower extremity strength would allow daily activities to be performed with less relative effort, would ensure adequate physical capacity to sustain activity throughout the day, reduces the need to modify tasks, and optimizes physical resiliency.[151]

RT was also effective for improving distance walked on the 6MWT; importantly, the observed mean difference of 16 m exceeding the 14-m minimally clinically important difference for older adults.[176] 6MWT distance is an indicator of submaximal aerobic capacity, and is predictive of community ambulation.[176] The findings from this review suggesting that RT may modestly improve aerobic capacity. During RT, there is a transient increase in heart rate, systolic and diastolic blood pressure, which may evoke cardiovascular training stimulus,[177] especially amongst individuals with more compromised fitness, such as those with significant mobility disability.

The effect of RT was modest for improving usual gait speed (mean difference 0.05 m/s), below the minimally clinically important difference of 0.1 m/s.[176] Several studies were 12-18 months in duration and in this case represents, at minimum, preservation in gait speed.[14,76,166,173] Declines in usual gait speed have been linked to many adverse health outcomes in older adults, including lower extremity limitation, incident ADL disability, hospitalization, cognitive decline and all-cause mortality.[178] Thus, even the maintenance of gait speed and prevention of further decline may be a relevant goal of RT for older adults living in the community with mobility disability. The remaining three studies included were of shorter duration (12-24 weeks) and prescribed exercise was of low intensity (no explicit mention of percentages of one repetition maximum were given).[127,159,162] Therefore RT may improve usual gait speed but higher-intensity prescriptions may yield better results.

Our study did not show an effect of RT on fast gait speed, which may be attributed to the types of RT protocols used. Fast gait speed is related to the capacity to generate force quickly and type II muscle fiber content, which decline more rapidly with age.[7] Power training (i.e., lower loads but moved with high velocity) may be a more appropriate modality to focus on increasing fast gait speed.[179] Only one study included in this review utilized power training (3 sets x 8 repetitions at 70-80% of one RM performed as quickly as possible for 12 weeks) in which fast gait speed was measured and found a statistically significant improvement in fast gait speed of 0.09 m/s.[165] Future research focused on power training for those with mobility disability may help discern its effect on fast gait speed.

In sensitivity analysis, we found that RT was superior to control for improving SPPB scores when provided as a sole intervention, although this result should be interpreted with caution with only three of nine studies included. A one-point change in SPPB score is considered a clinically meaningful change, where our analysis showed an improvement of 0.46 points. Arguably, the SPPB is a composite index that consists of three items, of which only five time sit-to-stand is specific to functional strength. RT interventions may have improved functional strength score of the SPPB, whereas multicomponent programs were variable in nature and not specific to RT and thus may have lacked the necessary training stimulus to improve the SPPB score.

Overall, findings from this review suggest that RT shows promise for its capacity to improve physical function in older adults with mobility disability. Relevant to knowledge translation and replication of interventions in the community, it is important that training variables, particularly those related to progressive overload, adaptation, and intensity, are considered when conducting research studies and explicitly stated in the methods sections of each intervention trial. Appropriate progression of RT loads (progressive overload) throughout training is necessary to continue to challenge the musculoskeletal system and prevent stalled progress due to adaption. Among the studies included in the current review, progression was described in half (n=12/24, 50%) and of those, only eight[115,126,162,166–168,170,172] (n=8/24, 33%) provided specific criteria for progression. The remaining studies[158,162,169,171] described progression without objective criteria, based on the quality of the movement or encouragement of the facilitator, which will be challenging for clinicians to replicate. Given that exercise progression using the outline of frequency, intensity, time, and type is critical to overcoming training adaptation, future RT interventions should establish a clear, objective progression schedule or criteria to facilitate knowledge uptake and implementation.

The intensity of RT is another critical variable of loading schemas. For RT protocols to effectively drive strength gains and functional improvements, prescription of load and volume of sets and repetitions must be sufficient to create stress on the body to allow for meaningful improvements. Despite the intensity of RT varying widely across interventions, ranging from "low-intensity"[127] to high loads of 80-90% of 1 RM,[115] we report training-related improvements in walking speed, walking capacity and lower limb strength. It is possible that even lower-intensity stimuli were of sufficient dosage to drive adaptation in deconditioned older adults.[180] While higher loading typically creates larger improvements, these may not be initially feasible for those with significant impairment levels.[180] Thus, minimal thresholds of exercise provide an opportunity for early functional gains to gradually increase activity towards optimal dosages of intensity.[180] Evaluating both minimally effective dosing and high-intensity loading are clinically relevant for this population to aid clinicians with RT exercise prescription.

Power training should also be specifically highlighted. Power training is a modality in which the concentric phase of a movement is performed as quickly as possible. In this review, four studies evaluated the use of power training for optimizing physical function in older adults, using an intensity of 70-80% of one repetition maximum.[158,165,167,168] Power training may be of particular benefit for older adults with mobility disability, as it has been shown the loss of muscular power occurs earlier and at a quicker rate in older adults than loss of muscular strength.[181]

Study Limitations

There were several limitations identified in this review. Firstly, many studies demonstrated a moderate or high risk of bias,[18] although this did not alter the conclusions of the study. Secondly, a lack of consistency in the criteria for mobility disability[18,147] contribute to heterogeneity in study populations evaluated in the present review. Establishing a consistent definition of mobility disability will help create consistency in study populations and thus aid in the determination of optimal resistance exercise prescription (e.g., dosage, duration, and progressive overload protocols) for individuals with mobility disability as well as those with its precursor, pre-clinical disability. Currently, at least six different definitions and cut-off scores have been identified across a variety of outcome measures.[47,49] Narrowing this down to a composite score of one or two outcomes or a gold standard outcome measure may allow for more homogeneous conceptualization of mobility disability. Finally, data was insufficient to conduct subgroup analysis by mobility status (mobility disability vs. pre-clinical disability). There may be different dosages or needs for individuals with preclinical disability as compared to those with established mobility disability. Given the spectrum of capacity described in mobility disability,[18,147] future research may establish unique parameters for the effectiveness of preventative programs for persons with preclinical disability.

2.6 Conclusions

Despite these gaps, RT appears to be a robust intervention, either in isolation or as part of a multi-component program, that incurs improvement in lower extremity strength, aerobic capacity, and usual gait speed for those with pre-clinical disability and mobility disability. RT can improve physical function, thereby allowing older adults to live independently for longer without the need for increased caregiver support, healthcare interventions or transitions into institutionalized care.

CHAPTER 3: High- Intensity Enhanced Resistance Training (HEaRT) to optimize independence and quality of life in older adults at-risk for or with established mobility disability: a pilot randomized controlled trial.

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Chapter formatted for submission to Physiotherapy Theory and Practice

3.1 Abstract:

Objectives: 1) To assess the safety and feasibility of a high-intensity resistance training program (HEaRT) in community-dwelling older adults with mobility disability or preclinical disability, and 2) To estimate the effect of HEaRT compared to a moderate-intensity program (MOD-RT) on outcomes related to mobility status, physical function, walking endurance and muscular strength.

Design, Setting, Participants: This was an assessor-blinded pilot randomized controlled trial of 49 adults aged 60-87 years with preclinical or mobility disability, conducted in community-based gyms.

Outcome Measures: Safety and feasibility of HEaRT were determined by 0% occurrence of intervention-related serious adverse events and >80% attendance, respectively. Clinical outcomes, assessed pre- and post-intervention, included transitions in mobility status, maximum isometric knee extensor strength, grip strength, the Short Physical Performance Battery (SPPB), 6-minute walk test (6MWT) distance, Timed Up and Go, Mini-Balance Evaluation Systems Test (Mini-BEST), Berg Balance Scale (BBS) and Activity-specific Balance Confidence (ABC) Scale.

Interventions: HEaRT and MOD-RT were performed twice weekly running for 12 weeks in group format. Exercises in HEaRT were prescribed 3 sets of 3-5 repetitions of multi-joint exercises at rate of perceived exertion (RPE) intensity 7-8/10; MOD-RT was prescribed 3 sets of 10-15 repetitions of single joint exercises at RPE 5-6/10.

Results: Of 49 participants enrolled, 46 completed the intervention (n=23 HEaRT; n=23 MOD-RT). There were no serious adverse events related to HEaRT. Average attendance was 82% of classes in the HEaRT group. More participants in the HEaRT group exhibited improvements in self-reported mobility status (12/23 (52%) reported improvements in HEaRT vs 5/23 (22%) in

MOD-RT; p=0.01). There were no significant group-time interactions in clinical outcomes (p=0.23-0.93), but a significant time effect was demonstrated in 6MWT distance (time effect p=0.01), TUG time (time effect p=0.02), and BBS score (time effect p=0.01). There was a small effect size in favor of HEaRT in 6MWT, ABC Scale, BBS and SPPB (d=0.2-0.3).

Conclusions. HEaRT is safe, feasible and effective for improving mobility status in older adults with preclinical disability or mobility disability and is similarly effective to MOD-RT in improving walking endurance, mobility, and balance. This study highlights that older adults can tolerate a high-load, low-volume resistance training schema using compound exercises that mimic activities of daily living.

Trial Registration: clinicaltrials.gov identifier: NCT02593084

3.2 Introduction

Mobility disability describes a state where persons experience difficulties completing activities of daily living.[18,73] In 2020, 31% of community-dwelling older adults reported mobility disabilities related to self-care.[50] Mobility disability has been linked to lower quality of life, risk of falls, and transition from independent living to institutionalized care.[18,73] Preceding overt mobility disability is preclinical disability (PCD), a state of subclinical decline.[73] Persons with PCD are at a heightened risk for falls,[52] and PCD is predictive of future mobility disability.[76] PCD may be a potential target for interventions to improve physical function and prevent transitions to worsening mobility.[76,182]

The risk of poor functional outcomes resulting from PCD may be mitigated through strategies to reverse age-associated losses in muscle strength, such as regular participation in resistance training (RT).[39] RT can increase muscular strength and physical function in community-dwelling older adults that report activity limitations.[39,120] However, the RT prescription must be at least moderate intensity (RPE 5-6/10) to provide a sufficient stimulus for muscular strength gain.[30] In clinical practice, healthcare practitioners often provide recommendations for low-intensity RT or "senior friendly" exercises due, in part, to a belief that older adults are unable to participate in high-load or high-intensity resistance training,[144] and likely compounded by the sparse body of research utilizing a high-load resistance training schema in those with mobility disability.[183] Indeed, underdosed exercise programs for older adults is a major issue in the physical therapy profession and highlighted it as a much needed knowledge translation initiative to increase the intensity of prescribed exercises for older adults in rehabilitation settings.[137]

Intensity in RT is achieved through increasing repetitions to approach muscular failure or an increase in external load lifted.[184,185] It is possible that high-intensity RT intensities may yield even greater benefits for physical outcomes for community-dwelling older adults.[30] The LIFTMOR trials were the first to demonstrate that high-load functional training (>85% 1RM) was safe and feasible in older persons with moderate-to-severe osteoporosis.[145,146] Their studies support the feasibility of high-load RT and its positive effects in improving femoral neck bone mineral density, lower extremity strength, grip strength and gait speed.[145,146]

Only three studies have specifically investigated the use of RT of any intensity in older adults with PCD.[14,172,186] The largest of these was the LIFE-P randomized controlled trial, which included over 1600 older adults with PCD, demonstrated that a walking intervention with very low-intensity RT utilizing ankle weights was more effective than health education in reducing transitions to mobility disability.[14,14,76]

To date, no studies have utilized a high-load RT schema for individuals with PCD or mobility disability. Thus, the objectives of this pilot randomized controlled trial were 1) to evaluate the safety (occurrence of intervention-related serious adverse events) and feasibility (attendance, attrition) of a high-intensity RT program in community-dwelling older adults with PCD or mobility disability utilizing high-load and low-volume, and 2) to estimate the effects of high-intensity RT relative to moderate-intensity RT on mobility status, walking endurance, strength, physical function, and balance. We hypothesized that: 1) there would be no adverse events among participants with PCD or mobility disability related a High-intensity EnhAnced Resistance Training (HEaRT) intervention and that participants will attend at least 80% of sessions and attrition will be <20%; and 2) that high-intensity RT would yield greater improvements in mobility status, walking endurance, strength, physical function, and balance compared to moderate-intensity.

3.3 Methods

3.3.1 Trial Design

This was a two-armed multi-center assessor-blinded pilot randomized controlled trial. Participants were randomized to one of two groups: HEaRT or Moderate-intensity Resistance Training (MOD-RT). Allocation was completed by an independent third party (AT) via computer-generated random number sequence using allocation concealment, random block sizes of 2, 4, or 6 participants, and stratified by sex. Safety and feasibility data were collected throughout the study using attendance sheets and reports of adverse events (objective 1), and clinical outcomes were assessed at baseline (pre-intervention, 0 weeks) and following study completion (post-intervention, 12 weeks) (objective 2). The trial was reported following CONSORT guidelines for pilot studies.[187] The trial took place in two community fitness settings in a dense urban center (population 828,000) and a small town location (population 21,000),[188] and programs were completed in three waves of recruitment (blocked enrollment) .The study was approved by the Hamilton Integrated Research Ethics Board (#0781) and registered on ClinicalTrials.gov (trial #NCT02593084).

3.3.2 Participants.

Participants were recruited between January 2016 and September 2017 through outreach to local primary care physicians, word of mouth referral in the community fitness gyms, and social media.

Persons were eligible to participate if they were over 60 years of age, residing in the community, and had self-reported preclinical disability or major mobility limitation (mobility disability) based on the Preclinical Disability and Mobility Scale.[48] The Preclinical Disability and Mobility Scale is a self-report measure which asks participants to rate their performance on three tasks: walking two kilometers, walking half a kilometer, and climbing a flight of stairs.[48] Individuals were classified with *major mobility limitation* (mobility disability) if they reported they were able to complete one or more tasks with minor difficulty, *PCD* if they were able to manage all tasks without difficulty but reported modifications such as slower performance or fatigue, or *robust* if they did not report difficulty or modifications to any task.[48]

Persons were excluded if they were participating in power sports (for example, pickleball) or RT, were medically unable to exercise based on current guidelines, [143] or presented with severe cognitive impairment (Montreal Cognitive Assessment score ≤10).[189] The Montreal Cognitive Assessment is a 30-point screening tool with items evaluating verbal memory, language, executive function, visuospatial sense and attention.[190,191] The Montreal Cognitive Assessment is sensitive to detect both mild cognitive impairment and dementia.[190] Individuals with mild to moderate cognitive impairment were included as it is estimated that this represents 15-26% of community-dwelling older adults.[192]

3.3.3 Outcomes

Primary outcomes: Safety and Feasibility of HEaRT. We used a priori thresholds for establishing the safety and feasibility of HEaRT. Relevant data were collected throughout the intervention period. Safety was defined as 0% occurrence of serious adverse events related to HEaRT, and feasibility was defined as attendance of more than 80% of HEaRT exercise sessions.

*Secondary outcomes: Clinical Outcome Measures***.** Assessments of all clinical outcomes were completed by an assessor blinded to group allocation within one week prior to intervention start date (baseline) and within one week of the intervention end date (post-intervention). Assessors had 2-5 years of clinical experience working with older adults and received on-site training on administering all outcome measures. Baseline demographics collected included age, sex, and the number of chronic conditions through a researcher generated questionnaire.

a) ***Mobility Status.*** Transitions in mobility status were evaluated via self-report using the Preclinical Disability and Mobility Scale.[48] Test-retest reliability (intraclass coefficient = 0.72-1.00) and predictive validity has been established for future mobility limitations over a 24-month period with those with PCD being 3-6x more likely to progress to major mobility disability compared to those without preclinical impairment.[48]

b) ***Mobility Measures.*** Ambulatory capacity was assessed as the primary clinical outcome using a 6-Minute Walk Test (**6MWT)** where participants walked at their usual pace for six minutes along a 25-meter pathway. Rest breaks were permitted as required. Total distance walked was recorded in meters. The 6MWT has established construct validity with peak oxygen consumption (r=0.63-0.79) and test-retest reliability (intraclass coefficient = 0.94-0.96) in community-dwelling older adults.[193] Physical function was assessed using the **Timed Up and Go (TUG).** Participants were asked to stand up from a standard chair, walk 3 meters over a line on the floor, turn around and return to sitting. Time was measured in seconds. The TUG has shown predictive validity for physical function and risk of falls, [194,195] and high intra- and inter-rater reliability (intra-class coefficient = 0.90-0.96, r=0.89-1.0) in community-dwelling older adults.[193]

c) ***Strength.*** **Maximum isometric knee extensor strength** (kg) of the participant's dominant leg was used to measure lower extremity strength.[196] The knee was placed in 45 degrees of flexion, and participants generated maximum force against a handheld dynamometer placed halfway between the lateral tubercle of the tibia and the lateral malleolus. The highest value of three trials was recorded (in kg). Knee extensor strength using dynamometry has high sensitivity (0.76-0.81) and specificity (0.78-0.94) for evaluating improvement in lower extremity strength in older adults.[196] **Maximum grip**

strength (kg) of the dominant hand**,** was measured using a handheld dynamometer, and was utilized as an indicator of global body strength.[197] The elbow was placed at 90 degrees of flexion, with the shoulder and forearm in the neutral position. The highest value of three trials was recorded (in kg). Grip strength has been shown to have test-retest and inter-rater reliability of r>80 and >0.98 in older adults, respectively.[198]

d) Physical Function. Functional performance was assessed using the **Short Physical Performance Battery (SPPB).** The SPPB evaluates three items: a sequential static balance task, usual gait speed and five-times sit-to-stand. Each item is scored from 0-4, with higher scores indicating greater physical function; the maximum score is 12. The SPPB has been shown to be reliable (internal consistency Cronbach α=0.6-0.83; test-retest intraclass coefficient = 0.6-0.83), with concurrent validity established with gait speed, community ambulation and lower extremity strength (r=0.36-0.75) in older adults with mobility disability.[49,154]

e) Balance Measures. Balance was assessed through the **Berg Balance Scale (BBS)** and **Mini-Balance Evaluations Systems test (Mini-BESTest).** The BBS involves 14 functional balance tasks ranging from seated transfers to single-leg stance, with a maximum score of 56. Higher scores indicate better balance. The BBS has established content validity with known measures (r=0.62-0.91), intra-rater reliability (r=0.96), test-retest reliability (intraclass coefficient =0.98) and a sensitivity of 0.64 and specificity of 0.9 to detect falls in community-dwelling older adults when score is < 45.[193] Since there can be a ceiling effect with the BBS,[199] the Mini-BESTest was also used. The Mini-BESTest is a 14-item outcome measure comprised of four subsections: anticipatory, reactive postural control, sensory orientation and dynamic gait evaluating tasks such as obstacle navigation, reaction to external perturbation and a dual-task Timed up and Go.[200] Higher scores are indicative of better balance in each subdomain. The Mini-BESTest is highly predictive of balance and falls in community-dwelling older adults (sensitivity =0.64-0.89; specificity =0.64-0.81).[200,201] Criterion validity has been established with the BEST-test and BBS (r=0.79-0.96), and reliability has shown to be excellent (inter-test reliability intra-class coefficient = 0.72-0.99 test-retest reliability intra-class coefficient = 0.80-0.97).[201] Balance confidence was assessed using the **Activity-Specific Balance Confidence Scale (ABC Scale).** Balance confidence is associated with fear of falling, an important consideration for community ambulation.[202] The ABC scale is a 16-item questionnaire that asks participants to rate their self-confidence in completing tasks of increasing complexity, from walking around the home to navigating on and off an escalator. Items are scored between 0-10, with a maximum score of 160 points. Higher scores indicate higher self-efficacy in balance.[203] The ABC scale has excellent internal consistency (Cronbach's alpha = 0.96) and concurrent validity with fear of falling outcome measures (r=0.88).[204]

3.3.4 Interventions

HEaRT and MOD-RT programs were 12 weeks in duration, consisting of twice-weekly sessions, approximately one hour in duration. Twelve weeks was selected as the training duration to provide sufficient exposure to high-intensity training to assess safety and feasibility and has been demonstrated as the minimally effective intervention length for strength improvements in healthy older adults with muscular weakness.[205,206] Both programs used a group-based format with 8-10 participants per class. Both interventions were delivered by a registered physiotherapist or trained kinesiologist. Both HEaRT and MOD-RT included a ten-minute aerobic warm-up, adding 5-10 pounds of weight each set until the desired intensity was achieved, and concluded with a five-minute cool-down of stretching exercises. Modifications to the range of motion or placement of load were made as needed in consideration of pre-existing musculoskeletal injury or functional ability. Attendance, exercises performed along with load, repetitions, sets and rates of perceived exertion were recorded in exercise logs by the participant. Sessions were scheduled on non-consecutive days to allow appropriate recovery time.

a) ***High-intensity Enhanced Resistance Training (HEaRT).*** HEaRT provided a higher-load, lower-repetition RT schema, consistent with evidence that programs with <6 repetitions at loads >80-85% of 1-Repetition Maximum may be most effective for building maximal strength. [143,207] Participants performed All exercises in HEaRT were complex, multi-joint movements selected to strengthen movement patterns associated with activities of daily living, including squats (standard or to a bench), step-ups, deadlifts, and overhead shoulder presses. Exercises were progressed through increasing repetitions or weight every 1-2 weeks or when perceived exertion was below 7/10.

b) ***Moderate-intensity exercise group (MOD-RT)***. MOD-RT utilized higher repetition schemas where participants completed three sets of 10 repetitions at a rating of perceived exertion of 5-6/10 or 60% of 1-Repetition maximum, the minimum load needed to drive change in muscular strength adaptation.[143,207] Exercises in MOD-RT were single-joint movements selected to target key muscle groups important for activities of daily living, such as knee extensions, standing hamstring curls, side-lying leg raises and bicep curls. Exercises were progressed through increasing repetitions or weight every 1-2 weeks or when RPE was below 5/10.

3.3.5 Sample Size

The primary objective of this pilot trial was to establish the safety and feasibility of HEaRT, thus we aimed to recruit approximately 50 individuals as this was deemed sufficient for pilot studies to assess feasibility.[208] This sample size would also be sufficient to detect a change in the 6MWT (primary clinical outcome) (sample size of 32 is required to detect a medium effect size (0.3) in the 6MWT (type I error 0.05, type II error 90%; 20% attrition rate).[209]

3.3.6 Data Analysis

Baseline characteristics were described as means and standard deviations for continuous data and counts and percentages for categorical variables.

To address objective 1, safety and feasibility data were analyzed using descriptive statistics (counts and frequencies). For objective 2, analysis was intention-to-treat. All clinical outcomes were first assessed for normality of baseline values using a Shapiro-Wilk test. Linear regression were conducted with the outcome of interest as the dependent variable, and group and time as the independent variables. Missing data was deemed missing at random; therefore a sensitivity analysis evaluating key covariates leading to participant drop-out and skewing of the data set was not performed.[210] Multiple imputation for continuous variables was used to ensure all data were accounted for. Change scores from pre- to post-intervention were calculated and effect size calculations were performed using Cohen's d (([mean change HEaRT minus mean change MOD-RT]/Pooled SD). A small effect size was considered if d=0.2-0.49, a medium effect size if d=0.5-0.79, and a large effect size was reported if d≥0.8.[211] Pearson's Chi^2 was utilized to assess transitions in mobility status. Analyses were conducted using STATA (Texas, United States, version 14.2) with an alpha level set at $p < 0.05$.

3.4 Results

The flow of individuals through the study is presented in Figure 3.1. Forty-nine individuals consented and were enrolled in the study. Baseline characteristics are presented in Table 3.1. Both groups presented with on average 3-4 different chronic conditions.

Cardiovascular disease (n=11 in HEaRT, n=13 in MOD-RT) and arthritis (n=14 in HEaRT n=13 in MOD-RT) were most prevalent. Three individuals withdrew from the study for reasons unrelated to interventions (HEaRT n=2; MOD-RT n=1); thus, 46 (HEaRT n=23; MOD-RT n=23) completed the trial. Missing data was deemed missing at random, and so missing data were imputed using linear regression.

FIGURE 3.1. Participant flow through study design

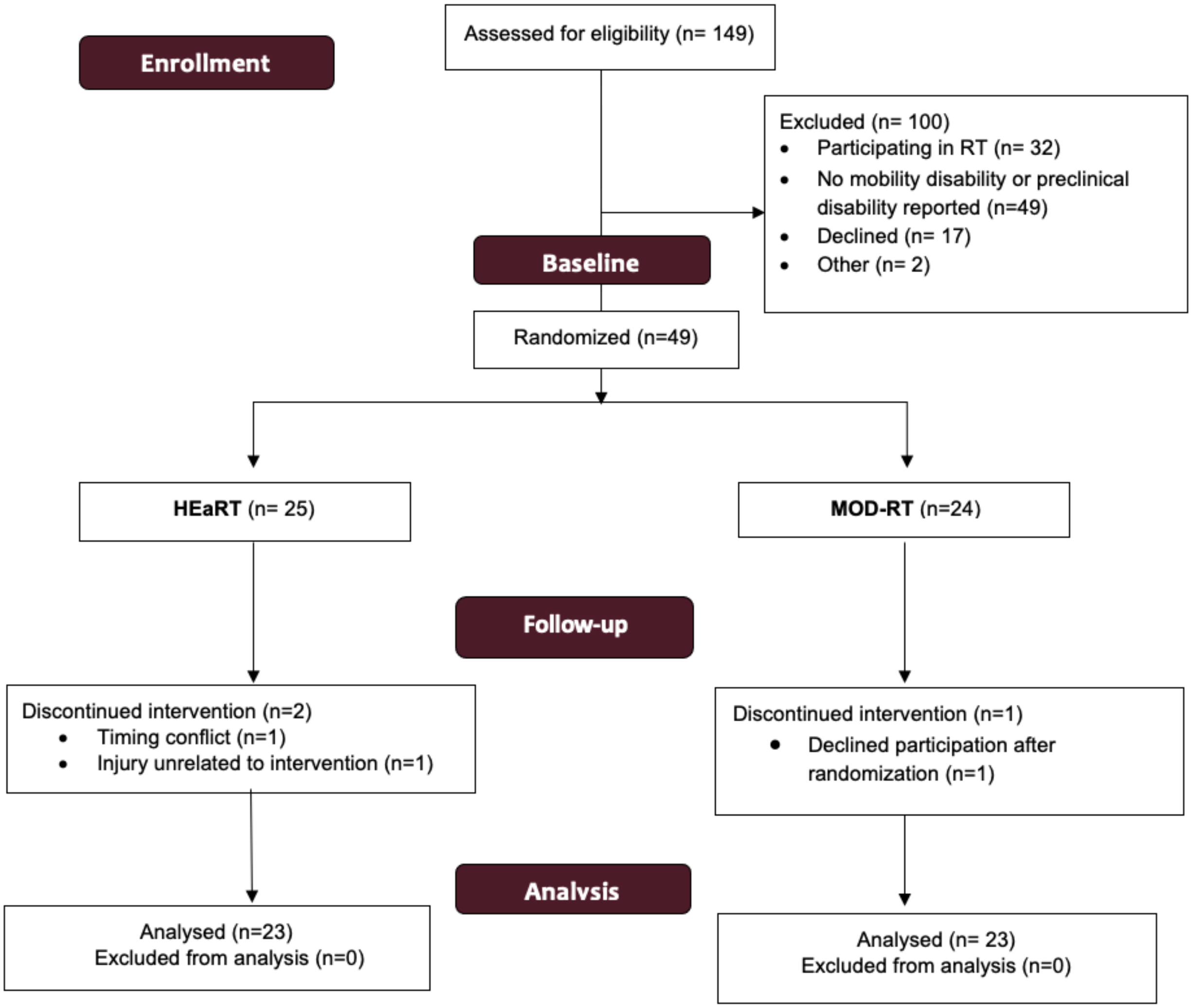


TABLE 3.1. Baseline characteristics by group

Variable	HEaRT N=25	MOD-RT N=24
Age, years	72 (9)	72 (7)
Sex n (%):		
Female	14 (56%)	16 (67%)
Male	11 (44%)	8 (33%)
Number of Chronic Conditions	3.4 (2.2)	3.4 (1.6)
Mobility Status, n (%):		
Preclinical Disability	16 (67%)	15 (63%)
Mobility Disability	8 (33%)	9 (37%)

Values are displayed as means (standard deviation) or counts as appropriate.
Abbreviations: HEaRT= High-intensity enhance resistance training; MOD-RT = moderate intensity resistance training

3.4.1 Safety and Feasibility

There were no serious adverse events related to the HEaRT intervention. One adverse event unrelated to the intervention (injurious fall) resulted in withdrawal from the study. Two individuals in the HEaRT group reported significant muscle soreness requiring modifications to the load applied (changed position of load or decreased for one week until soreness resolved) or to the range of motion of the movement (reduction in range of motion), which allowed individuals to remain in the study. Ratings of perceived exertion were maintained within the new parameters to continue with target intensity of the study intervention.

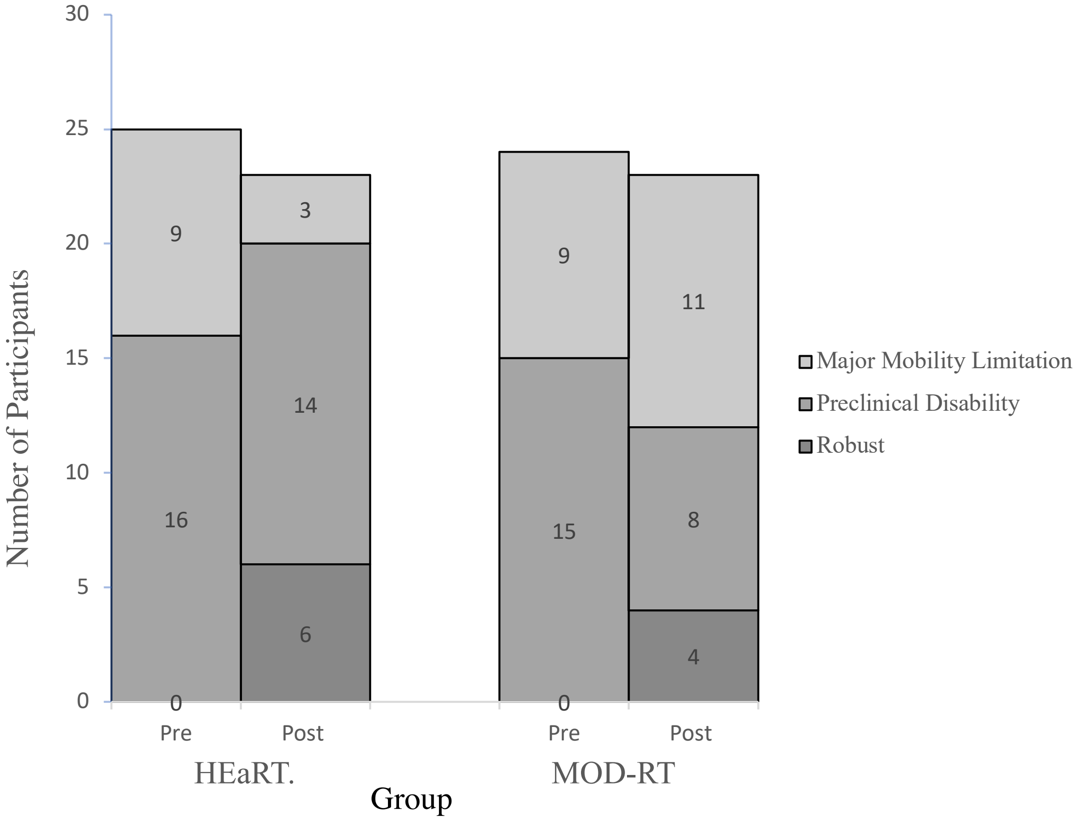
Participants in the HEaRT group attended 82% of classes (minimum 12 (50%), maximum 24 (100%) classes attended).

In the MOD-RT group, there was one incident of significant delayed onset muscle soreness. This was improved through modification of load and range of motion and the participant remained in the study. The MOD-RT group attended 87% of classes (minimum 11 (46%), maximum 24 (100%) classes).

3.4.2 Transitions in mobility status

Figure 3.2 depicts changes in mobility status for HEaRT and MOD-RT groups based on participant responses to the Preclinical Disability and Mobility Scale.

FIGURE 3.2. Transitions in mobility status pre- to post-intervention in High-intensity enhanced Resistance Training (HEaRT) and Moderate-intensity resistance training (MOD-RT) groups, as assessed by the Preclinical Disability and Mobility Scale.



More participants in the HEaRT group reported improvements in mobility compared to the MOD-RT (χ^2 (df 2, n=46): 8.25, p=0.01). Twelve of 23 participants in the HEaRT group (52%) reported improvements in mobility status (n=6 from major mobility limitation to PCD, n=6 from PCD to robust) compared to 5 of 23 (22%) participants in the MOD-RT group (n=2 from major mobility limitation to robust, n=1 from major mobility limitation to PCD, n=2 from PCD to robust). Five of 23 (22%) of individuals in the MOD-RT group (22%) reported worsening mobility states compared to 1 of 23 (4%) in the HEaRT group.

Clinical Outcome Measures. Table 3.2 outlines pre- to post-intervention outcome scores between groups for all strength, mobility, and balance measures. There were no group-time interactions in any clinical outcome measure (p=0.36-0.93). There was a within-group improvement in 6MWT, TUG, and BBS for both groups following intervention (time effect p=0.01-0.02, Table 3.2). There were no differences over time in the SPPB, Mini-BESTest, ABC Scale, maximum knee extensor strength or maximum grip (time-group interaction, p=0.05-0.93, Table 3.2).

There were small effect size improvements in favor of the HEaRT group in the 6MWT, ABC Scale, BBS and SPPB (d=0.2-0.3; Table 3.2).

TABLE 3.2. Changes in Clinical Outcomes by group, pre- to post-intervention. Values displayed are means ± standard deviations.

Outcome Measure	**Group Assigned**	**Pre Mean (SD)**	**Post Mean (SD)**	**ANOVA**		**Effect Size**
				Time* Group	Time	Cohen's d
6MWT distance (m)	HEaRT	321.5 (100.4)	400.5 (121.5)	0.48	0.01*	0.30
	MOD-RT	367.8 (100.8)	416.0 (88.7)			
TUG (s)	HEaRT	9.8 (2.4)	8.3 (1.7)	0.69	0.02*	0.13
	MOD-RT	9.7 (2.5)	8.5 (2.0)			
ABC Scale (points)	HEaRT	137.3 (25.1)	148.4 (10.0)	0.36	0.06	0.22
	MOD-RT	136.1 (17.9)	140.1 (20.3)			
BBS (points)	HEaRT	50.3 (3.8)	53.1 (2.6)	0.57	0.01*	0.20
	MOD-RT	51.1 (4.3)	53.2 (3.3)			
Mini BESTest (points)	HEaRT	22.1 (4.4)	23.9 (2.4)	0.93	0.09	0.03
	MOD-RT	21.7 (3.6)	23.4 (3.9)			
SPPB (points)	HEaRT	9 (2.3)	9.5 (1.8)	0.63	0.33	0.27
	MOD-RT	9.3 (2.1)	9.4 (1.9)			
	HEaRT	22.3 (16.6)	21.5 (8.3)	0.93	0.82	0.01

Max Knee extensor strength (kg)	MOD-RT	20.1 (14.7)	19.6 (6.7)			
Max Grip Strength (kg)	HEaRT	33.8 (18.0)	34.5 (12.1)	0.82	0.93	0.01
	MOD-RT	33.4 (24.1)	33.4 (16.8)			

Abbreviations: HEaRT= High-intensity enhance resistance training; MOD-RT = moderate intensity resistance training; 6MWT = Six-minute walk test; TUG = Timed up and Go; ABC Scale = Activity-specific balance confidence scale; BBS= Berg Balance Scale; Mini-BESTest= Mini Balance Evaluations systems Test; SPPB= Short Physical Performance Battery

3.5 Discussion

The results of this pilot study demonstrate that high-intensity RT using lower repetitions and higher load is safe and feasible for community-dwelling older adults with PCD and mobility disability. There were no serious adverse events and high attendance rates within the HEaRT program. Minor incidences of muscle soreness were effectively managed with modifications to the exercise program to reduce irritability, and enrolment in the study was maintained. Our study employed several strategies including involvement of, and supervision by, health and fitness professionals, a group format for a social atmosphere, and exercise logging for progression that have been shown to increase adherence to exercise interventions for older adults and those with chronic disease.[212]

Of importance to older adults, incident disability is predictive of future disability[51] and health events such as illness can result in permanent disabilities[213] and mobility limitations.[42] There is a critical need to identify appropriate and time-efficient interventions in the event of incident illness for older adults to improve physical function, mitigate transitions in mobility status, and thus maintain independent community living.[213] Our findings are similar to a much longer (18-month) multi-component program of walking and very low-intensity RT[76] but used a shorter (12 week) higher-intensity training program. The improvements in self-reported mobility status observed suggest that meaningful improvements can be observed in a condensed time frame when higher intensities of training are used. Moreover, the complex, functional movement patterns used in HEaRT were designed with the exercise principle of specificity in mind to enable older adults to see strength improvements in the movements involved in day-to-day tasks.[112,145] For example, we included movements such as a deadlift or hip hinge to mimic the motion of picking objects up from the floor, and an overhead shoulder press to mirror the action of putting items away in upper cabinets. This is in contrast to the MOD-RT group and the intervention in the LIFE-P study[214] which utilized single joint exercises and lower-load exercise prescriptions. Additionally, it is possible that the HEaRT paradigm exposed participants to external loads exceeding those typically encountered in daily tasks,[44,215] which may have contributed to higher confidence or self-efficacy in performing activities of daily living and thus self-reported mobility. We acknowledge however that we did not measure self-efficacy in ADLs, but future research may investigate the possible relationship between the role of high-load RT on perceived confidence in daily activities.

Contrary to our hypothesis, we did not observe greater improvements in 6MWT, TUG, and BBS in the HEaRT group compared to MOD-RT. It is possible that the exercise stimulus provided through both intervention arms was sufficient to benefit older adults with or at risk for mobility disability. This is aligned with previous studies just as the LIFE-P study[14] and may highlight that initiating any exercise program among previously sedentary, inactive individuals would likely incur benefits irrespective of intensity.[216] Indeed, we reported in Chapter 2 in our systematic review that RT is effective across a range of intervention intensities (low to high) in improving functional outcomes including the 6MWT in those with mobility disability.[217] We note that the exercise prescription and progression for the MOD-RT group met established RT guidelines for community-dwelling older adults.[121] We felt it was important to use two active intervention arms, rather than utilizing a no-intervention control arm. to examine the impact of load and types of exercises. The lack of between-group differences in functional outcomes however may be a product of an active comparator arm that met guideline recommendations was diligently progressed with pre-established parameters. Though not significant, the small effect size observed in several outcome measures (6MWT, ABC Scale, BBS and SPPB) suggests promise with HEaRT. It may be possible that a longer duration intervention period may be needed to observe differences over an active comparator arm such as MOD-RT. Nonetheless, our findings still have application to practice; given similar functional improvements with both moderate- and high-intensity RT, there may be opportunities to cater exercise to individual preferences.

We noted that 5 of 23 individuals (22%) in the MOD-RT group reported worsening mobility, compared to only one participant (4%) in the HEaRT group. Worsening states of mobility are concerning as they translate into to a greater need for caregiver support, assistance with activities of daily living and eventual transitions from community to institutionalized settings.[46] Perceived mobility, as measured by self-report, can influence participation in daily behaviors whereby individuals who self-report lower walking capacity tend to be more sedentary, despite scoring well on performance-based outcome measures.[218] While MOD-RT was dosed according to guideline recommendations,[121,124] its focus was primarily on simple, single-joint movements which may have lacked specificity to activities of daily living, limiting the opportunity to enhance mobility and physical function in daily tasks.

This study has several strengths. The interventions were administered by a registered physiotherapist and trained kinesiologists who carefully applied progression throughout the training protocol and expert supervision was given considering the high-intensity nature of this novel intervention. Secondly, this study took place in community fitness facilities demonstrating the broad potential of this program to be integrated into common community-based settings as no specialized equipment is required. As a pilot study, we selected an intervention duration of 12 weeks that would provide sufficient exposure to lower-repetition high-intensity RT to assess its safety and feasibility in this participant population.[219]

Several limitations for this study also exist. There was no follow-up after the end of the study, therefore we cannot determine whether exercise behaviors continued beyond the intervention phase and whether training-related benefits were sustained during a follow up period. However, as a pilot study, our primary objective was to first assess the safety and feasibility of this type of intervention in older adults with PCD and mobility disability. We acknowledge that the intervention duration may not have been sufficient to evaluate the between-group differences for other clinical outcomes. Future research might focus on a longer-duration intervention, determine whether the intervention results in changes in exercise behaviour beyond the program, and whether changes in self-reported mobility status may be maintained over time in older adults with PCD or mobility disability.

3.6 Conclusions

Our study was the first to demonstrate that low-repetition, high-load functional RT is safe and feasible for older adults with mobility limitations. RT programs incorporating complex, multi-joint movements may result in greater changes in self-reported mobility status and similar improvements in functional mobility compared to moderate-intensity RT. While we did not see improvements in our primary functional outcome measure, effect size estimates indicate that moving to a larger intervention trial is warranted.

Acknowledgements: We would like to thank Nicholas Prevett, Victoria Iantorno, and Bonnie Campbell for their contribution in the execution of this research study.

CHAPTER 4: An Ounce of Prevention: a substudy of pre-frail older adults from the HEaRT pilot randomized controlled trial

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Chapter will be formatted for submission to Physiotherapy Canada

4.1 Abstract

Objectives: To assess the safety and feasibility of a high-intensity enhanced resistance training program (HEaRT) for community-dwelling older adults with prefrailty; and to estimate the effect of HEaRT compared to a moderate-intensity program (MOD-RT) on functional outcomes related to physical function, muscular strength, balance, physical activity, health-related quality of life and physiological measures related to the muscular area and density.

Design, Setting, Participants: This was a substudy of an assessor-blinded pilot randomized controlled trial of persons with preclinical disability and mobility disability. This substudy included a subset of 36 participants (age 64-87 years) with prefrailty, defined as one or two physical phenotypes of frailty (muscular weakness, slow gait speed, fatigue, unexplained weight loss, physical inactivity). The trial was conducted in two community-based gyms. Participants were randomized in the larger trial into HEaRT or MOD-RT, and functional outcomes were assessed pre- and post-intervention. Participants with prefrailty were also assessed 8 weeks post-intervention.

Outcome Measures: Thresholds for safety and feasibility of HEaRT were established at 0% occurrence of intervention-related serious adverse events and >80% attendance, respectively. Functional outcomes included physical function (6-minute walk test (6MWT) distance, Short Physical Performance Battery (SPPB), Timed Up and Go), muscular strength (maximum isometric knee extensor strength and grip strength), balance (Mini-Balance Evaluation Systems Test (Mini-BEST), Berg Balance Scale (BBS)), balance confidence (Activity-specific Balance Confidence (ABC) Scale), and physical activity (Rapid Assessment of Physical Activity (RAPA)). For this substudy, participants with prefrailty were also assessed for health-related quality of life using the Short Form-36 and muscular mass and density using peripheral Quantitative Computed Tomography (pQCT).

Interventions: Interventions were conducted 2x/week for 12 weeks in a group format. HEaRT was prescribed at 3 sets of 3-5 repetitions of multi-joint exercises at a rating of perceived exertion of 7-8/10; MOD-RT was prescribed at 3 sets of 10-15 repetitions of single joint exercises at rating of perceived exertion of 5-6/10.

Results: Thirty-six participants from the larger trial presented with prefrailty (n=18 HEaRT, n=18 MOD-RT), of which 32 (89%) completed all assessments (n=15 HEaRT; n=17 MOD-RT). There were no serious adverse events related to HEaRT, and average attendance was 85% of classes. There were no group-by-time interactions in functional outcomes (p=0.15-0.86). Individuals in both groups reported improvements in the physical function subscale of the SF-36 (p=0.02) and increased participation in resistance training at 8-week follow-up as reported by the RAPA (p=0.01). A medium effect size in the SPPB (d=0.69) and a small effect size in the ABC scale (d=0.44) were seen. There was a medium effect size in favor of MOD-RT for grip strength (d=0.69).

Conclusions. HEaRT appears to be safe and feasible for older adults with prefrailty. Future studies examining the impact of high-load RT focused on those with prefrailty are warranted.

Trial Registration: clinicaltrials.gov identifier: NCT02593084

4.2 Introduction

With an increasing aging population, attention has turned to improving health status and preventing functional decline for older people.[220,221] Many older adults wish to age in place, highlighting the need for interventions to optimize physical function across the lifespan.[1] Clinical geriatric syndromes are spectrum conditions that arise from a constellation of signs and symptoms, presenting across multiple organ systems, which result in impairments in physical function.[222] Frailty is a geriatric syndrome that has been the target of much research due to its impact on health outcomes and mobility for older adults.[59,86,223] Frailty is characterized by an increased vulnerability to external stressors due to loss of physiological resiliency.[17,224] Individuals with worse frailty are at higher risk for negative health outcomes, including increased risk of mortality, hospitalization, institutionalization, and falls and have increased healthcare utilization compared to their non-frail peers.[59,86,223–226]

Frailty is not an all-or-none phenomenon; it exists across a spectrum.[54,224] Frailty is often conceptualized by changes in physical characteristics, most commonly by the Physical Phenotype of Frailty, which describes five physical attributes that may be present in those with frailty: muscular weakness, slow gait speed, fatigue/lethargy, unexplained weight loss, and physical inactivity.[17] Individuals presenting with three to five attributes are deemed frail, one or two physical attributes are prefrail, and zero attributes are considered robust.[17,224]

Estimates suggest that approximately 50% of community-dwelling older adults present with prefrailty and are at heightened risk for future frailty.[227,82] Researchers have explored interventions aimed at improving frailty once it has been established,[109,133,160] but longitudinal data suggest there may be a “point of no return” where the likelihood for clinically meaningful improvement in frailty status is significantly reduced.[228] This points to a need to look upstream at the prefrail state to take a preventative approach. Improvements in physical function for those with prefrailty may be critical for reducing the downstream impacts of frailty.[59,75,223,226]

Mobility disability and frailty overlap in their definitions and constructs. Both give rise to difficulties in physical function,[42,224,229] and both have precursor states (preclinical disability and prefrailty).[73,230,231] Moreover, low muscular mass and strength are hallmark features of mobility disability which are also often seen in both frailty and prefrailty.[17,125] Worth noting muscular weakness is the most common, and often the first, prefrailty criterion to manifest in community-dwelling older adults.[129]

In Chapter 3, we reported the results of a pilot RCT demonstrating that a high-intensity enhanced resistance training (HEaRT) is safe and feasible for older adults with mobility disability and may lead to greater improvements in self-reported mobility status compared to a moderate-intensity resistance training program. Given the overlap between mobility disability, frailty and their precursors states of preclinical disability and prefrailty, RT interventions such as HEaRT may benefit individuals living in the community with prefrailty.[232] Of note, the need for safety and feasibility data for the potential application of RT may be particularly relevant for this population, as individuals with prefrailty and frailty are considered to be a higher risk group than preclinical mobility disability.[233,234] This is due to added considerations of comorbidity, heightened proinflammatory biomarkers, and increased risk for all-cause mortality.[233,234]

To date, one quasi-experimental non-controlled study has provided preliminary evidence for applying high-intensity RT as part of a multicomponent program for those with prefrailty, although this study used a higher-repetition schema.[112] Safety, feasibility and preliminary estimates of the effectiveness of high-load, low-volume RT for prefrail individuals has yet to be examined within a randomized controlled design.

Participants identified as prefrail from the HEaRT study (Chapter 3) were included in this substudy, with additional clinical outcomes and an added follow-up timepoint. The objectives were: 1) to evaluate the safety (occurrence of adverse events) and feasibility (attendance and attrition) of HEaRT in community-dwelling older adults with pre-frailty, 2) to estimate effects of HEaRT on functional outcome measures (walking endurance, knee extensor strength, balance and health-related quality of life) and physiological outcomes (muscular mass and area) immediately post-intervention and at 8 week follow-up as compared to a moderate-intensity RT program (MOD-RT). We hypothesized that: 1) there would be no adverse events among participants with prefrailty related to the HEaRT intervention and that participants would attend at least 80% of sessions and attrition would be <20%; and 2) that high-intensity RT would yield greater improvements in mobility status, walking endurance, strength, physical function, and balance compared to moderate-intensity and those results would be sustained over an 8-week follow up period.

4.3 Methods

Trial Design. This was a substudy of the HEaRT study that was the focus of Chapter 3, a multi-center assessor-blinded pilot randomized controlled. This study included only the subset of participants who presented with prefrailty.

The design for the HEaRT study was previously described in Chapter 3 but in brief, the study took place in two community fitness settings (dense urban center, and smaller town location), and completed in three waves of recruitment (blocked enrollment with random block sizes of 2, 4, or 6 participants,). Randomization (1:1 into HEaRT or MOD-RT, stratified by sex) was completed through a computer-generated random number sequence by an independent third party (AT).

Assessors were blinded to group allocation. Assessments were conducted before and after the 12-week intervention period and at 8-week follow-up. Assessors (one physiotherapist and three kinesiologists) participated in a two-hour training session to administer functional outcomes. This study extended the HEaRT pilot trial to include additional measures of muscular area and density for a subset of participants, health-related quality of life for all participants, and a follow-up assessment 8 weeks beyond the intervention period.

Safety and feasibility data were collected throughout the 12-week exercise intervention through the use of exercise logs with anchoring questions (Objective 1), and functional outcomes were assessed at baseline (pre-intervention, 0 weeks), immediately post-intervention (12 weeks), and after 8-week follow-up (20 weeks) (Objective 2).

The HEaRT study was approved by the Hamilton Integrated Research Ethics Board (HiREB #0781) and amended for the current substudy to include muscular area and density for a subset of participants, health-related quality of life measurements and the 8-week follow-up timepoint. The research trial was registered on ClinicalTrials.gov (NCT02593084). Written informed consent was obtained from all participants.

Participants. Participants were recruited for the larger HEaRT trial between January 2016 and September 2017 at both sites. Persons were eligible for inclusion if they were over 60 years of age, spoke English, were residing in the community, and had self-reported preclinical disability or major mobility limitation (mobility disability) based on the Preclinical Disability and Mobility Scale.[48] Persons were excluded from participating in HEaRT if they were currently participating in power sports (racquetball, pickle ball, squash), a resistance training program using weights, or scored ≤10 on the Montreal Cognitive Assessment score indicating severe cognitive impairment[189] (15-26% of community-dwelling older adults present with mild to moderate cognitive impairment;[192] thus only those with severe impairment were excluded).

To be included in this analysis, individuals presenting with prefrailty were identified as having one or two physical attributes of the Physical Phenotype of Frailty (unintentional weight loss, physical inactivity as measured through the International Physical Activity Questionnaire,[235] slow gait speed, low muscle strength and fatigue; yes/no) (Table 4.1).[17]

TABLE 4.1. Operationalization of frailty. Definitions are based on Fried et al., 2001[17]

Frailty Characteristic	**Criterion for presence**
Weight Loss	Unintentional loss of > 10 lbs. in the last year
Exhaustion	Self-report of fatigue or feeling unusually tired or weak in the past month
Low Physical Activity	International Physical Activity Questionnaire: Category 1: “insufficiently active” as defined by <600 metabolic equivalent min/week
Slow Gait Speed	Usual walking speed < 0.6 m/s ≤159 cm or <0.67 m/s if height >159 cm as measured by the Six-Minute Walk Test
Muscle Weakness	Low grip strength as <17 kg of force for females and <29 kg of force for men measured by a hand-held dynamometer

Outcomes

Safety and Feasibility of HEaRT. We used a priori thresholds for establishing the safety and feasibility of HEaRT among individuals with pre-frailty as follows: 0% occurrence of serious adverse events related to HEaRT and attendance of more than 80% of HEaRT exercise sessions. Feasibility was defined as an attrition rate of less than 20% during the 12-week exercise intervention.

Changes in Function, Health-Related Quality of Life and Muscular Area and Density.

a) Physical Function Measures The **6-Minute Walk Test (6MWT)** was used to assess ambulatory capacity. Participants were instructed to walk at their usual pace along a 25-meter hallway for six minutes. Rest breaks were permitted. The total distance walked (meters) was recorded. The 6MWT has construct validity with peak oxygen consumption (r=0.63-0.79) and good test-retest reliability (intraclass coefficient = 0.94-0.96) in community-dwelling older adults.[193] Functional performance was assessed using the **Short Physical Performance Battery (SPPB)** and the **Timed Up and Go (TUG).** The SPPB evaluates three items (a sequential static balance task, usual gait speed, and five-time sit-to-stand), each scored from 0-4 for a maximum total score of 12.[236] Higher scores indicate better physical function. The SPPB has moderate to high internal consistency (Cronbach α=0.60-0.83),[154] moderate to high test-retest reliability (ICC= 0.6-0.83),[154] and concurrent validity with gait speed, community ambulation and lower extremity strength (r=0.36-0.75) in older adults with mobility disability.[49,154] For the TUG, participants were asked to stand up from a standard chair, walk three meters over a line on the floor, turn around and return to sitting, with time measured in seconds.[194,195] Intra- (ICC= 0.92-0.96) and inter-rater reliability (ICC = 0.98) of the TUG have been established in community-dwelling older adults.[193] The TUG has also shown predictive validity for physical function and risk of falls in this population.[194]

b) Strength Measures. **Maximum isometric knee extensor strength** of the dominant leg was used to measure lower extremity strength.[196] The knee was positioned at 45 degrees of flexion, and a handheld dynamometer was placed halfway between the lateral tubercle of the tibia and the lateral malleolus. Participants were asked to generate as much force against the dynamometer. Three trials were performed; the highest value (kilograms) was recorded. Handheld dynamometry has high sensitivity (0.76-0.81) and specificity (0.78-0.94) for evaluating improvement in strength in older adults.[196] **Maximum grip strength** of the dominant hand was used as an indicator of upper extremity strength.[197] Grip strength was assessed using a handheld grip dynamometer, with the elbow placed at 90 degrees of flexion and the shoulder and forearm in neutral position. Three trials were performed; the highest value (kilograms) was recorded. Grip strength has been shown to have high test-retest (r >0.80) and inter-rater reliability (r>0.98) in community-dwelling older adults.[198]

c) Balance Measures. The **Berg Balance Scale (BBS)** and **Mini-Balance Evaluations Systems test (Mini-BESTest)** were used to evaluate balance**.** The BBS is a 14-item scale that measures static and dynamic balance through various tasks ranging from seated transfers to stool stepping. With a maximum score of 56, higher scores indicate better balance.[193] The BBS has established content validity (r=0.62-0.91), intra-rater reliability (r=0.96), test-retest reliability (ICC=0.98) in community-dwelling older adults, and sensitivity of 0.64 and specificity of 0.9 to identify fallers if the score is <45. [193] Given that there may be a ceiling effect of the BBS for some community-dwelling older adults,[199] the Mini-BESTest was also administered. The Mini-BESTest is a 14-item test that evaluates four areas of balance: anticipatory, reactive postural control, sensory orientation and dynamic gait.[200] Tasks range from obstacle navigation to reaction to external perturbation, to a dual-task Timed up and Go.[200] Criterion validity has been established with the BEST-test and Activity-Specific Balance Confidence Scale (r=0.62) in a community-dwelling middle age to older adult population.[200] Reliability is excellent (inter-rater reliability intra-class coefficient = 0.72-1.0; test-retest reliability intra-class coefficient = 0.8-0.97) in data synthesized from a broad range of older adults from neurological populations to post-operative knee arthroplasty.[200] Finally, balance confidence was assessed using the **Activity-Specific Balance Confidence Scale (ABC**

Scale) as balance confidence is associated with fear of falling.[202] This 16-item questionnaire rates self-confidence in completing challenging balance tasks of increasing complexity, from walking around the home to navigating on and off an escalator. Each item is scored from 0-10, summed to a maximum possible score of 160, where higher scores indicate higher self-efficacy in balance.[203] The ABC scale has excellent internal consistency (Cronbach's alpha = 0.96) and concurrent validity with fear of falling outcome measures (r=0.88) in a population of community-dwelling older adults living in a rural community.[204]

d) Health-Related Quality of Life Measure. Health-related quality of life was evaluated using the **Short-Form 36 (SF-36)**, a self-report questionnaire comprising 36 items across six subscales and two composite indices encompassing multiple domains contributing to overall perceived quality of life.[237] Each subscale is scored out of 100 points, with higher values indicating better health-related quality of life. Internal consistency of the SF-36 is high across subscales (Cronbach's alpha=0.73-0.93), and test-retest reliability was moderate to excellent (r=0.6-0.81) in a sample of community-dwelling older adults.[237]

e) Physical Activity Measures. The Rapid Assessment of Physical Activity (RAPA) assessed exercise behaviors averaged over the last week. The RAPA is comprised of two subscales: 1) aerobic physical activity (RAPA1, scored from 1-5 where 1=sedentary and 5=active), and 2) resistance training, flexibility, and balance activities (RAPA2, where 0= no flexibility or resistance training, 1 = flexibility training only, 2 = RT only and 3 = flexibility and RT training).[238] For our evaluation, we were primarily interested in RAPA2 scores to capture participation in RT, and scores of 2 and 3 were combined for analysis. The RAPA has been validated for use with community-dwelling older adults (sensitivity 0.81, specificity 0.69 for identifying exercisers versus non-exercisers) and construct validity established against other physical activity questionnaires (r= 0.48-0.54).[238]

f) Muscle area and density. Muscle area and density were quantified using peripheral quantitative computed tomography (pQCT) at all three time points for a subset (n=11) of individuals with prefrailty. PQCT was performed to assess the total area of the calf, fat area, muscular area, and muscle density measures. Precision studies and calibration were completed before measurements were taken. The non-dominant leg was imaged unless a previous fracture or hardware was present. Muscle density and cross-sectional area were calculated at 66% ultra-distal of the tibia, corresponding to the approximate maximum cross-sectional area of the gastrocnemius and soleus muscle group. While no gold standard imaging technology exists, loss of muscular density, as seen through pQCT, has been correlated with losses in physical function (including grip strength) in older adults.[239,240]

Interventions. Interventions for both HEaRT and MOD-RT groups were described in detail in Chapter 3. In brief, both groups participated in 12-week, 2x/week RT programs. Programs incorporated a 10-minute warm-up, individualized exercise intensities were prescribed using the Rate of Perceived Exertion (RPE) scale,[241] exercise modifications were made as needed, and exercise progression was completed when intensity dropped below the prescribed level.

- ***High-intensity Enhanced Resistance Training (HEaRT).*** HEaRT participants were asked to complete 3-5 sets of 3-5 repetitions of each exercise at a rating of perceived exertion of 7-8/10 (“vigorous” intensity)

- ***Moderate-intensity exercise group (MOD-RT).*** Participants completed three sets of 10 repetitions of single-joint movement at a rating of perceived exertion of 5-6/10, the minimum load intensity needed to drive change in muscular strength adaptation as outlined by exercise guidelines.[121,124]

Sample Size. The current study was a substudy of the HEaRT study, which had a primary objective to establish the safety and feasibility of HEaRT. The current substudy included only participants who presented with prefrailty (n=36), which was sufficient to evaluate the safety and feasibility of HEaRT with this population. Preliminary estimates of the effect will be used to inform future fully powered trials to examine changes in clinical outcomes.

Data Analysis. Baseline characteristics were described as means and standard deviations for continuous variables or counts and percentages as applicable for categorical variables.

Addressing Objective 1, safety and feasibility data were analyzed using descriptive statistics (counts and frequencies). For clinical outcomes addressing Objective 2, analysis was intention-to-treat for those allocated and randomized. Imputation was completed if data was deemed to be missing at random. Multiple imputation via linear regression for continuous variables was used to ensure all data was accounted for. Data were considered missing at random; thus, sensitivity analysis was not completed. Effect sizes were calculated using Cohen's d. A small effect size was considered if $d=0.2-0.49$, a medium effect size if $d=0.5-0.79$, and a large effect size was reported if $d \geq 0.8$.[211] For the pQCT subgroup data, a repeated-measures analysis of variance was completed as all subjects completed pQCT testing. Analyses were conducted using STATA (Texas, United States, version 14.2) with alpha level set at $p < 0.05$.

4.4 Results

Baseline Characteristics. Participant flow through the study is outlined in Figure 4.1. Of the 49 in HEaRT, 36 were identified as prefrail and were included in this analysis. Baseline characteristics are outlined in Table 4.2. Both groups presented with mean 4.0 chronic conditions. Cardiovascular disease (n=8 in HEaRT, n=11 in MOD-RT) and arthritis (n=10 in HEaRT n=9 in MOD-RT) were most prevalent.

Safety and Feasibility. There were no serious adverse events related to the HEaRT intervention. One participant experienced a fall unrelated to the intervention and withdrew from the study. Two individuals reported significant muscle soreness requiring modifications to the training protocol for one exercise class to allow for muscular recovery (modifications included reducing the load and shortening the range of motion). Both individuals were able to complete the study intervention. The attrition rate was 11%: two participants were lost to follow-up prior to exercise program completion, and one individual was lost during the 8-week follow-up period due to illness.

The average attendance rate for the HEaRT group was 85% of classes (minimum-maximum 14 (60%)-24 (100%)).

Participants in MOD-RT attended an average of 83% of sessions (minimum-maximum 12 (50%)-24 (100%)). Attrition was 6%, with one participant lost to follow-up due to a scheduling conflict.

FIGURE 4.1: Flow of substudy participant flow.

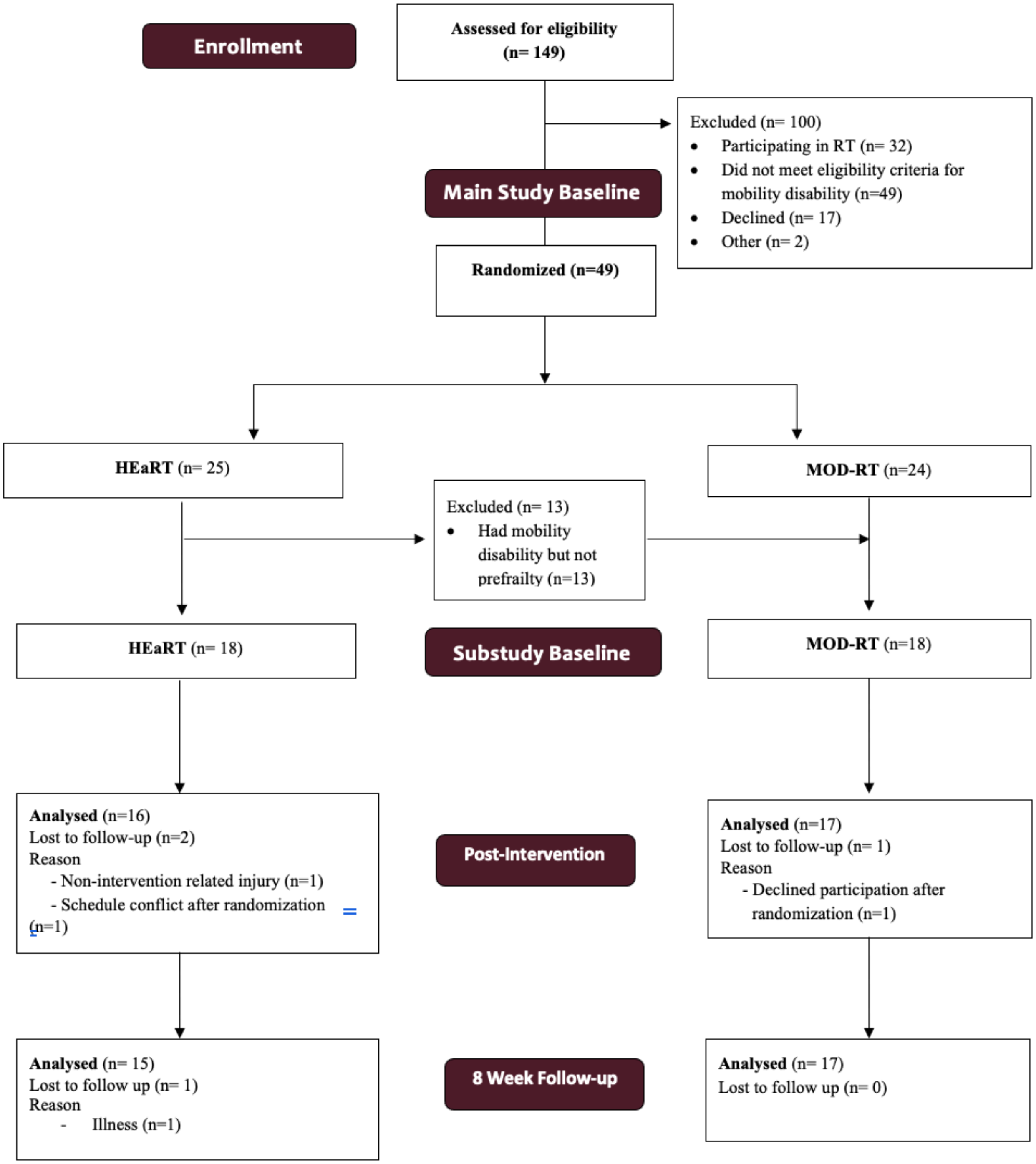


TABLE 4.2. Baseline Characteristics by group**.**

Baseline Characteristic	***HEaRT (n=18)***	***MOD-RT (n=18)***
Age, years	75 ± 8.5	74±6.5
Sex, n female (%)	9 (50)	11 (61)
Completed High School, yes (%)	18 (100)	15 (83)
Chronic Conditions, n	4 ± 2.2	4 ± 2.0
Montreal Cognitive Assessment Score, Points	22.9 ± 3.6	22.6 ± 5.2

Values are expressed as means ± standard deviation for continuous variables and counts (percentages) for categorical variables.

Functional Measures. There were no between-group differences in any functional outcome measures over time, including the 6MWT, SPPB, BBS, Mini-BEST, TUG or ABC Scale, nor for knee extensor or grip strength (Table 4.3).

There was a medium effect size improvement for the SPPB (d=0.69) and a small effect for the ABC scale (d=0.44). A medium effect size favouring MOD-RT was seen for grip strength (d=0.69; Table 4.3).

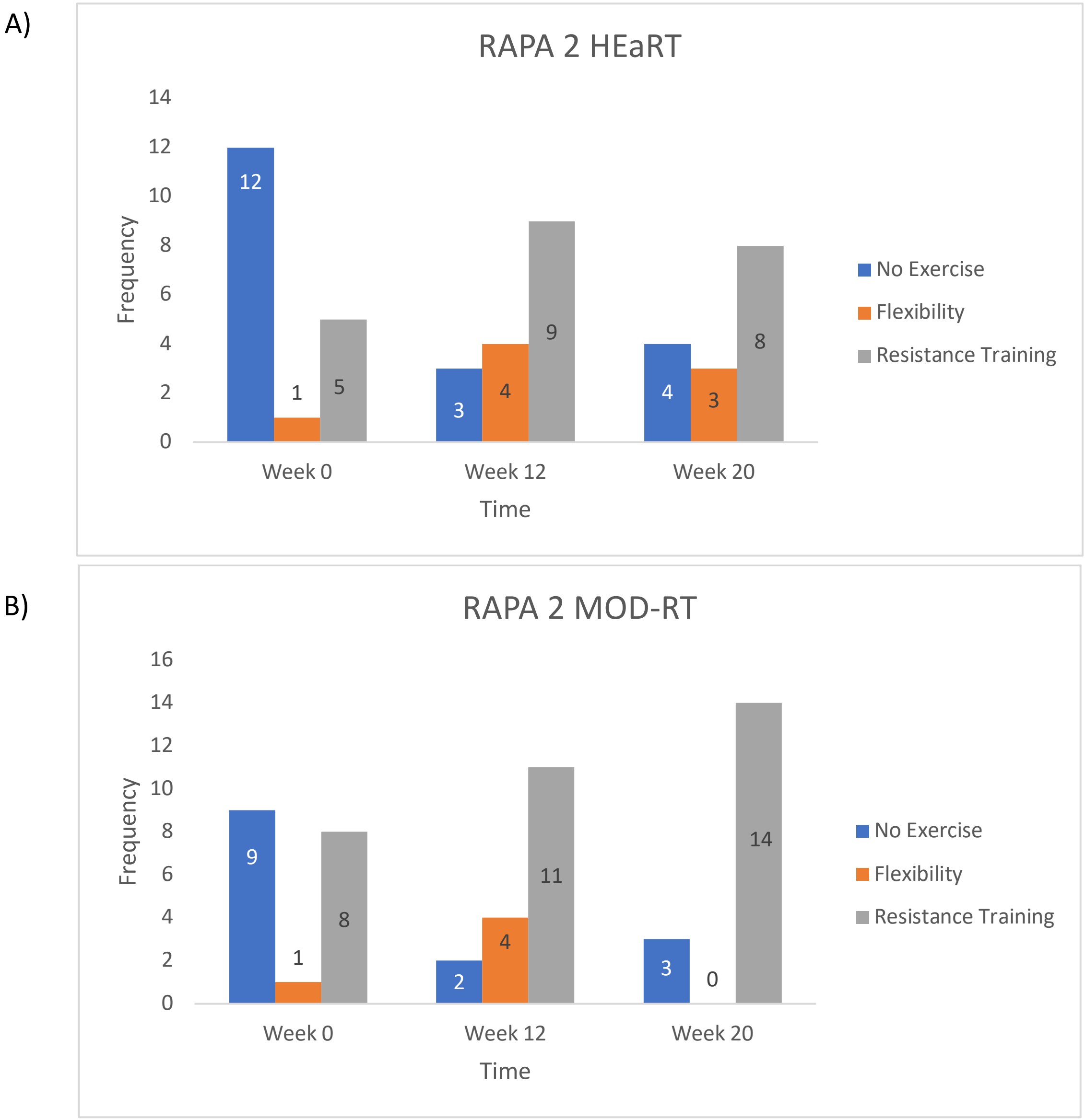
TABLE 4.3. Results of functional outcome measures, baseline versus post-assessment versus 8-week follow-up.

Outcome	**Group**	**Baseline (mean ± SD)**	**Post assessment (mean ± SD)**	**8 Week Follow Up (mean ± SD)**	**Group* Time p-Value**	**Effect Size (Pre-Post)**
6MWT (meters)	HEaRT	324.3 ± 19.7	370.1 ± 33.6	369.0 ± 25.7	0.67	0.09
	MOD-RT	334.5 ± 83.6	369.6 ± 22.8	371.9 ± 32.3		
SPPB (points)	HEaRT	8.6 ± 0.58	9.4 ± 0.5	9.6 ± 0.5	0.64	0.69
	MOD-RT	9.2 ± 0.52	9.3 ± 0.44	9.8 ± 0.51		
BBS (points)	HEaRT	50.6 ± 0.9	52.5 ± 0.9	52.3± 0.9	0.36	0.06
	MOD-RT	50.1 ± 1.1	52.0 ± 0.9	52.1±1.0		
Mini BEST	HEaRT	22.3 ± 1.1	23.7 ± 0.7	23.6 ± 0.9	0.74	0.06
	MOD-RT	21.8 ± 0.96	23 ± 1.0	22.8 ± 1.3		
TUG (s)	HEaRT	10.6 ± 0.7	8.9 ± 0.6	8.7± 0.6	0.18	0.19
	MOD-RT	10.1 ± 0.7	9.1 ± 0.5	8.5± 0.6		
ABC Scale	HEaRT	132.5± 6.2	145.1 ± 3.4	144.7± 4.8	0.21	0.44
	MOD-RT	132.0 ± 4.5	135.7 ± 5.2	136.9 ± 4.2		
Knee Extensor Strength (kg)	HEaRT	20.3 ± 3.9	17.4 ± 1.4	15.6 ± 1.5	0.66	0.09
	MOD-RT	19.6 ±2.9	16.5 ± 1.7	16.1 ± 1.6		
Grip Strength (kg)	HEaRT	38.9± 7	33.4 ± 3.9	31.1± 3.3	0.72	-0.69
	MOD-RT	29.9 ± 3.4	33.7 ± 4.3	30.3 ± 3.2		

Abbreviations: 6MWT = Six-minute walk test; SPPB = Short Physical Performance Battery; BBS = Berg Balance Scale; Mini BEST = Mini Balance Evaluation Systems Test; TUG = Timed up and Go; ABC scale = Activity-specific Balance Confidence Scale. Values are expressed as means ± standard deviations (SD).

Physical Activity Measures. Figure 4.2 depicts changes in RAPA 2 score over time for each group (HEaRT Week 0 vs Week 12: p=0.02; Week 0 vs Week 12: p=0.046; MOD-RT Week 0 vs Week 12; p=0.03; Week 0 vs Week 20: p=0.015). More individuals in both groups participated in resistance training post-intervention as per the RAPA 2 score Importantly, this increased participation was maintained at 8-week follow-up (HEaRT Week 12 vs Week 20:p=0.25; MOD-RT Week 12 vs Week 20: p=0.78).

FIGURE 4.2. Rapid Assessment of Physical Activity 2 scores for Week 0, 12, 20 for: A) HEaRT and B) MOD-RT



Health-related Quality of Life. No group-by-time interactions were observed for any subdomain of the SF-36. Both groups improved their self-reported physical function domain of the SF-36 (between-group effect 0.53, time effect p=0.006) (Table 4.4).

There was a small effect size improvement in the physical function, emotional health, and mental health subscales of the SF-36 in favour of HEaRT over MOD-RT (d=0.32-0.39) and a small effect size in favour of MOD-RT was seen for physical role (d=0.2; Table 4.4).

TABLE 4.4. Quality of Life using the Short-Form 36, baseline versus post-assessment versus 8-week follow-up.

Item	Group	Baseline	Post-intervention	Follow-Up	Time	Group* Time	Effect (Pre-Post)
Bodily Pain	HEaRT	66.2 ± 5.3	75.8 ± 4.0	76.1 ± 5.4	0.2	0.57	0.08
	MOD-RT	64.6 ± 6.3	72.4 ± 5.4	68.2 ± 6.9			
General Health	HEaRT	63.7 ± 5.0	64.9 ± 4.6	68.3 ± 4.2	0.85	0.98	0.16
	MOD-RT	67.8 ± 4.1	66.1 ± 4.7	66.3 ± 5.4			
Physical Function	HEaRT	61.4 ± 5.0	76.9 ± 3.8	76.9 ± 6.1	0.02*	0.14	0.32
	MOD-RT	64.4 ± 5.2	73.8 ± 4.2	72.8 ± 5.3			
Role Function (Physical)	HEaRT	55.6 ± 8.9	68.6 ± 9.1	60 ± 9.4	0.3	0.21	-0.2
	MOD-RT	65.3 ± 9.3	85.7 ± 5.7	73.1 ± 9.8			
Role Function (Emotional)	HEaRT	75.9 ± 8	91.8 ± 4.4	80.7 ± 6.7	0.15	0.74	0.39
	MOD-RT	79.6 ± 8.1	81.6 ± 8.2	76.4 ± 9.7			
Mental Health	HEaRT	75.9 ± 8	91 ± 4.4	80.7 ± 6.7	0.15	0.73	0.32
	MOD-RT	79.6 ± 8.1	81.6 ± 8.2	76.4 ± 9.7			
Energy/ Fatigue	HEaRT	60.6 ± 4.4	66.4 ± 2.9	64.7 ± 4.6	0.33	0.70	0.05
	MOD-RT	57.2 ± 4.9	63.9 ± 4.6	60.8 ± 4.5			
Social Functioning	HEaRT	80.8 ± 5.0	85.5 ± 4.7	89.7 ± 5.5	0.52	0.87	0.15
	MOD-RT	86.1 ± 4.7	87.1 ± 5.1	88.5 ± 5.9			

Data is presented as means +/- standard deviation.

pQCT. There were no changes between groups in the total area of the calf, fat area, muscular mass, or muscle density measures (Table 4.5).

TABLE 4.5. pQCT Muscular size and density measurements of the non-dominant calf.

Outcome	Group	Baseline (mean ± SD)	Post assessment (mean ± SD)	8 Week Follow Up (mean ± SD)	P Value
Total Area (mm^2)	HEaRT	5315.2 ± 2903.4	7864.4 ± 2472.2	7375.8 ± 2351.3	0.89
	MOD-RT	6437.6 ± 1024.4	5650.5 ± 2922.3	6800.3 ± 935.3	
Fat Area (mm^2)	HEaRT	4436.3 ± 4577.2	2138.4 ± 1645.5	2665.7 ± 1976.4	0.39
	MOD-RT	2097.5 ± 1537.4	3650.0± 3080.8	2665.7 ± 1139.4	
Muscular Area (mm^2)	HEaRT	5948.0 ± 436.1	7196.1 ± 1046.1	6662.4 ± 1025.1	0.21
	MOD-RT	5769.6 ± 396.7	6050.5 ± 439.5	6057.5 ± 327.8	
Muscular Density (mg/cm^3)	HEaRT	69.5 ±1.2	68.3 ± 2.3	67.0 ± 4.8	0.89
	MOD-RT	70.0 ± 2.4	69.7 ± 2.7	68.3 ± 1.6	

Data is presented as means +/- standard deviation. Subgroup of n=11 (HEaRT: n=5; MOD-RT: n=6)

4.5 Discussion

This study was a substudy of a pilot RCT investigating high-intensity resistance training for at-risk older adults with a specific focus on those with prefrailty. We demonstrated that individuals with prefrailty can participate in a high-load, low-volume resistance exercise program without serious adverse events. Delayed onset muscle soreness is common when initiating or progressing an RT program,[242] particularly in older adults,[243] and was the only reported adverse event in our protocol. In the current study, the two incidents of muscle soreness were successfully managed by temporarily reducing load and modifying the range of motion of the exercises undertaken. No participants dropped out of the intervention due to muscle soreness. Reducing dropouts in exercise interventions is a first step in encouraging lifelong RT participation.[121,244,245] Clinicians and fitness professionals may employ tools to manage delayed onset muscle soreness, such as exercise modifications and education about muscle soreness and its timeline for resolution will normalize the experience, help alleviate concerns about exercising, and minimize dropouts. Indeed, results from the RAPA demonstrating that participants continued

RT beyond the intervention phase are encouraging. Lifelong adherence to physical activity, particularly RT, is vital given that RT has been highlighted in multiple systematic reviews and guidelines as a cornerstone to managing and mitigating or preventing frailty.[125,232,246,247]

Two critical components of an effective exercise program are monitoring and progression of exercises over time. These were systematically applied in the current substudy to ensure adequate exposure to an effective RT dosage. It is important to apply progression through the monitoring of effort. To do this, in the current study, we used RPE as it is clinically feasible, accessible, and potentially equally effective.[248] In a randomized study of 82 community-dwelling older women participating in an 11-week RT program, there were no differences in upper or lower body strength improvements when progression was achieved through RPE as compared to 1RM monitoring.[249]

In theory,[250] increasing muscle strength through RT can potentially improve the attributes of muscular weakness, slow gait speed, fatigue/lethargy, and physical inactivity of the physical phenotype of frailty.[17] We did not observe improvements in functional outcome measures following 12 weeks of RT among those with prefrailty, although the medium effect in the SPPB and a small effect in the ABC scale suggest that we may see outcome improvement in a larger trial design. Of note, the 1.0-point improvement in SPPB score from pre-intervention to 8-week follow-up observed in the HEaRT group was clinically relevant, achieving the minimally clinically important difference.[209] The SPPB is a well-established outcome measure that has been shown to predict changes in function[251,252] such that researchers are investigating whether SPPB scores may be used to characterize prefrailty (<10 points) and frailty (<8 points).[253] Future research may use the SPPB as an alternative measure of frailty for intervention trials, and therefore, demonstrating meaningful changes in this measure may influence frailty trajectories.

One unexpected finding was related to strength measures of knee extensor and grip strength using handheld dynamometers. We found there was no improvement in strength following either study arm and an effect size in favour of MOD-RT for grip strength. Measuring knee extensor strength using handheld dynamometer is common in RT trials in the absence of gold standard isokinetic equipment, as it is more portable, feasible, and readily available in many settings.[254] We noted however that multiple participants reported discomfort in their hands and shins from the dynamometers, despite attempts to adjust positioning or increase padding for comfort. Participants' discomfort may have led to a lack of accuracy in our post-intervention measurements, as pain may have caused participants to modify how they performed the tests.

There was a surprising medium effect favouring the MOD-RT group in grip strength. Improvements in grip strength with RT in older adults are inconsistent.[255,256] In a systematic review of 32 studies (including RT, aerobic training, vibration platforms and Tai Chi) and 3018 older adults, improvements in grip strength were minimal and below clinically relevant thresholds.[255] Arguably, however, all exercise training groups were analyzed together, and no subgroup analysis was completed to establish whether this was specific to RT.[255] Grip strength is commonly prioritized in epidemiological studies[257,258] and used as a diagnostic criterion for frailty and sarcopenia as an indirect measure of overall body strength.[29,125,259] Indeed, we included grip strength as it is commonly used in defining muscular weakness for frailty.[17] However, some studies have proposed that grip strength may not be a useful measure for evaluating change in strength in intervention-based studies.[260] Further work is needed to evaluate the benefit of using grip strength as an outcome measure in exercise interventions for prefrailty and, if clinically useful, the influence of high-load versus moderate-load training on grip strength.

Given the pilot nature of this study, reflection on study methodology and potential areas for improvement to optimize an approach for a larger trial. Recent work has been done to validate other, potentially more comfortable, measures for grip strength, such as using a digital plastic tool.[261] Concerning lower extremity strength measures, in a subsequent trial, we would prioritize functional measures such as a 30 second sit-to-stand test (or modified with the use of hands) or a 3-5 repetition maximum test.[262,263]

Frailty is associated with worse health-related quality of life, particularly in health, independence, home and community ambulation, psychological well-being and leisure-time activities.[264] Less is known about the impact of prefrailty on health-related quality of life. Our pre-intervention SF-36 subscale scores aligned with values previously in community-dwelling older adults in the 70-79 age ranges for both males and females.[265] Interestingly, post-intervention scores exceeded reference normative values in every subscale. Additionally, both groups reported improvement in physical function on the SF-36. Regular participation in RT contributes positively to physical aspects of health-related quality of life, with some of the largest effects being seen in self-efficacy for completing daily activities.[266] We saw small effect size improvements in favour of HEaRT in the physical function, emotional health, and mental health subscales of the SF-36, which may be attributed to the design of the exercise program incorporating movements mirroring motor patterns of activities of daily living. Future research assessing the relationships between RT, ADL self-efficacy and health-related quality of life in those with prefrailty would improve our understanding of this potential relationship.

This study has several limitations. As this was a substudy, we acknowledge it was insufficiently powered to detect differences in functional or physiological outcomes between HeaRT versus MOD-RT. Our primary recruitment target was individuals with mobility disability or preclinical disability, and randomization was completed for the larger study. Thus, findings from this substudy must be interpreted with caution. Nonetheless, we demonstrated safety, feasibility, and a preliminary signal of the benefit of HeaRT among individuals with prefrailty, suggesting potential promise for future trials specifically for this population. We also acknowledge the limitations of the RAPA, which asks about participation in RT but does not measure intensity and duration. Future work may use physical activity questionnaires that more accurately describe the intensity of exercise behaviour.

4.6 Conclusions

This study demonstrated that a high-load resistance training program using appears safe and feasible for implementation in local gym facilities for individuals with prefrailty living in the community. While we did not see improvements in our functional outcome measures, effect size estimates indicate that moving to a larger intervention trial, particularly one specifically powered for changes in prefrailty, is warranted.

CHAPTER 5: Grand Discussion and Future Directions

The overarching aim of this thesis was to explore the role of RT for those with preclinical disability, mobility disability, and prefrailty. This aim was accomplished first by providing systematic review evidence for the use of RT in individuals with mobility disability (Chapter 2) and then establishing the safety and feasibility of higher-load RT programs for older adults with preclinical disability, mobility disability (Chapter 3) and prefrailty (Chapter 4).

The following sections will summarize the key messages of each chapter and will conclude with clinical applications and future directions for the paradigm of high-load resistance training for older adults with prefrailty or mobility disability.

Chapter Summaries

Chapter 2: The role of resistance training to improve or prevent mobility disability in community-dwelling older adults: a systematic review and meta-analysis.

In this systematic review and meta-analysis, we concluded that RT improves 6MWT distance, lower extremity strength, and usual gait speed in older adults with mobility disability if completed as a sole intervention or as part of a multicomponent program.

For those with mobility disability, performing ADLs are challenging and insufficient strength to complete these tasks may likely be why mobility disability has occurred.[267] Improving lower extremity strength through RT is an example of a conservative, low-cost intervention to increase the strength needed to complete daily tasks.[268]

Our analysis showed that much heterogeneity existed for program length, dosage, and exercise progression. No studies identified in the review that utilized a high-load, low-volume repetition schema for older adults with preclinical disability or mobility disability. Thus, results from this systematic review set the stage for Chapter 3.

Chapter 3: The use of High-Intensity Enhanced Resistance Training (HeaRT) to optimize independence and quality of life in older adults with or at-risk of mobility disability: a pilot randomized controlled trial.

This pilot RCT (n=49) demonstrated that older adults with preclinical disability or mobility disability could safely engage in high-load, low-volume RT (HeaRT). We reported no serious adverse events and low attrition related to our high-load intervention.

The HeaRT group was also compared to a moderate-intensity, higher-repetition, lower-load exercise protocol (MOD-RT). Protocols followed a strict loading progression to ensure that an adaptation stimulus was provided. Both groups improved in 6MWT distance, TUG time, and BBS score, with a small positive effect in favour of the HeaRT for the 6MWT, ABC Scale, BBS and SPPB.

Results from this pilot RCT provide evidence to support a future, larger-scale exercise trial.

Chapter 4: An Ounce of Prevention: The use of a high-load resistance training program (HeaRT) to improve physical function in pre-frail older adults, a substudy of a pilot randomized controlled trial

With an estimated 50% of older adults living in the community being pre-frail and muscular weakness being the most prominent prefrailty phenotype,[129] the next chapter of this thesis was a substudy of Chapter 3 that evaluated the safety and feasibility of HeaRT in a subgroup of 35 individuals also presenting with prefrailty. This substudy had an added eight-week post-intervention follow-up time point, an additional quality of life measure (SF-36), and measures of intervention-related changes in muscular density and area.

We report that HeaRT was safe and feasible with older adults with prefrailty. No between-group differences were seen in physical function, quality of life, and physiological outcomes of muscular density and area. However, the HeaRT and MOD-RT groups demonstrated self-reported improvements in physical functioning as assessed through the SF-36 and reported continuing to participate in RT exercise at the eight-week follow-up. Maintenance of health-related behaviours such as physical activity is an important public health objective for older adults to maintain physical function over time. [269]

Why RT Preventative Strategies are Needed for At-Risk Older Adults

Our aging population is creating unique challenges for our healthcare systems.[270] Health issues tend to accumulate with older age.[271] Age is a predominant risk factor in chronic disease[272] and is central to diagnosing clinical geriatric syndromes.[222] Healthcare utilization and need for healthcare resources increase with advancing age,[273] and sharply rise in those with concomitant clinical geriatrics syndromes such as frailty.[88,274] It is critical to establish effective strategies and available resources to meet this increase in demand.[269]

Curbing the strain on the healthcare system with an aging population has resulted in a rise in calls for preventative healthcare strategies.[275] Evidence is mounting on the utility of preventative programs, including health promotion counselling on lifestyle behaviours, such as exercise, for longevity, chronic disease management, and physical function.[232,276,277] Preventative interventions, and relevant to this thesis, RT can be used for community-dwelling older adults in primary prevention to reduce the risk of developing chronic disease, secondary prevention to target aging individuals with risk factors for chronic disease, or tertiary prevention to help with chronic disease management.[278,279] RT has a strong evidence base for optimizing health and physical function in the context of aging in general.[121,125] Our systematic review (Chapter 2) summarized the growing body of literature on the effectiveness of RT for those with mobility disability for improving muscular strength and function and is highlighted as an important exercise modality for health in published guidelines.[121,125]

Higher-Load RT as a Strategy to Improve Physical Function in those with Mobility Disability, Preclinical Disability and Prefrailty

The intensity, measured through effort, of RT is an important variable for optimizing physical function. With aging, there is a decline in the number of motor units, a reduction in collateral sprouting of motor units important for force production, and a preferential loss of type II (fast twitch) fibres.[142] When these losses approach a critical threshold, declines in overall muscle strength, power, and mass result in difficulties completing daily tasks. [29,65] The coupling of known age-related changes with our knowledge of muscular adaptations to RT justifies higher-load, low-repetition RT schemas such as those evaluated in our HEaRT interventions (Chapters 3 and 4). At higher loads of RT, motor unit recruitment is triggered by a need for higher rates of force development, leading to increased muscular fibre firing and selective type II muscular fibre activation.[121] This recruitment pattern is directly proportional to the effort, or intensity, exerted, which can be expressed as a percentage of absolute load or perceived effort.[121]

To maintain the absolute number of, and connections between, motor units and promote collateral sprouting to neighbouring muscle fibres, RT intensities of at least 70% of 1RM,[30] or a moderate intensity of RPE 5+/10 is required. [249] If the intensity is too low, no change or net loss in motor units results over time and absolute strength declines.[134] These minimum thresholds are recommended in exercise guidelines for community-dwelling older adults,[124] and those with clinical geriatric syndromes.[125] Intensities at or exceeding these thresholds were applied in the HEaRT (RPE 7-8/10) and active control arms (MOD-RT; RPE 5-6/10) in Chapters 3 and 4. While there is some expected loss of muscular strength with age, RT can mitigate those losses but must be at adequate intensities;[27,121,280] otherwise, underdosed exercise becomes insufficient to drive physiological changes to neuromuscular capacity.[30]

Underdosage reflects exercise prescriptions that are insufficient for adaptation to occur; in the case of RT prescription, may occur when loads or repetition do not provide the necessary stimulus for musculoskeletal adaptation[121]. Underdosage is potentially problematic when older adults face a loss of independence due to low physical resiliency and would benefit from improved physical reserve.[121] [121121] [281]Unfortunately, research demonstrates that health providers tend to encourage low-intensity exercise without emphasizing increasing physical function in older adults[282] and exercise physiology students lean towards “senior exercises” that lack loading.[137] The Choose Wisely campaign listed the underdosage of strength training programs in older adults as one of the biggest issues in physical therapy interventions.[141] Some of the reasons underpinning underdosage may come from the clinicians’ fear of injuring their patient, their beliefs that their client cannot tolerate high-intensity stimuli or a lack of self-efficacy in prescription and supervision on the provider’s side.[145,146]

Clinical Implications of High-Load RT

The pilot studies in Chapters 3 and 4 of this thesis add to the evidence from the earlier LIFTMOR trials[283] to provide evidence that higher-load paradigms are feasible in at-risk older adults to combat some of these fears.

Clinically, implementation of higher-load RT can take a variety of forms. If patient goals are associated with, or require, an increase in absolute raw strength, exposing older adults to high-load RT is justified. Prioritizing higher-load RT greater than the weights required for activities of daily living reduces the percent effort of tasks at home. For example, if a laundry basket is 10 kilograms and one older adult can deadlift 10 kilograms for exercise versus an older adult who consistently deadlifts 40 kg for exercise, the individuals exposed to higher loads in exercise will perceive the effort of doing their laundry as less taxing. The physical reserve of the individual participating in high-load RT is larger, and the odds of improved physical function are greater. Ways to incorporate this within a rehabilitation or exercise session include prescriptions of repetitions less than five per set or a gradual increase in load until rates of perceived exertion for 1-5 repetitions is 7+/10. Future work aiming to identify barriers and facilitators for clinicians to high-load RT in geriatric clinical practice would provide insights into how to implement high-load RT in rehabilitation settings.

Future Directions

This thesis establishes the first steps in exploring the application of high-load RT for these populations, laying the foundation for future work to expand to larger and longer studies utilizing this dosage schema. The need for longer-duration studies exists, as does the need for research evaluating the implementation of programs such as HEaRT into the community to investigate the long-term feasibility and viability of offering high-load programs to community-dwelling older adults.

Older adults with frailty and mobility disability present with a broad range of physical presentations; pragmatic interventions evaluating changes in physical function suitable across the range of presentations are needed.[283] We demonstrated that customizations and modifications to ROM and external loading were feasible and helped account for pre-existing musculoskeletal impairments, delayed onset muscle soreness and fatigue common in those with prefrailty and mobility disability. Future research can expand on this study by examining the effects of high-load RT on different subgroups of pre-frailty.

Qualitative studies to explore barriers to implementing high-intensity resistance training programs geared at older adults living with pre-frailty or mobility disability, rehabilitation professionals and fitness trainers are greatly needed. This will inform future research to address identified barriers and capitalize on facilitators to incorporate these programs and principles in clinical practice. Lastly, knowledge translation studies to examine the effectiveness of strategies to enhance clinician confidence in exercise prescription and progression may lead to clinically relevant changes in geriatric physical therapy practice.

Conclusions

The three studies in this thesis added to and challenged the current body of literature on the use of RT in at-risk older adults. In Chapter 2, we added to the literature by synthesizing the research on RT in mobility disability and reporting its effectiveness as a sole intervention or part of a multi-component program. In Chapters 3 and 4, we introduced a novel dosing schema not commonly seen in the geriatric literature with RT, utilizing a high-load training paradigm. We saw no adverse events, demonstrating the safety and feasibility of this intervention.

This work is a starting point to challenge providers' beliefs in prescribing exercise for older adults. Future work will continue to question the current norms in rehabilitation that lean towards more conservative, potentially underdosed programs for vulnerable older adults. This is a new and exciting opportunity to prescribe higher-load RT and optimize physical resiliency for older adults with prefrailty and mobility disability.

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