The impact of a six-month home-based resistance exercise program in adults with type 2 diabetes and chronic kidney disease on muscle function, frailty status, health related quality of life and health literacy

by

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Abstract

Background & Aims: Chronic kidney disease (CKD) coinciding with the presence of diabetes mellitus, known as diabetic kidney disease (DKD), is found in up to 50% of adults with type 2 diabetes (T2D). People suffering from DKD often have a high co-morbid burden that is associated with an increased prevalence of frailty and reduced muscle function, reduced health related quality of life (HRQOL) and increased healthcare utilization. The prevalence of this co-morbid burden and reduced muscle function in DKD highlights the need for effective strategies that can help to prevent or reverse the progression of these patients into a state of physical dysfunction. This thesis examined the primary outcomes specifically related to functional outcomes (short physical performance battery assessment [SPPB] and hand-grip) and frailty status (Edmonton Frailty Scale) and secondary outcomes of HRQOL (Short Form Health Survey [SF-36]) and health literacy (Functional, Communicative and Critical Health Literacy Scale) in an ongoing study called the FANTASTIC STUDY (The Development of an Innovative Home-based Strategy for Frailty Prevention in Adults with Diabetes and Chronic Kidney Disease). The hypothesis for this thesis is that participation in the 6-month resistance exercise program will result in improvements in functional outcomes, frailty status, HRQOL, and health literacy. Also examined was if participants with a higher level of baseline health literacy (HL) would have the greatest improvements in functional outcomes, frailty status and HRQOL.

Methods: An open-labelled, double block randomized controlled trial was conducted in adults aged 50 – 80 years with concurrent T2D and CKD (stages I-IV) who were screened at baseline for frailty using the Clinical Frailty Score. Participants were excluded if they did resistance-type exercise >1 times per week, were on dialysis, had functional/cognitive impairments, had recent

bone fractures or a history of skeletal muscle disorders. All participants attended baseline and 6-month visits at the Clinical Research Unit, with monthly home/virtual visits. Participants were randomized into intervention (resistance exercise + nutrition literacy) or standard of care (physical activity and nutrition education based on current Canadian guidelines).

Results: After 6 months, frail intervention participants showed significant percentage change in functional outcomes of balance (40%), sit-to-stand (38.5%), total SPPB scores (23%) and hand-grip (32%). Frail intervention participants also saw improvements in frailty status, as measured by the Edmonton Frailty Scale (-41%) and HRQOL domains of bodily pain (30.6%) and physical component scores (16%). Non-frail intervention participants saw significant percentage change in sit-to-stand (33%) and total SPPB scores (11%). Higher HL was associated with improvements in sit-to-stand and total SPPB scores for both frail and non-frail intervention participants ($p<0.01$).

Conclusions: Performing resistance exercise with resistance bands for 6 months improved functional outcomes, frailty status and HRQOL in older adults with T2D and CKD (stage I-IV). These findings are important as reduced functional performance and HRQOL is associated with negative outcomes such as fall risk and hospitalization. Studies that explore the role of HL may be valuable when developing RE interventions in older adults. Future studies examining frailty status as a direct outcome following RE only interventions are warranted.

Preface

This thesis is an original work by Chelsea Kamprath and Dr. Diana Mager's research group. The research project, of which this thesis is a part of, received ethics approval from the University of Alberta Research Ethics Board, Project Name: "The Development of an Innovative Home-based Strategy for Frailty Prevention in Adults with Type 2 Diabetes and Chronic Kidney Disease "No. Pro00089513 (08 March 2019).

Chelsea Kamprath, Rani Fedoruk, Maryah Robinson-Jackson, Kelsey Gordulic, Christine Lirette, Kristin Harms, Ashley Wilmott and Dr. Diana Mager contributed to conceptualization (D.M. only), resource development (C.K., R.F., K.G., K.H., D.M., only), data curation (C.K., R.F., M.R., C.L., and A.W. only), methodology, recruitment (C.K., R.F., M.R., A.W., D.M. only), project administration (C.K., R.F., M.R., and A.W. only), formal analysis (C.K., M.R., A.W., D.M. only), funding acquisition (R.F., as Kidney Foundation Grant, D.M., as grant funding), resources and software. Diana Mager PhD RD, Principal Investigator and Dr. Peter Senior, MBBS PhD, Co-Investigator, were responsible for all study aspects including design/inception, supervision of data collection, methodology, funding acquisition (operational funding), data analysis, intellectual and scientific interpretation, software, supervision and validation. Study design was also facilitated by Norman Boulé PhD, Dr. Angela Juby MD FRCPC, and Patricia Manns PhD, PT., all of whom provided expertise related to exercise and features of frailty. Operational funding was obtained from the University of Alberta Hospital Foundation in collaboration with the Government of Alberta and NovoNordisk Cananda, (RES0044176). Scholarship funding for C.K. was through the University of Alberta (Dr. Elizabeth A Donald MSc Fellowship in Human Nutrition, Alberta Graduate Excellence Scholarship).

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List of Abbreviations

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6MWT	Six minute walk test
A1C	Glycated hemoglobin
ADDQOL	Audit of Diabetes Dependent Quality of Life
AE	Aerobic exercise
BL	baseline
BMI	body mass index
BP	Bodily pain
CC	Case/Control
cm	Centimeters
COM	Combination exercise group
CoHL	Communicative health literacy
C	Cohort
CG	Control group
CFS	Clinical frailty scale
CHL	Critical health literacy
CKD	Chronic kidney disease
COVID-19	Coronavirus Disease 2019

DKD	Diabetic kidney disease
DM	Diabetes mellitus
DQOL	Diabetes quality of life measurement
EFS	Edmonton frail scale
EQ-5D-3L	European Quality of life 5 Dimensions
eGFR	Estimated glomerular filtration rate
F	Female
FANTASTIC	The development of an innovative home-based strategy for frailty prevention in adults with diabetes and chronic kidney disease
FBG	Fasting blood glucose
FCCHL	Functional, Communicative and Critical Health Literacy Scale
FHL	Functional health literacy
GH	General health
HG	Hand-grip
HL	Health literacy
HRQOL	Health related quality of life
HDL	High density lipoprotein
IPAQ	International physical activity questionnaire

IQR	Interquartile range
kg	Kilograms
LB	Lower body
M6	Month-6
M	Male
MDST	Maximum dynamic strength test
MCS	Mental component score
MH	Mental health
MS	Muscle strength
N	Sample size
n/a	Not available
OHA	Oral hypoglycemic agents
PCS	Physical component score
PF	Physical function
PP	Physical performance
RCT	Randomized controlled trial
RE	Resistance exercise
RM	Repetition maximum

RP	Role physical
SF-36	Short Form Health Survey
STS	Sit-to-stand
SD	Standard deviation
SPPB	Short Physical Performance Battery Assessment
SF	Social function
SOC	Standard of care
TUG	Timed up and go test
THL	Total health literacy
T2D	Type 2 diabetes
UP	Upper body
VT	Vitality
vs.	versus
y	years

Chapter 1 – Literature Review

1.1 INTRODUCTION

In Canada, it is estimated that up to 9% of the population has been diagnosed with Diabetes mellitus [1]. Diabetic kidney disease (DKD), which is chronic kidney disease (CKD) coinciding with the presence of diabetes, is found in up to 50% of diabetic adults greater than 65 years of age [2]. DKD is a progressive condition, with overt complications presenting typically only in later stages of the disease, with different stages requiring different levels of care (**Table 1.1**) [3]. People suffering from DKD often have a high co-morbid burden that includes conditions such as hypertension, neuropathy and frailty [4, 5]. This increased burden is associated with depression, reduced health related quality of life (HRQOL), increased healthcare utilization and reduced lean body mass [4, 6]. The impact of the co-morbid burden is compounded by an increased decline in muscle function [7, 8]. Reduced muscle function (muscle strength and power, balance and endurance), particularly in the presence of chronic disease, has been associated with a decreased ability to perform activities of daily living and an increased prevalence of frailty [9, 10]. The functional decline in muscle performance has also been associated with increased fall risk [11, 12]. Changes in skeletal muscle physiology and reduced muscle function in adults with type 2 diabetes (T2D) or DKD may be induced by co-morbid conditions such as uremia [13]. The prevalence of this co-morbid burden and reduced muscle function in T2D and CKD highlights the need for effective strategies that can help reverse or prevent the progression of these patients into state of physical dysfunction. Reducing the incidence of poor muscle function can help reduce morbidity, hospitalization, and mortality in this population [10, 14].

Table 1.1 Chronic kidney disease stages for all types and associated eGFR values [3]

Stages	eGFR (ml/min/1.73m^2)	Classification
I	>90	Normal (High)
II	89-60	Slight Decrease
III A **III B**	59-45 44-30	Mild To Moderate Moderate to severe
IV	29-15	Severe
V	<15	Kidney Failure

CKD= chronic kidney disease; eGFR= estimated glomerular filtration rate

1.2 DIABETIC KIDNEY DISEASE

1.2.1 Term Description and Prevalence of Diabetic Kidney Disease

CKD encompasses reduced kidney function or reduced estimated glomerular filtration rate (eGFR) irrespective of the etiology of kidney damage [15] (**Table 1.1**). Diabetes is known to be one of the leadings causes of CKD with up to 50% of T2D patients developing DKD [16, 17]. Following the diagnosis of T2D, kidney function may decrease over time progressing to the diagnosis of DKD. DKD is a specific type of kidney disease that is often defined as the presence of albuminuria (excretion of albumin in urine) along with a relatively slow reduction in eGFR levels in patients with diabetes mellitus (**Table 1.2**) [16]. DKD can span CKD stages I-IV (**Table 1.1**) [18, 19]. However, there is some controversy over this categorization as some definitions of DKD require an eGFR of <60 ml/min/1.73m^2 (CKD stages III-V) for a diagnosis [20]. Others define DKD with the presence of albuminuria, therefor DKD may be diagnosed even in the early stages of CKD (stage I and II) as defined by eGFR values [18, 19]. The progress of this disease can eventually lead to end-stage renal disease or kidney failure (CKD stage V) (**Figure 1.1**) [20]. Markers of chronic hyperglycemia (e.g., elevated glycated hemoglobin [A1C]) are associated with the development of DKD, indicating that poor glucose control likely has long-lasting effects on the progression of DKD [21, 22]. However,

hyperglycemia is not the only risk factor for the development of DKD. The presence of dyslipidemia, hypertension and obesity are also associated with the diagnosis of DKD [17, 20]. The presence of this cardiometabolic dysregulation can lead to an increased risk of adverse outcomes, such as heart attack and stroke in people with DKD [23] **(Figure 1.1)**. Hypertension alone or in combination with diabetes is a leading contributor to CKD in Canada, leading to a high prevalence of DKD [18].

Table 1.2 Conditions that favor the development of diabetic kidney disease vs other types of kidney disease

Conditions present that favour the development of Diabetic Kidney Disease	Conditions present that favour a diagnosis of a renal disease not Diabetic Kidney Disease
Diabetes diagnosis for > 5 years Presence of consistent albuminuria* Low eGFR, with proteinuria§ Slow disease progressionω	Diabetes diagnosis of < 5 years Presence of consistent hematuria Low eGFR with little proteinuria Rapid reduction of eGFR Family history of nondiabetic renal disease

eGFR = estimated glomerular filtration rate; information adapted from MacFarlane et al., 2018 [18]
**albuminuria (microalbuminuria = 30mg/day – 300 mg/day; macroalbuminuria = >300 mg/day)*
§low eGFR = <60 ml/min/1.73m²
ωslow disease progression refers a decrease in eGFR of 1-2 ml/min/1.73m² per year [18]

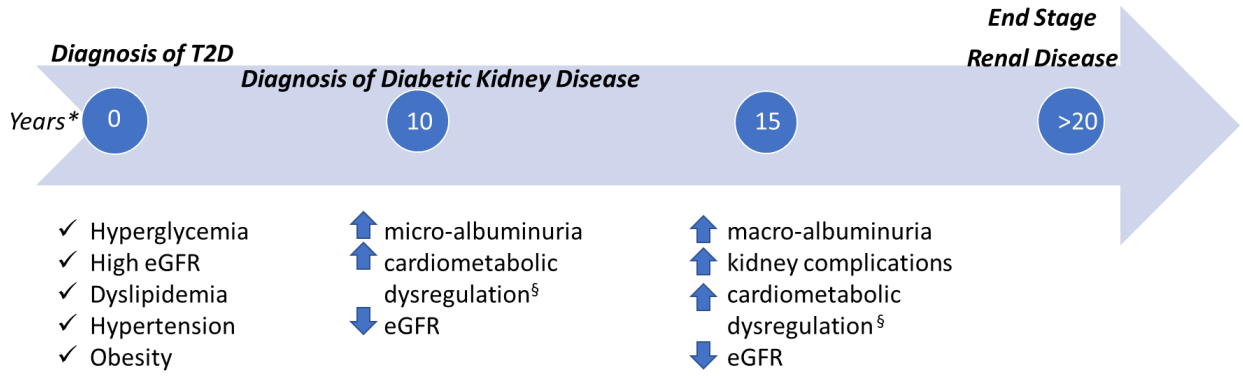

Figure 1.1 The progression of diabetic kidney disease following a diagnosis with type 2 diabetes adapted from Alicic *et al* [20] . T2D=type 2 diabetes; eGFR=estimated glomerular filtration rate
**time between progression to further stages is variable as it depends on many factors, such as glycemic control at and following diagnosis*
§cardiometabolic dysregulation encompasses the constellation of conditions associated with increased blood pressure, impaired glucose control, hypercholesterolemia and obesity [24]

1.2.2 Impact of Diabetic Kidney Disease

The presence of DKD is associated with several adverse outcomes, such as increased frailty, kidney failure and negative cardiovascular outcomes [20, 25, 26]. Recent research indicates that strategies that help to reduce the risks associated with DKD should be a key part of early clinical care for DKD [27]. Continuous management of glycemic control has been found to be one of the most important strategies for limiting DKD progression [27, 28]. While pharmacological interventions are effective at improving glycemic control, there is some research that multifactorial lifestyle modification (e.g., increased physical activity and dietary changes) can also be beneficial [29]. A 2015 review by Onyenwenyi et al., [29] found that personalized dietary counselling with a focus on protein and sodium reduction, as well as increased physical activity was associated with improvements (e.g., lower progression rate) in adults with DKD. These lifestyle changes appear to be particularly important to implement at time of T2D diagnosis as length of time since T2D diagnosis is related to a higher rate of DKD progression [29, 30].

1.3 FRAILTY

1.3.1 Term Description

Frailty is a complex condition that arises with age from a decrease in both physiological reserves and body function; reducing the ability of the body to respond appropriately to stress **(Figure 1.2)** [31]. Frailty often results in an increased risk for adverse outcomes such as falls, fractures and reduced HRQOL [4]. Considered to be a dynamic condition, the severity of frailty can change over time [32]. In 2001, Fried et al [33] reported that the frailty phenotype consisted of five physical symptoms of frailty: unintentional weight loss, self-reported exhaustion, slow gait speed, weak grip strength and low physical activity. If three or more of these criteria are

determined to be present, frailty exists. Two of the five physical frailty symptoms from the FRIED frailty phenotype are indicators of muscle function: gait speed (muscle endurance, physical performance) and hand-grip strength (muscle strength) [33]. Several other tools have been developed to help diagnose frailty and many of these use different markers of muscle function that encompass parameters related to muscle performance. These may include tests that measure functional endurance, muscle strength or physical performance.

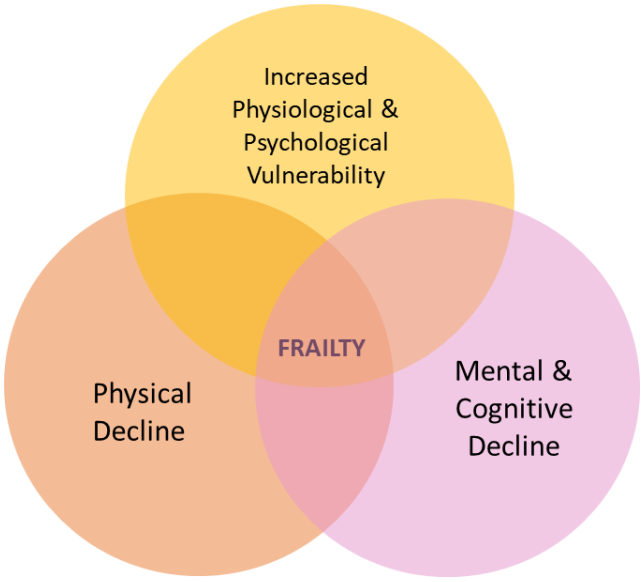

Figure 1.2 The three physical-psychosocial domains of frailty.

1.3.2 Prevalence of Frailty

Overall prevalence of frailty in adults ≥50 years was found to be 7.7% in a large multi-country European study with rates increasing alongside age [34]. Older adults with diabetes have been shown to have more than double the risk (odds risk ratio of 2.18) of developing frailty compared to older adults without diabetes [35]. One study by Casals *et al.* [36] found a frailty prevalence of 15% in a T2D population while another study found a 17% incidence in a population with both diabetes and CKD [4, 36]. Cross-sectional studies show that the incidence of frailty increases with

the severity of CKD stage (up to 43% in stages I-IV and 73% in patients on hemodialysis) [37, 38]. Renal dysfunction is known to adversely affect metabolic and muscle function through a variety of mechanisms. Pathophysiologic processes found in DKD like insulin resistance, chronic inflammation and increased protein wasting are all associated with increased frailty due to the functional consequences associated with them (e.g., decreased muscle mass) [39, 40]. Based on this, treatments in this population that focus on the prevention or reduction of the severity of frailty are needed.

1.3.3 Prevention of Frailty

Primary prevention in the pre-frail state, or early stages of frailty, should be targeted for the most effective management of frailty. Primary prevention is emphasized by changes in lifestyle factors (such as physical activity and diet) that will help to limit the progression of the patient into a more frail state [32]. Focusing on lifestyle interventions makes sense as self-care and self-management are important factors when considering the success of chronic disease management strategies [41]. Lifestyle factors are modifiable and have robust evidence for frailty prevention and treatment [42, 43].

1.4 RESISTANCE EXERCISE

1.4.1 Resistance Exercise as a Treatment for Muscle Dysfunction

Resistance exercise (RE) training is a well-known strategy for maintaining or increasing muscle function[44]. RE typically involves sets of brief repetitive movements with weights, weight machines, resistance bands or one's own body weight. Exercise interventions may include RE alone or in combination with other exercise modalities, such as aerobic exercise. Studies show that RE alone can improve body composition, muscle strength, power and functional endurance

in several clinical populations [44, 45]. RE may ameliorate physical dysfunction in older populations with T2D and CKD by contributing to increased muscle strength and physical performance [46]. Adherence to lifestyle interventions (such as exercise interventions) is critical for improvements in desired outcomes, such as increased muscle function [47]. However, many barriers have been identified that may prevent older adults from complying to recommended lifestyle interventions [48]. Health literacy (HL) is one factor that may influence a patients' adherence [49]. HL is a complex concept used to describe a persons' ability to obtain, process and implement information about their health [50].

The purpose of this literature review was to evaluate the current literature with regard to the efficacy of RE as a treatment to improve muscle function in adults with T2D and DKD. The implications of frailty and HL are also discussed in the context of how these factors may be examined in the overall context of rehabilitation of reduced muscle function in adults with DKD.

1.5 FACTORS THAT MAY INFLUENCE THE IMPACT OF RESISTANCE EXERCISE ON OUTCOMES SUCH AS PHYSICAL PERFORMANCE, MUSCLE STRENGTH AND HRQOL

1.5.1 Training Volume and Intensity

A summary of studies examining RE interventions in participants with T2D and DKD can be found in **Tables 1.3, 1.4, 1.5 and 1.6**. The RE interventions utilized structured, progressive programs designed to increase training volume and intensity levels over the study duration. Training volume (number of exercises, number of sets per exercise and number of repetitions per set) and the RE intensity are critically important factors when considering improvements in muscle function [51]. The majority of studies assigned high-intensity RE (≥70%) based on percentage of baseline 1 repetition maximum measurements (**Table 1.3**). This is the most

accurate method for determining appropriate RE intensity [51]. All studies in adults with T2D that prescribed RE by the 1 repetition maximum method reported significant improvement in measures of physical performance and muscle strength. However, the few studies that used self-reported rating of exertion scales (e.g., The Borg Scale of Perceived Exertion) [52] to assign a moderate level of RE intensity had inconsistent results in physical performance and muscle strength (**Table 1.4**). Self-reported exertion scales are participant-managed and easy to administer but have the drawback of inconsistencies in actual intensity of the exercise performed. Moreover, agreement between percentage of repetition maximum and self-perceived exertion scales is inconsistent [53, 54]. Due to potential lower training volumes and inconsistent intensity, studies that assign RE by self-perceived exertion scales may have varying levels of RE intensity compared to RE prescribed by 1 repetition maximum.

1.5.2 Conventional Resistance Exercise VS Resistance bands

RE can be accomplished by using a variety of methods. Conventional RE, the use of machines or free weights, was the most common method used in the literature reviewed (**Table 1.3**). RE using resistance bands was present in only a small number of studies (n=3) (**Table 1.3**). However, both types of RE found consistent improvements in physical performance (e.g., sit-to-stand) and measures of muscle strength (e.g., 1 repetition maximum). A 2019 systematic review from Lopes *et al.* [55] found that studies that used resistance bands had similar strength gains to studies that used conventional RE. However, this review was not specific to any population and included adults with and without chronic diseases (e.g., heart disease). However, a recently published review of RE interventions in frail older adults using resistance bands did not show any improvements in muscle strength or HRQOL at 12 or 24 weeks [56]. This review did find that frailty

status in adults older than 65 was reduced following 24 weeks of RE using resistance bands [56]. Studies with high intensity RE (≥80% 1 repetition maximum) using resistance bands have reported increases in physical performance, muscle strength and frailty status [57, 58], so it could be that appropriate intensity prescription is even more important when using resistance bands.

1.5.3 Location of Exercise (Supervised or Home-based)

There are many potential barriers to participation by older adults in exercise programming [59, 60]. Often, the cost of supervised, community-based exercise programs or limited transportation options impacts accessibility for older adults. Therefore, the feasibility of long-term supervised exercise programming for older adults may not be realistic. Some studies have illustrated that home-based programs are as effective as supervised programs at increasing muscle function in older adults living at home, with and without chronic disease (e.g., heart disease) [61, 62]. Jakicic *et al.* [63] found that access to home equipment was associated with increased adherence to exercise programs, and Valenzuela *et al.* [64] reported that adherence to technology-based exercise programs at home was quite high in the elderly. Home-based exercise protocols and supervised interventions both showed improvements in physical performance and muscle strength measures (**Table 1.4**).

1.5.4 Adherence to Resistance Exercise Programs

Another factor influencing improvements in muscle function may be adherence. In the studies reviewed, reported adherence ranged between 71% to 100% (**Table 1.4**). Adherence has been noted to have a dose-response relationship between clinical outcomes and interventions [65, 66]. Unfortunately, adherence to exercise is a well-documented challenge for older adults [59, 60, 67]. Participation in supervised exercise is thought to positively influence adherence [68].

Supervised exercise interventions report enhanced initial adherence, but similar adherence rates long term (>6 months) compared to home-based programs [68, 69]. The majority of the studies reviewed were supervised by exercise professionals with only small number of home-based studies (**Table 1.3**). Both supervised and home-based studies reported improvements in physical performance and muscle strength outcomes (**Table 1.4**).

1.6 ASSESSMENT OF MUSCLE FUNCTION IN ADULT POPULATIONS WITH TYPE 2 DIABETES AND DIABETIC KIDNEY DISEASE

1.6.1 Methods of Assessing Muscle Function

A list of reported tests used to assess muscle function in RE studies reviewed with T2D or DKD participants are found in **Appendix A: Table 1**. Studies used sit-to-stand, timed up and go, six-minute walk test, 10m gait speed and short physical performance battery assessment (SPPB) to assess physical performance. Three different types of muscle strength assessments were used: hand-grip (upper body strength), maximal dynamic strength test (MDST) (upper and lower body strength) and repetition maximum (upper and lower body strength).

1.7 IMPACT OF RESISTANCE EXERCISE INTERVENTIONS ON OUTCOMES IN ADULTS WITH TYPE 2 DIABETES AND DIABETIC KIDNEY DISEASE

1.7.1 Descriptive Characteristics of the Studies Reviewed

Exercise interventions often include RE alone, aerobic exercise alone or a combination of both exercise modalities. There is a large body of literature in RE only interventions that assess the impact of RE only interventions on muscle function in older participants with T2D. The T2D studies reviewed had intervention durations ranging from 8 to 52 weeks (**Table 1.3**). The mean age of the participants in these studies ranged from 49 to 78 years. Mean T2D duration was

between 3 and 18 years. The majority of the interventions were supervised by study staff (e.g., exercise specialists) (n=19/22 supervised; n=3/22 home-based) and used machines or free weights for resistance (n=19/22). Three studies used resistance bands. Five studies used self-perceived ratings of exertion for RE intensity (e.g., Borgs scale of perceived exertion [52]), while the rest prescribed RE intensity by percentage of 1 repetition maximum (n=17/22). There is very limited research (n=6) on RE only interventions in participants with DKD (**Table 1.3**). In the studies reviewed the stages of CKD ranged between II and IV with the majority of studies having participants that included participants with stage IV (n=6) (**Table 1.3**). Most of the studies had less than 40 participants (n=5). Intervention durations ranged between 8 weeks and 6 months. The mean age of participants in the DKD studies ranged from 46 to 76 years. Five studies were supervised and used machines for resistance while one home-based intervention utilized resistance bands. One study used a self-perceived rating of exertion scale and the other 5 prescribed intensity by percentage of 1 repetition maximum (**Table 1.3**).

Table 1.3 Description of studies measuring muscle function in resistance exercise only interventions with participants who have type 2 diabetes or diabetic kidney disease

Author, year	Study design	Population	Disease Duration (years)	eGFR *(mL/min per 1.73 m2)*	Baseline Anthropometrics	Age (years)	Sex	Sample size	Intervention Length	Control Group
Studies with RE only Interventions in T2D Participants										
Al-Shreef *et al.*, 2015[67][70]∗	RCT	T2D	n/a	n/a	Mean(SD) BMI: RE 31.3(4.1) AE 30.7(3.6)	Range: 40-55 RE 48.9(5.9) AE 47.8(5.3)	M=100	n=100	6 months	N
Bacchi *et al.*, 2012[68]∗	RCT	T2D	Mean(SD): RE 9.7(1.7) AE 10.7(1.4)	n/a	Mean(SD) BMI: RE 29.2 (1.0) AE 29.5(1.5)	Mean(SD): RE 55.6(1.7) AE 57.2(1.6)	F=12 M=28	n=40	4 months	N
Botton *et al.*, 2018[69][71]∗ω	RCT	T2D	Mean(SD): RE 10.7(7.9) CG 11.3(7.4)	n/a	Mean(SD) BMI: RE 28.2(3.6) CG 28.6(3.3)	Mean(SD): RE 70.6(6.7) CG 68.6(7.1)	F=18 M=26	n=44	3 months	Y
Castaneda *et al.*, 2002[70]∗	RCT	T2D	Mean(SD): RE 8(1) CG 11(1)	n/a	Mean(SD) BMI: RE 30.9(1.1) CG 31.2(1.0)	Mean(SD): RE 66(2) CG 66(1)	F=40 M=22	n= 62	16 weeks	Y
Cauza *et al.*, 2009[71]∗	C	T2D	n/a	n/a	Mean(SD) BMI: 31.3(0.9)	Mean(SD): 56.4(0.9)	F= 8 M=15	n=23	4 months	N
Cheung *et al.*, 2009[85]†ω	RCT	T2D	n/a	n/a	Mean (SD BMI: RE 39.7(9.0) CG 37.7 (9.2)	Mean(SD): RE 59.0(8.7) CG 62.0(6.7)	F=25 M=12	n=37	4 months	Y
Church *et al.*, 2010[86]⁎	RCT	T2D	Mean (SD) RE 7.2(5.5) COM 6.7(5.4) AE 7.4(6.0) CG 7.2(5.2)	n/a	Mean (SD) BMI: RE 34.1(5.4) COM 35.8(6.2) AE 34.7(6.1) CG 34.9(5.9)	Mean (SD) RE 56.9(8.7) COM 55.4(8.3) AE 53.7(9.1) CG 58.6(8.2)	F=165 M=97	n=262	9 months	Y
Celes *et al.*, 2017[84]∗ω	RCT	T2D	n/a	n/a	Mean (SD) Body Mass (KG) RE 75.1(16.7) CG 77.7(18.0)	Mean (SD) RE 62.1(10.5) CG 56.7(19.4	n/a	n=30	6 weeks	Y
Dunstan *et al.*, 2005[87]	RCT	T2D	Mean(SD): RE 7.6(5.4) CG 8.8(7.9)	n/a	Mean(SD) BMI: RE 31.5(3.7) CG 32.5(3.8)	Range: 60-80 RE 67.6(5.2) CG 66.9(5.3)	F=15 M=21	n=36	12 months	Y

Egger *et al.*, 2013[88]*	C	T2D	n/a	n/a	Mean(SD) BMI: HRE 29.9(4.7) ERE 29.8(5.3)	Mean(SD): HRE 64.5(7.1) ERE 65.2(8.6)	F=19 M=13	n=32	8 weeks	N
Geirsdottir *et al.*, 2012[89]*	RCT	T2D	n/a	n/a	Mean(SD) BMI: CG 28.46(4.79) Pre-T2D 29.80(3.88) T2D 31.69(5.71)	Range: 65-92 CG 73.2(5.5) Pre-T2D 77.0(5.3) T2D 75.2(6.7)	F=139 M=98	n= 237	12 weeks	Y
Gonela *et al.*, 2020[90]*	C	T2D	n/a	n/a	n/a	Mean (SD) 68.3(6.7)	F=18 M=5	n=23	16 weeks	Y
Hsieh *et al.*, 2018[91] *ω	RCT	T2D	Mean(SD): RE 11.1(7.8) CG 13.9(6.7)	n/a	Mean(SD) BMI: RE 25.6(2.6) CG 25.4(3.4)	Mean(SD): RE 70.6(4.2) CG 71.8(4.5)	F=19 M=11	n=30	12 weeks	Y
Ibanez *et al.*, 2005[92] *	C	T2D	n/a	n/a	Mean(SD) BMI: 28.2(2.7)	Mean(SD): 66.6(3.1)	M=9	n=9	16 weeks	N
Kwon *et al.*, 2010[93]*†	RCT	T2D	Mean (SD): RE 5.7(4.8) CG 6.1(6.3)	n/a	Mean(SD) BMI: RE 27.1(2.2) CG 27.6(2.8)	Mean(SD): RE 55.7(6.2) CG 57.0(8.0)	F=28	n=28	12 weeks	Y
Larose *et al.*, 2010[94]*	RCT	T2D	Mean(SD): RE 6.1(4.7) COM 5.2(4.8) AE 5.1(3.5) CG 5.0(4.5)	n/a	Mean(SD) BMI: RE 34.1(9.6) COM 35.0(9.6) AE 35.6(10.1) CG 35.0(9.5)	Mean(SD): RE 54.8(7.2) COM 53.5(7.3) AE 53.9(6.6) CG 54.8(7.2)	F=91 M=125	n=216	6 months	Y
Navarro-Peternella *et al.*, 2019[72]*ω	RCT	T2D	Mean(SD): RE 10(12) CG 9.0(4.1)	n/a	n/a	Mean (SD): RE 66.0(4.2) CON 66.6(4.8)	F=15 M= 15	n=30	12 weeks	Y
Park *et al.*, 2016[95]†	C	T2D	Mean(SD): Short T2D 3(2) long T2D 10(3)	n/a	Mean(SD) BMI: Short T2D 23.4(2.8) long T2D 25.0(3.1)	Mean (SD) Short T2D 54(8) Long T2D 59(6)	F=26	n=26	12 weeks	N
Plotnikoff *et al.*, 2010[73]	RCT	T2D	n/a	n/a	Mean(SD) BMI: RE 35(8) CG 26(5)	Mean (SD): RE 55.0 (12) CON 54.0 (12)	F=32 M=16	n=48	16 weeks	Y

Praet *et al.*, 2008[74]*	C	T2D	Mean(SD): 12.1(7.0)	n/a	Mean(SD) BMI: 32.2(4)	Mean(SD): 59.1(7.5)	M=11	n=11	10 weeks	N
Rodriguez-Manas *et al.*, 2019[75]*	RCT	T2D	Mean (SD): RE 15.1(12.2) CG 18.1(15.8)	n/a	Mean(SD) BMI: RE 29.3(4.96) CG 29.8(4.96)	Mean(SD): RE 78.4 (5.6) CG 77.6 (5.3)	F=473 M=491	n=964	16 weeks	Y
Takenami *et al.*, 2015[76]*	C	T2D	n/a	n/a	Mean(SD) BMI: 24.4(2.6)	Range: 55-80 Mean (SD) 68.2(9.7)	F=5 M=5	n=10	16 weeks	Y
RE only Interventions in DKD Participants that Measure Muscle Function										
Castaneda *et al.*, 2001[77]*	RCT	DKD (CKD stage IV)	n/a	Median: RE (24.76) CG (27.53)	Mean(SD) BMI: RE 29.3(6.6) CG 26.8(2.7)	Mean (SD): RE 65 (9) CG 64 (13)	F=9 M=17	n=26	12 weeks	Y
de Dues *et al.*, 2022[78]*	RCT	DKD (CKD stage II)	n/a	Mean (SD): RE 65.5(3.5) RE/BFR 65.0(2.5) CG 65.8(4.0)	Mean(SD) BMI: RE 33.6(2.0) RE/BFR 33.2(1.6) CG 33.3(1.9)	Mean (SD): RE 58(6) RE/BFR 58(7) CG 58.5(5.0)	F=33 M=72	n=105	6 months	Y
Gollie *et al.*, 2020[79]*	C	DKD (CKD stage III - IV)	n/a	Mean (range): 37.6(13.3-55.2)	Mean(range) BMI: 34.1(24.5-40.5)	Mean (range): 68.8 (57-78)	M=4	n=4	24 sessions	N
Heiwe *et al.*, 2005[80**(73)**]*	CC	DKD (CKD stage IV)	n/a	Mean (SD): RE 17.0(5) CG 17.0(5)	n/a	Mean(SD): RE 76 (8) CG 71 (5)	F=4 M=8	n=12	12 weeks	Y
Leaf *et al.*, 2003[82] ⌋	C	DKD (CKD stage III-IV)	n/a	Mean (SD) 33.7(5.3)	n/a	Mean (SD) 57(9)	M=5	n=5	6 weeks	N
Olvera-Soto *et al.*, 2020[82]†ω	CC	DKD (CKD stage IV)	n/a	Mean (SD): RE 20.6 (6.0) CG 24 (7.4)	n/a	Median (IQR): RE 48 (41.5-53) CG 46 (27.5-49.5)	F=23 M=16	n=39	12 weeks	Y
Watson *et al.*, 2015[83]*	RCT	DKD (CKD stage III-IV)	n/a	Median (IQR): RE 28.5 (19.0-2.0) CG 20.5(16.0-26.0)	Median (IQR): RE 32.7(30.3-38.5) CG 31.6(28.1-34.1)	Median (IQR): RE 63 (57-65) CG 66 (63-72)	F=13 M=25	n=38	8 weeks	Y

Note: AE= aerobic exercise; A1C= Glycated hemoglobin; baseline anthropometrics = may include (BMI, weight, Fat free mass %); C = cohort; CC = case/control; CG= control group; CKD= chronic kidney disease; DKD= diabetic kidney disease; eGFR= estimated glomerular filtration rate; F= female; M=male; n= sample size;

n/a= not assessed; RCT= randomized controlled trial; RE= resistance exercise only; RE/BFR= resistance exercise plus blood flow restriction; SD= standard deviation; T2D= type 2 diabetes mellitus

* = supervised intervention

† = used elastic/resistance bands for resistance

ω = used a self-perceived rating of exertion for intensity

Table 1.4 Results reported in studies with resistance exercise only interventions with participants who have type 2 diabetes and diabetic kidney disease that measure muscle function

Author, Year	T2D or DKD	Physical Function Assessment	Muscle Function Component Assessed	Other Outcomes Assessed (anthropometric, laboratory)	Subject Groups	Physical Function Results	Other outcomes Results	Adherence Reported, (%)
Studies with RE only interventions in T2D Participants								
Al-Shreef *et al.*, 2015[70]	T2D	HG	MS	BMI, albumin, A1C, FBG	RE only group, AE only group	↑HG($p<0.05$) in both RE and AE groups (within group); no other significant between group results reported	No results reported for changes to BMI, albumin, A1C, FBG	N
Bacchi *et al.*, 2012[74]	T2D	1 RM (UB & LB)	MS	BMI, A1C, FBG	RE only group, AE only group	↑1 RM (UP&LB)($p<0.0001$) was associated with RE; no other significant between group results reported	↓BMI(<0.0001) ↓A1C($p<0.0001$), ↓FBG($p<0.004$), were significantly reduced in RE, no significance found between groups ($p>0.05$)	Y (89%)
Botton *et al.*, 2018[71]	T2D	1 RM leg extension (LB), STS, TUG	MS, PP	BMI, A1C, FBG	RE only group, active control group (static stretching only)	↑1 RM($p<0.001$) was associated with RE, no significance found in STS ($p=0.18$), TUG ($p=0.26$)	No significant improvements found in BMI ($p>0.05$), A1C ($p=0.20$), FBG ($p=0.46$)	Y (87%)
Castaneda *et al.*, 2002[75]	T2D	1 RM (UB & LB)	MS	BMI, A1C, FBG	RE only group, control group with no activity changes	↑1 RM (UB & LB)($p=0.0001$) was associated with RE; no other significance between group results reported	↓A1C($p=0.01$) associated with RE, no other significant results in BMI ($p=0.89$), FBG ($p=0.34$)	Y (90%)
Cauza *et al.*, 2009[76]	T2D	MDST (UB & LB)	MS	BMI, A1C	One group of RE	**All within group analysis:** ↑MDST (UP & LB)($p<0.001$) was associated with RE, no other significant results found	↓A1C($p=0.001$) was significantly associated with RESIS, no other significant results reported in BMI ($p>0.05$)	N

Celes *et al*., 2017[77]	T2D	MDST(LB), STS, 6MWT, TUG	MS, PP	n/a	RE only group, control group did recreational activity (e.g. dance and yoga)	↑STS (p=0.019); ↑6MWT (p=0.003) was associated with RE; no significance between groups reported in TUG (p=0.86), MDST (LB) (p=0.777); Within RE group: ↑MDST(LB) (p=0.002); no significance found in TUG (p=0.102)	n/a	N
Cheung *et al*., 2009[78]	T2D	HG, TUG	MS, PP	BMI, A1C	RE group, one CG (standard of care)	no significant results reported in HG(p=0.26), TUG(p=0.19) between RE and CG; no results reported within groups	no significant results reported in BMI (p=0.22), A1C (p=0.30) between RE and CG; no results reported within groups	Y (90%)
Church *et al*., 2010[79]	T2D	MDST(LB)	MS	A1C	RE only group, COM group, AE only group, control group did standard of care	↑MDST (lower body) (p≤0.05) was associated with RE, no other significance between groups reported	no significant results reported in A1C for RE group(p=0.32)	N
Dunstan *et al.*, 2005[80]	T2D	1 RM (UB & LB)	MS	BMI, A1C, FBG	Weight loss diet + RE group, weight loss diet only control group	↑1 RM (UB&LB)(p=0.0001) was associated with RE; no other significance between groups reported	↓A1C(p<0.05) was associated with RE, no other significant results between groups in BMI (p>0.05), FBG (p>0.05), no significant changes in BMI (p>0.05), FBG (p>0.05) within RE group	Y (73%)
Egger *et al*., 2013[81]	T2D	MDST (UB)	MS	BMI, A1C, FBG	One group was high intensity RE exercise (10-12 reps), one group was endurance RE exercise (20-30 reps)	↑MDST(UB)(p=0.002) was significant between high intensity RE vs low intensity; no other significance between groups reported	↓BMI(p=0.03), ↓FBG(p=0.03) was associated with RE, no significant results reported in A1C (p=0.08)	N
Geirsdottir *et al*., 2012[82]	T2D	TUG, 6MWT, HG, MDST (LB)	MS, PP	BMI, A1C, FBG	Control (healthy elderly);	no significance between groups, **Within groups:** ↑TUG(p=0.012 T2D; p<0.001 control)	↓A1C(p<0.001) in control compared to T2D; No significance found	N

					prediabetic, T2D - all participants did RE only intervention	↑6MWT(p=0.002 T2D; p<0.001control); ↑HG(T2D group p=0.009; p<0.001control); ↑MDST(p=0.002 T2D; p<0.001 control); no other significant results found	compared to control in BMI (p>0.05) or FBG (p=0.05) no significant changes in T2D group in BMI (0.146), A1C (p=0.172), FBG (p=0.140);	
Gonela *et al.*, 2020[83]	T2D	1 RM (UB & LB), STS, 10m gait test	MS, PP	n/a	RE group only	↑1RM UB(p<0.05) LB (p<0.05); ↑STS (p<0.05); ↑10m walk test (p<0.05) was associated with RE; no other significant results reported	n/a	N
Hsieh *et al.*, 2018[84]	T2D	1 RM (UB and LB), STS, TUG	MS, PP	BMI, A1C, FBG	One RE group, one control group (standard of care)	↑STS(p=0.007) was associated with RE, no other between groups significant results, **Within groups**: ↑1 RM (LB)(p=0.001); ↑1 RM (UB)(p<0.05); ↑TUG(p=0.018) were significant within the RE group; no other significant results reported	No significant between group results; no significant results were reported in BMI (p>0.05); A1C (p>0.05), FBG (p>0.05)	Y (89%)
Ibanez *et al.*, 2005[85]	T2D	1 RM (UB & LB)	MS	BMI, A1C, FBG	4 week of no exercise, 16 weeks of RE exercise (participants were own control)	↑1 RM (UB&LB)(p<0.001) was significantly associated with RE; no other between or within group significance reported	↓ FBG(p<0.05) was associated with RE, no significant results were reported in BMI (p>0.05); A1C (p>0.05)	Y (99%)
Kwon *et al.*, 2014[86]	T2D	1 RM (UB & LB)	MS	BMI, A1C	RE only group, control group did not do RE program	↑1 RM (UB p<0.001; LB p=0.006) was significantly associated with RE; no other between or within group significance reported	No between groups significance found; ↓BMI(p=0.008) within RE; no significant results were reported in A1C (p=0.187) within RE group	N

Larose *et al.*, 2010[87]	T2D	1 RM (UB & LB)	MS	BMI, A1C	RE only group, COM group, AE only group, control group did standard of care	↑1 RM (UB&LB)(p<0.001) was significantly associated with RE compared to all groups; no other between group significance reported	↓A1C (p=0.04) in RE group compared to control; no significant results were reported in BMI (p=0.35) in RE compared to control	Y (85%)
Navarro-Peternella *et al.*, 2019[72]	T2D	MDST (ankle), 10 m gait speed	MS, PP	n/a	One group was RE only, control was standard of care	↑10m Gait speed(p=0.001) was significantly associated with RE; no significant results reported in MDST (ankle) (p>0.117)	n/a	Y (100%)
Park *et al.*, 2010[88]	T2D	HG, BCT, STS, BTS, CSRT, 8-foot TUG, 30s bicep curl, 30s abdominal curl up	MS, PP	BMI, A1C, FBG	one group had diabetes for short time (mean = 3 years) or long time (mean=10 years) all did RE intervention	**All within group analysis:** ↑HG(<0.001), ↑BCT(p<0.001), ↑STS(p<0.001), ↑CSRT(p<0.001), ↑8 foot TUG(p<0.001), ↑bicep curl(p<0.001), ↑abdominal curl(P<0.001) were all significantly associated with RE; no other significant results found	↓BMI(0.001), ↓A1C(p<0.001), ↓FBG(p<0.001) were significantly associated with RE, no other significant results were reported	N
Plotnikoff *et al.*, 2010[89]	T2D	1 RM (UP and LB)	MS	BMI, A1C, FBG	One group did RE only, control group was standard of care	↑1 RM (UB (p=0.002), LB (p=0.003), UB(p<0.001)) was significantly associated with RE; no other between group significant results	No significance between groups; no significant results reported in BMI (p=0.585), A1C(p=0.270), FBG (p=0.586) within RE group	Y (71%)
Praet *et al.*, 2008[90]	T2D	1 RM (UB and LB)	MS	BMI, A1C, FBG	One group total – did RE only	**Only within group analysis:** ↑1 RM UB(p=0.023) & LB(p=0.005) was significantly associated with RE	no significant results reported in BMI (p=0.870), A1C (p=0.386), FBG (p=0.568)	Y (83%)
Rodriguez-Manas *et al.*, 2019[91]	T2D	SPPB	PP	BMI, A1C	One group did RE + healthy living coaching, one group received	↑SPPB(p=0.003) was significantly associated with RE; no other between group significance reported	↓A1C(p=0.02) was associated with RE, no other significant results reported in BMI (p>0.05)	N

					standard of care			
Takenami *et al*., 2019[92]	T2D	MDST (LB), RM (LB)	MS	BMI, A1C, FBG	One group only; RE exercise	**Only within group analysis:** ↑(LB)(p=0.008); ↑MDST (LB)(p=0.021) were significantly associated with RE; no other significant results found	no significant results found in BMI (p=0.12), A1C (p=0.54), FBG (p=0.19)	N
Studies with RE only interventions in DKD Participants								
Castaneda *et al*., 2001[93]	DKD (CKD Stage IV)	1 RM (UB & LB)	MS	eGFR, creatinine, urea, albumin	Low protein diet with RE training, low protein diet control (no exercise)	↑1 RM (UP & LB)(p<0.001) was associated with RE; no other significant between group results reported	↑eGFR (p=0.05) was associated with RE; no significant results reported in creatinine(p>0.02), urea (p>0.02), albumin (p>0.02)	Y (91%)
de Dues *et al*., 2022[94]	DKD (CKD stage II)	1 RM (UP & LB)	MS	BMI, AIC, FBG, eGFR, albumin	RE group with CKD, RE group + blood flow restriction in UP & LB, CG did not do RE program	↑1 RM (UP & LB)(p<0.05) was associated with RE; no other significant between group results reported	↓A1C (P<0.001) was associated with RE, ↓eGFR (p<0.05) found in all groups, no significant results reported in BMI (P>0.05), FBG (P>0.05) or albumin (p>0.05)	Y (89%)
Gollie *et al*., 2020[95]	DKD (CKD stage III - V)	MDST (LB), SPPB, STS, TUG	MS, PP	BMI, eGFR, urea, creatinine, albumin	RE group only	↑MDST (LB), ↑SPPB, ↑STS, ↑TUG, p values not provided	↑eGFR, no changes reported in BMI, urea, creatinine, albumin, p values not reported	Y (100%)
Heiwe *et al*., 2005[73]	DKD (CKD Stage IV)	1 RM (LB)	MS	n/a	RE group with CKD, RE group without CKD, CG was standard of care with CKD	↑1 RM was associated in RE CKD group (p=0.0104), no other significant between group results reported	n/a	N
Olvera-Soto *et al*., 2020[96]	DKD (CKD stage IV)	HG	MS	eGFR, creatinine, urea, albumin	Cholecalciferol supplements + RE, CG took cholecalciferol without RE	↑HG (p=0.001) was associated with RE, no other significant between group results reported	eGFR changes were not reported, no significant results reported in creatinine(p=0.01), urea (p=0.260), albumin (p=0.748)	Y (77%)

Watson *et al.*, 2015[97]	DKD (CKD stage III-IV)	MDST (LB)	MS	n/a	RE group, CG group did standard of care	No significance improvements in LB MDST (p=0.09)	n/a	Y (92%)

Notes: *6MWT= 6 minute walk test; A1C= glycated hemoglobin; AE= aerobic exercise; BCT= biceps curl test; BMI=body mass index; BTS = back-scratch-test; CKD= chronic kidney disease; CSRT= chair-sit-and-reach test; COM=combination exercise group (both RE and AE); DKD= diabetic kidney disease; eGFR=estimated glomerular filtration rate; FBG=fasting blood glucose; HG= handgrip; LB= lower body; MDST= maximal dynamic strength test; MS= muscle strength; PP= physical performance; RE= resistance exercise only; RM= repetition maximum; SPPB= short physical performance battery; STS= sit-to-stand; T2D = type 2 diabetes; TUG= timed-up-and-go test; UB = upper body*

1.7.2 Impact of Resistance Exercise Interventions on Anthropometric and Laboratory Measures

The impact of RE only interventions in older adults with T2D or DKD on anthropometric (e.g., body mass index [BMI]) and laboratory values (e.g., glycated hemoglobin [A1C] and eGFR) is summarized in **Table 1.4**. The majority of T2D studies (n=15/22) did not find improvements in BMI (0.0 to 0.4 kg/m^2) following the RE interventions and none of the DKD studies reported on changes in BMI. The studies reviewed reported inconsistent changes in body weight (0.5 to -1.3 kg) and waist circumference (0.0 to -3.3 cm). Overall, the research is inconclusive regarding the impact of RE on anthropometric changes as assessed by BMI and body weight in older adults [98, 99]. BMI can be an imprecise measure and is insensitive to changes [100]. Changes in overall body weight may not be expected following RE interventions as the hypertrophic effect of RE may preclude overall weight change in older adults [44, 101]. Changes in waist circumference are also not typically associated with RE interventions in older adults [44, 101]. However, changes in overall body weight and waist circumference have been found in exercise interventions which include aerobic exercise along with RE [102, 103]. This may indicate that greater changes in anthropometric measures are more likely to be observed in combined interventions [102, 103].

Studies reporting associations between RE only interventions and laboratory measures for glucose control (A1C and fasting glucose) and renal function (eGFR, creatinine, urea and albumin) can be found in **Table 1.4**. Improvements in A1C (0.0 to 0.18%) were inconsistent in the studies reviewed with 7 studies reporting improvements and 11 seeing no changes. Improvements in fasting glucose (0 to -0.95 mmol/L) values were also inconsistent in the studies reviewed (n=4 improved; n=8 not improved). Two studies measured insulin resistance by homeostatic model for insulin resistance (HOMA-IR) and found no significant improvements

following the RE intervention [80, 85]. This variability could be due to the heterogeneity of the interventions (e.g., duration, exercise intensity, inclusion criteria) as several reviews indicate that RE is effective at improving glycemic control measures [104-106]. In the 6 studies that examined RE only interventions in DKD participants, changes in eGFR levels were reported in three studies (-1.18 to -0.04 ml/min/1.73m^2) and no significant improvements in creatinine, urea or albumin were reported in any study (**Table 1.4**). Two other randomized controlled trials in DKD (stages I-IV), that included aerobic exercise along with RE in their intervention, reported non-significant changes in eGFR (-0.5 and -1.9 ml/min/1.73m^2) [107, 108]. Overall, the literature has found exercise to have minimal impact on eGFR improvement but may limit the progression of decreasing function [109, 110].

1.7.3 Impact of Resistance Exercise Interventions on Body Composition (Lean Body Mass and Fat Mass)

Several of the studies reviewed assessed changes in lean body mass and fat mass in their participants with T2D. In the studies reviewed, a range of -0.2 to 3.2 kg change was reported in lean body mass [74-76, 79-82, 84, 86, 87, 89, 92]. Changes in fat mass were also inconsistent in the studies reviewed (0.0 to -3.7 kg) [75, 79, 80, 86-89, 92]. Due to the hypertrophy associated with RE, improvements in lean body mass have been associated with RE in older adults [44]. However, changes in other components of body composition, such as fat mass are less likely to be found following RE interventions in older adults [105, 111]. The loss of lean body mass is often observed as adults age and this is exacerbated by the presence of diseases like DKD [112]. This may mean that statistically significant changes in lean body mass and fat mass may not be consistently reported

following RE interventions but maintenance might be considered clinically important in older adults, particularly those with chronic disease like DKD [113].

1.7.4 Impact of Resistance Exercise Interventions on Physical Performance Measures

A summary of the impact of RE only interventions on physical performance tests in older adults with T2D is found in **Table 1.4.** One DKD study assessed physical performance tests following 24 sessions of RE (**Table 1.4**). Only one study in T2D participants used SPPB as an outcome, which did find improvements (increased by 0.94 points) following 16 weeks of supervised RE. The one DKD study found improvements in the SPPB score of 0.3 points. While the DKD study had smaller improvements, the T2D study had similar to improvements in SPPB scores in other-wise healthy frail older adults without specific diseases (increases of 0.8 to 1.4 points) [114-116] . An increase of 0.3 to 0.8 points on the SPPB in older adults is considered to be clinically significant and appears to be achievable in both T2D and DKD participants following RE interventions [117]. The SPPB is thought to be a highly valid and reliable tool to assess the functional status of older people [118]. Performance in the different domains (e.g., balance, gait speed and sit-to-stand) can be used to establish preventative strategies in multiple areas of functionality. Improvements in sit-to-stand scores (-0.94 seconds to -2.9 seconds) were also reported following RE interventions in T2D participants and the one DKD study found an improvement of -2.5 seconds. Studies examining the impact of RE interventions in older adults at risk for frailty found similar improvements in sit-to-stand scores (-0.9 to -1.9 seconds) [119-121]. Some of the studies reviewed showed that RE can elicit clinically significant changes in sit-to-stand as a change of -1.7 to -2.3 seconds in sit-to-stand score is considered to be clinically significant in older adults [122, 123]. The ability to complete the sit-to-stand movement is

predicative of functional independence and reduced capacity to perform on this test has been associated with many activities of daily living such as stair climbing, transfers and walking [124]. RE has been found to be an effective strategy to improve sit-to-stand performance in frail and pre-frail older adults [125, 126]. Significant improvements were also reported in physical performance tests that measure gait speed (e.g., six-minute walk test [24.7 to 51.2 meters] and 10m gait speed [+0.15 meters/second]). RE that targets the lower body has been shown to improve physical performance measures related to mobility [45, 127, 128]. However, heterogenous results were found regarding performance on the timed up and go test (-1.1 to 0.15 seconds). A systematic review on the impact of RE on physical performance in older adults found that RE did not improve overall timed up and go performance [129]. As clinically significant improvements in the timed up and go test are reported as changes of -0.9 to -1.4 seconds it seems like RE interventions in older adults are inconsistent in developing clinically relevant improvements in this test [130]. It may be that because the timed up and go test incorporates several types of movements and transitions, consistent improvements are less likely to occur after RE only interventions [131].

1.7.5 Impact of Resistance Exercise Interventions on Muscle Strength Measures

The results of RE interventions on measures of muscle strength in older adults with T2D and DKD is summarized in **Table 1.4**. There is a large body of evidence that RE in older adults with T2D will significantly increase muscle strength and the studies in DKD (CKD Stages II-IV) suggest the same. In T2D studies, improvements were found in measures of hand-grip (2.5 to 5.12 kg), upper and lower body 1 repetition maximum (upper body = 2.0 to 26 kg; lower body = 6.0 to 49.0 kg) and upper and lower body MDST (upper body = 10.8 to 15.1 kg; lower body = 5.1 to 54.3 kg) in almost all studies. One DKD study (CKD stage IV) found a 2.4 kg improvement in hand-grip

strength following 12 weeks of RE (**Table 1.4**). Three DKD studies (CKD stage II-IV) reported improvements in muscle strength as measured by 1 repetition maximum in upper body (7.8kg) and lower body (2.0 to 43.5 kg). Two studies (CKD Stage III-IV) measured lower body muscle strength by MDST and reported 6.1 and 18.3kg improvements. In randomized controlled trials in dialysis patients, improvements in hand-grip were smaller than in the T2D or DKD studies reviewed (0.4 and 1.2 kg) [108, 132]. Other randomized controlled trials found similar improvements (2.4 to 4.7 kg) in hand-grip in the frail elderly following RE interventions [114, 119, 120]. A systematic review by Liu *et al*., [129] reported that RE interventions consistently improved bother upper and lower body muscle strength in older adults, which was mostly measured by repetition maximum. There does not appear to be an agreed upon minimal clinically significant change in the literature for muscle strength measured by 1 repetition maximum or MDST and this is likely due to the wide variation in what muscle group these tests are used to assess [133]. However, clinically significant improvements in hand-grip have been reported to be between 5.0 to 6.5 kg [134]. These values indicate that some RE interventions in T2D participants improved hand-grip by a clinically significant value, but the DKD study did not. Hand-grip is often used to assess muscle strength in older and frail adults [135]. However, it is thought to be insensitive to changes in overall body strength (upper and lower body) [136]. Lower body strength is important to measure in older adults as it has been associated with predicting frailty, morbidity and mortality [9, 14].

1.8 HEALTH RELATED QUALITY OF LIFE

1.8.1 Health Related Quality of Life and Frailty

HRQOL is a term used to describe how well a person is able to function in their life along with a perceived level of well-being in terms of physical, mental and social health domains [137]. HRQOL and frailty have been consistently linked in the literature [138-140]. Frailty can lead to increased illness, hospitalizations, falls and mortality [4, 32, 141]. In turn, these adverse outcomes are likely to negatively impact HRQOL [142]. On the other hand, a reduction in frailty status is likely to improve the physical, mental and social domains of HRQOL [139, 143].

1.8.2 Impact of RE Interventions on Health Related Quality of Life in Adults with Type 2 Diabetes and Diabetic Kidney Disease

Only a few studies examine the impact of RE only interventions in T2D participants on HRQOL outcomes and are summarized in **Table 1.5**. No studies assessed HRQOL in studies with DKD (CKD stages I-IV). The results from these studies regarding HRQOL outcomes are found in **Table 1.6**. Overall, RE interventions reported inconsistent results regarding improved HRQOL. However, most of the studies (n=5/6) that used the 36 Item Short Form Survey (SF-36) [144] tool to measure HRQOL found improvements in some of the measured domains. Studies reported improvements in the SF-36 subdomains of general health (n=2, [2.4 and 3.0]), physical functioning (n=1, [9.0]), vitality (n=1, [10.5]), mental health (n=1, [3.1]) as well as the physical (n=3, [0.4 to 2.9]) and mental (n=2, [2.2 and 10.2]) component scores. A change of 5 points is considered clinically and socially relevant in the SF-36 tool [145]. All studies that used other HRQOL tools (n=3 [DQOL-Brasil, EQ-5D-3L, ADDQOL]) did not report any improvements in HRQOL. There is limited research on RE only interventions in populations with DKD or CKD (stage I-IV) prior to

dialysis. In one systematic review, RE was found to conclusively improve HRQOL in CKD hemodialysis participants [146]. All studies included in this review used the SF-36 tool and reported improvements in the physical component score [146]. The variable results reported in the T2D studies reviewed (**Table 1.6)** could be due to the heterogeneity of the HRQOL tool used (e.g., SF-36 vs Diabetes Quality of Life). A summary of the different HRQOL tools used in the studies reviewed is found in **Appendix A: Table 2**. Using a disease specific questionnaire (e.g., Diabetes Quality of Life) is thought to be helpful for quantifying changes in a patients' HRQOL following an intervention targeting specific disease outcomes (e.g., glycemic control) [147]. However, general HRQOL tools (e.g., SF-36) have been found to be more relevant to overall HRQOL and allow for comparison between populations [147, 148]. In a systematic review of RE interventions in older adults (not disease specific) RE interventions were found to conclusively improve HRQOL as measured by SF-36 [149]. The SF-36 is considered to be the gold standard for HRQOL research in physical activity so it is likely that this is the most appropriate tool to use in order understand the impact of RE interventions on HRQOL [150]. Disease specific tools (e.g., Adults with Diabetes Quality of Life) are more likely to elicit an understanding of how a disease itself impacts HRQOL [148].

Table 1.5 Description of studies measuring health related quality of life in resistance exercise only interventions in participants who have type 2 diabetes

Author, Year	Study design	Population	Disease Duration (years)	eGFR *(mL/min per 1.73 m2)*	Baseline Anthropometrics	Age (years)	Sex	Sample size	Intervention Length	Control Group
Botton *et al*, 2018[71] ∗ω	RCT	T2D	Mean(SD): RE 10.7(7.9) CG 11.3(7.4)	n/a	Mean(SD) BMI: RE 28.2(3.6) CG 28.6(3.3)	Mean(SD): RE 70.6(6.7) CG 68.6(7.1)	F=18 M=26	n=44	3 months	Y
Brazo-Sayavera *et al*., 2021[149]	C	T2D	n/a	n/a	Mean (SD) BMI: RE 30.0(3.40) CG 28.3(3.24)	Mean(SD): RE 74.7(4.5) CG 73.1(3.9)	F=22 M=13	n=35	12 weeks	Y
Cheung *et al*., 2009[85]†ω	RCT	T2D	n/a	n/a	Mean (SD BMI: RE 39.7(9.0) CG 37.7 (9.2)	Mean(SD): RE 59.0(8.7) CG 62.0(6.7)	F=25 M=12	n=37	4 months	Y
Hsieh *et al*., 2018[91]∗ω	RCT	T2D	Mean(SD): RE 11.1(7.8) CG 13.9(6.7)	n/a	Mean(SD) BMI: RE 25.6(2.6) CG 25.4(3.4)	Mean(SD): RE 70.6(4.2) CG 71.8(4.5)	F=19 M=11	n=30	12 weeks	Y
Lincoln *et al*, 2011[150]∗	RCT	T2D	n/a	n/a	Mean(SD) BMI: RE 30.9(5.7) CG 31.2(5.9)	Mean(SD): RE 66.0(7.9) CG 66.6(7.4)	F=37 M=21	n=58	16 weeks	Y
Meyers *et al*, 2013[151]∗	RCT	T2D	Mean (SD) RE 7.2(5.5) COM 6.7(5.4) AE 7.4(6.0) CG 7.2(5.2)	n/a	Mean (SD) BMI: RE 34.1(5.4) COM 35.8(6.2) AE 34.7(6.1) CG 34.9(5.9)	Mean (SD) RE 56.9(8.7) COM 55.4(8.3) AE 53.7(9.1) CG 58.6(8.2)	F=165 M=97	n=262	9 months	Y
Ng *et al*., 2011[152]∗†	RCT	T2D	Mean(SD): RE 11(9) AE 12(9)	n/a	Mean(SD) BMI: RE 27.4(4.7) AE 27.8(5.2))	Mean(SD): RE 57.0(7.0) CG 59.0(7.0)	F=41 M=19	n=60	8 weeks	N
Plotnikoff *et al*., 2010[89]	RCT	T2D	n/a	n/a	Mean(SD) BMI: RE 35(8) CG 26(5)	Mean (SD): RE 55.0 (12) CON 54.0 (12)	F=32 M=16	n=48	16 weeks	Y
Reid *et al*., 2010[153]∗	RCT	T2D	Mean(SD): RE 6.1(4.7) COM 5.2(4.8)	n/a	Mean(SD) BMI: RE 34.1(9.6) COM 35.0(9.6)	Mean(SD): RE 54.8(7.2) COM 53.5(7.3)	F=91 M=125	n=216	6 months	Y

			AE 5.1(3.5) CG 5.0(4.5)		AE 35.6(10.1) CG 35.0(9.5)	AE 53.9(6.6) CG 54.8(7.2)				

***Note**: AE = aerobic exercise; A1C= Glycated hemoglobin baseline anthropometrics = may include (BMI, weight, Fat free mass %); C = cohort; CC = case/control; CG = control group; CKD = chronic kidney disease; CON = control group; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; F= female; HRE= hypertrophy resistance exercise; HRQOL=health related quality of life; M=male; n= sample size; n/a= not assessed; RCT= randomized controlled trial; RE= resistance exercise only; SD= standard deviation; T2D= type 2 diabetes mellitus*

** = supervised intervention*

† = used elastic/resistance bands for resistance

ω = used a self-perceived rating of exertion for intensity

Table 1.6 Results of health related quality of life in studies with resistance exercise only interventions in participants with type 2 diabetes

Author, Year	T2D or DKD	HRQOL Tool	Subject Groups	HRQOL Results	Adherence Reported
Botton *et al.*, 2018[71]‖	T2D	DQOL-Brasil	RE only group, active CG (static stretching only)	No significant improvements found in HRQOL between RE and CG (p>0.05); no significant improvements found in HRQOL within RE group(p=0.37)	Y (87%)
Brazo-Sayavera *et al.*, 2021[151]	T2D	EQ-5D-3L	RE group who was frail or pre-frail, CG followed usual care and was robust	No significant improvements found in HRQOL between RE and CG (p=0.584); no significant improvements found in HRQOL within RE group(p>0.05)	N
Cheung *et al.*, 2009[78]	T2D	SF-36	RE group, one CG (standard of care)	No significant improvements found in HRQOL between RE and CG (p>0.24); except in general health category (p=0.02); no results within groups reported	Y (90%)
Hsieh *et al.*, 2018[84]	T2D	ADDQoL	One RE group, one CG (standard of care)	No significant improvements found in HRQOL between RE and CG (p>0.05); no significant improvements found in HRQOL within RE group(p>0.05)	Y (89%)
Lincoln *et al.*, 2011[152]	T2D	SF-36	One RE group, one CG (standard of care)	↑MCS was associated with RE (p<0.0001)	N

Meyers *et al*., 2013[153]	T2D	SF-36	RE only group, COM group, AE only group, control group did standard of care	↑PCS was associated with RE compared to CG(p=0.003); ↑PCS was found within RE group (p=0.005); no improvements were found in MCS in the RE group (p>0.05)	N
Ng *et al*., 2013[154]	T2D	SF-36	One RE group, one AE group	No significant differences found in HRQOL between groups (p>0.354); ↑physical functioning (p=0.04), ↑ general health (p<0.000), ↑vitality (p=0.004), ↑mental heath (p=0.02); ↑MCS (p=0.006) improvements in RE group; no significant improvements found in role physical (p=0.142), bodily pain (p=0.307), social function (p=0.330), role emotional (p=0.006), PCS (p=0.184) within RE group	N
Plotnikoff *et al.*, 2010[89]	T2D	SF-36	One RE group, one CG (standard of care)	No significant improvements found in HRQOL between RE and CG (PCS p=0.310; MCS p=0.131); no significant improvements found in HRQOL within RE group(p>0.05)	Y (71%)
Reid *et al*., 2010[155]	T2S	SF-36	RE only group, COM group, AE only group, control group did standard of care	↑PCS was associated with RE compared to CG(p=0.015); ↑MCS was associated with RE compared to CG(p<0.001)	Y (85%)

Notes: *6MWT = 6 minute walk test; A1C= glycated hemoglobin; ADDQoL=audit of diabetes dependent quality of life; AE= aerobic exercise; BMI=body mass index; CKD = chronic kidney disease; COM=combination exercise group (both RE and AE); DKD = diabetic kidney disease; DQOL=diabetes quality of life measurement; eGFR=estimated glomerular filtration rate; EQ-5D-3L=European quality of life 5 Dimensions; FBG=fasting blood glucose; HG= handgrip; HRQOL= health related quality of life; LB= lower body; MCS=mental component scores; PCS=physical component scores; QOL=quality of life; RE = resistance exercise only; SF-36=short form health survey; T2D = type 2 diabetes;*

1.9 HEALTH LITERACY

1.9.1 Term Description

HL has recently been recognized as a social determinant of health, due to its role in promoting and maintaining health [156]. At an individual level, HL encompasses the knowledge, motivation and skills that people use to access, comprehend, evaluate and implement information about health [156]. Nutbeam [50] describes HL as having three distinct types, each with increasing levels of complexity: functional, interactive (or communicative) and critical. Functional HL (FHL) encompasses basic literacy and numeracy skills (reading and writing) and the ability to partake in basic communication. FHL allows patients to understand health risks or navigate the healthcare system. Interactive (or communicative [CoHL]) HL is the ability to take in, extract meaning and apply information gathered regarding health. CoHL allows patients to seek out further support or information regarding their health. Critical HL (CHL) uses the most advanced cognitive skills to critically analyze relevant health information in order to take action and gain enhanced control over ones' life and health. Having CHL means a patient can take excess information regarding their health, filter through it and integrate the information into their personal behavioral actions.

1.9.2 Health Literacy and Health Outcomes

HL has been identified as a factor that has the potential to influence health outcomes [157]. Research has shown that patient HL status is associated with health outcomes (e.g., glycemic control) and is becoming increasingly important to consider when developing treatment strategies for chronic disease (**Figure 1.3**) [157]. Low levels of HL are associated with inappropriate use of health care services and poorer health status [157]. HL in older adults is particularly of

interest, as they often have a greater need for management of health and chronic conditions [48]. Older adults with low HL have an increased risk of frailty, higher healthcare costs and have higher mortality rates [157-159]. Higher levels of HL have been associated with engagement in self-care behaviors such as physical activity, eating a more healthful diet and participation in social events [160-162]. A systematic review done in 2013 [163] on the impact of HL on health outcomes in diabetes found inconclusive evidence regarding the influence of HL on glycemic control, hypoglycemia, blood pressure and diabetes complications. However, in this same review conclusive evidence associated higher HL with diabetes knowledge [163]. In a 2018 review [164] of the influence of HL on patient outcomes in CKD (included non-dialysis and dialysis studies), low HL was associated with increased hospitalizations and cardiovascular events in non-dialysis CKD. CKD participants (stage I-IV) with low HL also had lower disease knowledge [164]. Most of the studies included in these reviews looked only at FHL and did not include measures of CoHL or CHL. Along with the limited HL research available examining all components of HL, there is limited research on the influence of HL in DKD outcomes specifically. This area of research needs to be explored in order to understand how all the domains of HL may influence patient outcomes in people with DKD.

1.9.3 Health Literacy and Adherence

Adherence is a key component of the success of most medical treatment and advice [165]. Unfortunately, adherence to chronic disease treatments (e.g., medication regimens and lifestyle changes) has been found to be around 50% on average [166, 167]. Adherence is driven by many factors. It has been suggested that the relationship between HL and adherence may be part of the reason why HL is associated with poorer health outcomes [168, 169]. HL has been identified as a key indicator of patient compliance to prescribed treatments for chronic disease. Much of the

research on this has been done on the adherence to medication regimes, which generally show that higher HL is associated with higher medication adherence rates [166]. It has also been shown that adherence to non-medical recommendations (such as increased physical activity and dietary changes) are also associated with higher HL levels [166, 170]. A 2017 meta-analysis by Miller [166] showed that people with higher HL had a 14% higher rate of adherence to treatment. The relationship was strongest in non-medication interventions. One reason suggested was that lifestyle interventions require more guidance and learning, compared to a medication regimen. The increased need for understanding, implementation and decision making in lifestyle interventions may emphasize the increased dependency on HL in the patient [166].

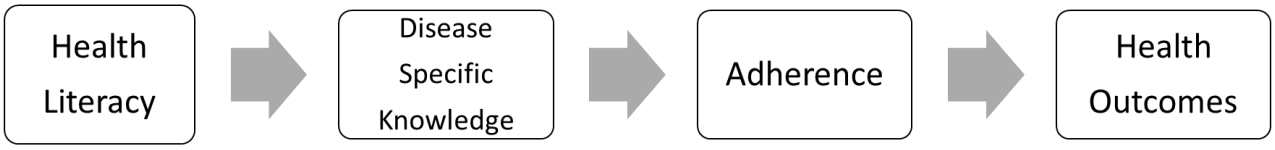

Figure 1.3 Proposed causal pathway linking health literacy and health outcomes. Adapted from Paasche-Orlow, M.K., and Wolf, M.S.; 2007 [171]

1.9.4 Health Literacy and Frailty

Adequate HL has been found to reduce the incidence of frailty and reduce the progression into a frailer state [159]. Assessment of physical function is an important component of monitoring frailty status [33]. Low HL has been associated with meaningful decline in physical function in older adults [157, 158, 172]. Gait speed, which is a direct indicator of reduced physical function, was found to be associated with HL in a 2020 study by Anami *et al.* [173]. Based on this, HL status is one predictor of frailty manifestation, and should be considered when developing treatment and intervention plans. Lifestyle interventions are often prescribed in order to prevent, or slow the progression of frailty. Increasing physical activity levels, improving body composition, as well as

improved physical performance are key determinants of the treatment of frailty. Different modalities of exercise, with an emphasis on resistance-type exercise, have been shown to be an effective treatment for the physical dysfunction that is found in frail or pre-frail adults [11, 57, 174, 175].

1.10 CONCLUSIONS

Chronic diseases like DKD require life-long involvement of the patient in the management of their disease [176]. Understanding variables that may influence patient compliance is important for multidisciplinary teams tasked with treating patients with complex diseases, such as DKD [176]. The relationship between HL and adherence to lifestyle interventions, like RE protocols, is important to investigate further as adherence is important for the success of interventions. HL is a complex, dynamic set of skills that can have a large impact on health outcomes in adults with chronic diseases like DKD. Having adequate HL is necessary for effective involvement of the patient in their own health care and to reduce the incidence of adverse conditions, such as frailty [159, 177]. This information is important in order to develop focused approaches that target improvements in muscle function that are aimed to increase accessibility and adherence to RE. These interventions are particularly important for adults with DKD at risk for frailty. Hence, this thesis will examine a) if a 6-month home-based RE program that uses digital technologies will result in significant improvements in functional outcomes, frailty status, HRQOL and HL **(CHAPTER 3**) and b) the impact of HL on the study outcomes (**CHAPTER 3**). Results from this thesis will help further research related to the treatment of frailty in adults with DKD.

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Chapter 2: Research Plan

2.1 STUDY RATIONALE

Frailty is a complex condition that arises with age from a decrease in both physiological reserves and body function, reducing the ability of the body to respond appropriately to stress. The presence of frailty often results in an increased risk for adverse outcomes (falls, fractures, and reduced HRQOL) [1, 2]. People with T2D and CKD often have a high co-morbid burden that includes conditions such as frailty. This increased burden is associated with depression, HRQOL, increased healthcare utilization, and reduced lean body mass [1, 3]. The impact of the co-morbid burden is compounded by an increased decline in muscle function and ability to perform activities of daily life [4, 5] The prevalence of this co-morbid burden alongside reduced muscle function in T2D and CKD highlights the need for effective strategies that can help reverse, or prevent the progression of these patients into state of physical dysfunction.

Resistance exercise (RE) training is a well-known strategy for maintaining or increasing muscle function in adults. RE has also been shown to have positive impacts on psychological factors as well, such as depression and cognitive decline [6, 7]. RE may ameliorate physical dysfunction in older populations by contributing to increased muscle strength, muscle power and physical performance [8]. As reduced muscle function is a key determinant of frailty, it is critical to understand the impact of RE in populations at high risk for frailty, such as patients who have both T2D and CKD [9, 10]. There is limited research that examines RE in older adults with both T2D and CKD. The purpose of this thesis was to examine the impact of a 6-month home-based RE program in older adults with T2D and CKD on frailty status and outcomes related to a specific domain of frailty: physical functioning. The findings from this randomized controlled trial will

provide robust contributions to the understanding of the role of RE in the development of future treatments for frailty in this population.

HL encompasses the knowledge, motivation and skills that people use to access, comprehend, evaluate and implement information about health [(11)]. HL has been identified as a factor that can be either a potential barrier or facilitator to health outcomes. Research has shown that patient HL status is associated with health outcomes and is becoming increasingly important to consider when developing treatment strategies for chronic disease [(12)]. It has been suggested that the link between HL and health outcomes is influenced by adherence to treatment plans [(13)]. The relationship between HL and adherence is important to investigate as adherence is a clear indicator of the success of interventions.

The findings from this thesis will provide insight regarding the impact a home-based RE program may have on functional outcomes, frailty status and HRQOL in older adults with T2D and CKD. It will also help to further our understanding regarding the role that HL may play in the success of rehabilitation programming on promoting improvements in muscle function in frail adults with T2D and CKD. Findings from this study will be applicable to other clinical populations where frailty is highly prevalent.

2.2 OVERALL OBJECTIVES AND HYPOTHESIS FOR THE FANTASTIC STUDY

Primary Study (FANTASTIC) Objective: To determine if an innovative home-based resistance exercise program using digital technologies and conducted over 6 months will result in significant improvements in functional outcomes, frailty status, body composition, HRQOL, physical activity patterns, diet quality, HL and nutrition literacy.

Primary Study (FANTASTIC Study) Hypothesis: Participation in the 6-month RE program will result in improvements in functional outcomes, frailty status, body composition, HRQOL, physical activity patterns, diet quality, health literacy and nutrition literacy.

2.2 THESIS SPECIFIC OBJECTIVES AND HYPOTHESIS

Thesis Objective 1: To determine if an innovative home-based resistance exercise program using digital technologies and conducted over six-months will result in significant improvements in functional outcomes (SPPB, hand-grip) and frailty assessments (Edmonton Frailty Scale).

Thesis Objective 2: To determine if an innovative home-based resistance training program using digital technologies and conducted over six-months will result in significant improvements in HRQOL (Short Form Health Survey [SF-36]) and health literacy (Functional, Communicative and Critical Health Literacy Scale [FCCHL]).

Thesis Objective 3: To determine the impact of health literacy on the primary (functional outcomes, frailty status) and secondary outcomes (HRQOL) of a home-based RE program in adults with T2D and CKD as measured by the FCCHL.

Thesis Hypothesis 1: The RE program will result in improved functional outcomes and frailty status.

Thesis Hypothesis 2: The RE program will result in improved HRQOL and health literacy.

Thesis Hypothesis 3: Participants with a higher level (above the median) of health literacy will have the greatest improvements in the measured outcomes of functional performance, frailty status and HRQOL over 6 months.

2.3 REFERENCES

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Chapter 3 – Impact of 6-month Home-based Resistance Exercise Program on Functional Outcomes, Frailty Status, Health Related Quality of Life and Health Literacy in Adults with T2D and CKD

3.1 INTRODUCTION

Frailty is a complex condition that arises with age from a decrease in both physiological reserves and body function; reducing the ability of the body to respond appropriately to stress [1]. Many lifestyle factors can influence the progression of frailty but the presence of chronic disease, such as type 2 diabetes (T2D), can be a major contributor to the development of frailty [2]. Kidney disease attributed to diabetes (diabetic kidney disease [DKD]) is one of the leading causes of chronic kidney disease (CKD) worldwide [3]. Patients with T2D and CKD are more likely to experience reduced health related quality of life (HRQOL) and increased prevalence of frailty [4, 5]. Frailty has been associated with depression, reduced HRQOL, increased healthcare utilization and fall risk [4-7]. The prevalence of this co-morbid burden highlights the need for interventions in people suffering from DKD. Interventions which aim to limit progression of frailty and muscle dysfunction in turn may help to reduce morbidity, hospitalizations and mortality in older adults with DKD [8, 9].

Resistance exercise (RE) is linked to many physiological and psychological benefits in adults of all ages. Studies show that RE can improve body composition, muscle strength, muscle power and functional endurance in older adults [10, 11]. Reduction in cognitive decline, improved quality of life and deceased depression in older adults have also been associated with RE [12, 13]. Consistent adherence to regular RE improves health outcomes from RE [14]. The American College

of Sports Medicine recommends that older adults with T2D participate in moderate or higher intensity RE a minimum of 2 times per week [15]. Related to the concept of adherence is health literacy (HL). HL encompasses the knowledge, motivation and skills that people use to access, comprehend, evaluate and utilize information about health [16]. HL has 3 domains, each with an increasing level of complexity: functional (FHL), communicative (CoHL) and critical (CHL). The level of HL contributes to the success of health outcomes experienced by any intervention [17]. Paasche-Orlow & Wolf [18]suggested that there is a causal pathway that links HL to adherence which is then linked to health outcomes. The relationship between HL and improved adherence to lifestyle interventions, such as RE, is important to investigate further as strategies to improve adherence are critical for the success of interventions [19].

The development of an innovative home-based strategy for frailty prevention in adults with Diabetes and Chronic Kidney Disease (FANTASTIC) study is examining the relationship between a 6-month home-based progressive RE program on functional outcomes, frailty status, HRQOL, body composition and other outcomes such as physical activity patterns, diet quality, HL and nutrition literacy in adults with T2D and CKD (pre-dialysis stage I-IV). This chapter addresses a preliminary data analysis that examines the relationships between the domains of HL (measured by Functional, Communicative and Critical Health Literacy Scale [FCCHL][20]) and adherence to the RE intervention on functional performance (Short Physical Performance Battery Assessment [SPPB], hand-grip), frailty status (Reported Edmonton Frail Scale [EFS]) and health related quality of life (HRQOL, [Short Form Health Survey (SF-36)]) in an ongoing randomized controlled trial (FANTASTIC Study). It was hypothesized that participation in the RE program would result in significant improvements in the primary outcomes of functional performance and

frailty status and secondary outcomes of HRQOL and HL. Additionally, it was hypothesized that the participants with higher (above the median) HL levels would have the greatest improvements in the measured outcomes of functional performance, frailty status and HRQOL over 6 months.

3.2 METHODS

An open-label, double-block randomized controlled trial was conducted in adults aged 50-85 years who had concurrent T2D and CKD (stages I-IV). This analysis is based upon 37 participants randomized into the study. Participants were recruited through the Alberta Kidney Care-North Renal Insufficiency (RIC) and Diabetic Nephropathy Prevention Clinics (DNCP) in Edmonton, Alberta and through community channels (e.g., word of mouth, social media channels of non-for-profit organizations). Inclusion criteria included adults aged 50-85 years with CKD stage (I-IV) who did resistance-type activity ≤1xweekly. Participants were excluded if they performed regular resistance-type exercise (≥1x weekly), were on dialysis, were pregnant, had severe or permanent vision loss, any functional or cognitive impairments (Mini Mental State Examination [21] scores <24), any recent bone fractures or a history of skeletal muscle disorders. Informed consent was obtained from the participants. This study was approved by the Human Research Ethics Board, University of Alberta (Pro00089513). Informed consent was obtained prior to study enrollment. Participants underwent initial screening of their medical record to confirm eligibility for study entry and then were screened for frailty using the Clinical Frailty Scale (CFS) [22] (**Appendix B: Figure 1**). Once eligibility was confirmed, participants were randomized to one of the arms of the study: intervention or standard of care (SOC). The randomization was done by an online number generator (randomizer.org) and designation was unknown to study staff until the participants baseline (month 0) university visit. The study protocol for each type of

study visit (baseline university, baseline home, monthly home visits, final university [month-6]) is depicted in **Figure 3.1**.

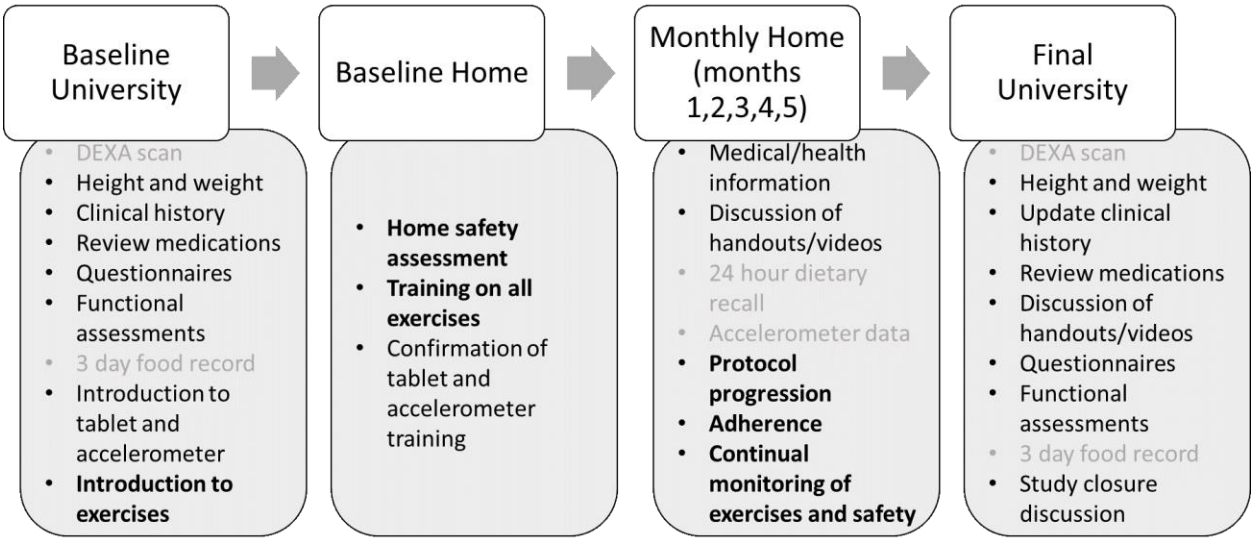

Figure 3.1 Flow diagram showing assessments done at different types of study visits. Regular text indicates activities done with both intervention and standard of care groups, **bold** text indicates activities done with intervention participants only and grey text indicates data collected but not included in this thesis.
DEXA=dual-energy X-ray absorptiometry

Primary outcomes measured in the FANTASTIC Study included functional outcome assessments (physical performance [SPPB] [23]; muscle strength [Jamar® dynamometer] [24]), frailty assessments (CFS; EFS; FRIED Frailty Phenotype) and body composition (Dual-Energy X-ray Absorptiometry). In this thesis, we examined the primary outcomes specifically related to SPPB, muscle strength and frailty assessments (EFS) only. Secondary outcomes presented in this thesis included HRQOL (SF-36) [25] and HL (FCCHL) [20]. A list of all outcomes measured in the FANTASTIC Study is found in (**Appendix B: Table 1**).

3.2.1 Measurement of Anthropometric, Demographic and Laboratory Data

Anthropometric and demographic data including height, weight, body mass index (BMI), age at study recruitment, age at diabetes diagnosis and sex were collected at the baseline and 6-month visits. Height (cm) and weight (kg) were measured to the nearest 0.01 cm and 0.1 kg. Height was measured without shoes using a digital stadiometer (Measurement Concepts & Quick Medical, Washington, USA). Weight was measured without shoes and while wearing light clothing using a Health o meter® Professional digital scale (Model 752KL, Illinois, USA) at university visits and using a Conair© portable precision electronic scale (Woodbridge, Ontario, Model WW12C) at home visits. BMI was calculated as weight(kg)/[height(m)]^2. Obesity was defined as a BMI ≥30kg/m^2 [(26)]. The number of co-morbidities, which was classified as any other condition that the participant was currently be treated for, (e.g., dyslipidemia or hypertension) was collected at the baseline university visit. Information on co-morbid conditions were collected verbally from participants, checked via medication lists as well as confirmed through online medical records. Phlebotomy collection was not included as part of the study protocol, however if recent laboratory results (≤3 months) were available from their online medical records the results were recorded. Laboratory parameters extracted from electronic medical records, if available, included kidney function tests (creatinine, estimated glomerular filtration rate [eGFR]), liver function tests (albumin, urea), diabetes control (Hemoglobin A1c [A1c], fasting- and random blood glucose), lipid panel (triglycerides, total cholesterol, high-density lipoproteins [HDL] cholesterol, low-density lipoproteins, cholesterol and cholesterol/HDL ratio), C-reactive protein [CRP] and minerals (sodium, potassium, chloride, magnesium, calcium and phosphorus). Laboratory data was available with a range of 2-111 days from the baseline university visits and

between 0-91 days from the final month-6 visit. All laboratory values were measured using validated methodologies by the Alberta Health Services Core Laboratory.

3.2.2 Measurement of Functional Outcomes

The SPPB test assesses both physical performance and level of physical functioning. The test is comprised of three components including balance, walking speed and sit-to-stand (**Figure 3.2)** [27]. Standing balance was measured in a progressive fashion beginning with a side-by-side stand, followed by semi-tandem stand and lastly a tandem stand. Before beginning the test, the researcher would demonstrate the position. When participants were in position and had released any support, the researcher began timing until 10 seconds had elapsed or the participant moved or held onto their support, whichever occurred first [23]. If the participant was unable to hold the position for 10 seconds they did not progress to the subsequent stance and the time they had held the stance for was recorded. Walking speed was measured as the time to complete a 3-meter walk. The walking course was clearly indicated with tape on the floor on either end and was free of any obstructions. Participants were instructed to walk from one end of the course to the other at their normal pace and to walk all the way past the taped line. If needed, participants could use a walking aid such as a walker or cane. The walk was performed twice and timed by the researcher; the faster of the two walks was used for scoring of the test [23]. To test the participant's sit-to-stand (STS) performance, the participant was seated in a chair with a straight back with their feet flat on the floor and their arms folded across their chest. They were then asked to stand up keeping their arms folded across their chest and the researcher demonstrated the movement. If the investigator deemed that it was safe to proceed, the participant was then asked if they felt it would be safe to attempt standing up from the chair without using their arms

five times as quickly as possible. If the participant agreed, the researcher would then time the participant from their initial sitting position until they stood up for the fifth time [23]. The test was stopped if the participant was unable to complete the first chair stand or did not feel comfortable completing five chair stands. The maximum SPPB score is 12 and the minimum is 0 as each component of the test is scored on a scale of 0-4 [27]. A score >10 is deemed normal while a score ≤10 is abnormal.

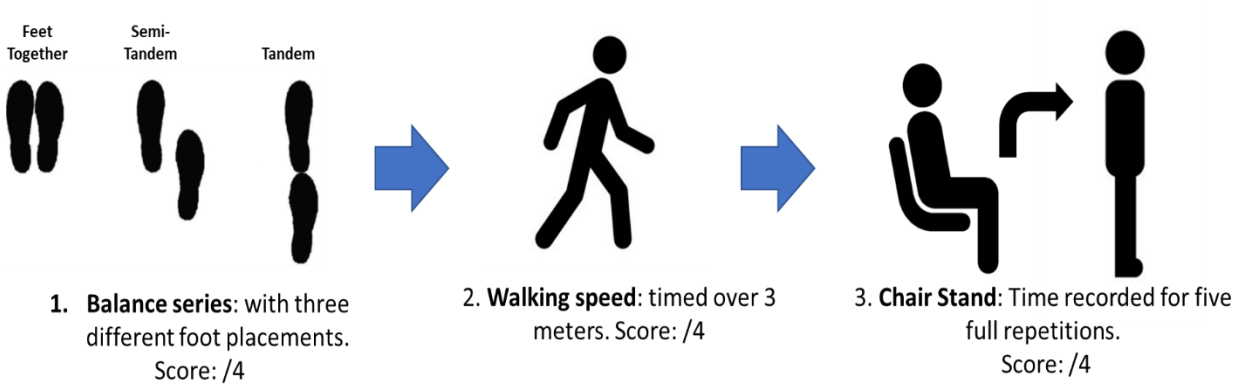

Figure 3.2 The three components of the Short Physical Performance Battery Assessment (SPPB). The maximum score for the entire test is 12 points. 1) The balance series is composed of three different foot placements, held for 10 seconds each for a maximum score of 4. 2) The walking (gait) speed series has participants walk their usual speed for 3 meters, two times. The fastest speed is scored for a maximum of 4 points. The chair stand, or sit-to-stand, series has participants complete 5 full repetitions as fast as possible for a maximum of 4 points.

Hand-grip was used to measure muscle strength using the Jamar® hand dynamometer following standardized methodology [28]. The participant's dominant hand and the dynamometer hand position were noted before beginning. Participants were seated with their feet flat on the floor with shoulders adducted and their elbow flexed at 90°. Forearm and wrist were in a neutral position and were not resting on anything. Measurements were taken in an alternating fashion until three measurements had been collected from each hand. The average of the three scores was when then used to assess hand-grip strength of each side. Hand-grip scores were compared to cut-off values corrected for BMI and sex determined by Fried *et al.* [29]. Participants whose

hand-grip score for their dominant hand was equal to or below the cut-off value were determined to have weakness and scores above the cut off value did not have weakness.

3.2.3 Frailty Assessments

Frailty status was assessed using 2 different assessment tools. The CFS was used by research staff at initial screening in order to categorize participants as frail or non-frail at study entry only. Participants that were ranked with a score of ≥4 were considered to be frail [22] (**Appendix B: Figure 1**). As well, a modified version of the reported EFS was administered at baseline and at month-6 [30, 31] (**Appendix B: Table 2**). The EFS is based on 9 categories which cover concepts that address: Cognition, General Health Status, Functional Independence, Social Support, Medication Usage, Nutrition, Mood, Continence and Self-Reported Performance of Daily Activities. Scores >5 are indicative of the presence of frailty. The validated modification to the EFS was to include the drawing component of the Mini-Mental State Exam instead of the standard clock test [21]. The EFS was used to assess changes in frailty status over the study duration.

3.2.4 Health Related Quality of Life Assessment

The self-administered SF-36 was used to assess HRQOL [32]. This tool is made up of 8 domains (Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, Role Emotional and Mental Health). There are also 2 summaries of components (Physical Component Summary and Mental Component Summary). The score is calculated from 0 to 100 for each domain, and a higher score is indicative of higher HRQOL. Scores from each domain and the component scores were then compared to Canadian normative data standardized for age and gender and were ranked [33]. Scores that met the

Canadian normative data standards were classified as normal HRQOL whereas scores that did not were classified as abnormal HRQOL [33].

3.2.5 Measurement of Health Literacy and Adherence (Protocol)

HL was measured by using the validated FCCHL questionnaire (**Appendix B: Figure 2**) [20]. This self-reported tool assesses FHL, CoHL, CHL and total HL (THL). High and low scores were determined for each section by categorizing the scores for above and below the median. Adherence to the protocol was self-reported by the intervention participants using a standardized form developed by the research staff (**Appendix B: Figure 3**). Participants were instructed on how to fill out the form for each month, and accuracy was verbally validated at each study visit by the researcher.

3.2.6 Standard of Care

The SOC group was trained by research staff on digital technology (tablet and accelerometer) to ensure consistency and adherence to the study protocol. Re-training was provided at monthly visits if necessary. The research staff provided the participants with new handouts and videos on the tablet monthly to review prior to the following month's visit. The handouts were Alberta Health Services materials with information regarding healthy eating, diabetes management, carbohydrates, sugar, sodium and physical activity. The videos were created by research staff and demonstrated the preparation and recipe of a healthy meal. Research staff reviewed the information in the documents with the participant at the subsequent visit.

3.2.7 Progressive Exercise Protocol

All participants were trained on the digital technology (tablets and accelerometry) and the exercise protocol to ensure consistency in exercise performance, safety and adherence to the study protocol. Re-training occurred as requested by participants. Research staff conducted a safety assessment and full training on all exercises during the baseline home study visit in the participants' home. Re-training on all of the exercises was done by research staff at month 2 and 4 in order to ensure continued participant safety, proper exercise technique and enhanced adherence. Participants were trained on 10 different exercises and each exercise day had 5 of those exercises assigned (**Table 3.1**). Participants were asked to do the exercises 3 times weekly, on non-consecutive days. In order to ensure proper technique, intervention participants were given instructional videos to follow for each exercise. These videos indicated what exercises to do, and how many sets and repetitions to complete each month for each exercise. Standardized set numbers were assigned based on what month of protocol the participant was in (e.g., months 1&2 = 1 set; months 3&4 = 2 sets; months 5&6 = 3 sets). The resistance exercise protocol used Theraband® resistance bands, with specific band colours representing different levels of resistance (**Table 3.2**). Participants were provided with the next level of band in the series at study visits when the participant indicated to study staff that the exercises were no longer challenging at the required number of sets and repetitions. Exercise personnel viewed exercise technique regularly to ensure that participants were performing the exercises with the appropriate level of intensity and performance.

Table 3.1 List of all exercises and targeted muscle groups included in protocol.

Exercise Name	Major Muscle Group(s)
Seated Row	Anterior and posterior arms, upper back
Biceps Curl	Anterior arms
Triceps Extension	Posterior arms
Overhead Press	Shoulders, anterior and posterior arms
Side Shoulder Raise	Shoulders
Reverse Fly	Posterior arms, upper back
Chest Press	Chest, anterior and posterior arms
Seated Flat-Back Lean	Abdominals
Sit-to-Stand	Legs
Leg Extension	Anterior thighs

List of all upper and lower body exercises, and associated muscle groups. Participants were asked to do 5 of these exercises (pre-determined by study protocol) on non-consecutive days, three days per week.

Table 3.2 Levels of resistance in pounds based on resistance band colour progression.

Band Colour	Resistance in Pounds at 100% elongation*
Yellow	3.0
Red	3.7
Green	4.6
Blue	5.8

**information was collected from Theraband™ website[(34)].*

3.3 STATISTICAL ANALYSIS

Data analysis was completed using SAS 9.0 statistical software (SAS, Version 9.4; SAS Institute Inc. Cary, NC. USA). Data was analyzed using a per-protocol approach. Data was expressed as mean ± standard deviation (SD) or median and inter-quartile range (IQR), unless otherwise specified. The normality of distribution was assessed by the Shapiro-Wilk test (**Appendix B: Table 3**). Chi squared/Fisher exact statistical analysis was used for categorical variables (e.g., sex). Repeated measures analysis of variances with post-hoc analysis was conducted to explore relationships between time, group allocation and primary (e.g., functional

outcomes and EFS score) and secondary outcomes (e.g., HRQOL domains, HL). Percentage change was calculated to determine magnitude of changes between baseline and month-6 for all primary (e.g., functional outcomes and EFS) and secondary outcomes (e.g., HRQOL domains, HL). To determine significance between values, T-tests were used for parametric data and Mann-Whitney tests were used for non-parametric data. Paired t-tests were used to compare baseline and month-6 values within groups (e.g., hand-grip). Post hoc tests done included Tukey's Test for parametric data (e.g., age) and the Bonferroni Test for non-parametric data (e.g., urea). A p value of ≤0.05 was considered significant, with the exception of post-hoc tests, where a p value of ≤0.0125 was considered significant.

3.4 RESULTS

3.4.1 Baseline Demographic, Anthropometric and Laboratory Data

Figure 3.3 shows the flow of participants through the FANTASTIC Study**.** Baseline demographic, anthropometric and relevant laboratory data by randomized group (RE or SOC) and frail or non-frail status is presented in **Table 3.3**. The overall median (interquartile range) age (years), BMI (kg/m^2) and duration of T2D (years) of the enrolled participants was 68.0(63.7-73.9), 33.0(28.1-35.1) and 15.2(10.2-19.0) respectively. Frailty was present in 38% (n=14/37) of participants. With the exception of eGFR and creatinine levels, there was no differences between frail and non-frail participants observed in demographic, anthropometric or laboratory variables at baseline. The majority of frail participants were on a combination of insulin therapies and oral hypoglycemic agents (OHA) while most non-frail participants were on OHA medications only (*p*=0.003) (**Figure 3.4**). Dyslipidemia (n=14 frail; n=20 non-frail) and hypertension (n=14 frail; n=19 non-frail) were the most common co-morbidities (**Figure 3.5 and Figure 3.6**). After 6

months, there was no changes in any laboratory values in either frail or non-frail RE or SOC groups($p>0.05$).

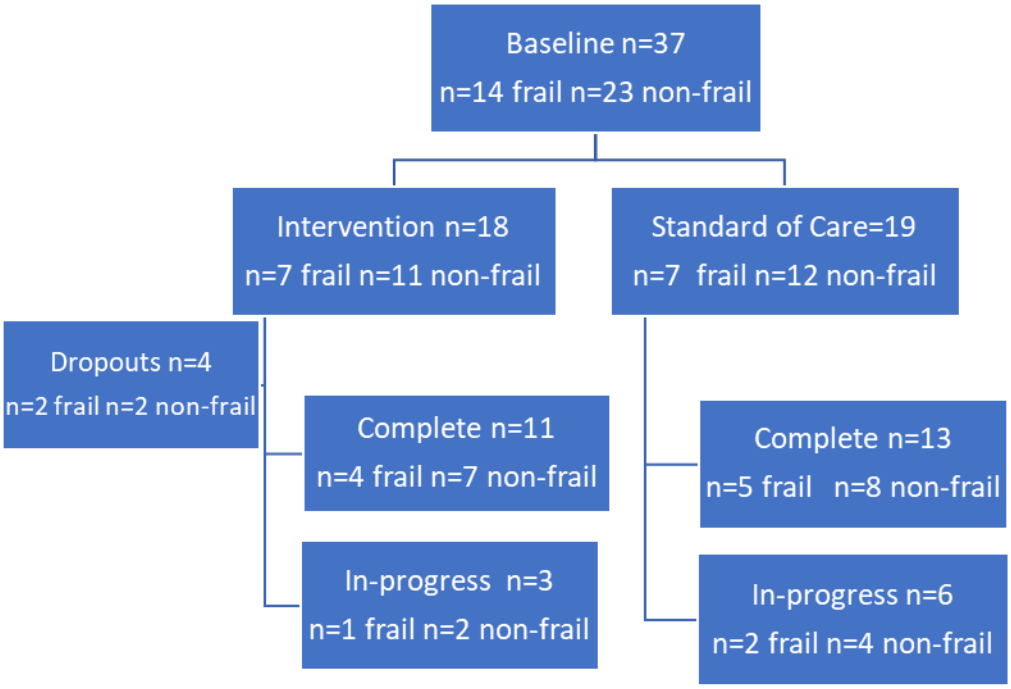

Figure 3.3 Participant flow diagram for data included this thesis. Participants were determined as frail or non-frail based on the Clinical Frailty Scale[22] at baseline enrollment. Following baseline enrollment, participants were randomized to intervention or standard of care group.

Table 3.3 Baseline demographic, anthropometric and laboratory data.

Variable	Resistance Exercise (n=18)		Standard of Care (n=19)		*P* values
	Frail (n=7)	Non-Frail (n=11)	Frail (n=7)	Non-Frail (n=12)	
Sex (F/M)	4/3	8/3	5/2	7/5	0.82
Age (years)	69.4 ± 7.3[a,b]	64.1 ± 6.3[a]	75.3± 6.0[b]	67.9 ± 6.2[a,b]	0.01
BMI (kg/m^2)	35.6 ± 5.1[a]	33.2 ± 6.7[a]	33.7 ± 6.5[a]	30.2 ± 3.7[a]	0.21
DM Duration (years)	22.4 ± 11.3[a]	15.3 ± 6.9[a]	22.4 ± 10.3[a]	11.5 ± 7.3[a]	0.02
Age at T2D Diagnosis	46.5 ± 16.4[a]	48.5 ± 9.3[a]	52.7 ± 9.2[a]	56.3 ± 10.2[a]	0.24
CKD Stage	3(2-4)[a]	2(2-2)[a]	3(2-4)[a]	3(2-3)[a]	0.89
eGFR (mL/min/1.73m^2)*	33.5 ± 17.2[a]	72.6 ± 13.7[b]	41.8 ± 27.5[a]	71.1 ± 21.5[b]	0.004
Comorbid Conditions (number)	5(3-5)[a]	3(2-5)[a]	5(3-6)[a]	4(2-4)[a]	0.07
Total Medication Number	10(8-14)[a]	8(7-10)[a]	11(8-12)[a]	7(6-9)[a]	0.14
HbA1c (%)*	8.4(6.7-8.4)[a]	7.3(6.8-8.1)[a]	7.9(7.5-8.9)[a]	6.7(6.2-7.6)[a]	0.14
Random glucose (mmol/L)*	5.4(5.4-5.4)[a]	8.8(6.3-13.4)[a]	8.0(6.4-10.8)[a]	5.6(5.0-8.6)[a]	0.88
Urea (mmol/L)*	-	6.4 ± 0.9[a]	12.1 ± 7.6[a]	7.3 ± 4.3[a]	0.26
Creatinine (mmol/L)*	185.0 ± 70.0[a]	89.0 ± 15.0[b]	150.0 ± 67.0[a]	93.0 ± 39.0[b]	0.006
Albumin (g/L)*	38.3 ± 6.5[a]	41.5 ± 0.7[a]	35.5 ± 8.1[a]	42.0 ± 3.0[a]	0.47

F=female, M=male, BMI=Body mass index (kg/m^2), T2D=type 2 diabetes, CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate (mL/min/1.73m^2), HbA1c=glycated hemoglobin. Data is expressed as mean ± standard deviation or median (interquartile range). Analysis of variance (ANOVA) was performed to assess differences between groups, followed by post-hoc analysis with either Tukeys Test (parametric data) or Bonferroni Correction (non-parametric data). A p value ≤0.0125 was considered significant; with the exception of categorical data where a p value of ≤0.05 was considered significant.

[a-b] Variables with different superscripts are significantly different.

**Number of patients for each laboratory measure varied according to availability. For all measures n≤27.*

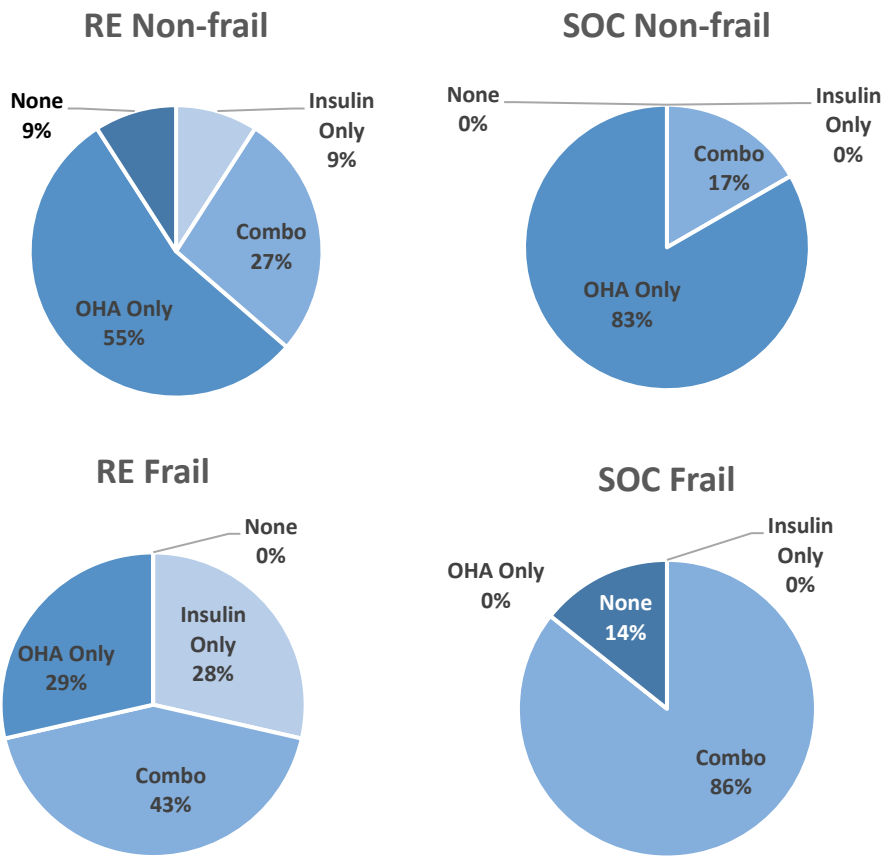

Figure 3.4 Percentages of participants at baseline on insulin only, oral hypoglycemic agents (OHA) only, a combination of both or no medications to manage type 2 diabetes. Intervention (RE) Non-frail (n=11), RE Frail (n=7), standard of care (SOC) Non-frail (n=12), SOC Frail (n=7). A Fisher's exact test was done to assess differences between the frail and non-frail participants (p=0.003).

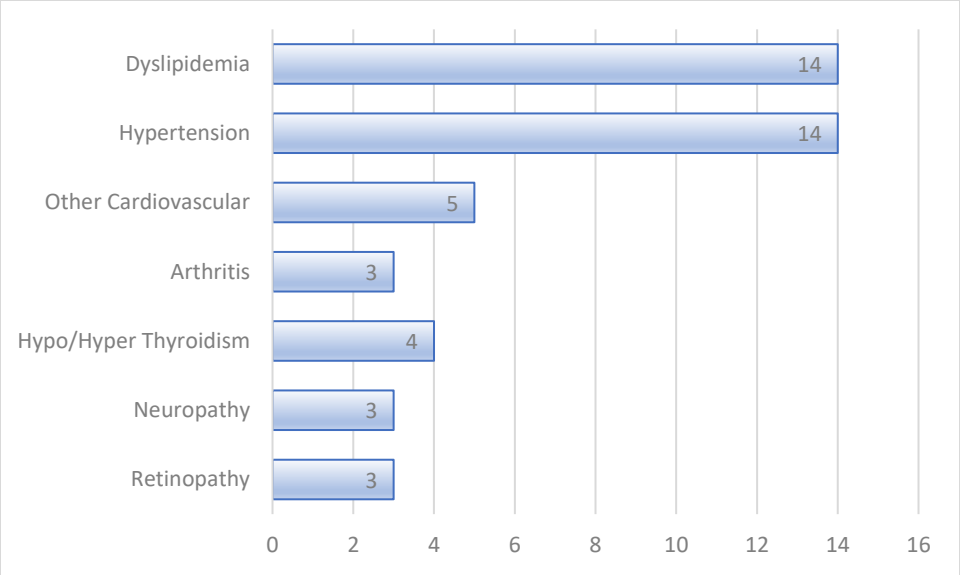

Figure 3.5 Most common co-morbidities reported in frail participants (n=14) at study entry. The "Other Cardiovascular" category included co-morbidities such as asthma, chronic obstructive pulmonary disease and heart disease.

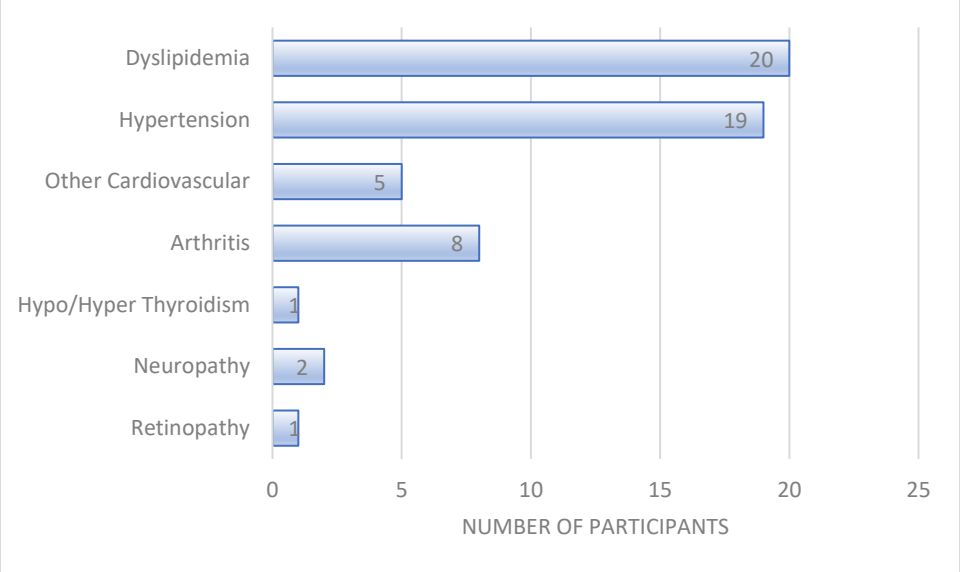

Figure 3.6 Most common co-morbidities reported in non-frail participants (n=23) at study entry. The "Other Cardiovascular" category included co-morbidities such as asthma, chronic obstructive pulmonary disease and heart disease

3.4.2 Impact of Intervention on Anthropometric, Demographic and Laboratory Variables

Data for demographic, anthropometric and laboratory variables after 6 months is presented in **Appendix B: Table 4 and Table 5**. After 6 months, there were no significant changes in any demographic, anthropometric or laboratory variables in frail RE, non-frail RE, frail SOC or non-frail SOC participants ($p>0.05$) (**Appendix B: Table 4**). As well, no significant changes were found in demographic, anthropometric or laboratory variables after 6 months in either RE (frail and non-frail RE participants combined) or SOC (frail and non-frail SOC participants combined) participants($p>0.05$) (**Appendix B: Table 5**).

3.4.3 Impact Intervention on Functional Outcomes

Data for SPPB scores and hand-grip is represented in **Figure 3.7 and 3.8**, respectively. After 6 months of RE, frail participants experienced significant percentage change in balance (40%), STS (38.5%) and total SPPB (23%) scores ($p\leq0.05$). Non-frail RE participants saw improvements in STS (33%) and total SPPB (11%) scores following the 6-month RE intervention ($p\leq0.05$). No changes were noted in SPPB scores in the SOC participants ($p>0.05$). Hand-grip significantly improved (32%) in frail participants following 6 months of RE ($p>0.05$). Non-frail RE participants and SOC did not experience significant changes in hand-grip after 6 months ($p>0.05$). No differences in balance, gait, STS, total SPPB score or hand-grip were seen for intervention participants above and below the median age (68 years), eGFR (61 $mL/min/1.76m^2$), T2D duration (15.2 years) or CKD stage (grouped by stage 1 and 2; 3 and 4) were observed ($p>0.05$) (**Appendix B: Table 6, 7, 8 and 9**). Between-sex differences were noted only in STS scores where frail women saw greater improvements compared to frail men following the intervention ($p=0.04$). No between sex differences were observed in any other functional outcome ($p>0.05$) (**Appendix B:**

Table 9). With the exception of hand-grip (p=0.01), RE participants (frail and non-frail combined) above the median age (≥68 years) did not have significant changes in any physical performance measures (SPPB) compared to SOC (frail and non-frail combined) participants (p>0.05) (**Appendix B: Table 11**). RE participants (frail and non-frail combined) below the median age (<68 years) did not have significant improvements compared to SOC (frail and non-frail combined) in any physical performance measures (SPPB) or hand-grip (p>0.05) (**Appendix B: Table 11**). No differences were noted between RE (frail and non-frail combined) and SOC (frail and non-frail combined) participants when compared by sex, CKD stage (grouped by stage 1 and 2; 3 and 4) or by above and below the median eGFR (61 mL/min/1.76m^2) and T2D duration (15.2 years) (p>0.05) (**Appendix B: Table 12, 13,14, 15**).

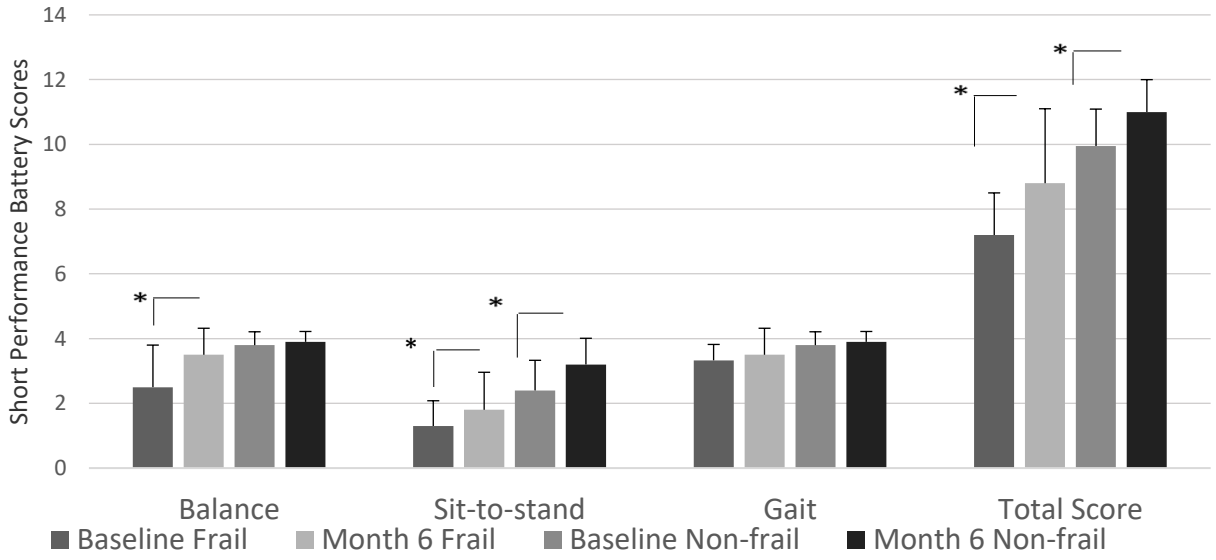

Figure 3.7 Effect of a 6-month home-based resistance exercise intervention on components of the Short Physical Performance Battery Assessment (SPPB) in frail and non-frail participants. Baseline Frail (n=7), month 6 Frail (n=4), Baseline Non-frail (n=11), month 6 Non-frail (n=7). Values are mean ± standard deviation. A t-test or Mann-Whitney test was conducted to determine if means between timepoints within groups were significantly different. Values with an asterisk are significantly different at p≤0.05.

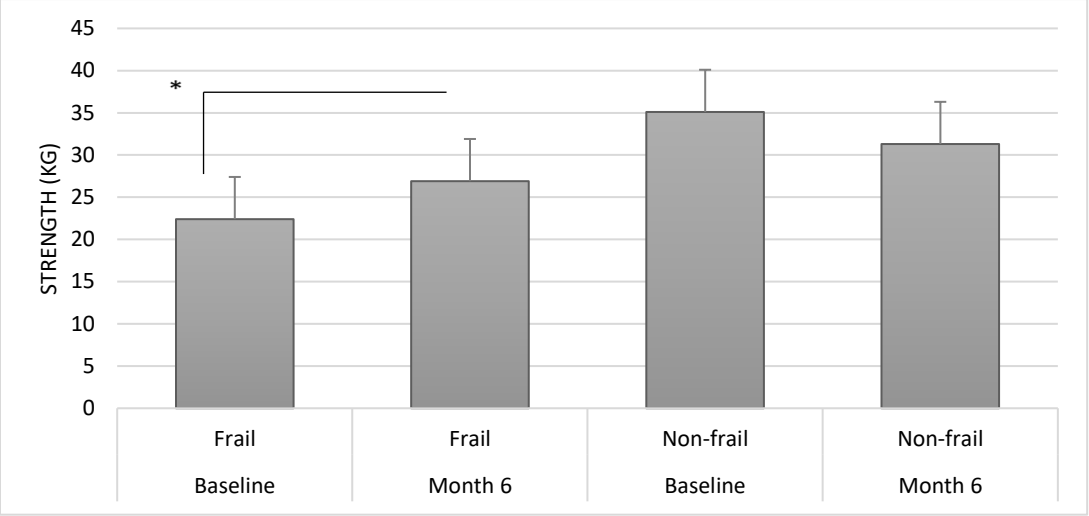

Figure 3.8 Effect of a 6-month home-based resistance exercise intervention on hand-grip strength (kg) in frail and non-frail participants. Baseline Frail (n=7), month 6 Frail (n=4), Baseline Non-frail (n=11), month 6 Non-frail (n=7). Values are mean ± standard deviation. A t-test or Mann-Whitney test was conducted to determine if means between timepoints within groups were significantly different. Values with an asterisk are significantly different at $p \leq 0.05$.

3.4.4 Impact of Intervention on Frailty Assessments

Data for EFS scores is found in **Figure 3.9** and in **Appendix B: Table 16**. Frail intervention participants saw a significant decrease (-41%) in EFS scores following 6 months of RE ($p \leq 0.05$). The intervention did not have any effect on EFS scores in non-frail participants ($p > 0.05$). No change in EFS score was observed in SOC participants after 6 months ($p > 0.05$). No difference in frailty status was noted for intervention participants above and below the median age (68 years), eGFR (61 mL/min/1.76m^2), T2D duration (15.2 years) or CKD stage (Grouped by 1 and 2; 3 and 4) ($p > 0.05$) (**Appendix B: Table 6, 7, 8 and 9**). Between-sex differences were observed only in frail intervention participants as women saw greater improvements in EFS scores compared to men ($p = 0.012$) (**Appendix B: Table 10**). There were no differences noted in frailty status between RE (frail and non-frail combined) and SOC (frail and non-frail combined) participants

when compared by above and below median age (68 years), sex, CKD stage (grouped by stage 1 and 2; 3 and 4) or by above and below median eGFR (61 mL/min/1.76m^2) and T2D duration (15.2 years) (p>0.05) (**Appendix B: Table 11, 12, 13, 14, 15**).

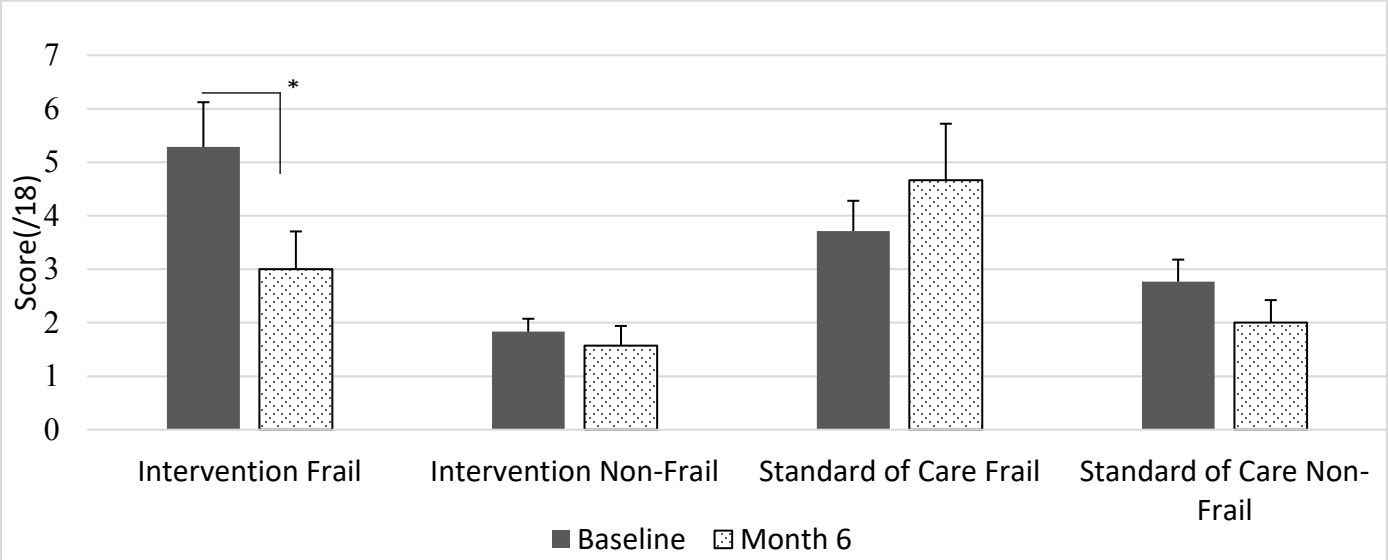

Figure 3.9 Changes in Reported Edmonton Frail Scale scores in frail and non-frail participants for intervention and standard of care (SOC) groups after 6 months. Baseline (BL) intervention Frail (n=7), month 6 (M6) intervention Frail (n=4), BL intervention Frail (n=11), M6 intervention Non-frail (n=7), BL SOC Frail (n=7), M6 SOC frail (n=5), BL SOC Non-frail (n=12), M6 SOC Non-frail (n=8). The scoring is as follows; 0-5 non-frail, 6-7 apparently vulnerable, 8-9 mildly frail, 10-11 moderate frailty and 12-18 severe frailty. Values are mean ± standard deviation. A t-test or Mann-Whitney test was conducted to determine if means between timepoints within groups were significantly different. Values with an asterisk are significantly different at p≤0.05.

3.4.5 Impact Intervention on Health Related Quality of Life

Data for HRQOL is found in **Figure 3.10**. Frail participants experienced significant improvements in the domains of bodily pain (30.6%) and physical component scores (16%) following 6 months of RE (p≤0.05). In contrast, non-frail participants did not see significant changes in any HRQOL domains following the RE intervention (p>0.05). No changes in any HRQOL domain was reported after 6 months in SOC participants (p>0. 05). There were no differences

between eGFR above and below the median (61 mL/min/1.76m^2) or sex in any HRQOL domain (**Appendix B: Table 7, 10**). Non-frail intervention participants above the median age (68 years) saw greater improvements in the physical functioning domain when compared to participants below the median age (p=0.02) (**Appendix B: Table 6**). Intervention participants with a T2D duration below the median (15.2 years) had greater improvements in the mental health domain (p=0.02) (**Appendix B: Table 8**). Conversely, participants with a T2D duration longer than the median (15.2 years) had greater physical composite score improvements (p=0.05) (**Appendix B: Table 8**). Frail intervention participants that were CKD stage 1 or 2 at baseline saw greater improvements in the mental health domain compared to frail participants in CKD stage 3 or 4 at baseline (p=0.04) (**Appendix B: Table 9**). No other differences in HRQOL domains were noted in participants above and below the median age (68 years), T2D duration (15.2 years) or CKD stage (p>0.05) (**Appendix B: Table 5**). When RE participants (frail and non-frail combined) were compared to SOC participants (frail and non-frail combined) by above and below the median age (68 years), sex, CKD group (grouped by stage 1 and 2; 3 and 4) and above and below median eGFR (61 mL/min/1.76m^2) and T2D duration (15.2 years) there were no differences in most HRQOL outcomes (p>0.05) (**Appendix B: Table 11, 12, 13, 14, 15**). Exceptions to this were female RE participants (frail and non-frail combined) saw improved mental component scores (p=0.01) compared to SOC females (frail and non-frail combined). As well, RE participants (frail and non-frail combined) with an eGFR above the median saw improved mental health scores (p=0.01) compared to SOC participants (frail and non-frail combined) (**Appendix B: Table 12, 14**). When compared to healthy norms for age and sex at baseline [34], frail participants had significantly lower scores in the general health (p<0.001) and social function (p=0.04) domains at baseline

compared to Canadian Normative Data. At baseline, non-frail participants had significantly lower scores in body pain (p=0.01) and general health (p=0.03) than Canadian normative data for age and sex[33]. No HRQOL domains were significantly different than Canadian Normative reference data after the 6-month intervention in either frail or non-frail RE participants. Data greater than 5 points below this normative data is considered clinically important [33].

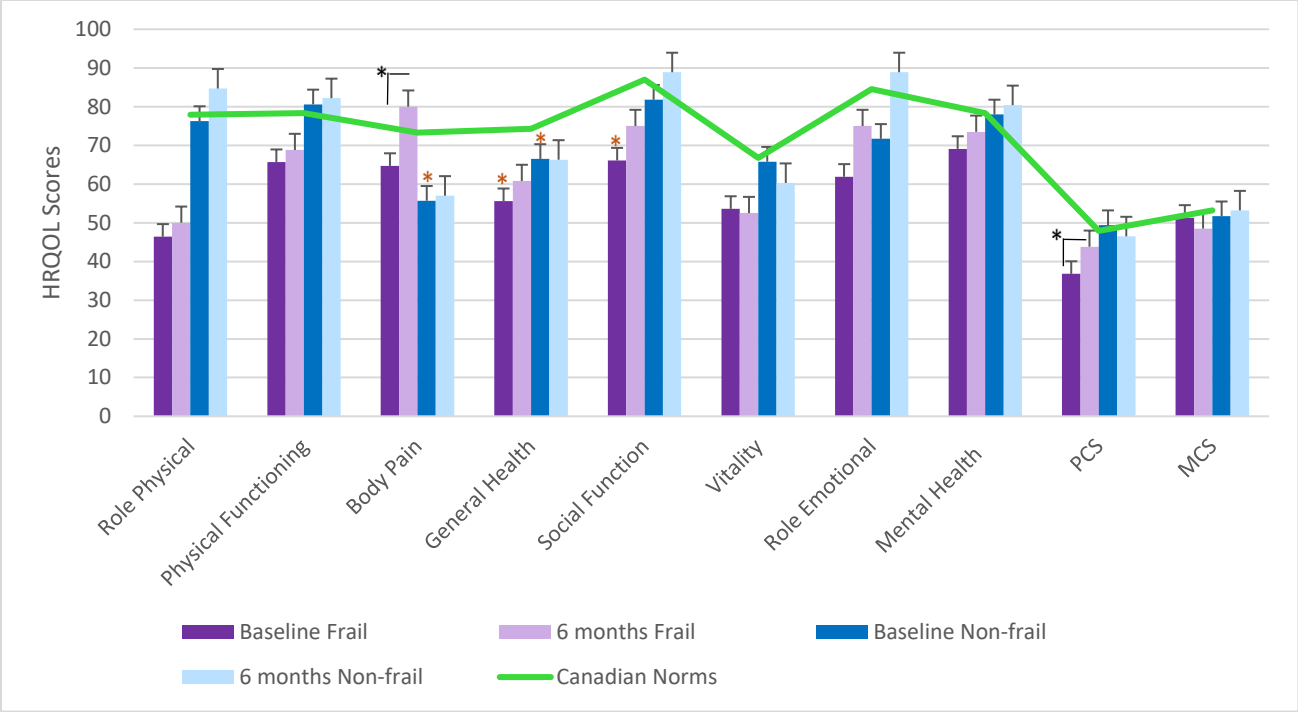

Figure 3.10 Effect of a 6-month home-based resistance exercise intervention on Health-Related Quality of Life (HRQOL) scores in frail and non-frail intervention participants. Baseline intervention Frail (n=7), 6-month intervention Frail (n=4), baseline intervention Non-frail (n=11),6 month intervention Non-frail (n=7). A higher score indicates higher HRQOL. Values are mean ± standard deviation. A t-test or Mann-Whitney test was conducted to determine if means between timepoints within groups were significantly different. HRQOL scores were compared using T-test or Mann-Whitney tests to Canadian Normative age and sex reference data [33]. Physical component scores (PCS) and mental component scores (MCS) are calculated by the transformation of the summary scores to T scores. PCS is calculated using scores from physical function, role physical, bodily pain and general health [25]. MCS is calculated using scores from mental health, role emotional, social function and vitality [25]. Values with a black asterisk are significantly different at p≤0.05. Values with a red asterisk are significantly different from the mean Canadian normative reference data at p≤0.05.
PCS=physical component scores; MCS= mental component scores

3.4.6 Impact of Health Literacy/Adherence After Intervention

Data are presented in **Figure 3.11 and 3.12** for baseline FHL and THL, respectively. Results for CoHL and CHL are found in **Appendix B: Figure 4 and 5**, respectively. No differences at baseline were found between groups in any domain of HL ($p>0.05$). After 6 months there were no significant changes in any HL category in RE or SOC groups ($p>0.05$). Higher levels of THL and CHL were related to improved adherence ($p<0.05$). Above median HL at baseline (FHL [2.8(2.6-3.6)], CHL [3.0(2.75-3.5)], THL [3.1(2.9-3.6)]) was associated with greater improvements in in STS and total scores for SPPB ($p<0.01$) in frail and non-frail intervention participants Higher HL had no impact on changes in hand-grip or HRQOL ($p>0.05$). Adherence to the RE protocol was 83% and 92% for frail and non-frail participants, respectively ($p=0.21$) (**Appendix B: Table 17**). No differences were noted in improvements in any HL domain between above and below the median eGFR (61 mL/min/1.76m^2) or T2D duration (15.2 years) or sex ($p>0.05$) (**Appendix B: Table 7,8 and 10**). Non-frail intervention participants above the median age (68 years) had significantly greater improvements in CHL compared to participants below the median age ($p=0.004$) (**Appendix B: Table 6**). Intervention participants who were in CKD stage 1 and 2 at baseline had significantly greater improvements in THL compared to those in CKD stages 3 and 4 ($p=0.01$) **(Appendix B: Table 9**). No other differences were found between participants above and below the median age (68 years) or by CKD stage in any other HL domains ($p>0.05$) (**Appendix B: Table 6 and 9**). There were no differences noted in FHL, CoHL, CHL or THL between RE (frail and non-frail combined) and SOC participants (frail and non-frail combined) when compared by above and below median age (68 years), sex, CKD stage (grouped by stage 1 and 2; 3 and 4) or by above and

below median eGFR (61 mL/min/1.76m^2) and T2D duration (15.2 years) (p>0.05) (**Appendix B: Table 11, 12, 13, 14, 15**).

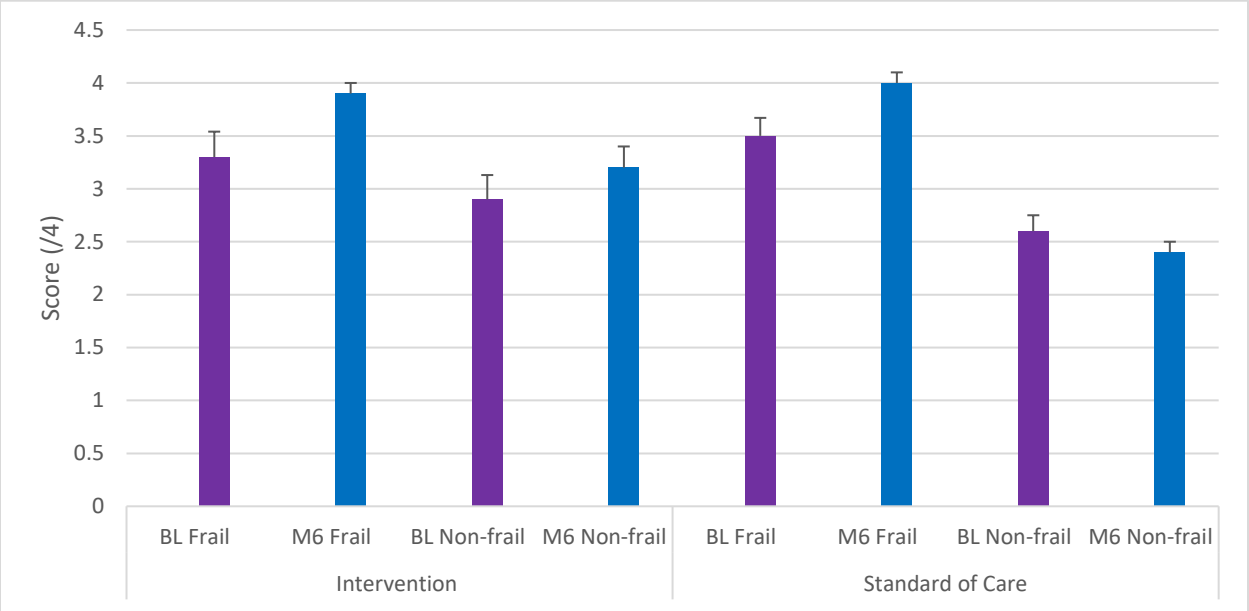

Figure 3.11 Functional health literacy (HL) in frail and non-frail participants for intervention and standard of care (SOC) groups as measured by the Functional, Critical and Communicate Health Literacy Scale. Baseline (BL) intervention Frail (n=7), month 6(M6) intervention Frail (n=4), BL intervention Frail (n=11), M6 intervention Non-frail (n=7), BL SOC Frail (n=7), M6 SOC Frail (n=5), BL SOC Non-frail (n=12), M6 SOC Non-frail (n=8). A higher score indicates higher functional HL. Values are mean ± standard deviation. A t-test was conducted to determine if means between timepoints within groups were significantly different. Values with an asterisk are significantly different at p≤0.05.
M6=month 6; BL=baseline

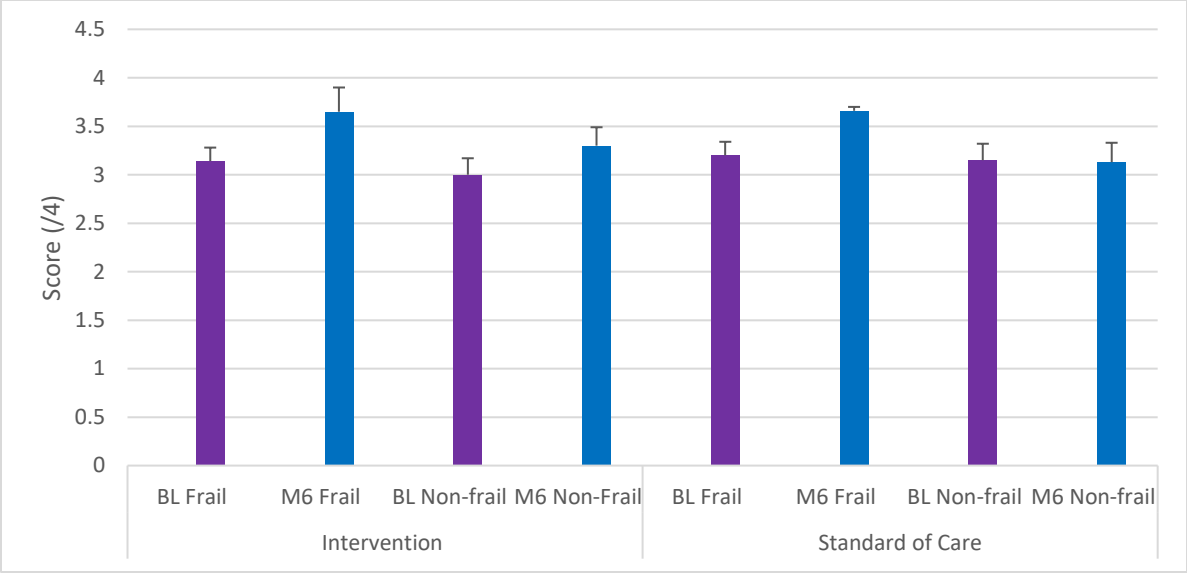

Figure 3.12 Total health literacy (HL) in frail and non-frail participants for intervention and standard of care (SOC) groups as measured by the Functional, Critical and Communicate Health Literacy Scale. Baseline (BL) intervention Frail (n=7), month 6(M6) intervention Frail (n=4), BL intervention Frail (n=11), M6 intervention Non-frail (n=7), BL SOC Frail (n=7), M6 SOC Frail (n=5), BL SOC Non-frail (n=12), M6 SOC Non-frail (n=8). A higher score indicates higher total HL. Values are mean ± standard deviation. A Mann-Whitney test was conducted to determine if means between timepoints within groups were significantly different. Values with an asterisk are significantly different at p≤0.05.
M6=month 6; BL=baseline

3.5 DISCUSSION

This thesis presented the preliminary results of a 6-month home-based RE program on functional outcomes, frailty scores, HRQOL and HL in a small subset (n=37) of older adults (50-85 years) with T2D and CKD (stages I-IV). The effect of the domains of HL on protocol adherence on these outcomes was also explored. After 6 months, intervention participants showed significant improvements in functional outcomes (e.g., SPPB score), frailty scores and HRQOL (e.g., physical composite scores). Frail participants were more likely to see improvements compared to non-frail participants following the intervention. Higher HL was associated with improvements in some functional outcomes (e.g., STS) in both frail and non-frail intervention participants. These

findings are important, as reduced functional performance and HRQOL is associated with negative outcomes, such as fall risk and increased hospitalizations [35, 36].

Improvements in physical performance and muscle strength were found following the intervention, particularly in the frail participants. RE has been shown to be effective at improving muscle strength, physical performance and stability in older adults [37-39]. Consistent with our findings, previous research in frail cohorts' report improved SPPB scores and muscle strength after RE training [40-42]. One reason for improvement in outcomes such as muscle strength in previously sedentary older adults following RE is the concept of adaptation [43]. Skeletal muscle is known to adapt to increased usage, thereby increasing its ability to perform tasks such as STS. In this study, the frail participants' performance on the functional tests was reduced at baseline compared to the non-frail participants. It may be that due to reduced muscle performance capacity, postural transition tasks (e.g., STS) and balance can be major issues for adults with frailty who are largely sedentary [44]. However, the frail participants had greater percentage change following 6 months of RE compared to non-frail participants in balance, STS and total SPPB scores. It may be that if greater disability is present, regular RE could elicit larger responses compared to participants with less pronounced disability in measures of functional performance. Our results have great significance as performance on the SPPB has been associated with fall risks, increased mortality and hospitalizations [45]. Strategies to improve performance on the SPPB have implications for potential treatments to prevent individuals who are pre-frail or frail from moving into a greater state of physical dysfunction. This can potentially reduce the risk of negative outcomes, such as falls.

Frail intervention participants did see a significant decrease in scores for the EFS after 6 months. This finding could be very important. While there is consistent evidence that regular RE can improve components of frailty assessments (e.g., muscle function), few studies report on the impact of RE alone and its ability to reverse the frailty phenotype [46]. Garcia Diaz *et al.* [47] found a significant decrease in frailty prevalence following 6 months of combined RE and aerobic exercise (AE). Nagai *et al.* [48] found that while overall frailty scores were reduced in older adults following 6 months of combined RE and AE, the frail status of participants did not change. As our research appears to be novel, in order to determine if RE alone can change frailty status future research should ensure to include frailty assessments as inclusion criteria as well as an outcome measure [46].

Improvements in two domains of HRQOL (physical composites scores and bodily pain) were found in frail participants following intervention completion. A few reasons may explain why limited impact on HRQOL was observed in non-frail participants. HRQOL is thought to be susceptible to ceiling effects, which could explain why non-frail participants did not see significant changes [49, 50]. Also, greater disability has been associated with reduced HRQOL [51]. Therefore, it might be expected that as the level of disability decreases in the frail participants, the level of HRQOL improves. Hence, the non-frail participants that had higher functioning at baseline had less room for improvement in HRQOL scores. A randomized controlled trial by Geirsdottir *et al.* [52] reported that improved performance in physical function was related to improved HRQOL (assessed by SF-36) in the elderly after 12 weeks of RE. Conversely, a much smaller randomized controlled trial found no improvements in HRQOL (assessed by the Audit of Diabetes-Dependent Quality of Life) following 12 weeks of RE in elderly participants with T2D.

Overall, the impact of RE alone on HRQOL in people with chronic disease is inconsistent, which may be partially explained by the wide variety of tools used to assess HRQOL [53-55].

While higher HL was associated with increased adherence to the protocol, this did not translate to a significant impact in most of the outcomes (e.g., hand-grip and HRQOL) following 6 months of RE. The one exception was that both frail and non-frail participants showed an association between higher HL and greater improvements in STS and total SPPB scores. Paasche-Orlow & Wolf [18] proposed that HL predicts greater adherence to lifestyle changes, which in turn predicts greater improvements in outcomes. However, limited research examines if HL moderates the efficacy of physical activity interventions [56]. One randomized controlled trial reported that HL levels did not impact intervention outcomes in sedentary women aged 18-65 years [57]. However, outcomes in this study differed slightly from ours as they examined minutes of physical activity per week, not direct measures of physical function. It may be that our study is unique in examining if each domain of HL moderated improvements in measures of functional outcomes following RE in older adults with chronic disease. When compared to two other studies that used this tool in a similar population, the levels of FHL, CoHL, and THL were comparable to the levels reported in the other studies. In our study, the CHL score was higher than in Ishikawa *et al.* [20] (**Appendix B: Table 18**). A high level of CHL may mean that our results support Nutbeam's [16] notion that the complex domain of CHL fosters the ability to instigate personal change, and therefore implement effective lifestyle choices. Overall, research shows a positive association between HL and physical activity levels [56]. Data on changes in physical activity patterns were not presented in this thesis but preliminary IPAQ data did not show any changes in total, moderate or vigorous levels of metabolic equivalents (METs) in any study group (**Appendix B: Figure 6, 7,**

8). However, significant increases in the number of metabolic equivalents (METS) spent in moderate activities within the home were found in frail intervention participants. As well, preliminary accelerometer results indicated that frail participants saw a significant decrease in sedentary activities (16.2%) and an increasing emphasis on improvements in leisure activities (52%). As these changes were independent of seasonal changes, it is probable that to some extent these changes are due to the home-based RE intervention. These results however, remain preliminary as this analysis only represents approximately 30% of the total data expected to be collected. Further research might be warranted to examine the potential influence of all HL domains (FHL, CoHL, CHL, THL) in adults with and without chronic diseases regarding improvements following physical activity interventions.

This thesis does have some limitations. The sample size in this analysis is small and underpowered in all variables with the exception of total SPPB score between intervention and control participants (**Appendix B: Table 19**). This may have impacted the findings in this preliminary analysis. However, this study is still ongoing and further relationships may be found as the sample size increases. When prescribing RE, it is important to consider intensity of the performed exercise itself [58]. As this intervention used resistance bands, a self-reported scale of exertion (e.g., The Borg Scale of Exertion [59]) would have been a valuable tool to incorporate. Self-reported scales of intensity have been found to be reliable and consistent measures of effort in older adults [60, 61]. After 6 months, participants varied in the colour of band they were using for the exercises and it may be that the addition of one of these tools could have improved the consistency of exercise intensity between participants (**Appendix B: Table 20**). With the exception of STS and EFS scores in frail RE participants, differences between sex were not noted

(**Appendix B: Table 9**). Sex differences could be important to consider as it is thought that women experience smaller improvements in muscle function compared to men [43]. However, sex differences in response to RE may wane as age increases [62]. Sarcopenia (loss of muscle mass) and reduced muscle function is known to increase with age [43]. However, age did not appear to be a factor in intervention participants who completed the protocol, with the exception of HRQOL physical functioning domain and CHL scores in non-frail participants (**Appendix B: Table 6**). The inclusion of age and sex matched non-frail participants may be valuable in order help determine if age and sex had moderating effects but the impact of this was difficult to determine in this analysis. Other potential confounders (eGFR, duration of T2D and CKD Stage) appeared to have no impact on the primary outcomes (physical function and EFS scores) and minimal influence on secondary outcomes (HRQOL and HL domains) but may be important to consider in future analysis (**Appendix B: Table 7, 8 and 9**). This study is relatively novel, as little research exists on RE alone in populations with DKD (CKD stages I-IV). An important element of this study was the use of frailty assessments at baseline and as an outcome measure as more research is needed to understand the impact of RE on frailty status, not just the individual components of frailty.

Performing RE with resistance bands for 6 months improved functional outcomes (e.g., STS), frailty scores and HRQOL in older adults with and CKD (stages I-IV). Participants classified as frail at study entry experienced overall greater changes in these outcomes. A higher level of HL (FHL, CHL and THL) was associated with improvements in some measures of physical performance. Studies that explore the role of HL, particularly CHL, may be valuable when developing RE interventions in older adults. Future studies examining frailty status as a direct outcome following RE only interventions are warranted.

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Chapter 4: Conclusions and Future Directions

4.1 INTRODUCTION

The presence of multiple chronic diseases is known to increase the risk of developing co-morbid conditions, such as frailty [(1)]. Frailty is a dynamic, complex condition which reduces the body's ability to overcome stress [(2)]. Frailty is associated with reduced HRQOL and increased morbidity and mortality in older adults [(3-5)]. One of the key indicators for the presence of frailty is reduced muscle function (characterized by diminished muscle strength, power or physical performance) [(6)]. Interventions which aim to decrease muscle dysfunction in adults with frailty may limit the progression of frailty and other co-morbid conditions, which may, in turn, help to reduce the hospitalizations, mortality and morbidity in older adults with diseases like diabetic kidney disease (DKD) [(7, 8)].

This thesis explored the efficacy of a home-based resistance exercise (RE) program for adults with type 2 diabetes (T2D) and chronic kidney disease (CKD) for 6 months to improve measures of functional outcomes, frailty status, health related quality of life (HRQOL) as well as a variety of other outcomes (body composition, diet quality, nutrition literacy, mental and cognitive health, activities of daily living and health care utilization). Results from this analysis contribute an overall larger randomized controlled trial, the FANTASTIC (Development of an Innovative Home-based Strategy for Frailty Prevention in Adults with Diabetes and Chronic Kidney Disease) Study. This thesis specifically focuses on outcomes related to physical function, change in frailty status, HRQOL and health literacy (HL). Also explored in this thesis was whether a higher level of HL in each domain [(functional [FHL], communicative [CoHL], critical [CHL]) at

baseline predicted improvements in physical function, frailty status and HRQOL. This analysis was done on the first 37 participants enrolled in the study.

4.2 SUMMARY OF RESEARCH FINDINGS

4.2.1 Changes in functional outcomes (SPPB, hand-grip) and frailty assessments (Edmonton Frailty Scale)

In this analysis, participants in the intervention arm who were frail experienced statistically significant improvements in every physical function assessment (balance, sit-to-stand [STS], total short performance battery assessment [SPPB] scores, hand-grip) with the exception of gait speed (**Hypothesis 1, Chapter 2**). This demonstrates that a 6-month home-based RE intervention improves measures of physical function in frail adults. Non-frail intervention participants, on the other hand, only experienced improvements in STS and SPPB total scores but not in balance, gait or hand-grip. These results may demonstrate that this particular RE intervention may be less effective in non-frail participants at improving physical function (**Hypothesis 1, Chapter 2)**. Neither frail or non-frail participants experienced changes in gait speed, one of the components of the SPPB. This was unexpected as progressive RE is thought to be effective at improving gait speed in both frail and non-frail older adults [9, 10]. However, for this particular test baseline assessments were close to maximum possible score for both frail and non-frail participants, indicating that this cohort may be considered higher functioning in terms of mobility. The assessment of gait used in the SPPB is done over a short distance and is highly relevant for assessing frailty status [11]. However, due to the limitation of the maximum possible score in the SPPB for gait speed, it may be that another gait assessment (e.g., six-minute walk test [12]) would have been a more appropriate measure for this population. Longer distance gait

speed tests, such as the six-minute walk test, are often used to assess the functional endurance and mobility of higher functioning older adults [13]. Gait assessments that cover longer distances or time intervals, like the six-minute walk test, could be more sensitive to changes in community-living older adults and are also considered predicative of frailty status [14]. Non-frail participants also did not show improvements in hand-grip strength. Hand-grip has been reported to be less sensitive to changes in overall strength (combination of upper and lower body) in older adults, so this may be why inconsistent results were found between the frail and non-frail RE participants [15]. As well, frail RE participants only saw improvements in frailty scores which was measured by the Edmonton frail scale (EFS) (**Hypothesis 1, Chapter 2).** Observing statistically significant improvements in non-frail adults as measured by the EFS may not be expected as the mean score in this cohort (1.8) was relatively close to the minimum available score (0). A minimum score on the EFS indicates that the participants do not have frailty [16].

4.2.2 Changes in Health Related Quality of Life and Health Literacy

Frail intervention participants saw statistically significant improvements in some domains of HRQOL (bodily pain, physical component scores) following the RE intervention (**Hypothesis 2, Chapter 3**). These findings are comparable to other studies as improvements in HRQOL domains, particularly in the physical domain (which include bodily pain and physical component scores) have been reported following exercise interventions in frail adults [9, 17]. Non-frail participants did not see significant improvements in any category of HRQOL (**Hypothesis 2, Chapter 2**). One reason that non-frail participants did not see improvements may be that they had HRQOL scores that were similar to Canadian Normative reference data for age and sex in most categories. These results suggest that the participants in this analysis may be less likely to experience a significant

change in HRQOL. As well, HRQOL is likely to reduce over time in people at risk for or with frailty and the stability in the participants scores might be considered optimal and clinically significant [18]. Further, at the time the follow-up assessment occurred, there was a global pandemic that also may have influenced the participants perceptions of their current physical, mental and social wellbeing. In a longitudinal study of older adults confined due to Government restrictions, the HRQOL domains of role physical and physical component scores reduced over the course of the confinement [19]. In a cross-sectional survey of older women, all eight domains of the SF-36 tool were reduced following the implementation of social isolation requirements [20]. These effects were noted independent of becoming sick with the virus and were related to the cancellation of regular activities and forced social isolation [19, 20]. Therefore, it's possible that the impact of the global pandemic may have precluded any benefit from the intervention. No changes were noted in any domain of HL in either intervention or standard of care participants indicating that this RE intervention did not impact HL status (**Hypothesis 2, Chapter 2**). There is limited research on the impact of lifestyle interventions (such as resistance exercise) on the domains of HL. HL is a complex concept that can be influenced by many factors but has been shown to improve in older adults following multi-component, targeted interventions that include strategies to improve FHL, CoHL and CHL [21].

4.2.3 The Impact of Health Literacy on Primary (functional outcomes, frailty status) and Secondary Outcomes (Health Related Quality of Life)

Baseline FHL, CoHL, CHL and THL levels were not associated with most of the study outcomes (balance, gait speed, frail status or HRQOL). However, higher baseline FHL, CHL and THL were associated with greater improvements in STS and SPPB scores in both frail and non-

frail intervention participants. These results indicate that baseline HL did impact some of the outcomes, particularly those related to physical performance but not those related to muscle strength or HRQOL (**Hypothesis 3, Chapter 2**). Older adults with lower HL may be less aware of the importance of regular participation in lifestyle interventions [22]. The associations found in this thesis suggest that HL level may impact study outcomes related to physical performance. However, more work needs to be done to further understand these findings.

4.3 STRENGTH AND LIMITATIONS

One of the strengths of this study is the robust design, which utilized a double-block, randomized controlled trial format. The double block design (frail vs non-frail, intervention vs standard of care) allowed evaluation of the participants who entered the study as frail or non-frail, which was assessed consistently by study staff using the Clinical Frailty Scale (CFS) [23]. As well, more than one frailty assessment tool was used in this study. Though not presented in this thesis, Fried's frailty phenotype was also measured, which will allow for the future comparison of different frailty tools in further analysis between the frail and non-frail cohorts [24]. Another strength of the overall FANTASTIC study is the exploration of the different domains of frailty (physical and cognitive). While not presented in this thesis, mental health was also assessed. Examining frailty with multiple lenses could help to determine which components of frailty are more responsive to a home-based RE intervention. These differences are important to understand as the existence of a heterogenous response could have implications for future strategies to help reduce the severity of frailty in adults with T2D and CKD. The use of the SF-36 questionnaire is thought to be the gold standard in physical activity research [25]. However, this self-assessed tool does have a high participant burden associated with it as it quite long. It may

be that a shorter HRQOL tool, such as the SF-12 may have been a better fit for this study which already had a high participation burden. The SF-12 questionnaire has been found to replicate SF-36 results and is thought to be a more efficient tool to assess HRQOL [26]. The design of this study may have benefited from blinding the researchers who assessed the study outcomes. This could reduce the potential for outcome assessor bias and increase the overall quality of the study design [27]. To help mitigate this, the majority of the tools used in this study were objective measures which can help to reduce the risk of outcome assessor bias [28]. Selection bias may have also been a concern in this study. Participants who self-selected to participate (consented to participate) may have shared socio-demographic characteristics (e.g., HL, income level or education status) that could influence the outcomes of this study. One of the challenges with lifestyle interventions, such as resistance exercise (RE) programs, is that adherence to the prescribed protocol is often low [29]. There can be many barriers to adherence in lifestyle interventions, particularly in programs that are not supervised [30]. However, one of the things that made this study unique was that it took place within the participants' own home. Designing the program to be self-directed and highly accessible was an important part of addressing some of these barriers to exercise. A review of interventions in older adults by Martin *et al*., [31] found that average reported adherence to prescribed exercise was 78%. In other studies, home-based RE interventions have found adherence to be around 73% [32, 33]. The relatively high adherence in the participants (>83%) in this preliminary analysis suggests that the design of this study may have been effective in supporting adherence by addressing some of the barriers to participation commonly observed in exercise (e.g., accessibility). This is important, as higher adherence (>75%) has been associated with improved health outcomes in rehabilitation interventions [34]. This study

may have benefited from incorporating a tool to measure intensity of exercise. While the lack of participant reported intensity may have been mitigated by the progression of bands to increase the resistance level, the utilization of a scale to report intensity (e.g., Borgs Scale of Perceived Exertion [35]) may have improved the consistency of intensity between participants. This was not analyzed in the current analysis but will be part of the overall efficacy of the intervention once the study has been completed. Often, a limitation in the literature about frailty reduction is that participants with chronic diseases (such as T2D and CKD) are excluded or not examined specifically, even though chronic disease is considered a risk factor for the presence of frailty [36, 37]. The specificity of this study provides much needed further understanding about the unique responses to RE, with a focus on frailty, in the population of diabetic kidney disease (DKD).

4.4 IMPLICATIONS FOR CLINICAL CARE

People with chronic diseases, such as DKD, are at an increased risk for a heightened co-morbid burden, therefore the findings of this research are relevant to clinical care. Performance on functional tests is widely used clinically as these assessments are sensitive to changes in health status, which may help clinicians to provide timely interventions [38]. The improvements of the SPPB score in both frail and non-frail participants is particularly important as reduced performance has been shown to be related to increased hospitalizations, fall risk and mortality [39]. The changes in frailty status and the HRQOL domains by frail intervention participants is also relevant, as changes in both factors have been known to predict mortality and morbidity in older adults [40, 41]. This means that strategies which target to reduce or limit frailty progression should consider including RE. The results indicate that this type of intervention could help to enable

community living frail adults with DKD to continue to maintain independence and reduce the co-morbid burden of chronic disease **(Figure 4.1)**.

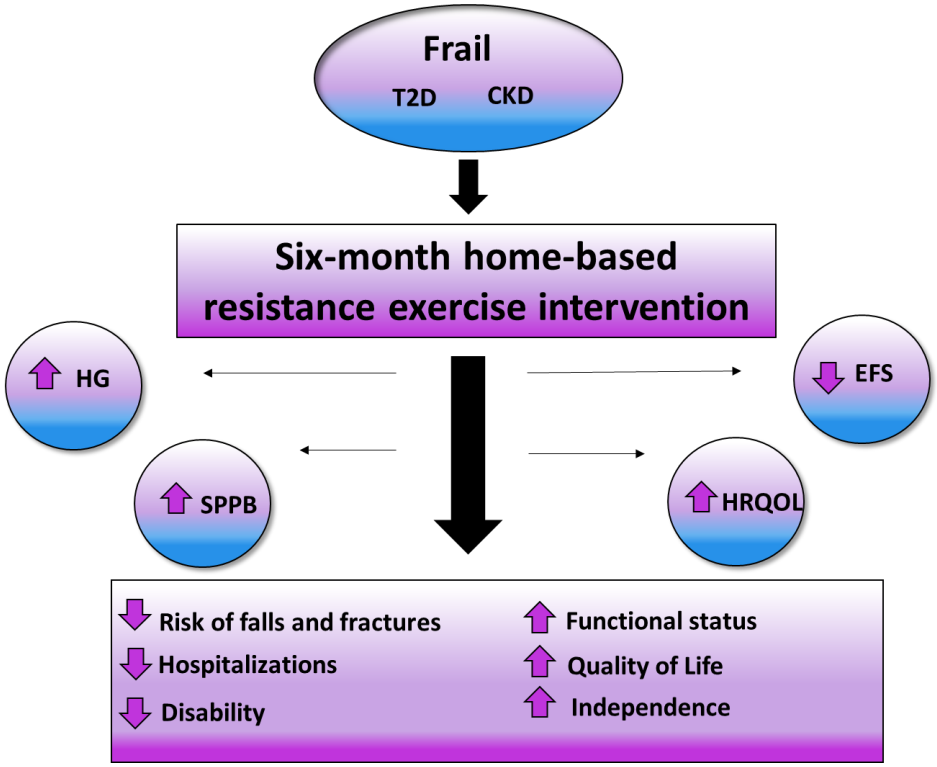

Figure 4.1 Flow diagram showing the impact of a six-month home-based resistance exercise (RE) intervention on frail people with type 2 diabetes (T2D) and chronic kidney disease (CKD). HG=hand-grip; SPPB=short physical performance battery assessment; EFS=Edmonton frail scale; HRQOL=health related quality of life.

While not analyzed in this thesis, body composition and diet quality are also known to be important predictors of frailty [42, 43]. The loss of lean muscle mass (sarcopenia) is highly prevalent in people with frailty and is an important risk factor for disability and mortality [44]. Diet quality, especially the presence of nutrient deficiencies related to lean-body mass are particularly important. Previous research indicates that diets with enough protein and vitamin D are protective of the loss of muscle mass [45]. The completion of the analysis, which will include body composition and diet quality, will help to develop a better understanding of the role these factors

can play in understanding the impact of a multi-dimensional 6-month RE program in people with DKD and frailty. The addition of this knowledge to future interventions may help to create multifaceted approaches to encompass as many of the targeted domains of frailty as possible.

It is widely recognized that lifestyle interventions can be challenging to implement in community dwelling older adults. Accessibility, cost and availability are just some factors that can limit the likelihood of participation in programs. However, the FANTASTIC study addressed these issues by providing a home-based program using virtual technology which utilized simple equipment. Home-based exercise programs have been shown to be effective at increasing physical function and HRQOL in the frail elderly. The implications from this study may be highly relevant in situations where older people find themselves unable to participate in community-based programming, particularly those living in remote or rural locations within Alberta. A timely example of isolated people needing options for physical activity programming occurred during the global pandemic of Coronavirus Disease of 2019 (COVID-19). This study was able to show people who are at risk for frailty and other complications that can arise from the lack of physical activity were able to continue to participate in the program (e.g., high adherence). Even during a global pandemic which required people to substantially reduce activities outside of the home, improvements were observed.

4.5 FUTURE RESEARCH

Future research aimed at reducing the severity and prevalence of frailty in populations with chronic diseases like DKD should consider the findings presented in this thesis. A key characteristic of the FANTASTIC Study is the successful and critically important use of technology within the home environment to deliver consistent guidance to participants during the

intervention. Improvements in technology has enabled programming to be delivered within a participants' home with ease. The development of an app-based platform which could bring lifestyle interventions directly to the patient will likely be a valuable tool for an interdisciplinary team treating a patient with chronic diseases moving forward. Having the ability to bring programs directly to the patient in their home and communicate via the same platform would drastically increase the accessibility and feasibility of future interventions [46]. In addition, as the literature is limited in understanding the impact of exercise on functional outcomes, frailty status and HRQOL on people with DKD, consideration of other exercise modalities (e.g., balance and aerobic exercise) would enrich the understandings presented in this thesis. Future randomized controlled trials in DKD populations should include groups that undergo balance training only, aerobic exercise only, a combination of all exercise modalities (balance, resistance and aerobic) a RE only group as well as control groups. This would help to gain further understanding about the best exercise treatments for prevention and reduction of frailty in older adults with DKD. A more in-depth analysis about the impact of all three domains of HL on lifestyle interventions should also be considered in future research. Much of the research on HL and various health outcomes present inconsistent findings. There are several reasons why this might be the case. Self-reported tools (e.g., The Functional, Communicative and Critical Health Literacy Scale [47]) tend to have a greater relationship with self-care behaviors, but performance-based measures of HL (e.g., Newest Vital Sign [48]) appear to have a stronger relationship with outcomes like glycemic control [49]. Few studies have used tools that assess all three dimensions of HL, FHL, CoHL and CHL, as described in 2008 by Nutbeam [50] and only measure FHL (e.g., numeracy). While FHL has been shown to be a predictor for some outcomes (e.g., lower number of physician visits); it may

be that associations between HL and other outcomes (e.g., physical activity) might not be found if the other dimensions of HL are not assessed [51].

4.6 OVERALL CONCLUSIONS

Frailty is a complex condition that arises with age and is characterized by a reduced physical and physiological ability to respond appropriately to stress. Strategies to prevent or slow-down the progression into a frail state are especially important in populations with high co-morbid burdens. While this 6-month intervention shows that people who have DKD can see improvements from a simple home-based training program, more work needs to be done to understand the best strategies to ameliorate frailty. Understanding the impacts of interventions at all stages of frailty (e.g., pre-frail) is important as frailty is a highly complex, dynamic condition. Consideration of factors that may impact the outcomes of these strategies, such as HL, will help with the development of robust, impactful strategies.

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Appendix A

Table 1 Muscle function component and muscle groups of muscle function tests in studies reviewed

Muscle Function Tests	Components Tested	Major muscle groups involved
	Upper Body	
Hand Grip	Strength	Flexor, extensor muscles of forearm
	Lower Body	
STS	Strength and Power	Quadriceps, hamstrings, core muscles
6MWT	Gait, Cardiorespiratory Endurance	Quadriceps, hamstrings, gluteal, calf and shin muscles
Timed Up and Go	Gait, balance	Core muscles, quadriceps, hamstrings, gluteal, calf and shin muscles
10m gait speed	Gait	Quadriceps, hamstrings, gluteal, calf and shin muscles
	Full Body Tests	
Repetition Maximum	Strength	Any muscle can be evaluated
Maximal dynamic strength test	Strength	Any muscle can be evaluated
	Multiple Component Test	
SPPB - combines STS, gait speed and balance tests	Balance, strength and power, gait speed	Quadriceps, hamstrings, core muscles

List of upper body, lower body, full body and multicomponent muscle functions tests. STS=sit-to-stand, SPPB=short physical performance battery assessment

Table 2 Brief Description of Health Related Quality of Life Tools used in Studies Reviewed

Name of Tool	Target Population	Domains Assessed	Self-Reported (S) or Objective (O)
DQOL-Brasil[1]	Adults with diabetes, in Brasil	self-care behavior, satisfaction with diabetes control	**S**
EQ-5D-3L[2]	General Population	mobility, self-care, usual activities, pain/discomfort, anxiety/depression	**S**
SF-36[3]	General Population	physical functioning, role physical, bodily pain, general health, vitality, social function, role emotional, mental health, mental composite scores, physical composite scores	**S**
ADDQoL[4]	Adults with diabetes	leisure activities, working life, physical health, social factors, self-confidence, motivation, financial factors, dependence on others	**S**

ADDQoL=audit of diabetes dependent quality of life; EQ-5D-3L= European quality of life 5 Dimensions; DQOL=diabetes quality of life measurement; SF-36= SF-36=short form health survey

1. Correr CJ, Pontarolo R, Melchiors AC *et al.* (2008) [Translation to portuguese and validation of the Diabetes Quality Of Life Measure (DQOL-Brazil)]. *Arq Bras Endocrinol Metabol* 52, 515-522.
2. Oppe M, Devlin NJ Szende A (2007) *EQ-5D value sets: inventory, comparative review and user guide*: Springer.
3. Elizabeth AS, Judith AE, Jacqueline D-J *et al.* (1998) Health-Related Quality of Life in Chronic Disorders: A Comparison across Studies Using the MOS SF-36. *Quality of Life Research* 7, 57-65.
4. Bradley C, Todd C, Gorton T *et al.* (1999) The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res* 8, 79-91.

Appendix B

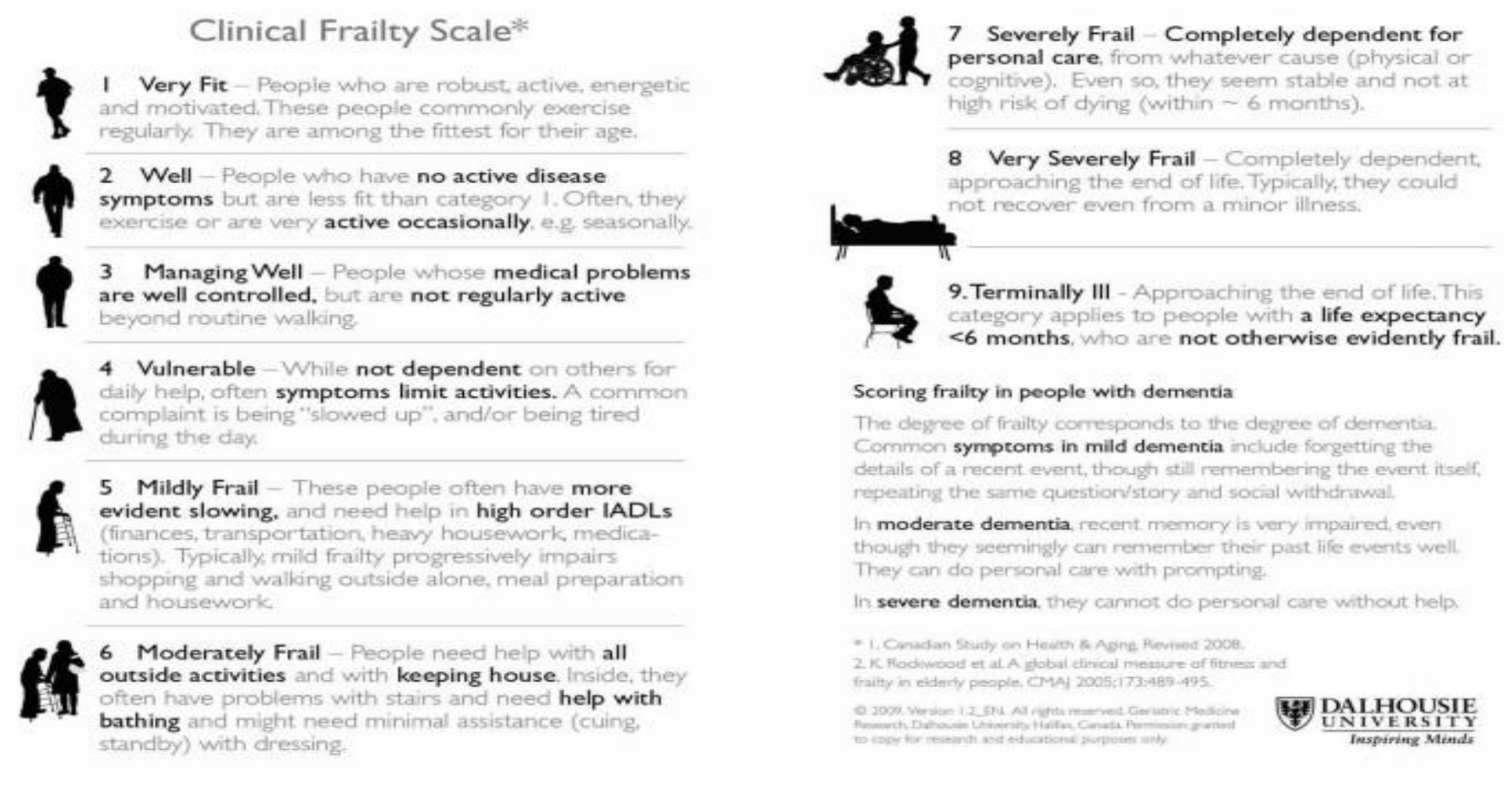

Figure 1 Clinical Frailty Scale[1]. Study staff scored participants after consent was received and screening was complete. A score of ≤3 was considered non-frail, a score of ≥4 was considered frail[1]. Participants with a score of ≥7 are considered to be ineligible for the study.

Table 1 List of all assessments administered in the FANTASTIC study.

Name of Questionnaire	Self-Reported (SR) or Administered (A)	Primary (P) or Secondary (S) Outcome in FANTASTIC Study	Included in this Thesis (Y=yes N=No)
Functional Outcomes (Short Physical Performance Battery [SPPB][(1)], hand-grip)	A	P	Y
Reported Edmonton Frail Scale (EFS)[(3)]	A	P	Y
Functional, Communicative and Critical Health Literacy Scale (FCCHL)[(2)]	SR	S	Y
Modified Barthel ADL Index[(4)]	A	S	N
General Activities of Daily Living Scale (GADL)[(5)]	A	S	N
Short Form Health Survey (SF-36)[(6)]	SR	S	Y
Major Depression Inventory (MDI)[(7)]	SR	S	N
Mini-Mental State Examination (MMSE)[(8)]	A	S	N
International Physical Activity Questionnaire (IPAQ)[(9)]	A	S	Y
Nutrition Literacy Scale (NLS)[(10)]	SR	S	N
Body Composition	A	P	N
Diet Information	A	S	N
Anthropometric Data	A	S	Y
Demographic Data	S	S	Y
Phlebotomy Values*	A	S	Y
Health-care Utilization[#]	A/S	S	N
Accelerometer Data	A	S	N
Adherence to Protocol	S	S	Y

SR=self-reported, A=administered, P=primary outcome in FANTASTIC Study; S=secondary outcomes in FANTASTIC Study; Y=yes; N=no; SPPB=short physical performance battery assessment; EFS=reported Edmonton frail scale, FCCHL=functional, communicative and critical health literacy scale, ADL=activities of daily living, GADL= general activities of daily living, SF-36=short form health survey, MDI=major depression

inventory, MMSE=mini-mental state examination, IPAQ=international physical activity questionnaire, NLS=nutrition literacy scale
** phlebotomy were collected if available through online medical records for the 3 months prior to baseline visit*
[#] health-care utilization was collected both verbally from participants at study visits, and if available through online medical records

Table 2 Items, frailty domain and scores used in the FANTASTIC Study for the reported Edmonton Frail Scale.

Item	Frailty Domain	Score
• **drawing from MMSE**	Cognition	No errors = 0 Points Minor spacing errors = 1 points Other errors = 2 points
• **Hospital admissions in the last year** (use clinical history)	General Health Status	0 times = 0 points
• **first question from SF-36**	General Health Status	Excellent/very good/good = 0 points Fair = 1 points Poor = 2 points
• **List of 8 activities of daily living they need assistance with**	Functional Independence	0-1 activities = 0 points 2-4 activities = 1 points 5-8 activities = 2 points
• **Do they have someone to depend on**	Social Support	Always = 0 points Sometimes = 1 points Never = 2 points
• **≥ or < than 5 medications** (use clinical history)	Medication Use	< = 0 points ≥ = 1 points
• **Forget medications**	Medication Use	No = 0 points Yes = 1 points
• **Recent weight loss** (use clinical history)	Nutrition	No = 0 points Yes = 1 points
• **Use MDI to determine if they feel sad or depressed**	Mood	No = 0 points Yes = 1 points
• **Use Barthel to determine continence**	Continence	No = 0 points Yes = 1 points
• **Can they do heavy housework without help?**	Self-reported performance	No = 0 points Yes = 1 points
• **Can they walk up a flight of stairs without help?**	Self-reported performance	No = 0 points Yes = 1 points
• **Can they walk 1 KM without help**	Self-reported performance	No = 0 points Yes = 1 points

Study staff administered the questionnaire[(3)] during the baseline and end of study visits at the university. Score total: 0-5 = not frail; 6-7 = apparently vulnerable; 8-9 = mildly frail; 10-11 = moderate frailty; 12-18 = severe frailty. MMSE= mini-mental stage exam[(2)], MDI= major depression inventory[(3)]

Functional, Communicative and Critical Health Literacy (FCCHL)

Participant Code: _____

Date: __ __/ __ __/ __ __(YY/MM/DD)

These questions ask about how you interact with information regarding your health.

This is not a test! There are no wrong answers. Think about how you usually do things.

In reading instructions or leaflets from hospitals/pharmacies, have you had the following experiences during the past one year?

You have…	Never Rarely Sometimes Often
1) found that the print was too small to read	1---------2----------3----------4
2) found characters and words that you did not know	1---------2----------3----------4
3) found that the content was too difficult	1---------2----------3----------4
4) needed a long time to read and understand them	1---------2----------3----------4
5) needed someone to help you read them	1---------2----------3----------4

Since being diagnosed with <u>diabetes</u>, have you had any of the following experiences in seeking information related to diabetes (e.g. diagnosis, treatment, self-care issues, alternative therapy, etc.)?

You have…	Never Rarely Sometimes Often
6) collected information from various sources	1---------2----------3----------4
7) extracted the information you wanted	1---------2----------3----------4
8) understood the obtained information	1---------2----------3----------4
9) communicated your thoughts about your health to someone	1---------2----------3----------4
10) applied the obtained information to your daily life	1---------2----------3----------4

Adapted with permission, 2019. HREB *(Pro00089513).* Ishikawa H., Takeuchi T., Yano E. Measuring functional, communicative, and critical health literacy among diabetes patients. Diabetes Care 2008; 31: 874-879.

You have…	Never Rarely Sometimes Often
11) considered whether the information was applicable to your situation	1---------2----------3----------4
12) considered the credibility of the information	1---------2----------3----------4
13) checked whether the information was correct	1---------2----------3----------4
14) collected information to make decisions about your health	1---------2----------3----------4

You're Finished. Thank you for your time.

Figure 2 Functional, Communicative and Critical Health Literacy Tool[2]. Questionnaire[2] was self-administered by participants at baseline and end of study university visits. Scores for questions 1-5 were reversed upon calculation. Total health literacy was calculated by combining scores from a) functional health literacy b) communicative health literacy and c) critical health literacy. A higher score was indicative of higher health literacy.

MONTH: #____ **From: _____ To: _____**

For each day please fill the table in as follows:

- **COMPLETED** if you completed all or most of the exercises as shown on the video for that day
- **HALF COMPLETED** if you completed about half of the exercises as shown on the video for that day
- **NOT COMPLETED** if you did not complete or completed very little of the exercises as shown on the video for that day

	WEEK 1	WEEK 2	WEEK 3	WEEK 4
First Exercise Day				
Second Exercise Day				
Third Exercise Day				
Nutrition Video				

Figure 3 Monthly exercise tracking sheet for intervention participants to determine adherence to the exercise protocol. Participants were asked to record if they had completed, half completed or not completed the exercises on each designated day during the 4 weeks between study visits. Participants are also asked to record if they watched the assigned nutrition literacy videos in weeks 1 and 3. Participants completed a sheet for month 1, 2, 3, 4, 5 and 6.

Table 3 Shapiro-Wilk test for normality

Variable	Shapiro-Wilk Test >0.05=normal <0.05=not normal	Parametric (P) >0.05 or Non-parametric (N) <0.05
Baseline demographic, anthropometric, Laboratory		
SOC age	0.54	P
RE age	0.43	P
SOC Non-frail age	0.80	P
SOC Frail	0.61	P
RE Non-frail	0.45	P
RE Frail	0.27	P
SOC BMI	0.72	P
RE BMI	0.78	P
SOC Non-frail BMI	0.91	P
SOC Frail BMI	0.99	P
RE Non-frail BMI	0.81	P
RE Frail	0.70	P
SOC T2D Duration	0.002	N
RE T2D Duration	0.13	P
SOC Non-frail T2D Duration	0.001	N
SOC Frail T2D Duration	0.02	N
RE Non-frail T2D Duration	0.71	P
RE Frail T2D Duration	0.29	P
SOC Age of T2D Diagnosis	0.23	P
RE Age of T2D Diagnosis	0.08	P
SOC Non-frail Age of T2D Diagnosis	0.17	P
SOC Frail Age of T2D Diagnosis	0.73	P
RE Non-frail Age of T2D Diagnosis	0.87	P
RE Frail Age of T2D Diagnosis	0.03	N
SOC eGFR	0.009	N
RE eGFR	0.38	P
SOC Non-frail eGFR	0.009	N
SOC Frail eGFR	0.26	P
RE Non-frail eGFR	0.24	P
RE Frail eGFR	0.18	P
SOC meds	0.20	P
RE meds	0.20	P
SOC Non-frail meds	0.03	N
SOC Frail meds	0.76	P

RE Non-frail meds	0.34	P
RE Frail meds	0.07	P
SOC Comorbid	0.009	N
RE Comorbid	0.52	P
SOC Non-frail Comorbid	0.66	P
SOC Frail Comorbid	0.09	P
RE Non-frail Comorbid	0.71	P
RE Frail Comorbid	0.26	P
SOC a1c	0.50	P
RE a1c1	0.13	P
SOC Non-frail a1c	0.18	P
SOC Frail a1c	0.54	P
RE Non-frail a1c	0.60	P
RE Frail a1c	<0.001	N
SOC rbg	0.014	N
RE rbg	0.19	P
SOC Non-frail rbg	0.02	N
SOC Frail rbg	0.70	P
RE Non-frail rbg	0.63	P
RE Frail rbg	-	-
SOC urea	0.03	N
RE urea	0.005	N
SOC Non-frail urea	0.07	N
SOC Frail urea	0.70	P
RE Non-frail urea	0.63	P
RE Frail urea	-	-
SOC creatinine	0.01	N
RE creatinine	0.02	N
SOC Non-frail creatinine	0.03	N
SOC Frail creatinine	0.19	P
RE Non-frail creatinine	0.19	P
RE Frail creatinine	0.27	P
SOC alb	0.05	P
RE alb	0.73	P
SOC Non-frail alb	0.02	N
SOC Frail alb	0.51	P
RE Non-frail alb	1	P
RE Frail alb	0.92	P
Physical Function		
SOC balance BL	<0.0001	N

SOC balance M6	0.002	N
RE balance BL	<0.0001	N
RE balance M6	<0.0001	N
SOC % change balance	0.005	N
RE % change balance	<0.0001	N
SOC STS BL	0.03	N
SOC STS M6	0.06	P
RE STS BL	0.008	N
RE STS M6	0.02	N
SOC % change STS	0.001	N
RE % change STS	0.10	P
SOC gait BL	<0.0001	N
SOC gait M6	0.0001	N
RE gait BL	<0.0001	N
RE gait M6	<0.0001	N
SOC % change gait	0.009	N
RE % change gait	<0.0001	N
SOC SPPB BL	0.41	P
SOC SPPB M6	0.08	P
RE SPPB BL	0.01	N
RE SPPB M6	0.01	N
SOC % change SPPB	0.67	P
RE % change SPPB	0.20	P
SOC R HG BL	0.004	N
SOC R HG M6	0.04	N
RE R HG BL	0.49	P
RE R HG M6	0.37	P
SOC % change R HG	0.35	P
RE % change R HG	0.17	P
SOC L HG BL	0.003	N
SOC L HG M6	0.17	P
RE L HG BL	0.07	P
RE L HG M6	0.89	P
SOC % change L HG	0.26	P
RE % change L HG	0.91	P
Frailty Status		
SOC EFS BL	0.53	P
SOC EFS M6	0.05	P
RE EFS BL	0.008	N
RE EFS M6	0.45	P

SOC % change EFS	0.001	N
RE % change EFS	0.003	N
Health Literacy		
SOC FHL BL	0.19	P
SOC FHL M6	0.06	P
RE FHL BL	0.30	P
RE FHL M6	0.06	P
SOC % change FHL	0.85	P
RE % change FHL	0.77	P
SOC CoHL BL	0.0003	N
SOC CoHL M6	0.004	N
RE CoHL BL	0.25	P
SOC CoHL M6	0.001	N
SOC % change CoHL	0.001	N
RE % change CoHL	0.017	N
SOC CHL BL	0.1	P
SOC CHL M6	0.31	P
RE CHL BL	0.09	P
SOC CHL M6	0.002	N
SOC % change CHL	0.22	P
RE % change CHL	0.05	P
SOC THL BL	0.57	P
SOC THL M6	0.44	P
RE THL BL	0.15	P
SOC THL M6	0.19	P
SOC % change THL	0.68	P
RE % change THL	0.002	N
Health Related Quality of Life		
SOC PF BL	0.15	P
SOC PF M6	0.14	P
RE PF BL	0.06	P
RE PF M6	0.02	N
SOC % change PF	0.02	N
RE % change PF	0.84	P
SOC RP BL	0.001	N
SOC RP M6	0.001	N
RE RP BL	<0.0001	N
RE RP M6	0.0003	N
SOC % change RP	0.001	N
RE % change RP	0.0002	N

SOC BP BL	0.36	P
SOC BP M6	0.08	P
RE BP BL	0.30	P
RE BP M6	0.25	P
SOC % change BP	0.01	N
RE % change BP	0.58	P
SOC GH BL	0.34	P
SOC GH M6	0.05	P
RE GH BL	0.38	P
RE GH M6	0.89	P
SOC % change GH	0.04	N
RE % change GH	0.78	P
SOC VT BL	0.54	P
SOC VT M6	0.08	P
RE VT BL	0.36	P
RE VT M6	0.09	P
SOC % change VT	<0.0001	N
RE % change VT	0.15	P
SOC SF BL	0.0005	N
SOC SF M6	0.0002	N
RE SF BL	0.0004	N
RE SF M6	0.0002	N
SOC % change SF	0.004	N
RE % change SF	0.009	N
SOC MH BL	0.20	P
SOC MH M6	0.35	P
RE MH BL	0.07	P
RE MH M6	0.37	P
SOC % change MH	0.001	N
RE % change MH	0.018	N
SOC PCS BL	0.06	P
SOC PCS M6	0.13	P
RE PCS BL	0.19	P
RE PCS M6	0.28	P
SOC % change PCS	0.18	P
RE % change PCS	0.27	P
SOC MCS BL	0.17	P
SOC MCS M6	0.12	P
RE MCS BL	0.13	P
RE MCS M6	0.31	P

SOC % change MCS	<0.0001	N
RE % change MCS	0.49	P

Results for Shapiro-Wilk test for normality. Results >0.05 were considered normally distributed while results <0.05 were considered not normally distributed. P=parametric data; N=non-parametric data; SOC=standard of care; RE=resistance exercise intervention; BMI=body mass index (kg/m^2); T2D=type 2 diabetes; eGFR=estimated glomerular filtration rate (mL/min/1.73m^2); meds=medication number; Comorbid=number of co-morbidities; a1c=glycated hemoglobin; rbg=random glucose; alb=albumin; BL=baseline; M6=month 6; % change=percentage change; STS=sit to stand; SPPB=short physical performance battery assessment; R=right hand; HG=hand-grip; L=left hand; EFS=Edmonton Frail Scale; FHL=functional health literacy, CoHL=communicative health literacy, CHL=critical health literacy; THL=total health literacy; HRQOL=health related quality of life; PF=physical function domain; RP=role physical domain; BP=body pain domain; GH=general health domain; VT=vitality domain; SF=social function domain; MH=mental health domain; PCS=physical component score; MCS=mental component score

Table 4 Month-6 demographic, anthropometric and laboratory data in entire cohort (frail intervention, non-frail intervention, frail standard of care and non-frail standard of care participants)

Variable	Resistance Exercise (n=11)		Standard of Care (n=13)	
	Frail (n=4)	Non-Frail (n=7)	Frail(n=5)	Non-Frail (n=8)
Sex (F/M)	2/2	5/2	3/2	3/5
Age (years)	73.0 ± 3.4	64.6 ± 6.8	74.7± 6.3	68.7 ± 7.2
BMI (kg/m^2)	32.8 ± 4.8	34.7 ± 6.9	32.7 ± 5.9	30 ± 3.3
DM Duration (years)	20.0 ± 13.2	15.3 ± 7.0	17.1 ± 2.7	13.5 ± 8.5
Age at T2D Diagnosis	52.5 ± 15.0	49.1 ± 7.3	57.4 ± 4.8	55.1 ± 11.3
CKD Stage	3(2-4)	2(2-3)	3(2-4)	4(2-3)
eGFR (mL/min/1.73m^2)	50.3 ± 28.3	76.3 ± 16.8	46.4 ± 28.8	60.0 ± 26.4
Comorbid Conditions (number)	5(4-5)	3(3-4)	4(3-6)	3.5(3-4)
Total Medication Number	10(9-11)	7(6-11)	10(9-12)	7(5-8)
HbA1c (%)	7.6(7.3-7.8)	7.9(7.6-8.0)	-	7(6.6-7.1)
Random glucose (mmol/L)	6.8(6.8-6.9)	7.4(6.7-8.0)	-	7.5(7--8)
Urea (mmol/L)	6.4 ± 0.9	-	9.8 ± 6.9	-
Creatinine (mmol/L)	145 ± 101.6	72.7 ± 11.7	136 ± 57	111 ± 40
Albumin (g/L)	41 ± 3.6	-	41.7 ± 2.9	-

F=female, M=male, BMI=Body mass index (kg/m^2), T2D=type 2 diabetes, CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate (mL/min/1.73m^2), HbA1c=glycated hemoglobin. Data is expressed as mean ± standard deviation or median (interquartile range). A t-test or Mann Whitney test was done to assess the difference in means between baseline and month-6. A p value ≤0.05 was considered significant.

[a] Variables superscripts are significantly different from baseline

Table 5 Baseline and month-6 demographic, anthropometric and laboratory data in entire cohort (intervention and standard of care participants)*

Variable	Resistance Exercise		Standard of Care	
	Baseline (n=18)	Month 6 (n=11)	Baseline (n=19)	Month 6 (n=13)
Sex (F/M)	12/6	7/4	12/7	6/7
Age (years)	66.1 ± 7.0	67.7 ± 7.0	70.6 ± 7.0	71.0 ± 7.3
BMI (kg/m^2)	34.1 ± 6.1	34.0 ± 6.0	31.5 ± 5.1	31.1 ± 4.4
DM Duration (years)	18.1 ± 9.3	17.0 ± 9.3	15.5 ± 9.9	14.9 ± 6.9
Age at T2D Diagnosis	47.8 ± 12.1	50.4 ± 10.1	55.0 ± 9.7	56.0 ± 9.1
CKD Stage	2(2-3)	3(2-3)	2(2-3)	3(2-3)
eGFR (mL/min/1.73m^2)	51.3 ± 25.5	61.4 ± 26.2	61.3 ± 26.8	52.4 ± 27.0
Comorbid Conditions (number)	4(3-5)	4(3-5)	4(3-5)	4(3-4)
Total Medication Number	9(7-11)	9(7-11)	8(6-11)	7(6-10)
HbA1c (%)	7.7(6.8-8.4)	7.7(7.3-8.1)	7.4(6.7-7.6)	6.6(6.0-7.1)
Random glucose (mmol/L)	7.3(5.4-10.2)	6.8(6.5-7.4)	7.2(5.6-9.2)	7.9(7.1-8.0)
Urea (mmol/L)	6.4 ± 0.9	7.1 ± 1.7	8.9 ± 5.6	8.3 ± 5.5
Creatinine (mmol/L)	141 ± 70.8	114 ± 81.9	112 ± 55.5	123 ± 48.0
Albumin (g/L)	39.6 ± 4.9	38.8 ± 6.8	41.7 ± 2.9	42.0 ± 3.6

** frail and non-frail participants were pooled in resistance and standard of care groups. F=female, M=male, BMI=Body mass index (kg/m^2), T2D=type 2 diabetes, CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate (mL/min/1.73m^2), HbA1c=glycated hemoglobin. Data is expressed as mean ± standard deviation or median (interquartile range). A t-test or Mann Whitney test was done to assess the difference in means between baseline and month-6. A p value ≤0.05 was considered significant.*

[a] Variables superscripts are significantly different from baseline

Table 6 Assessment of differences by age (above and below median) in functional outcomes, frailty status, health related quality of life and health literacy in intervention participants*

Outcome	Age		
	Intervention (frail and non-frail) (above and below the median <68 years and ≥68 years) (n=5 below; n=6 above)	*Intervention Frail: above and below median (<68 and ≥68) (n=0 below; n=4 above)*	*Intervention Non-frail: above and below median (<68 and ≥68) (n=5 below; n=2 above)*
Physical Function			
Balance	0.39	n/a	0.12
Gait	0.39	n/a	n/a
STS	0.65	n/a	0.86
SPPB	0.87	n/a	0.82
Right HG	0.19	n/a	0.53
Left HG	0.45	n/a	0.72
Frailty Status			
EFS	0.61	n/a	0.78
Health Related Quality of Life			
RP[§]	0.85	n/a	0.18
PF[ω]	0.41	n/a	**0.02**
BP[§]	0.99	n/a	0.92
GH	0.74	n/a	0.80
SF	0.08	n/a	0.15
VT	0.28	n/a	0.39
RM	0.43	n/a	0.26
MH	0.37	n/a	0.28
PCS[±]	0.79	n/a	0.95
MCS[ν]	0.14	n/a	0.36
Health Literacy			
FHL	0.23	n/a	0.07
CoHL	0.35	n/a	0.42
CHL	0.20	n/a	**0.004**
THL	0.17	n/a	0.41

Calculations for significance in percentage change for physical function, frailty status, health related quality of life and health literacy outcomes in participants that finished the resistance exercise protocol between: age below and above the median age. STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy, n/a= unable to calculate value due to lack of data in that category. A p value ≤0.05 was considered significant.

**calculations were done in completed intervention participants (frail and non-frail combined), then by frail and non-frail in completed intervention participants only*

[§]*had data available for n=4 participants below the median age*
[ω]*had data available for n=3 participants below the median age*
[±]*had data available for n=2 and n=5 participants below and above the median age, respectively*
[√] *had data available for n=2 participants below the median age*

Table 7 Assessment of differences by eGFR (above and below median) in functional outcomes, frailty status, health related quality of life and health literacy in intervention participants*

Outcome	eGFR *Intervention (frail and non-frail): (above and below the median <61 and ≥61 mL/min/1.76m^2) (n=3 above; n=2 below)*
Physical Function	
Balance[†]	n/a
Gait	0.50
STS	0.92
SPPB	0.89
Right HG	0.79
Left HG	0.76
Frailty Status	
EFS	0.24
Health Related Quality of Life	
RP	0.72
PF[±]	n/a
BP	0.48
GH	0.41
SF	0.40
VT	0.96
RM	0.57
MH	0.13
PCS[±]	n/a
MCS[±]	n/a
Health Literacy	
FHL	0.33
CoHL	0.49
CHL	0.90
THL	0.17

Calculations for significance in percentage change for physical function, frailty status, health related quality of life and health literacy outcomes in participants that finished the resistance exercise protocol between: eGFR below and above the median. eGFR= estimated glomerular filtration rate (mL/min/1.76m^2); STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical

component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy, n/a= unable to calculate value due to lack of data in that category. A p value ≤0.05 was considered significant.
**calculations were done in completed intervention participants only (frail and non-frail combined); not enough data available to do by frail and non-frail on their own*
[†]unable to do calculation as no change was experienced for any variable
[±]unable to do calculation as no data was available for one category

Table 8 Assessment of differences by diabetes duration (above and below median) in functional outcomes, frailty status, health related quality of life and health literacy in intervention participants*

	T2D Duration		
Outcome	*Intervention (frail and non-frail) (above and below the median <15.2 years and ≥15.2 years) (n=6 below; n=5 above)*	*Frail Intervention: above and below median (<15.2 and ≥15.2) (n=2 below; n=2 above)*	*Non-frail Intervention: above and below median (<15.2 and ≥15.2) (n=4 below; n=3 above)*
Physical Function			
Balance	0.30	n/a	0.29
Gait	0.39	0.42	n/a
STS	0.58	0.81	0.71
SPPB	0.39	0.50	0.82
Right HG	0.91	0.66	0.77
Left HG	0.62	0.71	0.96
Frailty Status			
EFS	0.43	0.89	0.44
Health Related Quality of Life			
RP[§]	0.41	0.69	0.54
PF[ω]	0.32	0.30	0.93
BP[§]	0.28	0.16	0.73
GH	0.94	0.99	0.92
SF	0.46	0.56	0.89
VT	0.43	0.30	0.91
RM	0.55	0.13	0.44
MH	**0.02**	0.32	0.08
PCS[±]	**0.05**	0.17	0.24
MCS[v]	0.25	0.30	0.65
Health Literacy			
FHL	0.32	0.19	0.92
CoHL	0.54	0.46	0.82
CHL	0.41	0.30	0.95
THL	0.95	0.92	0.77

Calculations for significance in percentage change for physical function, frailty status, health related quality of life and health literacy outcomes in participants that finished the resistance exercise protocol

between: duration of diabetes below and above the median duration of diabetes. T2D=type two diabetes; STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical composite scores; MCS=mental composite scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy, n/a = unable to calculate value due to lack of data in that category. A p value ≤0.05 was considered significant.
**calculations were done in completed intervention participants (frail and non-frail combined), then by frail and non-frail in completed intervention participants only*
[§]had data available for n=4 participants above the median disease duration
[ω]had data available for n=4 participants below the median disease duration
[±]had data available for n=4 and n=3 participants below and above median disease duration, respectively
[v] had data available for n=4 and n=4 participants below and above median disease duration, respectively

Table 9 Assessment of differences by CKD stage (1 and 2; 3 and 4) in functional outcomes, frailty status, health related quality of life and health literacy in completed intervention participants*

	CKD Stage by Group		
Outcome	*Intervention (frail and non-frail): CKD stages 1 and 2; CKD stages 3 and 4) (n=8 CKD stage 1 and 2; n=3 CKD stage 3 and 4)*	*Frail Intervention: (1 and 2 CKD stage n=1; 3 and 4 CKD stage n=3)*	*Non-frail Intervention: (1 and 2 CKD stage n=7; 3 and 4 CKD stage n=0)*
Physical Function			
Balance[†]	n/a	n/a*	n/a
Gait	0.13	0.67	n/a
STS	0.83	0.44	n/a
SPPB	0.64	0.67	n/a
Right HG	0.63	0.43	n/a
Left HG	0.95	0.39	n/a
Frailty Status			
EFS	0.50	0.30	n/a
Health Related Quality of Life			
RP[§]	0.38	0.82	n/a
PF[ω]	0.97	0.95	n/a
BP[§]	0.62	0.86	n/a
GH	0.36	0.19	n/a
SF	0.17	0.82	n/a
VT	0.55	0.94	n/a
RM	0.33	0.12	n/a
MH	0.28	**0.04**	n/a
PCS[±]	0.44	0.84	n/a
MCS[v]	0.76	0.23	n/a
Health Literacy			

FHL	0.21	0.21	n/a
CoHL	0.24	0.63	n/a
CHL	0.25	0.12	n/a
THL	**0.01**	0.32	n/a

Calculations for significance in percentage change for physical function, frailty status, health related quality of life and health literacy outcomes in participants that finished the resistance exercise protocol between: kidney disease stage grouped by stages 1/2 (n=7) and stages 3/4 (n=3). CKD=chronic kidney disease; STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy, n/a= unable to calculate value due to lack of data in that category. A p value ≤0.05 was considered significant.

**calculations were done in completed intervention participants (frail and non-frail combined), then by frail and non-frail in completed intervention participants only*

[†]*unable to do calculation as no change was experienced for any variable*

[§]*had data available for n=6 participants in the stage 1/2 group*

[ω]*had data available for n=5 participants in the stage 1/2 group*

[±]*had data available for n=4 and n=2 participants in the stage 1/2, and stage 3/4 group, respectively*

[√] *had data available for n=4 and n=3 participants in the stage 1/2, and stage 3/4 group, respectively*

Table 10 Assessment of differences by sex in functional outcomes, frailty status, health related quality of life and health literacy in completed intervention participants*

	Sex		
Outcome	*Intervention (frail and non-frail) (n=4 male; n=7 female)*	*Frail Intervention: (n=2 male; n=2 female)*	*Non-frail Intervention: (n=2 male; n=5 female)*
Physical Function			
Balance	0.48	n/a	0.58
Gait	0.20	0.42	n/a*
STS	0.27	**0.04**	0.86
SPPB	0.21	0.17	0.99
Right HG	0.95	0.29	0.70
Left HG	0.45	0.32	0.96
Frailty Status			
EFS	0.24	**0.012**	0.24
Health Related Quality of Life			
RP[§]	0.43	0.32	0.54
PF[ω]	0.13	0.30	n/a
BP[§]	0.31	0.96	0.26
GH	0.58	0.16	0.45
SF	0.30	0.43	0.91
VT	0.93	0.30	0.39
RM	0.70	0.78	0.86
MH	0.90	0.68	0.80

PCS[±]	0.30	0.50	n/a
MCS[v]	0.67	0.95	n/a
Health Literacy			
FHL	0.75	0.42	0.48
CoHL	0.58	0.46	0.40
CHL	0.06	0.30	0.28
THL	0.11	0.06	0.32

Calculations for significance in percentage change for physical function, frailty status, health related quality of life and health literacy outcomes in participants that finished the resistance exercise protocol by sex. STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical composite scores; MCS=mental composite scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy, n/a=unable to calculate value due to lack of data in that category. A p value ≤0.05 was considered significant.

**calculations were done in completed intervention participants (frail and non-frail combined), then by frail and non-frail in completed intervention participants only*

[§]*had data available for n=6 women*

[ω]*had data available for n=2 men*

[±]*had data available for n=1 men and n=6 women*

[v] *had data available for n=2 men and n=6 women*

Table 11 Assessment of differences by age (above and below the median) in functional outcomes, frailty status, health related quality of life and health literacy in completed participants*

	Age	
Outcome	*RE vs SOC (frail and non-frail combined) (below the median <68 years) (n=5 RE; n=5 SOC)*	*RE vs SOC (frail and non-frail combined) (above the median ≥68 years) (n=6 RE; n=8 SOC)*
Physical Function		
Balance	0.17	0.57
Gait	0.14	0.91
STS	0.60	0.59
SPPB	0.70	0.92
Right HG	0.56	**0.01**
Left HG	0.13	0.57
Frailty Status		
EFS	0.28	0.66
Health Related Quality of Life		
RP[§]	0.52	0.74
PF[ω]	0.39	0.90
BP[§]	0.37	0.95
GH	0.62	0.53

SF	0.28	0.15
VT	0.19	0.47
RM	0.19	0.54
MH	0.96	0.74
PCS[±]	0.50	0.70
MCS[v]	**0.05**	0.87
Health Literacy		
FHL	0.09	0.70
CoHL	0.86	0.27
CHL	0.07	0.20
THL	0.28	0.50

Calculations for significance in percentage change in participants that finished either invention (RE) or standard of care (SOC) protocol for physical function, frailty status, health related quality of life and health literacy outcomes between participants of the RE group and SOC group in age below the median age (n=10 RE; n=8 SOC) and above the median age (n=8 RE; n=11 SOC). STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy. A p value ≤0.05 was considered significant.

**calculations were done between all completed intervention participants (frail and non-frail combined) and standard of care participants (frail and non-frail combined)*

[§]*had data available for n=4 RE; n=4 SOC participants below the median age and n=6 RE; n=5 SOC above the median age*

[ω]*had data available for n=3 RE and n=4 SOC participants below the median age, and n=6; n=7 SOC above median age*

[±]*had data available for n=3 RE, n=4 SOC participants below the median age and n=5 RE; n=6 SOC above the median age*

[v] *had data available for n=3 RE; n=4 SOC participants below the median age and n=6 RE; n=6 SOC above the median age*

Table 12 Assessment of differences by sex in functional outcomes, frailty status, health related quality of life and health literacy in completed participants*

	Sex	
Outcome	*RE vs SOC Males (frail and non-frail combined) (n=4 RE; n=7 SOC)*	*RE vs SOC Females (frail and non-frail combined) (n=6 RE; n=6 SOC)*
Physical Function		
Balance	0.19	0.45
Gait	0.74	0.32
STS	0.77	0.63
SPPB	0.23	0.28
Right HG	0.07	0.30
Left HG	0.38	0.26

Frailty Status		
EFS	0.20	0.06
Health Related Quality of Life		
RP[§]	0.81	0.29
PF[ω]	0.68	0.36
BP[§]	0.24	0.06
GH	0.46	0.54
SF	0.30	0.18
VT	0.21	0.19
RM	0.21	0.74
MH	0.68	0.09
PCS[±]	0.84	0.32
MCS[ν]	0.27	**0.01**
Health Literacy		
FHL	0.24	0.68
CoHL	0.55	0.31
CHL	0.93	0.33
THL	0.35	0.10

*Calculations for significance between percentage change in participants that finished either invention (RE) or standard of care (SOC) protocol for physical function, frailty status, health related quality of life and health literacy outcomes by sex ([n=4 male RE; n=7 male SOC]; [n=6 female RE; n=6 female SOC]). STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy. A p value ≤0.05 was considered significant. *calculations were done in all completed intervention participants (frail and non-frail combined) and standard of care participants (frail and non-frail combined)*

[§]had data available for n=4 RE; n=5 SOC male participants and n=6 RE; n=5 SOC female participants

[ω]had data available for n=2 RE; n=6 SOC male participants and n=4 RE; n=5 SOC female participants

Table 13 Assessment of differences by CKD stage (1 and 2; 3 and 4) in functional outcomes, frailty status, health related quality of life and health literacy in completed participants*

	CKD Stage by Group	
Outcome	*RE vs SOC (frail and non-frail combined): CKD stages 1 and 2) (n=6 RE; n=6 SOC)*	*RE vs SOC (frail and non-frail combined): CKD stages 3 and 4) (n=1 RE; n=4 SOC)*
Physical Function		
Balance	0.22	0.18
Gait	0.80	0.46
STS	0.66	0.88
SPPB	0.22	0.54
Right HG	0.40	0.07

Left HG	0.65	0.62
Frailty Status		
EFS	0.15	0.51
Health Related Quality of Life		
RP[§]	0.16	0.38
PF[ω]	0.49	0.97
BP[§]	0.82	0.52
GH	0.61	0.39
SF	0.98	0.39
VT	0.12	0.54
RM	0.84	0.26
MH	0.12	0.34
PCS[±]	0.13	0.67
MCS[v]	0.59	0.40
Health Literacy		
FHL	0.99	0.61
CoHL	0.66	0.18
CHL	0.53	0.21
THL	0.90	0.12

Calculations for significance between percentage change in participants that finished either invention (RE) or standard of care (SOC) protocol in physical function, frailty status, health related quality of life and health literacy outcomes between participants of the RE group and SOC group by kidney disease grouped by stages 1/2 (n=11 RE; n=11 SOC) and stages 3/4 (n=5 RE; n=7 SOC). CKD=chronic kidney disease; STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy. A p value ≤0.05 was considered significant.

**calculations were done in all completed intervention participants (frail and non-frail combined) and standard of care participants (frail and non-frail combined)*

[§]*had data available for n=5 RE; n=4 SOC participants in CKD stage 1/2 and n=1 RE; n=3 SOC in CKD stages 3/4*

[ω]*had data available for n=4 RE and n=5 SOC participants in CKD stage 1/2 and n=1 RE; n=4 SOC in CKD stages 3/4*

[±]*had data available for n=3 RE, n=4 SOC participants in CKD stage 1/2 and n=1 RE; n=3 SOC in CKD stages 3/4*

[v] *had data available for n=3 RE; n=4 SOC participants in CKD stage 1/2 and n=1 RE; n=3 SOC in CKD stages 3/4*

Table 14 Assessment of differences by eGFR (above and below median) in functional outcomes, frailty status, health related quality of life and health literacy in completed participants*

	eGFR	
Outcome	*RE vs SOC (frail and non-frail combined) (below the median <61 mL/min/1.76m^2) (n=2 RE; n=5 SOC)*	*RE vs SOC (frail and non frail combined) (above the median ≥61 mL/min/1.76m^2) (n=2 RE; n=5 SOC)*
Physical Function		
Balance	0.18	0.57
Gait	0.46	0.67
STS	0.88	0.67
SPPB	0.54	0.39
Right HG	0.07	0.21
Left HG	0.62	0.13
Frailty Status		
EFS	0.51	0.08
Health Related Quality of Life		
RP[§]	0.38	0.45
PF[ω]	0.96	n/a
BP[§]	0.52	0.53
GH	0.39	0.46
SF	0.39	0.76
VT	0.54	0.91
RM	0.60	0.18
MH	0.34	**0.01**
PCS[±]	0.67	n/a
MCS[√]	0.40	n/a
Health Literacy		
FHL	0.61	0.93
CoHL	0.18	0.98
CHL	0.21	0.52
THL	0.12	0.95

Calculations for significance between percentage change in participants that finished either invention (RE) or standard of care (SOC) protocol in physical function, frailty status, health related quality of life and health literacy outcomes between participants of the RE group and SOC group in estimated glomerular filtration rate (eGFR) below the median eGFR (n=5 RE; n=7 SOC) and above the median eGFR (n=6 RE; n=8 SOC). eGFR=estimated glomerular filtration rate; STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy; n/a=not available. A p value ≤0.05 was considered significant.
**calculations were done in all completed intervention participants (frail and non-frail combined) and standard of care participants (frail and non-frail combined)*

[§]had data available for n=2 RE; n=5 SOC participants below the median eGFR and n=2 RE; n=5 SOC above the median eGFR
[ω]had data available for n=1 RE and n=5 SOC participants below the median eGFR, and n=0 RE; n=4 SOC above median eGFR
[±]had data available for n=1 RE, n=5 SOC participants below the median eGFR and n=0 RE; n=4 SOC above the median eGFR
[v] had data available for n=2 RE; n=5 SOC participants below the median eGFR and n=0 RE; n=4 SOC above the median eGFR

Table 15 Assessment of differences by diabetes duration (above and below median) in functional outcomes, frailty status, health related quality of life and health literacy in all completed participants*

	T2D Duration	
Outcome	*RE vs SOC (frail and non-frail combined) (below the median <15.2 years) (n=5 RE; n=6 SOC)*	*RE vs SOC (frail and non-frail combined) (above the median ≥15.2 years) (n=4 RE; n=4 SOC)*
Physical Function		
Balance	0.59	0.65
Gait	0.85	0.51
STS	1.00	0.90
SPPB	0.78	0.87
Right HG	0.14	0.18
Left HG	0.63	0.57
Frailty Status		
EFS	0.43	0.78
Health Related Quality of Life		
RP[§]	0.27	0.64
PF[ω]	0.53	0.74
BP[§]	0.51	0.10
GH	0.95	0.13
SF	0.32	0.19
VT	0.21	0.40
RM	0.51	0.50
MH	0.09	0.19
PCS[±]	0.06	0.57
MCS[v]	0.58	0.31
Health Literacy		
FHL	0.27	0.87
CoHL	0.36	0.44
CHL	0.64	0.85
THL	0.52	0.69

Calculations for significance between percentage change in participants that finished either invention (RE) or standard of care (SOC) protocol in physical function, frailty status, health related quality of life and health literacy outcomes between participants of the resistance exercise (RE) group and standard of care (SOC) group in duration of diabetes below the median duration (n=7 RE; n=11 SOC) and above the median age (n=11 RE; n=8 SOC). T2D=type two diabetes; STS=sit-to-stand; SPPB=short physical performance battery assessment; HG=hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical component scores; MCS=mental component scores; FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy. A p value ≤0.05 was considered significant.
**calculations were done in all completed intervention participants (frail and non-frail combined) and standard of care participants (frail and non-frail combined)*
[§]had data available for n=5 RE; n=5 SOC participants below the median diabetes duration and n=3 RE; n=3 SOC above the median diabetes duration
[ω]had data available for n=3 RE and n=6 SOC participants below the median diabetes duration, and n=3 RE; n=2 SOC above median diabetes duration
[±]had data available for n=3 RE, n=5 SOC participants below the median diabetes duration and n=2 RE; n=2 SOC above the median diabetes duration
[v] had data available for n=3 RE; n=5 SOC participants below the median diabetes duration and n=3 RE; n=2 SOC above the median diabetes duration

Table 16 Ranges of values for the reported Edmonton Frail Scale for all participants at baseline and month 6

Study Group	Baseline EFS Scores	Month 6 EFS Scores
Frail RE	1-9 (n=7)	1-4 (n=4)
Non-frail RE	0-3 (n=11)	0-3 (n=7)
Frail SOC	2-6 (n=7)	2-7 (n=5)
Non-frail SOC	0-5 (n=12)	1-4 (n=8)

Values for reported Edmonton Frail Scale (EFS) for resistance exercise (RE) and standard of car (SOC) participants at baseline and month 6. Values are presented as a range within each category.

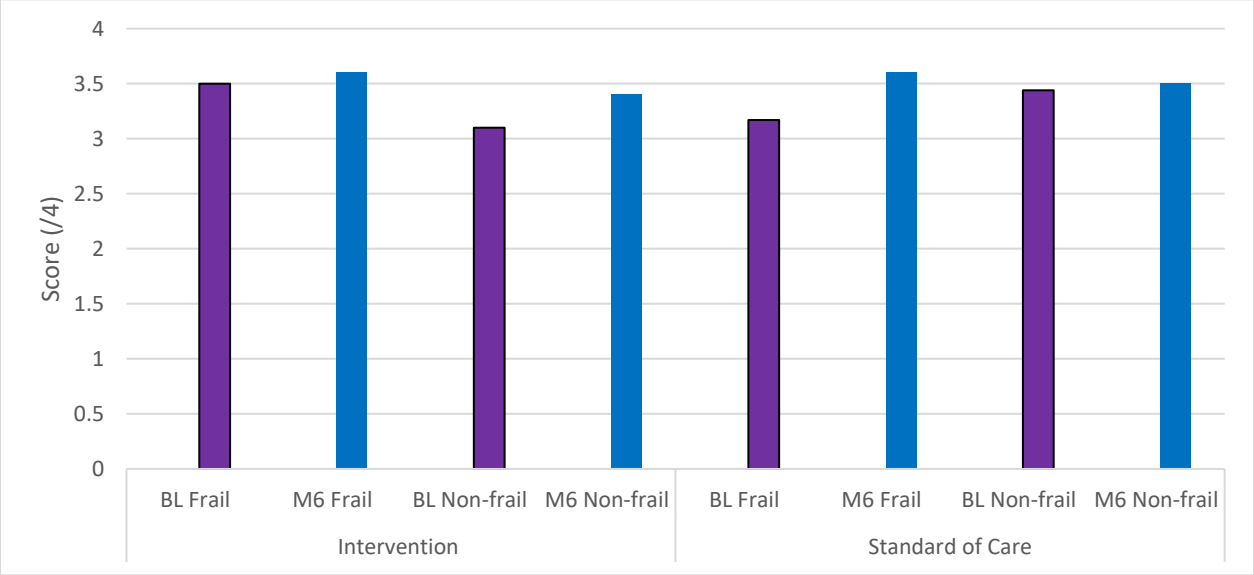

Figure 4 Communicative healthy literacy (HL) in frail and non-frail participants for intervention and standard of care (SOC) groups as measured by the Functional, Critical and Communicate Health Literacy Scale. Baseline (BL) intervention frail (n=7), month 6(M6) intervention frail (n=4), BL intervention frail (n=11), M6 intervention non-frail (n=7), BL SOC frail (n=7), M6 SOC frail (n=5), BL SOC non-frail (n=12), M6 SOC non-frail (n=8). A higher score indicates higher communicative HL. Values are mean ± standard deviation. A t-test was conducted to determine if means between groups were significantly different. Values with an asterisk are significantly different at $p \leq 0.05$.
M6=month 6; BL=baseline

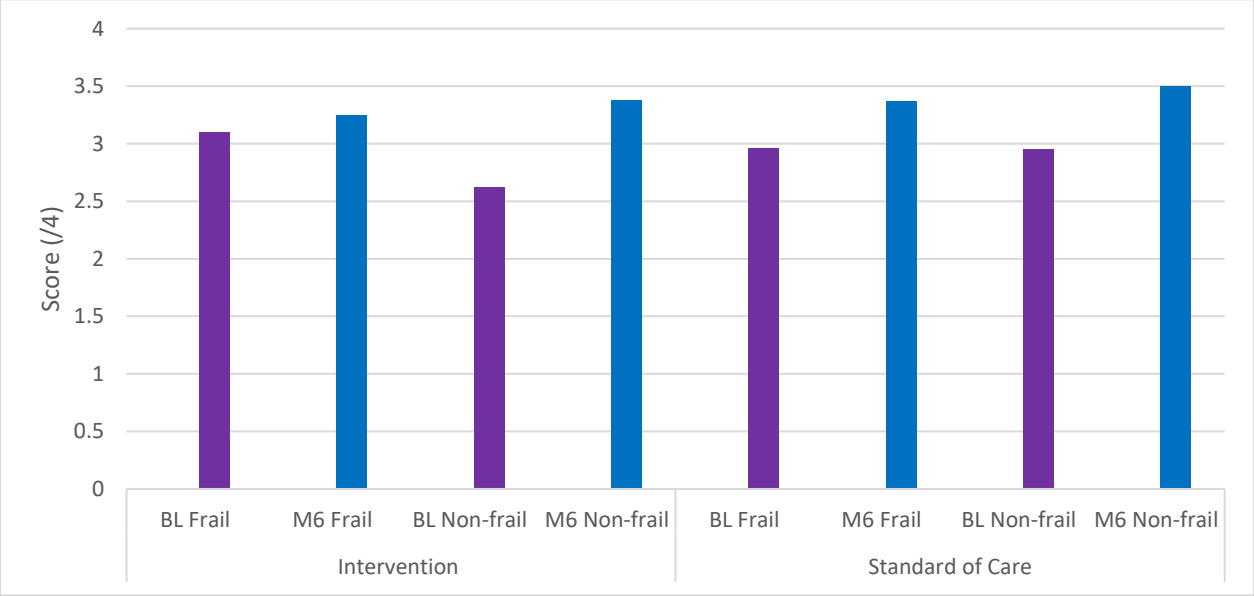

Figure 5 Critical healthy literacy (HL) in frail and non-frail participants for intervention and standard of care (SOC) groups as measured by the Functional, Critical and Communicate Health Literacy Scale. Baseline (BL) intervention frail (n=7), month 6(M6) intervention frail (n=4), BL intervention frail (n=11), M6 intervention non-frail (n=7), BL SOC frail (n=7), M6 SOC frail (n=5), BL SOC non-frail (n=12), M6 SOC non-frail (n=8). A higher score indicates higher critical HL. Values are mean ± standard deviation. A t-test was conducted to determine if means between groups were significantly different. Values with an asterisk are significantly different at p≤0.05. *M6=month 6; BL=baseline*

Table 17 Adherence to protocol for frail and non-frail participants

	Frail Intervention	Non-frail Intervention	p value
Adherence (%)	83(44-96)	92(59-100)	*p*=0.21

Protocol adherence of frail and non-frail participants. Data is expressed as median (interquartile range). A p value ≤0.05 was considered significant.

Table 18 Comparison of health literacy scores in FANTASTIC at study entry to other studies that use the Functional, Communicative and Critical Health Literacy Scale

Category	FANTASTIC (n=37)	Heijmans et al (n=1256)	Ishiwaka et al (n=138)
FHL	3.0±0.7	3.2±0.7	3.4±0.75
CoHL	3.3±0.6	3.1±0.7	2.66±0.7
CHL	3.1±0.6	2.7±0.8	2.0±0.63
THL	3.1±0.4	3.0±0.6	n/a

Health literacy (HL) mean scores from FANTASTIC Study along with mean scores from 1) Heijmans et al. [4] and 2) Ishikawa et al. [5]. FHL=functional HL, CoHL=communicative HL, CHL=critical HL, THL=total HL, n/a=not available

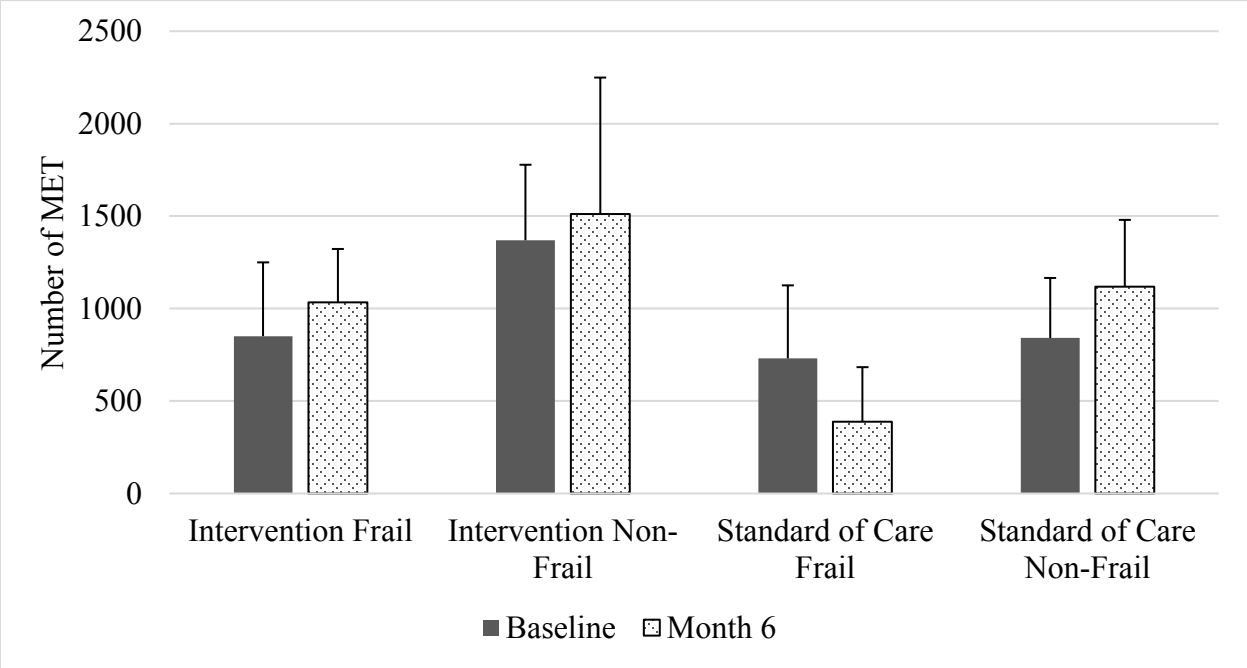

Figure 6 International Physical Activity Questionnaire Total Walking Metabolic Equivalents (METs) in frail and non-frail participants for intervention and standard of care (SOC) groups. Baseline (BL) intervention frail (n=7), month 6(M6) intervention frail (n=4), BL intervention frail (n=11), M6 intervention non-frail (n=7), BL SOC frail (n=7), M6 SOC frail (n=5), BL SOC non-frail (n=12), M6 SOC non-frail (n=8). A higher score indicates higher average of sitting minutes/day. Values are mean ± standard deviation. A t-test was conducted to determine if means between groups were significantly different. Values with an asterisk are significantly different at p≤0.05.

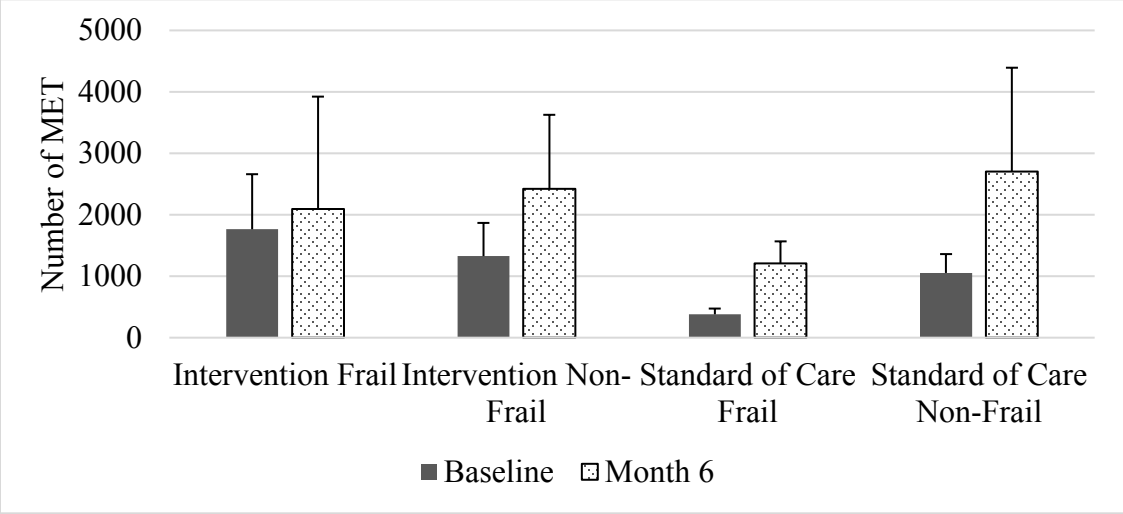

Figure 7 International Physical Activity Questionnaire Total Moderate Metabolic Equivalents (METs) in frail and non-frail participants for intervention and standard of care (SOC) groups. Baseline (BL) intervention frail (n=7), month 6(M6) intervention frail (n=4), BL intervention frail (n=11), M6 intervention non-frail (n=7), BL SOC frail (n=7), M6 SOC frail (n=5), BL SOC non-frail (n=12), M6 SOC non-frail (n=8). A higher score indicates higher average moderate MET's/day. Values are mean ± standard deviation. A t-test was conducted to determine if means between groups were significantly different. Values with an asterisk are significantly different at p≤0.05.

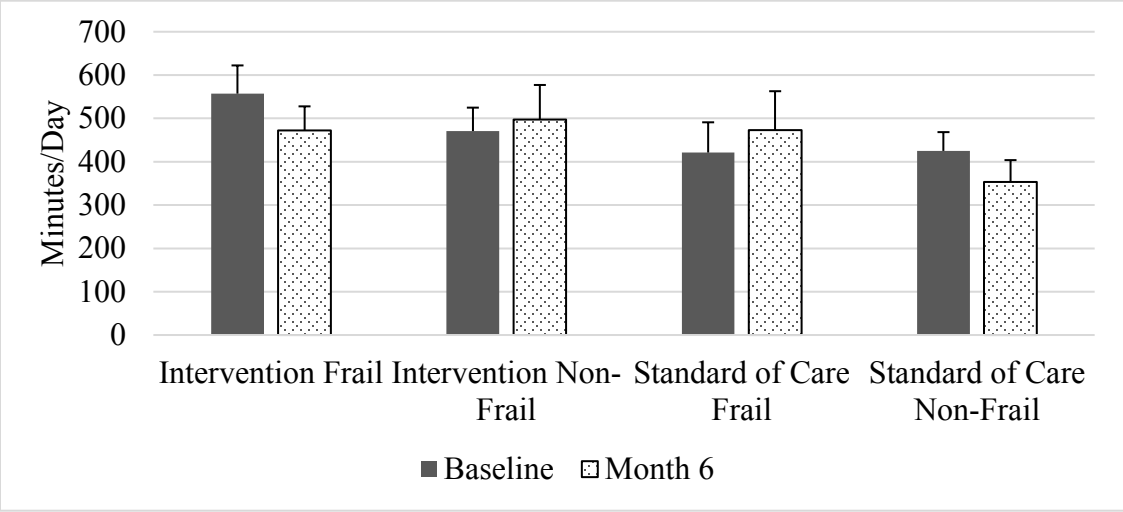

Figure 8 International Physical Activity Questionnaire Average sitting minutes/day in frail and non-frail participants for intervention and standard of care (SOC) groups. Baseline (BL) intervention frail (n=7), month 6(M6) intervention frail (n=4), BL intervention frail (n=11), M6 intervention non-frail (n=7), BL SOC frail (n=7), M6 SOC frail (n=5), BL SOC non-frail (n=12), M6 SOC non-frail (n=8). A higher score indicates higher average of sitting minutes/day. Values are

mean ± standard deviation. A t-test was conducted to determine if means between groups were significantly different. Values with an asterisk are significantly different at $p \leq 0.05$.

Table 19 Post hoc power calculations for physical function, frailty status, HRQOL and HL outcomes

Variable	RE and SOC M6	RE Frail BL & M6	RE Non-frail BL & M6	SOC Frail BL & M6	SOC Non-frail BL & M6
Physical Function					
Balance	0.74	0.46	0.0	0.41	0.0
Gait	0.19	0.20	0.0	0.05	0.0
STS	0.43	0.15	0.12	0.18	0.14
Total SPPB	**0.80**	0.37	0.06	0.12	0.08
R HG	0.04	0.13	0.05	0.03	0.05
L HG	0.10	0.06	0.06	0.05	0.18
Frailty Status					
EFS	0.22	0.40	0.0	0.13	0.43
Health Related Quality of Life					
RP	0.03*	0.03	0.07	0.09†	0.69$^{\lceil}$
PF	0.09‡	0.04	0.11$^{£€}$	0.15†	0.20$^{\lceil\lrcorner}$
BP	0.09*	0.27	0.03$^{€}$	0.18	0.59
GH	0.06	0.10	0.03	0.10	0.08
SF	0.04	0.66	0.34	0.03	0.13
VT	0.29	0.03	0.06	0.29	0.34
RM	0.03	0.08	0.06	0.06	**0.76**
MH	0.03	0.32	0.05	0.24	0.22
PCS	0.03$^{\omega\ddagger}$	0.04	0.04$^{£\int}$	0.03†	0.39$^{\|\lrcorner}$
MCS	0.16 $^{\omega\ddagger}$	0.25	0.26$^{£\int}$	0.10†	0.17$^{\|\lrcorner}$
Health Literacy					
FHL	0.16	0.12	0.05	0.23	0.09
CoHL	0.11	0.07	0.0	0.0	0.0
CHL	0.06	0.04	0.18	0.05	0.06
THL	0.07	0.08	0.08	0.21	0.0

Post hoc power calculations for physical function, frailty status, health related quality of life and health literacy outcomes between: resistance exercise (RE) and standard of care (SOC) participants at month 6 (M6), frail RE participants at baseline (BL) and M6, non-frail RE participants at BL and M6, frail SOC participants at BL and M6 and non-frail SOC participants and BL and M6. RE participants at M6 (n=11); SOC participants at M6 (n=13); frail RE participants at BL (n=7); frail RE participants at M6 (n=4); non-frail RE participants at BL (n=11); non-frail RE participants at M6 (n=7); frail SOC participants at BL (n=7); frail SOC participants at M6 (n=5); non-frail SOC participants at BL (n=12); non-frail SOC participants at M6 (n=8). STS=sit-to-stand; SPPB=short physical performance battery assessment; R HG=right hand-grip; L HG=left hand-grip; EFS=Edmonton frail scale; RP= role physical; PF= physical functioning; BP=body pain; GH=general health; SF=social functioning; VT=vitality; RM=role emotional; MH=mental health; PCS=physical composite scores; MCS=mental composite scores;

FHL=functional health literacy; CoHL=communicative health literacy; CHL= critical health literacy; THL=total health literacy. Power calculations were based on an alpha of 0.05.
**had data available for n=10 RE participants*
[ω]had data available for n=9 RE participants
[‡]had data available for n=12 SOC participants
[£]had data available for n=10 BL RE non-frail participants
[€]had data available for n=6 M6 RE non-frail participants
[ʃ]had data available for n=5 M6 RE non-frail participants
[†]had data available for n=6 BL SOC frail participants
[⌈]had data available for n=11 BL SOC non-frail participants
[‖]had data available for n=10 BL SOC non-frail participants
[⌋]had data available for n=7 M6 SOC non-frail participants

Table 20 Level of Theraband™ at month-6 for frail and non-frail participants finished protocol

Category	Yellow	Red	Green	Blue
RE Frail	0	2	2	0
RE Non-frail	1	5	1	0

Bands increase in intensity in the order of yellow, red, green and blue from least intense to most intense.

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