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The Feasibility of Square-Stepping Exercise as a Universal Intervention for Older Adults with Chronic Disease to Improve Cognitive and Physical Function

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Kinesiology

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The Feasibility of Square-stepping Exercise as a Universal Intervention for Older Adults with Chronic Disease to Improve Cognitive and Physical Function

Abstract

Square-stepping exercise (SSE) is a cognitive training program with a physical component. An instructor demonstrates a stepping pattern across a gridded mat and participants are required to memorize and repeat the patterns on their own. In community-dwelling older adults, SSE has demonstrated some benefits on global cognitive functioning (GCF), balance, functional fitness, and social interaction.

Aims: to investigate the feasibility and efficacy of SSE in varied populations and settings to improve mobility and cognition. Populations included older adults with: knee osteoarthritis (OA), type 2 diabetes mellitus (T2DM) and self-reported cognitive complaints (sCC), and those living in long-term care (LTC) and continuum care (CC) homes.

Methods: We conducted 3 pilot randomized controlled trials ranging from 12- to 24-weeks of SSE. Feasibility was determined through recruitment and attendance.

Participants were assessed on a host of cognitive, functional, and gait outcomes before and after SSE.

Results: We found that SSE was not feasible in older adults with knee OA and results were inconclusive whether it effected mobility in this population. SSE demonstrated improvements in the planning domain in older adults with T2DM and sCC. However, attendance remained a challenge in this group due to high disease burden (i.e. appointments and illness), and therefore it was not feasible. In LTC and CC homes, SSE was not feasible because recruitment and attendance were low. However, we showed that adults living with dementia improved on mood and behaviour symptom scores.

Conclusions: Square-stepping exercise is not a feasible program as implemented in this thesis and SSE showed limited benefit to cognitive and mobility outcomes. These pilot studies demonstrated the challenges of feasibility in adults with diverse cognitive and mobility impairments. Future studies should focus on addressing recruitment and adherence strategies for chronic disease populations.

Keywords

Knee osteoarthritis

Type 2 diabetes mellitus

Cognitive decline

Self-reported cognitive complaints

dementia

Mobility

Long-term care

Retirement living

Cognitive Training

Statement of Co-Authorship

This thesis was written in full by Erin M. Shellington, with review and edits from Dr. Robert Petrella (primary supervisor). Dr. Dawn Gill (advisory committee member) assisted with edits on Chapter 2-4b. Dr. Matthew Heath (advisory committee member) assisted with review and edits of Chapters 3 and 4b. Dr. Sonja Reichert (advisory committee member) assisted with review and edits of Chapter 3. The study design of Chapter 4a was in collaboration with the Schlegel Villages and Schlegel-University of Waterloo Research Institute for Aging, which is represented in authorship in addition to Western University staff who assisted in study design and data collection – none of the individuals were involved in the writing or editing of this document. Dr. Ryosuke Shigematsu is the primary developer of the Square-stepping exercise program on which this thesis is based and therefore provided support of this work and study designs; however, he did not participate in the writing or editing of this document.

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List of Abbreviations, Symbols, Nomenclature

< = less than

> = greater than

η_p^2 = partial eta squared, effect size for analysis of variance test

6MWT = 6 metre walk test, m/s

A1C = glycated hemoglobin

ABC = Activities-specific Balance Confidence Score

AD = Alzheimer's disease

ANCOVA = Analysis of Co-variance

ANOVA = analysis of variance

ApoE = Apolipoprotein E

BDNF = brain derived neurotrophic factor

BMI = body mass index, kg/m²

CBS = Cambridge Brain Sciences

CC = continuum care

CES-D = Centre for Studies in Epidemiology Depression Scale

CI = confidence intervals

CIHR = Canadian Institutes for Health Research

cm = centimetre

cm/s = centimetre per second

DASH = dietary approaches to stop hypertension

DPDA = difficulty performing daily activities, from WOMAC™

F = F-statistics, ratio of variances from analysis of variances statistical test

FAB = Fullerton Advanced Balance Scale

GCF = global cognitive functioning

GLA:D = GoodLife for osteoArthritis in Denmark

Hz = hertz

IGF-1 = insulin like growth factor 1

IGR-1R = insulin like growth factor 1 receptor

kg/m² = unit for Body Mass index, kilograms per meter squared

km = kilometres

LTC = long-term care

MCI = mild cognitive impairment

min = minute

MMSE = Mini-Mental State Examination, scored out of 30

MoCA = Montreal Cognitive Assessment, scored out of 30

ms = milliseconds

N, n = sample size

No. = number

NPIQ = Neuropsychiatric Inventory Questionnaire

OA = osteoarthritis
OARSI = OsteoArthritis Research Society International
p = statistical probability value
PHAC = Public Health Agency of Canada
 $pV_{O_{2max}}$ = predicted maximum volume of oxygen consumption, ml/kg/min
RCT = randomized controlled trial
RIA = Schlegel – University of Waterloo Research Institute for Aging
RL = retirement living
RT = reaction time
sCC = Self-reported cognitive complaints
SD = standard deviation
SEM = standard error of the mean
SPPB = Short Performance Physical Battery
SPSS = Statistical Package for the Social Sciences computer software
SSE = Square-stepping exercise
t = t-statistic, obtained from chi-square test
T2DM = type 2 diabetes mellitus
TIA = transient ischemic attack
TrkB = tyrosine receptor kinase B
TUG = Timed up and go test, seconds
V0 = visit 0, baseline visit, pre-intervention assessment
V1 = visit 1, refer to methods in each paper for specific time point
V2 = visit 2, refer to methods in each paper for specific time point
vs = versus
WHO = World Health Organization
WOMAC™ = Western Ontario and McMaster Universities Osteoarthritis Index
 X^2 = chi-square value
z-score = standardized score, distance between raw score and population mean

Introduction

The Canadian population is aging, and with this comes increased incidence of chronic disease and an increase in health care needs that the Canadian public funding model will struggle to maintain. Adults with chronic diseases have varying levels of impaired mobility and cognitive decline, which are risk factors for one another. As such, there is a need for interventions, such as cognitive training, that are efficacious and economical.

We sought to determine if a novel cognitive training program, called Square-stepping exercise (SSE), was feasible and could improve mobility and/or cognition in older adults with chronic disease as a universal intervention. We conducted three pilot randomized controlled trials (RCTs) in older adults with: knee osteoarthritis (OA), type 2 diabetes mellitus (T2DM) with self-reported cognitive complaints (sCC), and adults in long-term care (LTC) and continuum care (CC) homes as example populations.

The dictionary definition of feasibility is ‘the state or degree of being easily or conveniently done’ [1]. The journal, *Pilot and Feasibility Studies*, acknowledges that there remain discrepancies and no agreed upon definition for the term feasibility in intervention studies. However, Bowen et al. have proposed the following definition for feasibility: “the feasibility for intervention efficacy is: meeting intended behavioural outcomes under ideal circumstances, whereas feasibility of intervention effectiveness is: evaluating success in the real-world” [2]. In the context of this thesis we will use Bowen et al.’s definition of feasibility for intervention efficacy, which we measured via recruitment and attendance in accordance with Thabane et al.’s recommendations for pilot studies [3].

Mobility defined by the International Classification of Functioning, Disability, and Health (ICF) Framework is: “moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation” [4]. We focused on a functional approach and therefore, mobility as defined for this thesis was the ability to complete everyday functional movements, and tasks without considerable external aids. Adults with chronic disease, including physical and cognitive impairments, have reduced mobility. We measured mobility in several ways in this thesis including the timed-up and go, 30 second chair stand, and walking speed.

Cognition refers to mental processes, including the ability to think and make logical thoughts and conclusions, including several domains such as memory and executive function (higher-ordered thinking). We discuss four cognitive domains in this thesis that combine to create a global cognitive functioning (GCF) score, which are: planning, memory, concentration, and reasoning, as defined by one of our outcomes, Cambridge Brain Sciences [5].

The following literature review discusses the chronic disease pandemic, defines the chronic diseases this thesis will cover, mechanisms for disease development, mechanisms of cognitive training and exercise, and problems with current interventions. It concludes with the current state of evidence for our proposed intervention, SSE.

Prevalence and Cost of Chronic Disease

The World Health Organization (WHO) attributed 88% of deaths in Canada to non-communicable chronic disease, which included hypertension and obesity as the leading risk factors [6]. The Public Health Agency of Canada (PHAC) calculated the direct and indirect costs of all chronic diseases and injury to be \$192.8 billion annually,

which was an increase of 13.8% over a three-year period [7]. Many chronic diseases are associated with reduced function, including mobility and cognitive impairments.

Examples of chronic diseases that contribute to reduced mobility and cognitive decline that will be discussed are knee OA, T2DM, and cognitive impairment. Within the scope of chronic disease in Canada, 16% of Canadians are effected by all types of arthritis, including 10% who are effected by OA [8,9]; by 2036, arthritis is expected to effect 20% of Canadians [8]. Osteoarthritis alone contributes \$6.4 billion annually to direct and indirect health care costs [7,8]. Type 2 diabetes mellitus effects 9.3% of Canadians, with an expected increase to 12.1% by 2025 [10]. Over a ten-year period, costs associated with T2DM have nearly doubled, reaching \$12.2 billion per year [11]. An estimated 45% of people (over the age of 45 years) who live in LTC, have a diagnosis of dementia [12]. In 2016, dementia effected 564000 Canadians and costed Canadian health care \$10.4 billion; by 2031 the prevalence is expected to increase to 937000 and cost \$16.6 billion [13].

People with chronic diseases have varying disease burden, measured by morbidity and quality of life. Cerebrovascular and neurological conditions are associated with the worst physical and mental health quality of life scores amongst the spectrum of chronic diseases; OA and T2DM are associated with high disease burden [14,15]. Reduced participation in social activities and depression are associated with reduced activities of daily living and poor quality of life as well as cognitive decline [16–18]. Arthritis is the leading cause of disability for women and second leading cause of disability for men [8,19]. Quality of life decreases with increased complications associated with T2DM [20,21]. With a public health care model in Canada, there is an urgent need to slow the incidence of chronic disease as well as develop cost effective treatment strategies to

improve health and quality of life amidst the aging Canadian population in a feasible, scalable, and pragmatic way.

Diseases, mechanisms, and interventions

Osteoarthritis

Osteoarthritis is defined as radiographic (X-ray) evidence of cartilage loss at a joint, with or without joint symptoms, most commonly pain and functional limitations [22]. Osteoarthritis is primarily a disease whereby the articular cartilage in a joint is worn down from unequal joint pressure, resulting in joint space narrowing, and inflammation, which leads to pain, disability, and reduced function and proprioception [22]. These symptoms (pain, reduced function) are associated with increased falls risk and decreased physical activity in adults with knee and hip OA [23,24]. An increased risk of falling is associated with mobility and cognitive impairments [25,26]. Osteoarthritis is caused by modifiable risk factors including obesity, physical inactivity, and acute injury and non-modifiable risk factors including, age, sex, and joint malformation [22,27].

There is no cure for OA, and current treatments are primarily based on symptom and pain relief, and improving mobility and function. Current treatments do not address prevention of disease progression. For example, the gold standard treatment for knee OA is total knee replacement surgery; other non-surgical treatment options are pharmacological and non-pharmacological. Non-pharmacological treatments for OA are based on guidelines created by the Osteoarthritis Research Society International (OARSI), which include: land-based exercise, weight management, strength training, water-based exercise, self-management, and education. Pharmacological treatments include anti-inflammatory and pain management injections, drugs (e.g., non-steroidal anti-inflammatory drugs, capsaicin, duloxetine, and acetaminophen) and topical treatment

[28]. For the purposes of this thesis we focused on land-based exercises recommended by OARSI.

T'ai Chi has strong favourable benefits for pain reduction and improvement of physical function. Two meta-analyses found that T'ai Chi interventions reduced pain and to some extent, improved physical function for adults with knee OA [28–30]. A neuromuscular training program, which has been implemented into clinical practice in Denmark and investigated in Canada, has demonstrated improvements in pain as well as lower extremity functional fitness in prospective cohort studies [31,32]. However, in randomized controlled trials, there was not a superior effect of the neuromuscular training program compared to controls or other types of training [33–35]. It is likely that the lack of evidence for improvements in physical function, such as balance, through the proposed mechanisms of proprioception or neuromuscular function is due to the low number of trials that appropriately assess these outcomes [24]. A recent systematic review of T'ai Chi interventions found that 72% of trials did not measure balance using a test of proprioception and/or neuromuscular function [36]. Nevertheless, in those studies that did include these measurements, there was evidence for improved balance and proprioception or neuromuscular function, which supports the hypothesis that T'ai Chi improves balance by changes in proprioception [36].

The feasibility, as measured by attendance in programs, was >80% in most studies, demonstrating that interventions appear to be feasible in adults with knee OA [37–39]. In practice, these interventions (neuromuscular training and T'ai Chi) require specialized training and certification to administer. As well, in further evaluation of the neuromuscular training program, it was only adopted by 20% of municipalities, demonstrating continued issues of cost, which limits its full scalability as an intervention

for OA [39]. Thus, there still appears to be limited ability to scale interventions and increase accessibility of programs to everyone effected by OA. Further development of intervention studies is required to determine a program that will improve neuromuscular function, and proprioception to improve falls risk and physical function in adults with OA, that is feasible and scalable.

Type 2 diabetes mellitus

Type 2 diabetes mellitus is defined as primary systemic insulin resistance with reduced beta cell function [40]. The two main risk factors for T2DM are physical inactivity and obesity. Physical inactivity leads to insulin resistance through reduced function of insulin receptor substrate 1, disruptions of phosphoinositide 3 kinase activation, and glucose transporter 4 translocations, which causes a reduction of glucose entering cells, and leads to hyperglycemia [40]. Obesity causes chronic general inflammation via adipose tissue, which leads to insulin resistance through increased intracellular fatty acids and disrupted glucose metabolism through competition between fats and glucose, thereby decreasing glucose oxidation, resulting in hyperglycemia [40]. While obesity and physical inactivity are major risk factors for T2DM, other risk factors include: increasing age, diet, family history, polycystic ovary syndrome, mental illness, hypertension, hyperlipidemia, and cardiometabolic disturbances [41].

The support for exercise as an intervention for prevention, treatment and management of T2DM is well established with demonstrated evidence and national guidelines. Similar to OA, T2DM has no known cure and treatments are prescribed to manage the disease, reduce symptoms, and reduce risk of co-morbidity. Diabetes Canada (formerly the Canadian Diabetes Association) has published clinical practice guidelines, which include a healthy lifestyle as the primary recommended treatment at the onset of

diagnosis, specifically exercise [41]. Exercise improves glycated hemoglobin (A1C), and controls blood glucose to prevent micro- and macro-vascular complications associated with T2DM [40,41]. Vascular complications are arguably the most important clinical outcomes for people with T2DM; however, one such vascular complication that has been overlooked is dementia [42].

Few studies have examined the effect of exercise on the prevention of cognitive decline in adults with T2DM. Those that have been conducted are generally of poor quality, design, and have small sample sizes as well as limited adherence reporting. A 24-week lifestyle intervention elicited a decline in immediate and delayed recall in adults with T2DM, n=17; however, there was no control group in this study [43]. A sub-study compared adults with T2DM to adults without T2DM on a cycling or cyber-cycling protocol, n=20; they found improvements in executive function in the T2DM group [44]. A third study found that adults with T2DM improved global cognitive functioning compared to a control group; this improvement was not seen in adults without T2DM (n=415 at baseline) [45]. These studies demonstrate that there is potential to improve cognition in adults with T2DM and without cognitive deficits. However, more studies with robust methodology are needed, in addition to investigating alternative interventions, such as cognitive training, to specifically target cognitive function.

Attendance rates of feasibility studies reported between 50-100% attendance rates, with most averages in the range of 60-80% [43–45]. Further, dropout rates are reported between 10-43% [44,45]. It is likely that there are high dropout rates because adults with T2DM have high disease burden, as demonstrated by higher vascular burden (i.e., cardiovascular risk) compared to non-diabetes controls [45]. Additionally, two of the three studies discussed were sub-analyses of larger randomized controlled trials. Thus, the

feasibility of cognitive training and exercise interventions for adults with T2DM need better reporting.

Cognitive Impairment

Cognitive decline is on a spectrum with subjective cognitive decline (SCD) as the earliest phase and dementia and Alzheimer's disease (AD) at the end stages, and therefore, there are several definitions. Subjective cognitive decline or a self-reported cognitive complaint (sCC) is identified when a person or partner/family member reports a decline in memory and/or thinking skills, which can occur with or without objective impairment [46,47]. Evidence suggests SCD increases the likelihood of developing dementia and those who are concerned or worried about their declining cognition further increase their risk of dementia [48,49]. Mild cognitive impairment (MCI) includes objective evidence of cognitive decline in memory or thinking domains, which is usually assessed using standardized tests, such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) [48]. Dementia is the clinical diagnosis of overt disease, which is defined as a decline in memory and/or thinking skills that impairs function [50]. The underlying mechanism for dementia and AD are likely multifactorial and thus the interactions of several mechanisms result in disease [51–54].

Proposed mechanisms and accepted risk factors of cognitive decline are summarized in an updated review by Santos et al. 2017. In brief, cardiometabolic changes (e.g., impaired heart function, hypertension, hypercholesterolemia, hyperglycemia) are accepted risk factors [55]. The mechanism is related to reduced cerebral blood flow, chronic microvascular injury, endothelial damage (stiffness, nitric oxide decrements), changes to the blood brain barrier (leak of ion balance, glucose exchange), build-up of Tau tangles, and amyloid plaques, which results in impaired cognitive function over time.

Additionally, it is accepted that the Apolipoprotein E (ApoE) gene is related to AD risk [55]. However, much of the cellular changes related to the development of dementia remain to be elucidated. Midlife vascular risk factors, disease, and events, such as stroke, transient ischemic attacks (TIA), heart disease, and T2DM are risk factors for dementia [51,52]. Furthermore, a recent study evaluating meta-analyses on 76 environmental risk factors for dementia found convincing evidence that depression (any age and late life), benzodiazepine use, and low social contact increase the risk for all types of dementia [56].

In adults with subjective cognitive decline, MCI, or dementia, the treatment options available are aimed at slowing progression and reducing symptoms, rather than stopping or reversing cognitive decline. Further, pharmaceuticals have failed to demonstrate any cognitive benefit to dementia or AD [57,58]; however, exercise and cognitive training intervention trials are showing promise.

Exercise improves cognition in adults primarily through increased cerebral blood flow [59]. Aerobic exercise increases levels of brain derived neurotrophic factor (BDNF) and its receptor, tyrosine receptor kinase B (TrkB), which in turn increases hippocampal volume and synaptic plasticity [53,60], resulting in improvements in memory and executive function. Resistance training appears to increase insulin-like growth factor 1 (IGF-1) and its receptor IGF-1R, which increases prefrontal cortex volume and improves response inhibition and conflict resolution [52,53,61].

In 2003, a meta-analysis found aerobic exercise to have a positive effect on cognitive function [62]. In healthy older adults, it was found that a six-month study of aerobic exercise improved conflict resolution and attention (executive function) as well as preserved brain structures [59]. A similar one-year study of walking, found a two percent

increase in hippocampal volume and improvements in memory, which is equivalent to reducing one to two years of age-related volume loss [63]. In a nine-year longitudinal study, it was found that walking 1.6 km (1 mile) per day was enough to maintain gray matter in older adults [64]. In adults with subjective cognitive decline or MCI, a 24-week, three times per week exercise intervention found improvements in global cognition and memory; in comparison the control group declined in global cognition over that same period [65]. A six-month study of four days per week of high intensity exercise in adults with MCI, found improvements in executive function, and females demonstrated greater improvements than males [66]. In adults with dementia, exercise interventions appear to provide cognitive benefit; however, the results are less robust. It appears that the benefits associated with exercise on cognition may only provide maintenance of cognitive function rather than improvements, despite interventions lasting up to 12-months in adults with dementia [67,68].

As an alternative to exercise interventions, cognitive training has been under investigation in recent years to determine its efficacy on cognition, and thus, meta-analyses have been conducted. Two recently published meta-analyses found small, but significant, benefits of cognitive training on cognition, specifically memory. Further, the data suggest that cognitive training imparts a lasting effect; however, it should be noted that these studies were conducted in healthy older adults and not in adults with cognitive impairments [69–71].

The mechanism by which cognitive training improves cognition is still under investigation. However, Chapman et al., have demonstrated it appears to be, at least in part, related to increased activation of the frontal, temporal and parietal areas as a result of the cognitive stimulus of the intervention (i.e., the cognitive training task) that

increases activation in specific brain regions. There is increased global and regional blood flow at resting state due to overall increased metabolic demand from cognitive training (i.e., increased periods of activation), and increased resting state activation (default mode network, and executive-related areas), as well as greater connectivity in associated regions, and increased white matter [72]. These changes: hemodynamic, neural activation, connectivity, and structure, appear to be associated with functional improvements in cognitive function. These changes were seen in healthy older adults. However, in adults with cognitive impairments there is evidence for brain plasticity because compensatory pathways are activated in response to cognitive training, rather than the ‘traditional’ neural pathways shown in healthy older adults [73,74]. Further study on the efficacy of cognitive training is needed.

The feasibility, that is recruitment and attendance, of cognitive training studies to improve cognition in older adults is poorly reported [72,75]. Additionally, some studies exclude participants from analysis who did not adhere to the cognitive training program [76]. Exercise intervention studies have somewhat better attendance reporting, for reference, a range of 60-80% average attendance rates are reported in exercise trials to improve cognition [77–79]. Interestingly, programs that are administered in retirement and assisted living communities have higher attendance rates, averaging closer to 80% [68,80]. However, in studies in assisted living homes in adults with dementia (i.e., higher disease burden), recruitment rates (17%), and dropout rates (36%) are low, as well as high incidence of adverse events [68]. Thus, there remains to be problems with the feasibility of interventions in adults with cognitive impairments.

Scalability of interventions

Overall, disease burden is a barrier to participation in interventions [81–83], and therefore limits feasibility and scalability of interventions. To date, there are very few intervention trials that have demonstrated scalability. In order to combat the overarching burden of chronic disease, it would be advantageous to have an intervention that is efficacious for multiple chronic conditions, multi-morbidity and well tolerated for varying levels of fitness. A robust example of successful scalability and implementation of an intervention is the DASH diet (Dietary Approaches to Stop Hypertension) [84]. Originally designed to reduce hypertension through reduced sodium diet, randomized controlled trials have also demonstrated it can prevent osteoporosis [85], colorectal cancer [86], heart disease, stroke [87], and help prevent diabetes complications [88]. This program has been endorsed by Diabetes Canada, Heart and Stroke Foundation, Hypertension Canada, and Dietitians of Canada, and thus, has demonstrated its clinical benefits, feasibility, and scalability. In contrast, the only scaled intervention for multiple chronic conditions is aerobic exercise [89]. However, recommendations for aerobic exercise vary amongst chronic diseases for primary, secondary, and tertiary prevention, and the recommendations differ in frequency, intensity, time, and type (e.g., aerobic, resistance and alternative forms, such as T'ai Chi) of exercise. Further, there are many contraindications for each disease, making recommendations difficult to interpret for disease populations [28,41]. Because of the varied guidelines, primary care clinicians do not feel confident prescribing aerobic exercise despite its benefits and therefore, further scaling of interventions is needed [90–92]. Additionally, aerobic exercise has not translated into real world settings, as only 12% of Canadian adults over 60 years of age regularly achieve recommended physical activity guidelines [93]. The burden chronic

disease imparts on an individual has a detrimental effect on adherence to interventions; therefore, an intervention is needed that will improve adherence for adults with all types of chronic diseases to promote secondary disease prevention, including mobility and cognitive decline.

A universal intervention – Square-stepping exercise (SSE)

As a potential universal intervention for chronic disease populations, we chose to investigate the use of a novel cognitive training program, Square-stepping exercise (SSE). Square-stepping exercise was designed as a falls prevention program for community-dwelling older adults by Shigematsu and Okura in Japan [94]. It is a cognitive training program that is best described as a progressive, visuospatial working memory task with a cued stepping response. An instructor demonstrates a stepping pattern across a gridded mat and participants are required to memorize and repeat the patterns (see Figure 1). The mat is 250 cm by 100 cm divided into 10 rows and four columns. The program includes over 200 patterns that range from beginner to intermediate to advanced [94]. Steps can be forward, backward, horizontal, or diagonal in direction. Square-stepping exercise has been primarily investigated as a twice weekly program for approximately 45 minutes. It is a low-cost activity that is group-based and designed to be a social program. Thus, SSE is cognitively stimulating and socially engaging; further, because of its range of steps it can also be considered a type of neuromuscular training.

Square-stepping exercise has shown improvements in mobility, in both randomized (RCT) and non-randomized (non-RCT) study designs in community dwelling older adults. SSE has shown improved lower limb functional fitness and strength over 3- [95,96] , 4- [97], and 6-month [94] interventions in RCT and non-RCT study designs compared to active and non-active control groups. Further, in non-RCT studies, it has

shown to improve balance over 4 months, equivalent to an active control group [97]. SSE has exhibited similar adherence to a walking program after four years (63% vs 65% respectively; non-RCT) [98]. Square-stepping exercise has also shown cognitive benefit in non-RCTs lasting 4- and 6- months, with improvements in global cognition, specifically attention and flexibility as well as memory and executive function, respectively [99,100]. Further, SSE has been studied in a 6-month randomized design in combination with multi-modality exercise and dual-task training, and demonstrated improvements in global cognition [78].

In previous studies, SSE has established good feasibility, with average attendance rates of >80% over three to six month interventions [78,94–96,100,101]. It should be noted that these studies were completed in healthy community-dwelling older adults and therefore have low disease burden. To determine if SSE could provide any secondary prevention for chronic diseases in older adults, we investigated it as a universal program for adults with chronic disease based on its demonstrated benefits in community-dwelling older adults.

The primary aims of this thesis were: to determine if SSE is feasible in adults: 1) living with knee OA, 2) living with T2DM and sCC, and 3) living in LTC and CC homes, as relevant examples of chronic diseases with a spectrum of mobility and cognitive impairments. Secondary aims were to assess the potential efficacy of SSE on mobility and/or cognitive outcomes in the proposed populations. Tertiary aims were to determine if the intervention group improved in executive control in adults with T2DM and elderly individuals in CC homes.

The remainder of the contents of this thesis are described here. Chapter two is a 24-week pilot RCT in adults with knee OA, which we assessed the feasibility of SSE and

its efficacy on mobility and OA symptoms. Chapter three is a 24-week pilot RCT in adults with T2DM and sCC which assessed the feasibility of SSE and its efficacy on cognition (including oculomotor function via antisaccade eye-tracking). Chapter four(a) is a 12-week pilot cluster RCT in LTC and CC homes, where we assessed the feasibility of implementing SSE and its efficacy on cognition, and mobility (via balance and gait) and Chapter 4(b) is a sub-study of oculomotor function (via antisaccade eye-tracking) in elderly adults with cognitive impairment. Chapter 5 is a discussion and conclusions of the results of the thesis.

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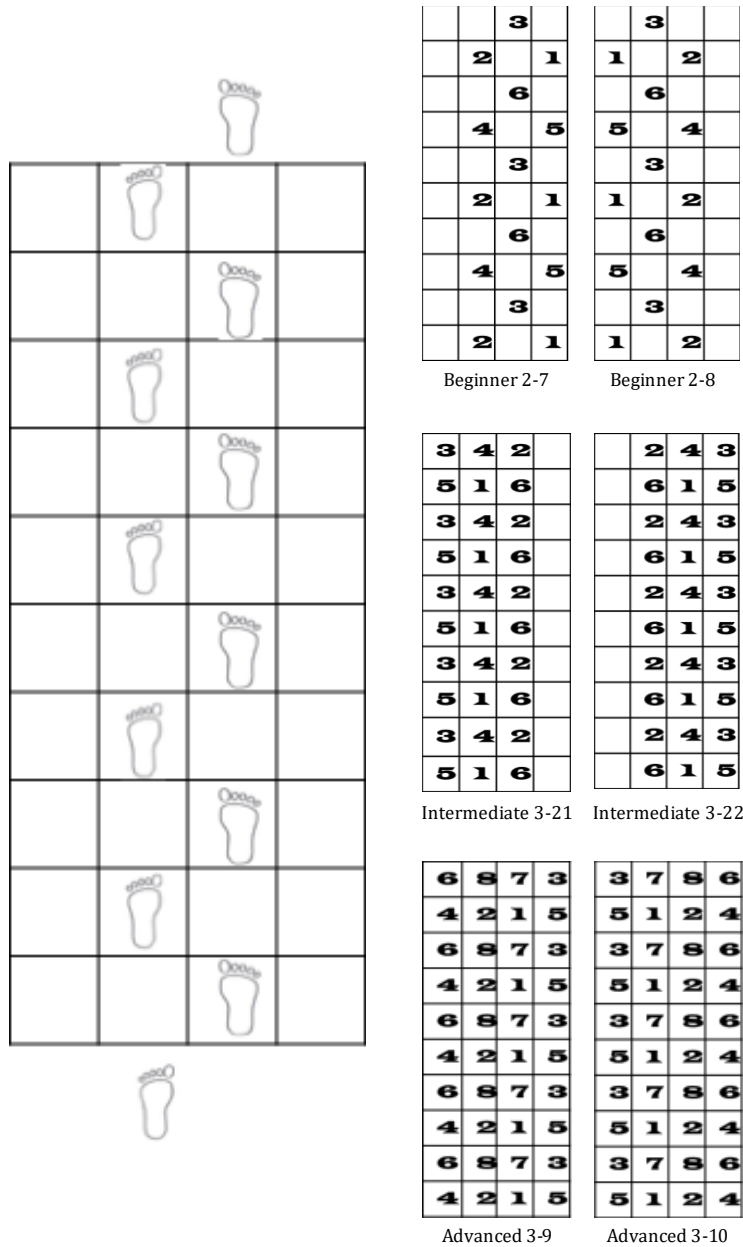


Figure 1: Depicted is an graphic of the Square-stepping exercise program, with examples of beginner, intermediate and advanced stepping patterns.

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Square-stepping exercise as an innovative intervention for older adults with knee osteoarthritis: results from a pilot feasibility study.

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Abstract

We conducted a 24-week, 2x/week, randomized study of a novel intervention, Square-stepping exercise (SSE), in older adults with knee osteoarthritis (OA) to determine feasibility (recruitment and attendance) and efficacy on: symptoms (WOMAC), balance (Fullerton), mobility (30-sec chair stand), and walking speed. Participants (n=22) were 69.5 (SD 7.4) years, 68% female, mean BMI of 30.7 kg/m² (SD 5.6). For all participants randomized to the SSE group the overall attendance rate was 49% (n=10). For the participants who completed the intervention the overall attendance rate was 70% (n=7). The SSE group showed non-significant trends toward a small-medium effect of improved 30-second chair stand test at 12-weeks, $F=1.8$, $p=0.12$, $\eta_p^2=0.16$, and 24-weeks, $F=3.4$, $p=0.09$, $\eta_p^2=0.18$, and walking speed at 24-weeks, $F=2.4$, $p=0.14$, $\eta_p^2=0.14$ compared to the control group, adjusting for baseline. There were no differences in knee OA symptoms. Because of the low attendance rates, SSE in older adults with knee OA was not feasible and the efficacy of SSE on mobility was inconclusive. In the future SSE should be investigated to improve feasibility through alternative recruitment and implementation strategies.

Background

In 2010, 4.4 million Canadians were living with osteoarthritis (OA); the prevalence is expected to increase to 10.4 million by the year 2040, which will represent 71% of adults over the age of 70 years [1]. Osteoarthritis costs approximately \$6.4 billion annually in direct and indirect health care costs [1–3], and is associated with high disease burden [4,5].

Hallmarks of knee OA are: pain, increased disability, and functional decline. There is high inter-individual variation in how people with knee OA experience symptoms of pain, stiffness, and activities of daily living, as well as how these symptoms interact with radiographic evidence of joint disease [6]. Knee OA is associated with reduced mobility, decline in physical activities, and decreased ability to do functional tasks. These functional limitations challenge independence among older adults [7,8].

The Osteoarthritis Research Society International (OARSI) recommends the following core exercise treatments for knee OA: land-based exercise, strength training, and water-based exercise [9]. Indeed, a recent Cochrane review of exercise interventions for the treatment of knee OA concluded that land-based therapeutic exercise can improve knee OA symptoms of pain, physical function, and quality of life, with lower limb muscle strengthening and aerobic exercise as the most efficacious exercise modalities [10]. These authors judged the quality of evidence to be high but that the dosage (i.e. duration, frequency, and intensity) of exercise remains to be elucidated.

Symptoms of OA appear to be dependent on how effected people are by their knee OA, thus the heterogeneity of knee OA symptoms remains to be a limiting factor [10]. In the Cochrane review, T'ai Chi was noted to have a small benefit on pain as compared to a more robust effect with strengthening or aerobic exercise; however, in a T'ai Chi only

review, it effectively reduced knee pain in adults with knee OA [11]. Similarly, yoga appears to have a positive benefit on pain in a review of knee OA participants, although more high quality research is needed [12–14].

Patients with knee OA experience reduced knee proprioception at a rate that is greater than normal aging and their reduced proprioception is associated with reduced functional status [15]. Reduced knee proprioception is linked to reduced neuromuscular control, thereby contributing to increased fall risk [16]. By improving knee proprioception and neuromuscular control through dynamic physical activity, it may be possible to reduce fall risk and maintain mobility in older adults with knee OA through improved functional mobility and balance [15,16]. The only known example of a neuromuscular training program for adults with OA is the Good Life with osteoArthritis in Denmark (GLA:D) program. It includes functional exercises aimed at improving sensorimotor control and dynamic stability combined with education sessions to continue the exercises at home [17,18]. This program shows promise in implementation studies on functional outcomes of neuromuscular control (e.g., chair stand, walking speed); however, in randomized controlled trials it has not been shown to be superior to a strength training program [19,20].

Square-stepping exercise (SSE) is a visuospatial working memory task with a cued stepping response; thus, it can be considered a type of proprioception or neuromuscular training task since proprioception and visuospatial tasks are associated with frontal and parietal lobe activation [21,22]. It was originally developed as a fall prevention program for older adults by Shigematsu and Okura [23]. Specifically, an instructor demonstrates a stepping pattern across a gridded mat and the participants are required to memorize and repeat the pattern. The program is progressive, whereby the

patterns increase in difficulty from beginner to intermediate to advanced patterns; thus, challenging mobility, balance, and visuospatial skills, a surrogate for proprioception, through wide horizontal, diagonal, and backwards steps into specific small squares on the mat.

We were interested in examining whether SSE could enhance mobility and balance through visuospatial training in adults with knee OA. Square-stepping exercise is similar in administration and intensity to T'ai Chi and yoga because it is also a form of mind-motor exercise, thus stimulating visuospatial skills. In community-dwelling older adults there is some evidence that SSE can improve balance, strength [24,25], and lower-extremity functional fitness [26–28]. Square-stepping exercise may have comparable benefits on mobility in community-dwelling older adults to those shown through T'ai Chi and yoga in adults with knee OA. These types of mind-motor interventions (yoga and T'ai Chi) may enhance proprioception and neuromuscular control that could lead to reduced fall risk and improved mobility in adults with knee OA.

The primary aim of this study was to determine if a SSE program is feasible in an older adult population with knee OA, assessed via recruitment and attendance. Secondary aims of the study were to determine if: 1) knee OA symptoms (pain, stiffness, and difficulty performing daily activities), 2) static and dynamic balance, 3) balance confidence, 4) mobility, 5) fitness, or 6) walking speed were improved in the SSE group compared to the control group at either 12- or 24-weeks. Thus, we hypothesized SSE to be a feasible and potentially efficacious intervention in adults with knee OA as well.

Methods

Study Design

We conducted a 24-week pilot randomized controlled trial, whereby participants were randomized to a SSE program (SSE group) or wait-list control group (control group). Randomization sequence was computer-generated, with one to one allocation, balancing every four participants (i.e., block randomization). A study investigator who was not involved in the assessments completed the number generation and used concealed envelopes for randomization. The group allocation was revealed at the end of the baseline assessment by a study investigator not involved in the randomization sequence. This study was un-blinded for both participants and study personnel due to logistical reasons (i.e., assessors also conducted SSE sessions). It was run concurrently with a different study of the same intervention and run over three waves of enrolment (intervention start dates: June 2015, October 2015, and November 2015) to increase the size of groups per wave as well as convenience. Locations for the intervention included the YMCA Stoney Creek (London Canada) and YMCA Woodstock (Woodstock Canada). There was no cost to participate in the program and no compensation provided, other than to cover the cost of parking at assessment sites. The study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario (No. 106537) and the study was done in accordance with the Declaration of Helsinki. All participants were provided with a letter of information and written informed consent was obtained prior to any data collection or study procedures.

Eligibility

Participants were ambulatory, 45 to 85 years old, diagnosed with knee OA (self-reported diagnosis), had a Western Ontario and McMaster Universities Arthritis Index

(WOMAC™) pain score of four or greater for their index knee, and were available twice weekly for the duration of the study. Exclusion criteria included: index knee replacement, or planned knee surgery for either knee during the study duration, uncontrolled hypertension, psychiatric or psychotic disorder, and any other reason the study investigators felt would intervene with study evaluations or intervention.

Recruitment

Participants from previous research studies were pre-screened for OA and contacted by phone regarding their interest to participate in this study (i.e., if they had previously indicated interest in participating in future research studies). Additionally, advertisements in local newspapers, community centre newsletters, local doctor offices, and physiotherapy clinics were utilized. Recruitment for the study began in May 2015 and was completed in November 2015.

Assessments

Assessments were completed at community locations in London and Woodstock Canada at baseline (V0), 12-weeks (V1), and 24-weeks (V2).

Baseline participant characteristics included: age, sex, race, marital status, a self-reported general health rating question, blood pressure, height, and weight [Body Mass Index (BMI)]. The Charlson Co-morbidity index score was calculated through the number of medical conditions (self-report) as per the weighted Charlson criteria [29].

Feasibility was defined using Bowen's definition for intervention efficacy: "meeting intended behavioural outcomes under ideal circumstances" [30]. To assess feasibility of the SSE program in older adults with knee OA, recruitment and attendance were determined [31].

The assessments for knee OA symptoms (WOMAC), mobility (30-second chair stand), balance [Activities-specific balance confidence (ABC) scale and Fullerton Advanced Balance (FAB) scale], Leisure activities (cognitive and physical), fitness (STEP Test), and walking speed (6 metre walk test) are summarized (See Table 1).

Intervention – SSE group

Square-stepping exercise (SSE) is a visuospatial working memory program well suited for older adults to improve lower-extremity functional fitness and reduce fall risk [23,25]. An instructor demonstrated a stepping pattern across a gridded mat, which is 250 cm x 100 cm and divided into four columns of 10 rows, totalling 40 squares. The participants are required to try to remember and repeat the patterns four times; the group would move onto the next pattern after 80% of the group completed the pattern correctly. There are over 200 patterns that are progressive; the SSE program begins with beginner patterns and progresses to intermediate and advanced patterns. The number of steps in a pattern range from two to 16 steps, and steps can be forward, backward, horizontal, or diagonal in direction, which challenges mobility, balance, and visuospatial skills. Each pattern has a right and left foot start. SSE is a group-based program that increases social engagement through peer assistance.

The program duration was 24-weeks and sessions were held twice per week for one hour at a local YMCA. During the one hour sessions, a five- to ten-minute warm up and five- to ten-minute cool-down were done at the beginning and end to reduce the risk of injury, with a focus on stretching the muscles of the neck to reduce neck strain from looking down at the mat. SSE was done for 45 minutes each session. A warm up pattern from the beginner protocols was completed, which was followed by the last completed pattern from the previous session. Attendance and pattern progression were recorded at

each session. Light music was played in the background to help motivate and encourage participants.

Wait-list control group

Participants randomized to the wait-list control group participated in all the assessments (V0, V1, V2). After completing the final assessment (V2), they were invited to participate in the SSE program for 24-weeks to ensure that everyone was given the opportunity to participate in the program. Further, a wait-list design was chosen to have a comparator group and logistical constraints prevented having an active control group.

Sample Size

For this pilot trial, we proposed that 40 participants (20 per group) was a reasonable sample size for our secondary outcome, the 30 second chair stand test. With 18 participants per group, our study would have 80% power at the 5% significance level to detect an effect size (mean difference divided by standard deviation) of 0.95, a large effect size [32]. We estimated a dropout rate of 10%, which increased our calculation to 20 participants per group (40 total). We felt that this was a conservative dropout rate given our experience.

Statistical analyses

Statistical analyses were conducted in SPSS, version 24. Analysis of covariance (ANCOVA) was used to assess between group differences at assessment time points (V1 and V2), controlling for baseline (V0) values. Frequency tables and descriptive statistics were used to assess attendance and recruitment rates. Effect size, reported as partial eta squared (η_p^2 , where 0.1 is small, 0.25 is medium, and 0.4 is large [33]), was included because this was a pilot study and the focus was not statistical significance.

Results

Recruitment

Ninety people were identified as potential participants from May to November 2015. Twenty-two participants provided written informed consent and enrolled in the study, 10 were randomized to the SSE group and 12 were randomized to the control group (See Figure 1).

Attendance

The total possible number of sessions was 48 (i.e., 2 times per week for 24-weeks), however a range of 45-48 SSE sessions were offered due to poor weather conditions and instructor availability across the three intervention waves. In the SSE group, the average attendance rate was 49.3% for all participants (n=10), 69.9% for study completers (n=7) and 90.5% in participants who attended >50% of sessions (n=5).

Participants

Participants (n=22) were an average of 69.5 (SD 7.4) years of age, 68% female, with a mean BMI of 30.7 kg/m² (SD 5.6) and a mean Charlson Index of 2.1 (SD 1.1) (See Table 2).

Western Ontario and McMaster Universities Arthritis Index (WOMACTM)

ANCOVAs were conducted to assess differences between groups at V1 and V2, controlling for V0 and no significant differences were found (See Table 3 and Figure 2). There may be a small effect on pain at V1, however all other effect sizes were negligible.

Balance, Mobility, Leisure Activities, Fitness, and Walking Speed

ANCOVAs were conducted to assess differences between groups in balance, mobility, leisure activities, fitness, and walking speed at V1 and V2, controlling for V0 (See Table 4 and Figure 3). The SSE group trended toward improvements in the 30-

second chair stand test at V1 and V2, as well as walking speed at V2 when controlling for V0; these were supported by small to medium effect sizes; however, these were not significant findings.

There were no significant differences in Activities-specific balance confidence (ABC) scale, Leisure activities, or fitness at any time points. There was a small positive effect on the ABC scale at V1, and other effect sizes were negligible.

Adverse events

There were three adverse events related to the study. One participant in the SSE group fell during a balance assessment; one participant in the control group fell during an SSE session; and one participant in the control group reported headaches due to neck strain during several SSE sessions. There were no serious adverse events related to the study, specifically death or hospitalization.

Discussion

Overall, we found SSE was not a feasible program for older adults with knee OA; our aim was to recruit 40 participants, we were only able to recruit 22 participants out of a potential 90 over a six-month period. Further, in the SSE group, the mean attendance rate was 49.3% for all participants, although the adherent participant's (i.e., attended more than 50% of sessions) average attendance rate was 90.5% (n=5), this was only in 50% of enrolled participants. Our methods of recruitment were to contact previous participants in clinical research studies from our laboratory, poster advertisements at physiotherapy clinics, doctors' offices, and seniors' community centres as well as advertisements in local newspapers. Recruitment for exercise programs in healthy populations is challenging, therefore recruitment in a population with functional impairments and knee pain likely further limited our recruitment [9,34,35]. In the SSE group, we had two people

drop out of the program due to ongoing health related issues and one participant lost interest. We can relate our issues with recruitment and dropout to the Charlson Index score, which indicated that many participants had a co-morbid condition beyond knee OA, which likely effected attendance and adherence. Other barriers to program participation include: time commitment of six-months, daytime sessions, and location (i.e., not central location or accessed via transit). We chose the location and time of day based on the availability of our community partners' space. Increasing flexibility of time of day for the program and/or a shorter duration intervention may have improved our recruitment and attendance; however, as currently investigated, SSE is not feasible for adults with knee OA.

Trends towards improvements in the 30-second chair stand suggest that SSE may improve lower-extremity functional mobility. Additionally, trends toward improvements in walking speed suggest that the SSE program may reduce risks associated with low walking speed, such as frailty [36,37]. Although speculative, SSE may improve lower-extremity mobility and walking speed, which may be in part due to improvements in neuromuscular control and proprioception, thus potentially reducing fall risk in adults with knee OA [16]. We must highlight the results are not significant. Due to this lack of significance, we are unable to conclude improvements in physical function at the present time. Additionally, we cannot ignore the fact that the trends we see may in fact be due to natural variation or random chance due to the small sample size, in addition to the fact that SSE may not impart benefits on physical function in adults with knee OA.

In our analyses, we did not see any significant differences between groups in any knee OA symptoms, assessed by the WOMACTM, at any time point (V0, V1 or V2). There was much variability in both groups, where standard deviations were more than

50% of the WOMAC™ scores, demonstrating a lot of inter-individual variation – a common occurrence in knee OA studies despite its common use [6]; however, we did have a small sample size which could have introduced much of the variation. If we had administered the WOMAC™ more often than the three time points, we may have seen more consistent profiles of knee OA symptoms, which may have reduced variability in the WOMAC™ data and shown trends. The efficacy of SSE on older adults' knee OA symptoms of pain, stiffness, and difficulty performing daily activities (DPDA) remains to be elucidated.

Limitations

Our main limitation was the small sample size, which did not allow us to conclusively evaluate efficacy in our secondary outcomes. The lengthy study duration, time of day, and location may have been limiting factors for recruitment and attendance. Lastly, having a direct measure of proprioception would have been beneficial; however, it was beyond the scope of this feasibility study. Our measures of neuromuscular function using the chair stand and TUG are similar to other OA studies [38] and therefore, elucidating the mechanism of improved mobility is a limitation in most studies in this field and thus, it should be a focus in future investigations.

Future Directions

In the future, studies should focus on ways to improve the feasibility of exercise interventions for adults with knee OA. From our experience, simple ways to improve feasibility would be to allow for more flexibility in the time of day participants can attend sessions, as well as optimize the locations of interventions and/or have more than one location. Other ways to improve the feasibility would be to incorporate SSE into existing senior's fitness programs as an addition to currently offered classes or as an additional

class. This would be more pragmatic and may improve recruitment. Further, initiating a collaboration with OA researcher-clinicians may aid with recruitment, specifically targeting individuals on waiting lists for knee replacement surgery or in physiotherapy for knee OA treatment.

Recommendations for future studies of SSE in adults with knee OA would be to have an active control group and/or GLA:D program group and/or usual care to have more appropriate comparator groups. Further, it would be advantageous to implement *a priori* criteria for feasibility, for example 70% of recruitment fulfilled and 70% attendance rate [31]. If we extrapolate to a larger trial, based on the current results, to see an improvement of 1 point on WOMAC pain scale we would need a sample of 240, or a sample of 58 to see an improvement of 1 in the 30-second chair stand test [32].

Conclusions

Recruitment was challenging, and we found that adults with knee OA had low adherence to the SSE program, with an average attendance of 49%. The efficacy of SSE on mobility in older adults with knee OA should be further investigated as our results showed trends and therefore were inconclusive. Additionally, we did not see any changes in knee symptoms as a result of the intervention. We conclude that SSE is not feasible in adults with knee OA and we cannot conclude if it imparts symptom relief nor improved physical function based on the current results.

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Table 1: Study assessment and outcome measures, which were assessed at baseline, 12-weeks and 24-weeks in all participants.

Assessment	Outcome	Description
Knee OA symptoms: WOMAC™	Knee pain	Self-report questionnaire of: 5 pain, 2 stiffness and 17 questions on difficulty performing daily activities. The WOMAC™ is a well validated and used scale [39].
	Knee stiffness	
	Difficulty performing daily activities (DPDA)	
	Global Assessment	
Balance	Activities-specific Balance Confidence (ABC) Scale	Self-report questionnaire of 16 questions on balance confidence [40,41]. It is reliable in a knee osteoarthritis population [42].
	Fullerton Advanced Balance (FAB) Scale	A test of 10 static and dynamic balance assessments and it is valid and reliable [43].
Mobility	30 Second Chair Stand	Participants are required to stand up and sit down as many times as they can in 30-seconds; recommended by OARSI [44][45].
	Timed-up and Go test (TUG)	Participants are required to stand from a seated position, walk around a cone 3 metres away; recommended by OARSI [45,46].
Leisure Activities	Cognitive Activities	A self-report questionnaire of participation in 6 cognitive and 11 physical activities [47].
	Physical Activities	
Fitness	STEP™ Test	Participants are required to step up and down a set of two stairs 20 times at a comfortable pace which is timed; their radial pulse is measured. To calculate predicted VO_{2max} , heart rate, time to complete the steps, sex, age, height and weight are used [48,49].
Walking Speed	6 metre walk test	A self-paced walking test where a person walks 8-metres and is timed through the middle six[50][36].

Table 2: Participant characteristics at baseline, by randomization group.

	SSE Group (n=10)	Control Group (n=12)
Age, years, mean (SD)	69.7 (9.3)	69.3 (5.9)
Female sex, No. (%)	6 (60.0)	9 (75.0)
Caucasian No. (%)	9 (90.0)	10 (83.3)
Height, cm, mean (SD)	163.8 (7.9)	163.3 (9.6)
Weight, kg, mean (SD)	88.9 (16.6)	79.1 (13.2)
BMI, mean (SD)	32.0 (7.2)	29.6 (3.7)
Index knee = right knee, No. (%)	8 (80.0)	7 (58.3)
Charlson Index^a, mean (SD)	1.8 (0.9)	2.3 (1.3)
Predicted V_{O2max}^b, mean (SD)	32.5 (5.7)	24.7 (6.7)
Systolic Blood pressure, mean (SD)	149.2 (21.5)	137.8 (11.4)
Diastolic blood pressure, mean (SD)	82.9 (7.7)	79.5 (9.8)
Self-rated health, \geqgood^c, No. (%)	8 (80)	11 (92)

^aCharlson Co-morbidity Index [29]

^b Predicted V_{O2max} is calculated from the STEP™ Test [48].

^cSelf-rated general health rating question: poor, fair, good, very good and excellent.

Table 3: WOMAC™ results at 12 (V1) and 24-week (V2) assessments during a SSE intervention¹.

	Visit	F-statistic	p-value	η_p^2
Pain	V1	2.11	0.17	0.12
	V2	0.01	0.93	<.01
Stiffness	V1	0.07	0.79	<.01
	V2	0.16	0.70	0.01
DPDA²	V1	0.08	0.78	<.01
	V2	1.38	0.27	0.08
Total Score	V1	0.04	0.85	<.01
	V2	0.36	0.56	0.02
Global Assessment	V1	0.07	0.80	<.01
	V2	0.98	0.34	0.06

¹ Analysis of covariance between groups with wait-list control group as comparator and adjusted for baseline (V0) values.

² Difficulty performing daily activities

Table 4: Results for functional outcomes at 12-weeks (V1) and 24-weeks (V2) during a SSE intervention¹.

	Time	F-statistic	P-value	η_p^2
Balance				
ABC Scale	V1	1.54	0.23	0.09
	V2	.003	0.96	<.01
FAB Scale	V1	0.42	0.84	<.01
	V2	0.83	0.34	0.06
Mobility				
30s Chair Stand	V1	1.81	0.12	0.16
	V2	3.39	0.09	0.18
TUG	V1	0.83	0.38	0.06
	V2	0.09	0.77	<.01
Leisure Activities				
Cognitive	V1	1.11	0.31	0.07
	V2	0.33	0.57	0.02
Physical	V1	0.32	0.58	0.02
	V2	0.83	0.38	0.05
Fitness				
Predicted V0_{2max}	V1	0.02	0.88	<.01
	V2	0.20	0.66	0.02
Walking Speed	V1	0.57	0.46	0.04
	V2	2.43	0.14	0.14

¹ Analysis of covariance was used with wait-list control group as comparator and controlled for baseline (V0) values.

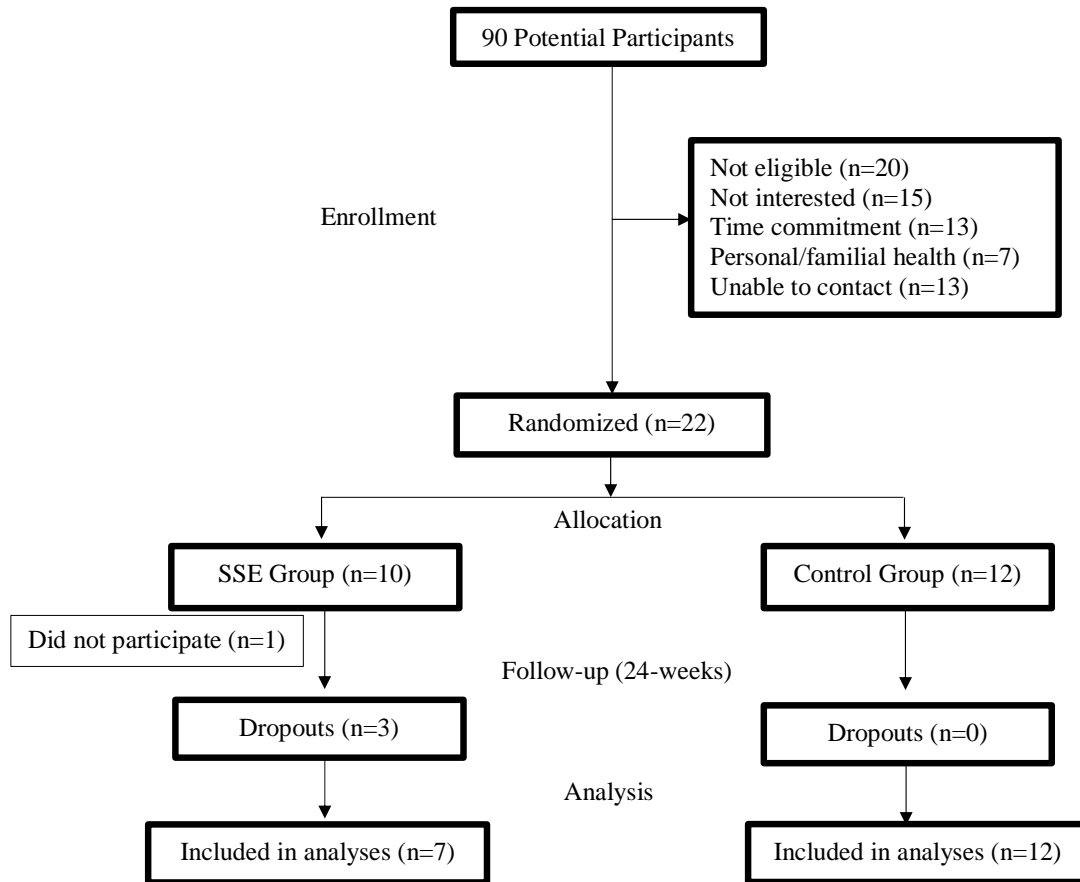


Figure 1: Study flow diagram to 24-weeks follow-up (end of intervention).

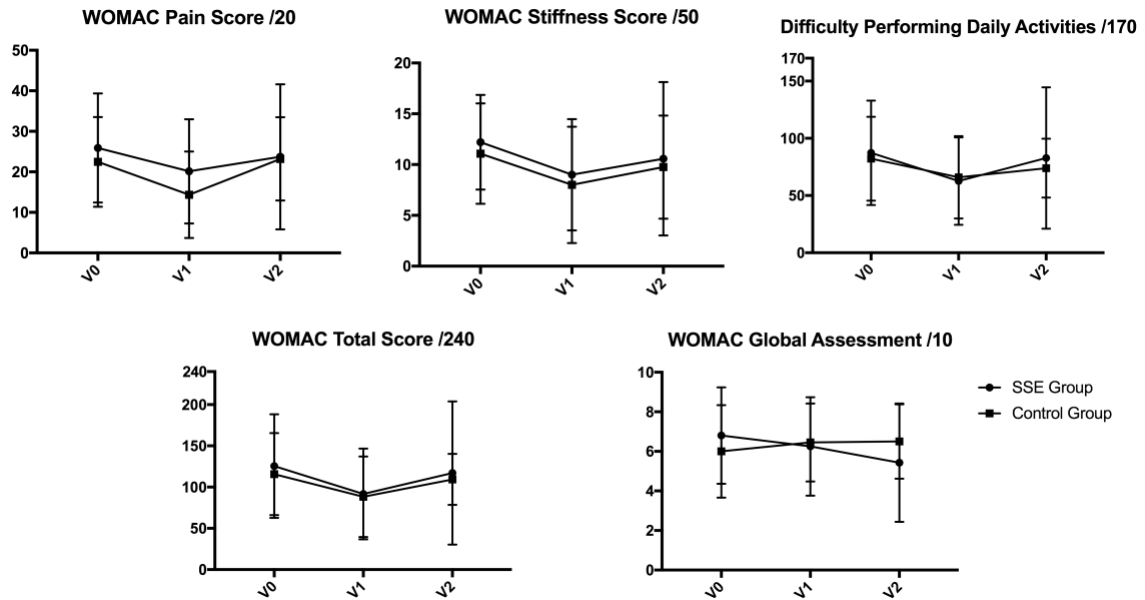


Figure 2: WOMAC™ scores for Pain, Stiffness and Difficulty performing Daily Activities (DPDA), total score and global assessment, separated by group allocation, Square-stepping exercise (SSE) group (n=7) and Control group (n=12). Lower scores indicated less symptoms, except global assessment; mean score at baseline (V0), 12-weeks (V1) and 24-weeks (V2) with standard deviation error bars.

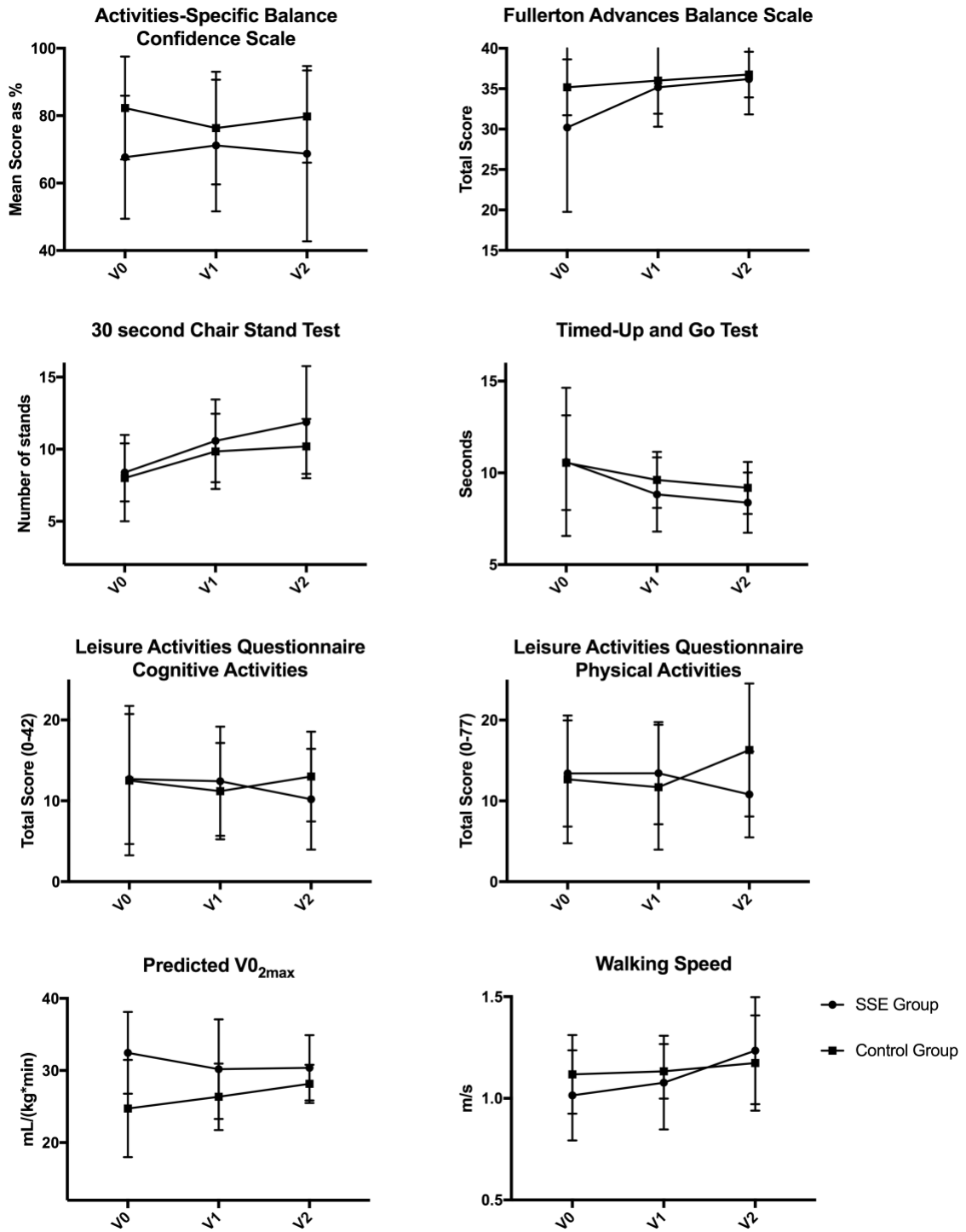


Figure 3: Mobility outcomes scores, by randomization group, Control group vs Square-stepping exercise (SSE) group at baseline (V0), 12-weeks (V1) and 24-weeks (V2).

Square-stepping exercise improves executive function in older adults with type 2 diabetes mellitus and self-reported cognitive complaints.

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Key Words

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Abstract

Adults with type 2 diabetes mellitus (T2DM) have an increased risk of dementia. We proposed a cognitive training program, called Square-stepping exercise (SSE). Aims of the study were to determine: 1) feasibility of SSE in adults with T2DM and self-reported cognitive complaints (sCC); 2) if 24-weeks of SSE improved cognition; and 3) if SSE improved antisaccade reaction time (RT) - a measure of executive-related oculomotor control.

Methods: Adults >49 years with T2DM and sCC were randomized to a SSE Group (2x/week for 24-weeks of SSE), or control group. Feasibility was assessed via recruitment and attendance. Participants were assessed at baseline (V0), 12-weeks (V1) and 24-weeks (V2) on global cognitive function (GCF), memory, planning, reasoning, and concentration via a computer-based cognitive battery (Cambridge Brain Sciences), in addition to antisaccade RT measured via eye-tracking (at V0 and V2 only).

Results: Participants in the SSE group, were [mean, (SD)]: 65.9 (5.2) years old, 33% female, with a BMI of 33.3 kg/m² (4.8) (n=12). Participants in the control group, were: 71.2 (6.9) years old, 31% female, and had a BMI of 31.9 kg/m² (4.6) (n=13). Over 24-weeks, the average attendance was 34% for all participants (n=12), 47.3% for study completers (n=8), and 70.2% for participants who attended >50% of sessions (n=4). The SSE group improved in the planning domain (mean change scores from V1-V2), $F=5.8$, $p=0.03$, $\eta_p^2=0.28$, compared to controls. In the SSE group, we found a non-significant improvement in antisaccade RT of 37 ms (SD 16), n=2, compared to the control group, which had a mean antisaccade RT improvement of 9 ms (SD 45), n=8.

Conclusions: SSE is not feasible in older adults with T2DM and sCC due to the low attendance rate; however, this study provides some evidence that SSE may improve

executive function, specifically planning domain change scores, in adults with T2DM and sCC.

Background

Older adults with type 2 diabetes mellitus (T2DM) are at increased risk of cognitive decline [1,2]. This increased risk is thought to be caused by vascular and metabolic disturbances associated with T2DM which effect the brain [3,4]. Importantly, cognitive decline in T2DM is associated with poor diabetes self-management that can lead to poor glycaemic control and increased vascular risk – a risk ‘cycle’ associated with further increased risk of cognitive decline [5,6]. This can lead to a downward spiral of poor health; thus, an efficacious intervention to maintain cognitive function is needed.

Older adults who self-report cognitive complaints (sCC), otherwise referred to as subjective cognitive decline, are at increased risk of cognitive decline [7,8]. Further to that, those who express concern or worry about their worsening memory have further increased risk of cognitive decline [7]. Therefore, older adults with T2DM and sCC are an important population to target to reduce the risk of cognitive decline. Reducing cognitive decline, thereby delaying the incidence of dementia, has the potential to save millions of dollars in health care costs [9,10].

Cognition is measured in a variety of ways and separated into several domains. In this report we describe global cognitive function (GCF), which is a composite of four domains: memory, planning, concentration, and reasoning [11]. Additionally, we discuss executive function which is higher ordered thinking that includes planning and inhibitory control. Maintaining executive control in older adults with T2DM is essential for self-management of diabetes, including insulin therapy [12].

Cognitive training studies in older adults with or without cognitive impairments have demonstrated benefits in cognition, including executive function [13,14]. Furthermore, our group has previously demonstrated that a long-term (24-week) multiple

modality exercise intervention improved executive control in community-dwelling older adults with and without cognitive decline and that the improvement was present not only immediately following the intervention, but also following a 24-week washout period [15–17].

In addressing the improved executive control in sCC identified above, our group employed the antisaccade task. Antisaccades are a cognitively challenging task requiring that a participant makes a saccade mirror symmetrical to the location of a visual stimulus (i.e., look to the opposite side of the computer screen of where a target is presented) [18]. Notably, the top-down demands of the task require executive-related cognitive control mediated via an extensive frontoparietal network - an area linked to cognitive decline in dementia [19–23].

Few interventional studies have investigated cognition as a primary outcome in adults with T2DM. Some examples are exercise interventions, which showed inconclusive results [24–27], thus the efficacy remains to be elucidated. The limitations of these studies include, a lack of consistency in results, lack of control groups, as well as studies that analyse T2DM participants as sub-groups and compare T2DM to non-T2DM participants. Therefore, further interventional research is needed to improve cognition in adults with T2DM.

We proposed a novel cognitive training program, called Square-stepping exercise (SSE). Square-stepping exercise was originally developed as a fall prevention program in Japan [28]. SSE is a visuospatial working memory task with a cued stepping response, and thus combines cognitive training with a physical component in a unique way. An instructor demonstrates a stepping pattern and participants must try to memorize and repeat the pattern. The program is progressive because patterns increase in difficulty from

beginner to intermediate to advanced. Additionally, SSE is a group-based program and therefore, social engagement is encouraged. SSE has led to improvements in GCF, memory, and executive function in community-dwelling older adults [29–31], in addition to improvements in mobility and functional fitness [32–34]; however, SSE studies have been of varied quality, specifically not all randomized trials, and thus more evidence is needed.

Square-stepping exercise has not been previously studied in older adults with T2DM and therefore, the primary aim of this study was to determine whether a SSE program is feasible in older adults with T2DM and a sCC, assessed via recruitment and attendance. Secondary study aims were: 1) to determine if GCF and domain specific cognitive function (memory, reasoning, concentration, and planning) improved in the intervention group compared to the control group at either 12- or 24-weeks. The tertiary study aim was to assess antisaccade reaction time (RT) at baseline and 24-weeks to identify improvements in executive control.

Methods

Study Design

We conducted a 24-week pilot randomized controlled trial (RCT), whereby participants were randomized to a SSE program (SSE group) or wait-list control group (control group). Randomization sequence was computer-generated, with 1:1 concealed allocation, balancing every 4 participants (i.e., block randomization). This study was unblinded for both participants and study personnel due to logistical reasons. This study was run concurrently with a different study of the same intervention and run over 3 waves of enrolment (both studies have their own randomizations, recruitment, and measurements; the studies had the same intervention only). Intervention start dates were: June 2015,

October 2015, and November 2015. Locations for the intervention included the YMCA Stoney Creek (London Canada) and YMCA Woodstock (Woodstock Canada). There was no cost or compensation to the participants, apart from parking reimbursement. The study was approved by the Health Sciences Research Ethics Board (No. 105883) at the University of Western Ontario and the study was done in accordance with the Declaration of Helsinki. Additionally, all participants were provided with a letter of information and written informed consent was obtained prior to any data collection or study procedures.

Eligibility

Participants were eligible if they: had stable T2DM [i.e., 6 months of glycated haemoglobin (A1C) below 9.0%], were aged 50 or older and answered yes to: “Do you feel your memory and/or thinking skills have gotten worse recently?” [35]. Participants were excluded if they had: a diagnosis of dementia, Mini mental state examination score (MMSE) of <24 [36], other neurological disorder, or Centre for studies of epidemiology depression scale (CES-D) score of >15. Additional exclusion criteria included: history of cardiovascular event(s) that would prevent participation, not ambulatory, uncontrolled diabetes (A1C >9.0%), unstable angina, untreated retinopathy, foot ulcers, severe sensory impairment (i.e., vision was required to be normal or corrected-to normal vision) or not being able to commit to attending at least 75% of sessions during the intervention period. Furthermore, we excluded adults with type 1 diabetes mellitus due to the inherent differences in disease mechanism, progression to vascular risk, and longer disease duration. Participants were excluded from eye-tracking assessment if they had eye diseases that preclude accurate eye-tracking, such as retinopathy, cataracts, macular degeneration, and/or glaucoma.

Recruitment

Participants were recruited from the St. Joseph's Primary Care Diabetes Support Program (London Canada), advertisements in local newspapers, community centre newsletters, local doctor offices, and at the YMCA where the intervention took place. Additionally, participants from previous research studies from our group were pre-screened for diabetes and contacted by phone call regarding their interest to participate if they had previously consented to being contacted about future research studies. Recruitment for the study began in February 2015 and was completed in November 2015.

Assessments

Assessments were completed at the St. Joseph's Primary Care Diabetes Support Program at baseline (V0), 12-weeks (intervention mid-point, V1) and 24-weeks (post-intervention, V2).

Baseline participant characteristics included: age, sex, race, a self-reported general health rating question, blood pressure, height and weight [Body Mass Index (BMI)], waist circumference (cm), diabetes duration, A1C, medications (to identify those on insulin for safety during exercise), highest level of education obtained, and duration of sCC. The Montreal Cognitive Assessment (MoCA) [37] and the Clock Drawing Test [38,39] were administered. To calculate the Charlson Co-morbidity index score, participants were asked about the number of their medical conditions (self-report) and added as per the weighted Charlson criteria [40]. Finally, participants were asked if they were concerned or worried about their worsening memory and/or thinking skills [8].

To assess feasibility of the SSE program in older adults with T2DM and sCC, recruitment and attendance were determined; feasibility was defined using Bowen et al.'s definition for intervention efficacy: "meeting intended behavioural outcomes under ideal

circumstances” [41,42]. Our four cognitive outcome domains were: memory, concentration, planning, and reasoning, and a combined GCF score. These were assessed using the 12-item computer-based Cambridge Brain Sciences (CBS) cognitive battery (for a detailed description of the games see supplement to Hampshire et al 2012 [43] and/or Table 1). The CBS games are based on well-established neuropsychology paradigms and are well supported by the literature [11,43]. The games provide an objective measurement of cognition and minimize assessor bias as they do not require a clinician to administer them like traditional paper-based neuropsychiatric assessments. Furthermore, the CBS games are dynamic and change with the participant’s responses, thus there is not a learning effect associated with the CBS games. The participants completed a familiarization session of the games prior to completing the assessment at V0, V1, and V2. The games were completed on the participants’ home computers when possible or with study personnel on laptops.

For the eye-tracking experiment, participants sat in a height adjustable chair placed in front of a table with their head in a head/chin rest. A 30-inch LCD monitor (1280 x 960 pixels, DELL 3007WFP, Round Rock, TX, USA) 550 mm from the table’s front edge was midline centered on the participant and the gaze location of the participants’ left eye was assessed using a video-based eye-tracking system, sampling 360 Hz (Eye-Trac6; Applied Sciences Laboratories, Bedford, MA, USA). Oral and written instructions were provided for the participants before each block of pro- and anti-saccades. Computer and experimental trials were controlled via MATLAB (MathWorks, Natick, MA).

For the oculomotor eye-tracking assessment, participants completed both pro- and antisaccades. A prosaccade required a rapid response to the target’s veridical location

(look to a presented target/cross on the screen). An antisaccade required suppressing the stimulus-driven prosaccades (i.e. response suppression) and completing a response mirror-symmetrical to the target's location (i.e., 180-degree spatial transformation). In both pro- and antisaccade tasks, a trial was initiated with a midline and eye-level central fixation cross (1-degree diameter) presented on the computer monitor. Following the attainment of a stable fixation (+1.5 degrees for 450 ms), a 1000-2000 ms interval for initiation of a target stimulus (50 ms duration) appeared left or right of the fixation cross at a proximal or distal eccentricity. The onset of the target serves as the movement imperative to pro- or antisaccade as quickly as possible. Pro- and antisaccades were completed in separate and randomly ordered blocks (2 blocks of 80 trials) and the location (i.e., left or right of fixation) and eccentricity (proximal, distal) of a target was ordered randomly and presented on 20 occasions during a block. For further reading on the antisaccade task, see Everling and Fischer, 1998 [23].

Intervention – SSE group

Square-stepping exercise is a cognitive training program well suited for older adults to improve memory and executive function. For this task, an instructor demonstrated to the group, a stepping pattern across a gridded mat, which is 250 cm x 100 cm and divided into four columns of 10 rows, totalling 40 squares. The participants are required to try to remember and repeat the patterns four times; the group would move onto the next pattern after 80% of the group had completed the current pattern correctly. There are over 200 patterns that are progressive; the SSE program begins with beginner patterns and progresses to intermediate and advanced patterns. The number of steps in a pattern range from 2 to 16 steps, and steps can be forward, backward, horizontal, or diagonal in direction, which challenges memory, and executive skills. Each pattern has

both a right and left foot start. Although each individual completes the patterns on their own, SSE is completed in a group setting and therefore it increases social engagement through peer coaching of the patterns.

The program duration was 24-weeks and sessions were twice per week for 1 hour at a local YMCA with study personnel, a seniors' fitness instructor, and/or student volunteers. During the 1 hour sessions, a 5 to 10 minute warm-up and 5 to 10 minute cool-down was done at the beginning and end to reduce the risk of injury, with a focus on stretching the muscles of the neck to reduce neck strain from looking down at the mat. SSE was done for 45 minutes each session. A warm up pattern from the beginner protocols was completed, which was followed by the last completed pattern from the previous session. Attendance and pattern progression were recorded at each session. Light music was played in the background to help motivate and encourage participants.

Wait-list control group

Participants randomized to the wait-list control group participated in all the assessments (V0, V1, V2). After completing the final assessment (V2), they were invited to participate in the SSE program for 24-weeks; however, they were not assessed on attendance. This was to ensure that everyone was given the opportunity to participate in the program. Further, a wait-list design was chosen to have a comparator group and logistical constraints prevented having an active control group.

Sample Size

We proposed that 60 participants (30 per group) was a reasonable sample size for this pilot study. Specifically, with 25 participants per group, our study would have 80% power at the 5% significance level to detect an effect size of 0.80, a large effect size [44] for our secondary outcome of GCF. We estimated a dropout rate of 20%, which increased

our calculation to 30 participants per group (60 total). We felt that this was a conservative dropout rate given our experience.

Statistical Analyses

Statistical analyses were conducted in SPSS, version 24. For our cognitive outcomes, from the CBS games, there were 2 planning tasks, 4 memory tasks, 3 reasoning tasks, and 3 concentration tasks. We created standardized composite z-scores for each domain (planning, reasoning, concentration, memory); then to create a GCF score, the 4 domain-specific z-scores were averaged.

For GCF and domain specific function, we used ANCOVA to assess between group differences at assessment time points (V1 and V2), controlling for baseline values (V0) in addition to exploratory analyses of change scores from V0-V1, V1-V2 and V0-V2. For our saccade RT outcome, we used a 2 (group) x 2 (time) x 2 (task) ANOVA. Frequency tables and descriptive statistics were used to assess attendance and recruitment rates. Effect size, reported as partial eta squared (η_p^2 , where 0.1 is small, 0.25 is medium, and 0.4 is large [45]), was included because this was a pilot study and the focus was not statistical significance.

Results

Feasibility

Recruitment

Recruitment was from February 2015 to November 2015 and we identified 139 people as potential participants; following screening, 25 participants were enrolled and randomized (See Figure 1).

Participants

Participants in the SSE group (n=12) were [mean, (SD)]: 65.9 (5.2) years old, 33% female, with BMI 33.3 kg/m² (4.8), and Charlson index of 2.2 (0.7) with a median diabetes duration 10.0 (IQR 6) years. Participants in the control group (n=13) were: 71.2 (6.9) years old, 31% female, with BMI 31.9 kg/m² (4.6), and Charlson index of 2.2 (1.1) with a median diabetes duration of 10.0 (IQR 15) years (See Table 2).

Attendance

The initial program design included 2 SSE sessions per week, over 24-weeks to total 48 sessions; however, due to inclement weather, the number of sessions ranged from 42-48 over the 3 waves. In the SSE group, the average attendance rate was 34% for all participants enrolled (n=12), 47.3% for study completers (n=8), and 70.2% for participants with >50% attendance (n=4).

Cognition

Global cognitive functioning, and domain specific function (memory, planning, reasoning, and concentration) were assessed between groups at V1 and V2, controlling for baseline scores (V0), diabetes duration, and age (See Figure 2). No significant differences between groups were found in our primary analyses (all p>0.05). Effect sizes for memory at V1 ($\eta_p^2=0.13$) and planning at V2 ($\eta_p^2=0.17$) were small in favour of the SSE group; the remaining effect sizes were negligible.

We found a significant difference between groups in the planning domain (mean change score from V1-V2), where $F=5.8$, $p=0.03$, $\eta_p^2=0.28$; the SSE group had greater improvements in planning scores from 12- to 24-weeks compared to the control group with medium effect. As an exploratory analysis, we conducted within group t-tests of GCF change scores; we found improvement in the mean change of GCF between V0-V2,

$t=2.8$, $p=0.03$ and trends toward improvement in the GCF mean change between V1-V2, $t=2.4$, $p=0.06$. There were no improvements seen in the control group (all $p>0.05$). CBS scores at baseline as well as population norms are summarized (See Table 3).

Prosaccade and Antisaccade Reaction Time

In group x time x task there was no interaction or main effects of group or time; but there was a main effect of task, $F=61.0$, $p<0.01$, that is antisaccades had longer RT than prosaccades.

Within the SSE group, we did not see significant improvements in antisaccade RT, all $p>0.05$; the SSE group's antisaccade RT at post-intervention was 336.4 ms (SD 1.1) - a decrease of 37 ms (SD 16) from V0, and the control group's antisaccade RT at post-intervention was 347.0 ms (SD 42) – a decrease of 9 ms (SD 45) from V0 (See Figure 3).

In this assessment, there were few participants who were able to complete the assessment at V0 and V2 due to eye related issues associated with T2DM, which was determined during attempts to track stable eye fixation. Furthermore, several participants who completed this assessment at V0 were dropouts and therefore did not complete the V2 assessment. Our n-sizes between groups at V2 were: SSE group, $n=2$ and control group, $n=8$ and therefore we did not have enough power to detect between group differences (see Table 4).

Adverse Events

There was 1 adverse event related to the study; a participant developed headaches from looking down at the SSE mat, which was aggravated from a previously diagnosed issue. The participant stopped attending SSE sessions at week six.

Discussion

The primary aim of this study was to determine the feasibility of the SSE program in older adults with T2DM and sCC. We had difficulty with recruitment and retention of participants in this study. We were only able to recruit 25 participants out of a target sample size of 60 (i.e., 42%) despite 10 months of recruitment. Recruitment was primarily through St. Joseph's Family Medical and Dental Centre and newspaper advertisements, with many patients stating that the time commitment for the study was too much. Of those enrolled and randomized to the SSE group, we had an average attendance of 34% for all participants, and only 4 (33%) participants attended 50% or more of sessions, at a mean attendance rate of 70%. Many of the absences were due to doctors' appointments and illness, indicating that the high disease burden of T2DM may be a potential barrier to participation [46]. Based on the participants Charlson index, they had average of more than 2 co-morbidities beyond T2DM and sCC, further supporting that our population had high disease burden which limited their adherence [40]. Overall, we must conclude the current delivery of SSE is not feasible for individuals with T2DM and sCC.

Our secondary aims included: GCF and domain specific cognitive function (memory, reasoning, concentration, planning). We found that the SSE group improved in the planning domain between 12- and 24- weeks, although no other domains or GCF were significant. It is likely the trends in improvement for GCF were driven by improvements in the planning domain. Additionally, the improvement in the planning domain scores may be related to the nature of the SSE program, whereby participants must memorize the patterns and then plan their foot placements correctly across the mat. It is reasonable that improvements in cognition may be initiated later in the intervention, as previous cognitive

training interventions that have demonstrated benefits were long duration (at least 20 hours in duration), as well as cognitive benefits resulting from exercise interventions are at least 6 months in duration [13,47]. We must note that SSE is a social program which encourages peer coaching and thus, it may also impart cognitive benefit. Overall, these results support SSE as a program to improve cognitive function, even with improvements in a small sample such as ours.

The improvements in executive function, as demonstrated by improvements in the planning domain, are supported by the non-significant improvements in antisaccade RT. Antisaccades had longer RT than prosaccades and represent a cognitively challenging task [15–17]. Both the planning domain and antisaccade RTs are measures of executive control, which is known to be reduced with age [1,21] and improved with exercise [15,48]. Unfortunately, the sample size employed in our oculomotor assessment, coupled with the unequal distribution of participants in SSE and control groups precluded a reliable basis for determining efficacy of executive-related oculomotor improvements - a result most likely linked to dropouts and eye-related issues associated with T2DM. We must highlight the results in antisaccade RT are not significant and due to this lack of significance, we are unable to conclude improvements in executive-related oculomotor control at the present time. Additionally, we cannot ignore the fact that the trends we see may in fact be due to natural variation or random chance due to our small sample size.

Although not measured here, to briefly speculate on the mechanism for which SSE improves executive function, as seen through improved planning domain scores, we would expect it to be similar to previous cognitive training literature. Previous literature has demonstrated that cognitive training increases activation in the frontal, parietal and temporal regions of the brain - regions associated with executive control [19]. And this

increased activation remains high at rest, which results in region-specific increased blood flow, metabolism, and synaptic connectivity, which in turn is associated with improved cognitive function [49].

Maintaining executive control in older adults with T2DM and sCC is especially important as diabetes self-management, specifically insulin administration, can become increasingly difficult with impaired cognitive function [5,6]. If maintenance of cognition can be achieved through cognitive training programs, such as SSE, it would be beneficial to the overall health of people with T2DM to reduce co-morbidity.

Limitations

A major limitation to this study was the small sample size and poor retention of participants – as a result, this study was underpowered and therefore, not feasible. However, we were still able to demonstrate trends in improvement of cognitive function, specifically executive function in our population. Older adults with T2DM and sCC have a high disease burden and therefore future studies should allow for more flexibility of SSE sessions. Additionally, SSE is a group-based program, where social interaction is encouraged and thus there is a possibility that the improvements in cognition we have shown may in part be due to the social aspect of SSE.

We originally began recruitment for this study from the Primary Care Diabetes Support Program exclusively. This program is a specialized diabetes referral program that serves patients referred by other healthcare providers or through patients' self-referral, but in general, often serves a population that may be more medically complex, and living with a longer duration of diabetes than patients not referred to such a clinic. This likely impacted our recruitment and participant dropout rates due to high disease burden.

Future Directions

In the future, it would be important to improve the feasibility of this program. A strategy to improve attendance could be to create a more flexible intervention schedule. For example, increasing the number of sessions available to participants per week as well as different times throughout the day would allow participants to have flexibility in when they choose to attend. This would account for absences due to doctor's appointments and illness that may arise. Additionally, having a more convenient location or multiple locations of the program may help to increase adherence. Other ways to increase flexibility of the program would be to incorporate SSE into pre-existing senior's community centres, which may also help with recruitment. Further, collaborations with other researchers and community members that have diabetes-specific programming, such as educational programs, may improve recruitment. Other potential ways to improve accessibility of the program would be to add onto scheduled appointments or mobile health such as the SSE HealthBrain smartphone application [50]. Lastly, in future study design, implementing *a priori* criteria for feasibility would improve study quality, for example 70% of recruitment fulfilled and 70% of attendance rate as 'acceptable' feasibility [42].

Conclusions

SSE is not feasible in adults with T2DM and sCC with an average attendance of only 34%. A 24-week SSE program shows promise in improving cognitive function, specifically executive control, in older adults with T2DM and sCC, a population with high chronic disease burden and risk for cognitive decline. Future studies should focus on minimizing barriers to participation through improved ease of accessibility in alternative implementation methods.

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Table 1: Cambridge Brain Sciences cognitive computer battery games

Game Name and Domain	Brief description of game
Monkey Ladder: Memory	Sets of numbered squares are displayed all at the same time at random locations within an invisible 5*5 grid. After a variable interval, the numbers are removed leaving just the blank squares visible and a tone cues the participant to respond by clicking on the squares in ascending numerical sequence. After 3 errors the test ends.
Verbal Reasoning: Reasoning	Problems of the form “The square is not encapsulated by the circle” are displayed on the screen and the participant must indicate whether the statement correctly describes a pair of objects displayed in the centre of the screen. To achieve maximum points, the participant must solve as many problems as possible within 90 seconds.
Double Trouble: Reasoning	A coloured word is displayed at the top of the screen, for example the word RED drawn in blue ink. The participants must indicate which of two coloured words at the bottom of the screen describes the colour that the word at the top of the screen is drawn in. The colour word mappings may be congruent, incongruent, or doubly incongruent, depending on whether the colour that a given word describes matches the colour that it is drawn in, solving as many problems as possible within 90 seconds.
Odd One Out: Reasoning	A 3* 3 grid of cells is displayed on the screen. Each cell contains a variable number of copies of a coloured shape. The features that make up the objects in each cell (color, shape, number of copies) are related to each other according to a set of rules. The participant must deduce the rules that relate the object features and select the one cell whose contents do not correspond to those rules, solving as many problems as possible in 3 minutes.
Spatial Span: Memory	16 squares are displayed in a 4 * 4 grid. A sub-set of the squares flash in a random sequence at a rate of 1 flash every 900 ms. Subsequently, the mouse cursor is displayed and a tone cues the participant to repeat the sequence by clicking on the squares in the same order in which they flashed.
Rotations Task: Concentration	In this variant, two grids of coloured squares are displayed to either side of the screen with one of the grids rotated by a multiple of 90 degrees. When rotated, the grids are either identical or differ by the position of just one square. To gain maximum points, the participant must indicate whether the grids are identical, solving as many problems as possible within 90 seconds.

Feature Match: Concentration	Two grids are displayed on the screen, each containing a set of abstract shapes. In half of the trials the grids differ by just one shape. To gain maximum points, the participant must indicate whether or not the grid's contents are identical, solving as many problems as possible within 90 seconds.
Digit Span: Memory	Participants view a sequence of digits that appear on the screen one after another. Subsequently, they repeat the sequence of numbers by entering them on the keyboard. After 3 errors the test ends.
Hampshire tree task: Planning	Numbered beads are positioned on a tree shaped frame. The participant repositions the beads so that they are configured in ascending numerical order running from left to right and top to bottom of the tree, solving as many problems as possible in 3 minutes.
Paired Associates: Memory	Boxes are displayed at random locations on an invisible 5*5 grid. The boxes open one after another to reveal an enclosed object. Subsequently, the objects are displayed in random order in the centre of the grid and the participant must click on the boxes that contained them.
Polygon Task: Concentration	A pair of overlapping polygons is displayed on one side of the screen. To gain maximum points, the participant must indicate whether a polygon displayed on the other side of the screen is identical to one of the interlocking polygons, solving as many problems as possible within 90 seconds.
Spatial Search: Planning	Sets of boxes are displayed on the screen in random locations within an invisible 5*5 grid. The participant must find a hidden "token" by clicking on the boxes one at a time to reveal their contents. When the token is found, it is hidden within another box. After 3 errors the test ends.

Table 2: Participant characteristics by randomization group.

	Control Group n=13	SSE Group n=12
Age, years, mean(SD)	71.2 (6.9)	65.9 (5.2)
Female sex, No. (%)	4 (31)	4 (33)
Caucasian No. (%)	13 (100)	5 (40)
Health Rating \geqGood^a, No. (%)	8 (61.5)	9 (75)
Height, m, mean (SD)	1.7 (0.1)	1.7 (0.1)
Weight, kg, mean (SD)	88.4 (11.4)	94.5 (19.6)
BMI, mean (SD)	31.9 (4.6)	33.3 (4.8)
Waist circumference, cm, mean (SD)	110.9 (8.9)	113.6 (15.3)
Systolic blood pressure, mean (SD)	135.8 (20.5)	131.7 (12.3)
Diastolic blood pressure, mean (SD)	77.2 (10.4)	79.9 (6.2)
Diabetes duration, years, median (IQR)	10.0 (15)	10.0 (6)
A1C (%), mean (SD)	6.9 (0.5)	7.2 (1.0)
Charlson Index^b, mean (SD)	2.2 (1.1)	2.2 (0.7)
Medications, No., mean (SD)	9.1 (5.4)	7.4 (4.3)
Memory worse^c, No. (%)	10 (76.9)	9 (75.0)
Duration of sCC^d, years, median (IQR)	3.0 (8.0)	1.5 (3.8)
Concern, re: memory/thinking^e, No. (%)	7 (53.8)	6 (50.0)
Total Education, years, mean (SD)	13.4 (2.1)	13.7 (2.5)
MMSE^f, /30, mean (SD)	28.5 (1.2)	28.9 (0.9)
MoCA^g, /30, mean (SD)	25.9 (2.7)	25.4 (2.7)
Clock Drawing Test, /13, mean (SD)	12.4 (0.7)	12.0 (1.0)

^aParticipants were asked to rate their health: excellent, very good, good, fair, poor.

^bCharlson Co-morbidity Index [48]

^cParticipants were asked what do you feel has gotten worse: memory, thinking skills or both.

^dsCC = subjective cognitive complaint

^eParticipants were asked if they were concerned about their worsening memory and/or thinking skills: yes or no.

^fMMSE= Mini Mental State Examination

^gMoCA= Montreal Cognitive Assessment

Table 3: Cambridge Brain Sciences online computer game scores at baseline, separated by randomization group and population norms; mean and standard deviations presented.

CBS Game - Domain	Control Group N=13	SSE Group N=12	Participants N=25	Population Norms^a
Memory				
Monkey Ladder	6.2 (0.6)	7.0 (1.5)	6.5 (1.3)	6.7 (1.4) n=4361
Spatial Span	4.6 (1.0)	4.5 (1.1)	4.6 (1.0)	5.1 (1.0) n=4366
Digit Span	6.1 (1.3)	6.5 (1.0)	6.3 (1.2)	6.9 (1.6) n=4379
Paired Associates	3.9 (1.0)	4.0 (1.7)	4.0 (1.4)	4.5 (1.1) n=4365
Reasoning				
Verbal Reasoning	8.1 (5.4)	10.5 (5.3)	9.2 (5.3)	14.8 (4.7) n=4378
Double Trouble	6.7 (11.2)	7.7 (14.7)	1.2 (12.7)	18.9 (14.0) n=4376
Odd One Out	7.2 (3.1)	8.8 (4.5)	12.6 (1.9)	9.6 (4.1) n=4369
Concentration				
Rotations	52.8 (27.0)	49.5 (33.0)	51.2 (29.4)	67.3 (31.0) n=4345
Feature Match	78.0 (17.8)	77.5 (35.6)	77.8 (27.2)	104.3 (28.7) n=4397
Interlocking Polygons	20.8 (15.9)	19.3 (19.1)	20.1 (17.1)	35.2 (21.6) n=4399
Planning				
Tree Task	14.9 (6.1)	14.2 (9.1)	14.5 (7.5)	15.3 (7.9) n=4124
Token Search	6.7 (1.8)	5.8 (2.0)	6.3 (1.9)	6.6 (2.1) n=4323

^aData obtained from Cambridge Brain Sciences normative data, age range 55-90 years.

Table 4: Participant baseline characteristics for eye-tracking assessments, separated by randomization group.

	Control (n=8)	SSE (n=2)
Age, mean(SD)	73.4 (5.3)	63.5 (7.8)
Female sex, No. (%)	1 (13)	1 (50)
Height, m, mean(SD)	1.69 (0.05)	1.65 (0.05)
Weight, kg, mean(SD)	86.1 (11.2)	101.6 (6.4)
Blood pressure (systolic/diastolic), mean(SD)	140.4/74.5 (23.3/11.7)	144.0/84.5 (5.7/14.8)
Diabetes duration, years, mean (SD)	14.1 (9.4)	7.0 (7.1)
Years of education, mean (SD)	13.25 (2.6)	16.0 (2.8)
MMSE /30, mean (SD)	28.6 (1.2)	29.0 (1.4)
MoCA /30, mean (SD)	25.5 (2.6)	25.5 (3.5)
HbA1c, %, mean (SD)	6.9 (0.5)	7.1 (0.1)

Figure 1: Study flow of participants.

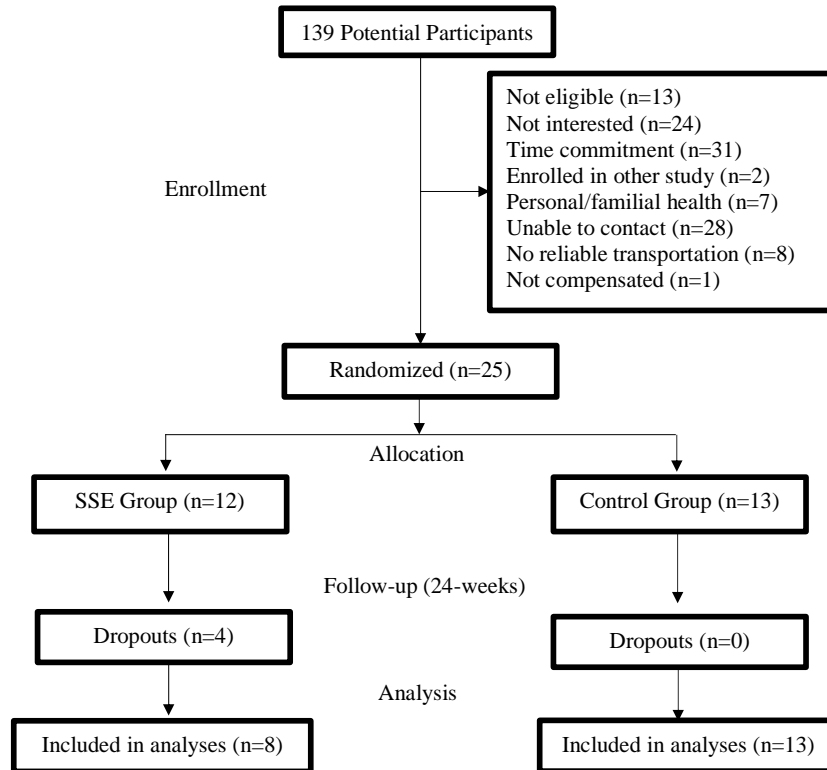
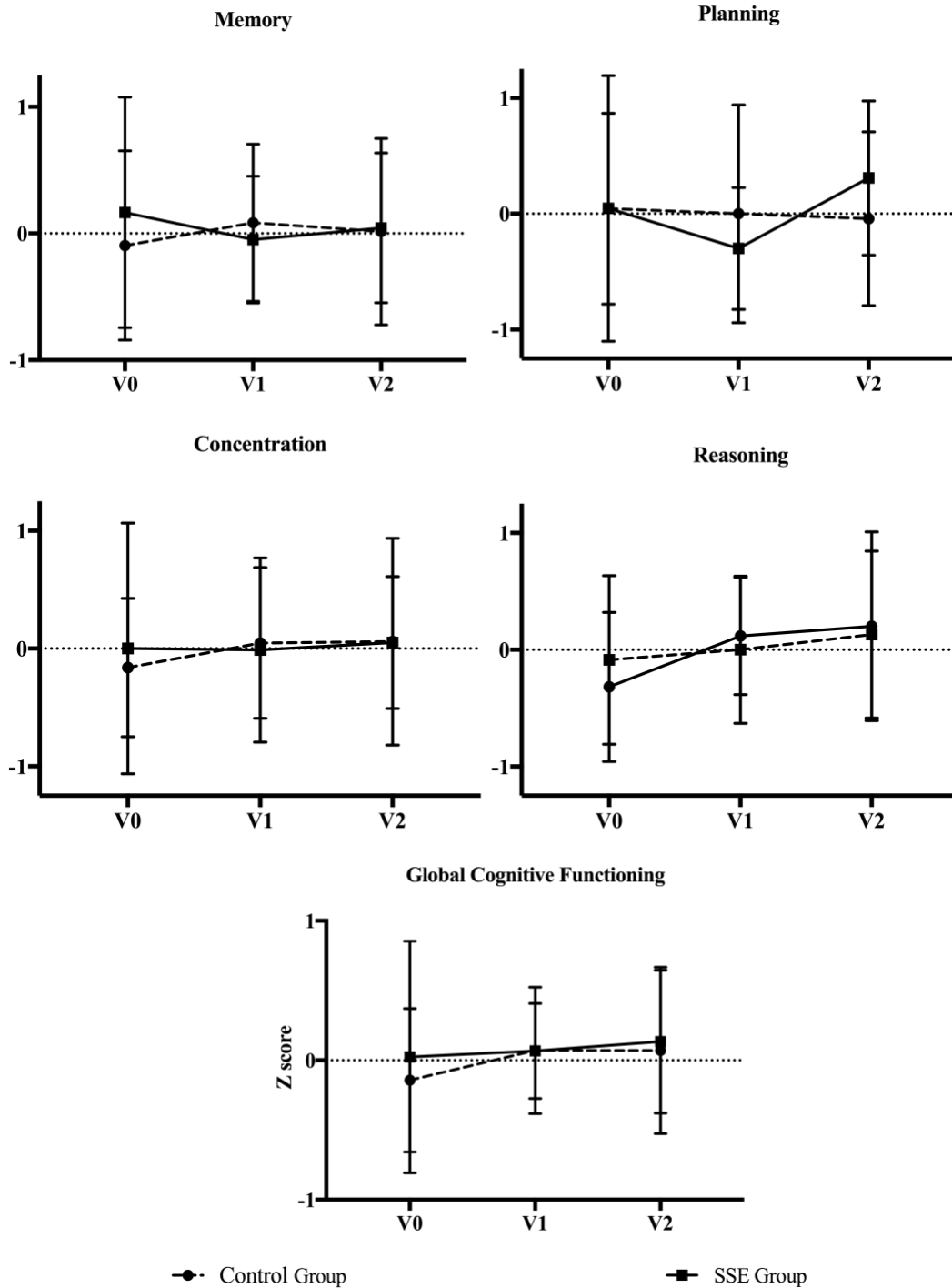
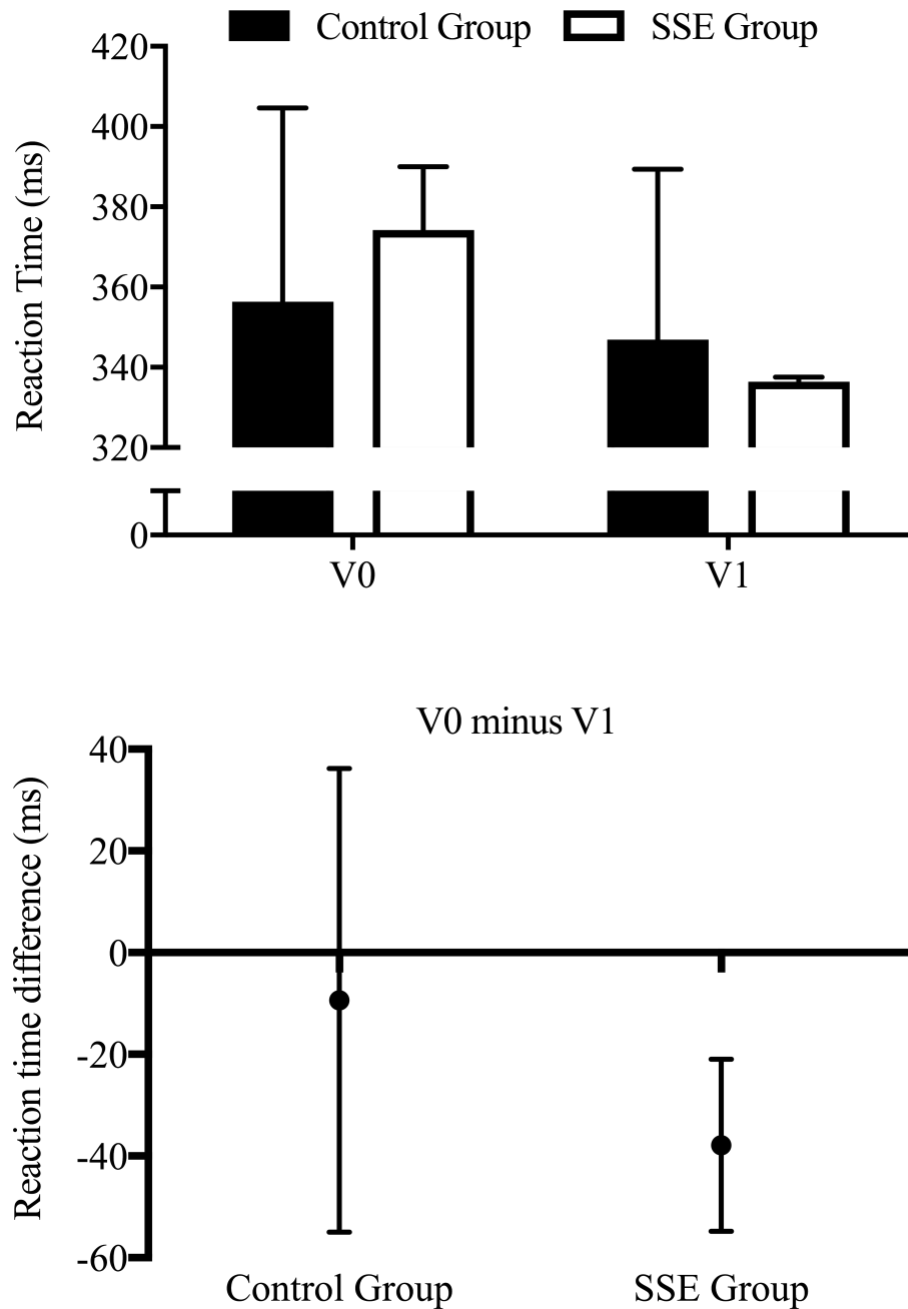


Figure 2: Cognitive function outcomes for older adults with type 2 diabetes mellitus and self-reported cognitive complaints.



Global and domain-specific cognitive functioning standardized z-scores, separated by randomization groups, Control group (circles) and Square-stepping exercise (SSE) group (squares) at baseline (V0), 12-weeks (V1) and 24-weeks (V2). Group means with standard deviation error bars represented.

Figure 3: Antisaccade reaction time sub-study



The top panel depicts mean antisaccade reaction time (ms) as a function of Control group (black bars) and Square stepping exercise (SSE) groups (white bars) at pre- (V0) and post-intervention (V1) assessments. Error bars represent standard deviation. The bottom panel represents antisaccade reaction time difference scores contrasting performance at V1 and V0 as a function of each group (i.e., Control and SSE). Error bars represent standard deviation. Control group, $n=8$; SSE group, $n=2$.

Results from a feasibility study of a Square-stepping exercise program in continuum care and long-term care homes in Ontario Canada: The Mind Fun Study

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Key Words

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Abstract

We conducted a pilot cluster randomized trial of a cognitive training intervention, called Square-stepping exercise (SSE), in continuum care (CC) and long-term care (LTC) homes [2 SSE sites (2x/wk for 12-weeks) and 2 control sites]. Primary aim: to determine feasibility of SSE via recruitment, attendance, and program fidelity. At baseline (V0) and post-intervention (V1) we assessed: cognition (Cambridge Brain Sciences), gait (GaitRITE), balance (balance test), and mood [participants with dementia (questionnaire)]. Participants (n=71) were 81.7 (SD 11.4) years old, and 75% female. Mean attendance rate across all participants was 40%. SSE improved mood and behaviour symptom scores (total, frequency, and severity), all $F > 1$, $p < 0.05$. No between group differences in cognition, balance or dual-task gait were seen. SSE was not feasible in CC and LTC due to low attendance; however, it benefited social engagement and improved mood and behaviours in participants with dementia. Further research is needed to determine the efficacy of SSE on cognition and mobility in this population with diverse cognitive and mobility impairments.

Background

The number of adults older than 85 years of age is growing [1], as is the number of older adults living in collective dwellings (i.e., seniors residences or health care facilities) [2]. Adults living in long-term care (LTC), continuum care (CC) and retirement living (RL) homes have higher prevalence of cognitive impairment and dementia than their community-dwelling counterparts, which for many, is the reason they are in assisted living home [3,4].¹ Assisted living is related to social isolation and loneliness, which are associated with reduced cognitive function [5,6], as well as physical inactivity and depression [7]. Furthermore, reduced cognition is associated with lower physical functioning and mobility [8,9]. Overall, adults living in CC and LTC homes have a high level of chronic disease burden that is related to social isolation, and mobility and cognitive impairments.

Aerobic, resistance, and multiple modality exercise interventions, as well as cognitive, and dual-task training programs, have shown benefits for improving cognition [10–19] and reducing depression [20,21] in older adults with and without cognitive impairments. However, these studies are primarily conducted in healthy community-dwelling older adults.

Little interventional research has been conducted in CC and LTC homes assessing the efficacy of programs on cognitive function. A six-month, twice weekly, multiple modality exercise program in older adults with mild cognitive impairment living in assisted or independent living showed decline in cognitive function; however, there was no control group [22]. And an eight week study of exergaming in adults in assisted living

¹ Continuum care refers to a range of assisted living situations, from retirement (i.e., independent) living to LTC (i.e., nursing care).

without cognitive impairments saw no changes in cognition [23]. The efficacy of interventions on cognition in LTC and CC homes remains equivocal, which is likely largely a function of: the variability and limited interventions that have been investigated, cognitive and mobility impairments of the participants, and the variability of chronic disease burden in assisted living homes.

In this study, we proposed a cognitive training program with a physical component, known as Square-stepping exercise (SSE), which was developed as a fall prevention program for community-dwelling older adults in Japan [24]. It is a visuospatial working memory task with a cued stepping response that challenges balance skills and fosters positive social interactions through feedback from peers. An instructor demonstrates a stepping pattern across a gridded mat and participants are required to memorize and repeat the patterns. Square-stepping exercise has been shown to improve balance, lower extremity functional fitness, and strength as well as global cognitive functioning, memory, and executive functioning in community-dwelling older adults in randomized and non-randomized studies [24–28]. SSE is a group-based program that is simple to implement, requires minimal equipment, and staff requirements and thus, is an appropriate intervention to assess in LTC and CC homes.

Feasibility of intervention studies is poorly defined in the literature; however, Bowen et al. define feasibility for intervention efficacy is “meeting intended behavioural outcomes under ideal circumstances” [29]. Therefore, many studies measure feasibility as recruitment and attendance of participants throughout the intervention [30]. There have been few feasibility studies in assisted living homes and the results have been as variable as the interventions. A five-minute sit-to-stand activity administered by nurses, twice per day for nine-weeks, had an adherence rate of 13% (n=25), whereas an eight-week group-

based exergame program of seven participants had an attendance rate of 100% [23,31]. Feasibility is known to be influenced by: the type of activity, group vs. individual sessions, and the amount of staff burden [23,31–34]. Known positive predictors of program adherence in assisted living homes include: group-based activity, social support, staff support, and convenience of the program [34,35]. Thus, when developing an intervention in assisted living homes, many factors should be considered in program design for both residents and staff.

Our primary aim was to determine if the SSE program was feasible in LTC and CC homes, through assessment of recruitment, attendance rates, and program fidelity. Our secondary aims were to assess whether our outcome measures were feasible in populations with diverse cognitive and mobility impairments, as measured by the number of participants who could complete the assessments. Additionally, we aimed to determine if a 12-week SSE program improved: global cognitive functioning (GCF), memory, concentration, planning, reasoning, single or dual-task gait characteristics, and balance in residents in CC or LTC homes with diverse cognitive and mobility impairments compared to a control group. Lastly, we aimed to determine if a 12-week SSE program improves mood and behaviours symptoms in residents living with dementia compared to a control group (with dementia).

Methods

Study Design

We collaborated with the Schlegel Villages and the Schlegel-University of Waterloo Research Institute for Aging (RIA). The Schlegel Villages are a group of 16 LTC and CC homes in Ontario Canada. Of the 16 homes, four sites volunteered to be involved in the study. The Schlegel staff kinesiologists (i.e., Registered Kinesiologists

and/or Exercise Therapists) develop monthly programs for the residents at each of the sites, both one-on-one and group programs, specific to the level of care (e.g., retirement living or long-term care). The kinesiologists implemented the SSE program as a part of their regular monthly programming with the residents. The kinesiologists were trained to deliver SSE during a one hour SSE training session conducted by study personnel and they were given a written protocol of the program.

We conducted a pilot cluster randomized controlled trial (RCT), whereby four sites (two LTC and two CC homes) were stratified by level of care and randomized to the SSE program or wait-list control.² Randomization sequence was computer generated with concealed one to one allocation. Using a wait-list control group allowed assessment of SSE feasibility, after changes from the intervention sites were implemented as well as provide a comparator group for outcome measurements. To keep anonymity of the sites, they will be referred to as: site 1 (SSE group; LTC site), site 2 (SSE group; CC site), site 3 (control group; LTC site) and site 4 (control group; CC site). Therefore, the SSE and control group each contained one LTC and one CC home.

All residents from the four sites were invited to participate in the program, regardless of cognitive or mobility impairments (i.e., no exclusion criteria). The purpose was to maintain a pragmatic approach to the study design.

To recruit the residents, information sessions were held and an article was included in the monthly newsletter at each of the four sites. Additionally, the kinesiologists at each site approached residents or their family members for their interest.

² Chapter 4a includes participants from all levels of care in continuum care homes, while Chapter 4b only includes residents in retirement living within the continuum care home.

Participants (decision makers) provided written informed consent prior to baseline assessments. The study was approved by the University of Western Ontario Health Sciences Research Ethics Board (No. 107891), and the RIA research ethics. It was conducted in accordance to the Helsinki Declaration.

Participant Characteristics

To describe our population, the following participant characteristics were obtained at baseline: sex, age, marital status, race, years of education, blood pressure, presence of depression, height, weight, use of a walking aid, and transfer status. We also collected a list of medications and diagnoses. The diagnoses were added to create a Charlson Comorbidity index score as per the weighted criteria [36]. When available, these data were obtained from residents' charts at each of the homes, which was extracted by Schlegel Village or RIA staff to maintain confidentiality or by self-report when not available.

In participants without previously diagnosed cognitive impairments, we conducted a Montreal Cognitive Assessment (MoCA). Evidence suggests that adults who self-report cognitive complaints are at higher risk of cognitive decline and expressing worry about declining cognition further advances this progression of cognitive decline [37–39]. Therefore, we asked the following questions regarding the participant's opinion on their cognition: do you feel your memory and/or thinking skills have gotten worse recently (yes or no)? For the participants who responded 'yes', two additional questions were asked: 1) what would you say has gotten worse (memory, thinking skills or both)? and 2) are you concerned/worried about your worsening memory and/or thinking skills (yes or no) [37]?

Intervention

Residents participated in a progressive 12-week SSE intervention. An instructor demonstrated stepping or walking patterns across the gridded SSE mat (250cm x 100cm, partitioned into four columns with 10 rows). The residents were required to try and remember stepping patterns and then repeat the patterns on their own. There are more than 200 validated patterns that range from beginner to advanced with two to sixteen steps; to increase difficulty, steps are forward, backward, horizontal, and diagonal in direction.

In order to be inclusive of residents with severe mobility impairments who were interested in the program, we developed a 'hand SSE mat'. It was a miniature version of the large SSE mat (25cm x 10cm), which was fastened to a legal length clipboard. The residents were required to remember the pattern and repeat the pattern on the miniature mat with their fingers instead of walking across the large mat. This helped to increase engagement in the program and to provide cognitive and social stimulus to those with physical impairments.

The program ran for 12 weeks (2 days/week; 60 minute sessions) at each of the sites. Each session consisted of five to ten minutes of warm-up exercises and stretching, 45 minutes of SSE and five to ten minutes of cool down and stretching. There was a focus on stretching of the neck due to previous experiences with SSE, as residents are required to look down to ensure proper foot placement. Attendance was taken at each session and program progression was monitored via attendance logs. Because SSE was implemented as a part of the kinesiologists scheduled programming, residents who were not enrolled in the study were still able to participate in the SSE program.

Wait-list Control

The two sites that were randomized to the wait-list control group completed the study assessments (i.e., completed pre- and post-intervention assessments) without any intervention. After the post-intervention assessments, the control sites were invited to implement the SSE program so that all residents had an opportunity to participate. Further, a wait-list design was chosen to have a comparator group and logistical constraints prevented having an active control group.

Feasibility of the intervention

The primary outcome was to determine the feasibility of SSE in LTC and CC homes. To assess feasibility, we examined: 1) recruitment through the number of participants enrolled, 2) attendance rates through the number of residents who attended each SSE session, and 3) program fidelity to determine if the program was delivered as intended through anecdotal feedback from kinesiologists. No formal interviews were conducted; however, kinesiologists were asked about SSE implementation during the intervention period, either by email, phone or in person, specifically “how is the Square-stepping going? Any concerns or questions?” and post-intervention was more open discussion based on things that went well, did not go well, and recommendations for future implementation and potential modifications.

We also kept track of the number of residents who participated in SSE but were not enrolled in the study, to determine if there was further interest in participating in SSE without enrolment in the research study. Feasibility was assessed at all four sites, regardless of group allocation. The kinesiologists who implemented the program at each of the sites were told at the beginning of the study that they should alter the SSE intervention as they felt appropriate for their residents.

Outcomes and Assessments

The assessments were completed at pre-intervention (V0; June 2016) and post-intervention (V1; September-October 2016), during one-and-a-half-hour time blocks with the research team at each of the sites.

Mood and Behaviour Questionnaire

The kinesiologists completed the Neuropsychiatric Inventory Questionnaire (NPIQ) for participants living with dementia only (identified from demographics, i.e., previous diagnoses), in both SSE and control groups. The NPIQ is a 12-item questionnaire that assesses mood and behaviours and has shown to be valid and reliable [40]. The questionnaire is scored based on: 1) presence of symptoms (0, 1), which are totalled for a score out of 12; 2) frequency of symptoms (1-3); and 3) severity of symptoms (1-4) for each applicable questionnaire item.

Cognition

Our cognitive outcomes were: global cognitive functioning (GCF) and the four cognitive domains (memory, concentration, planning, and reasoning). These were assessed using the computer-based Cambridge Brain Sciences (CBS) cognitive battery [41]. These games are based on well-established neuropsychology paradigms and are well supported by literature [42–53]. A subset of eight games were used, instead of the full battery of 12 to minimize participant fatigue (See Table 1). The CBS games are an objective measurement of cognition and minimize assessor bias; additionally, they do not require a clinician to administer them like traditional paper-based neuropsychiatric assessments. Furthermore, the CBS games are dynamic and change with the participant's responses and cognitive ability, thus there is not a learning effect associated with the CBS games.

The CBS games were completed based on individual's abilities, therefore participants with diagnosed dementia did not complete the games. Those with some cognitive impairments completed some of the games, while the remainder completed the battery of eight games.

When possible, the CBS games were completed on touch screen computers at each of the four sites, otherwise laptops with an external mouse were used. The participants completed a familiarization session of the games prior to completing the assessment at V0 and V1. The residents were assisted by study personnel during the familiarization session to ensure they understood how to use the computer and navigate the games, after which the participants completed the games on their own.

Gait

Our gait outcomes included both single (usual) and dual-task gait, which was recorded on an electronic walkway, GAITRite ® System (Peekskill, NY, USA). In total, there were six gait outcomes. The outcomes were: gait velocity, step length, and stride time variability, under both single and dual-task conditions. If the participants needed to, they could use their walking aid (e.g., walker, cane, etc), which leave digital imprints and were removed in post-processing of data. All participants who were mobile, completed single task gait, which was walking across the mat twice at a usual pace (i.e. normal walking).

Participants completed the dual-task conditions dependent on their cognitive and mobility abilities and therefore gait assessments were individualized. Participants were asked to walk across the mat under a dual task condition. Dual-task conditions included: walking across the mat while counting backwards by ones (starting from 60 at V0 or 80 at V1), semantic fluency walking (naming animals at V0 or vegetables at V1) and serial

sevens walking (counting backwards by seven, starting from 70 at V0 or 90 at V1). Dual task gait conditions were averaged to create a composite dual-task score.

Balance

Participants who were ambulatory completed, to the best of their ability, the balance portion of the Short Performance Physical Battery Test (SPPB)[54]; the balance test is comprised of three parts. Test A was the side-by-side stand, where participants were asked to stand with their feet together for ten seconds without holding onto anything (scored 0 or 1); if they could not complete this, the test would end. Test B was a semi-tandem stand, where participants were asked to stand for ten seconds with their feet together but one foot was offset half a foot length (scored 0 or 1); if they could not complete this, the test would end. Test C was the tandem stand, where participants were asked to stand for ten seconds with one foot directly in front of the other (scored 2, if held for ten seconds, scored 1 if held 3-9.99 seconds, scored 0 if held for < 3 seconds). Therefore, total balance scores ranged from zero to four.

Feasibility of the outcome measurements

Feasibility of the outcome assessments was determined to assess whether the outcomes chosen were appropriate for our study population. This was done through assessing the number of participants who were successfully able to complete the measurements pre- and post-intervention. The purpose was to determine the acceptability of the outcome measurements for a larger, pragmatic trial. We employed several cognitive and mobility assessments to allow for diverse cognitive and mobility impairments to be assessed (as described above).

Power and sample size

The primary outcome of this study was feasibility, however we calculated a sample size based on the secondary study outcome, GCF, measured using CBS. Based on previous literature that used CBS in older adults for an 8-week brain training program, they found 2 medium (0.37, 0.80) and 1 large (1.09) effect sizes for 3 specific tests within the CBS games that we used [55]. If we used an effect size of 0.5 (medium), we required a sample of $n=125$ [56]. To account for statistical efficiency in randomization by clusters, the sample size has been inflated to 1.29 (based on intraclass correlation coefficient of 0.01) resulting in a total of 161 participants, assuming an average cluster size of 30, which requires 5 sites [57,58]. The aim of this study was not necessarily to find significance in GCF, but rather to obtain an understanding of the feasibility of the program in CC and LTC homes. We recruited all willing participants interested in the program at each of the four Schlegel Villages which volunteered to be a part of the study.

Statistical Analysis

SPSS version 24 was used to analyze data and we used Analysis of Covariance (ANCOVA), controlling for baseline. For all continuous variables of interest, distributions were examined to assess normality and presence of outliers. For categorical variables, frequency tables were examined to ensure there were no out-of-range values.

From the CBS, there were two planning tasks, two memory tasks, two reasoning tasks, and two concentration tasks. We created composite standardized z-scores for each domain as follows: 1) calculate means and standard deviations from each task, 2) for each task, subtract the mean and divide by the standard deviation; 3) within each domain, the tasks were averaged to create a domain specific z-score. Then to create a GCF, the four domain-specific z-scores were averaged. We did not generate a GCF if any domain-

specific score was missing. Since this was a pilot cluster RCT and our primary outcome was feasibility, we did not account for clustering in our model because it was not statistically possible.

Dual-task gait scores were obtained from the three tasks (counting backwards, semantic fluency, and serial sevens) and averaged to generate one score. We did not generate a dual-task score if any task score was missing.

We examined outcomes as descriptive statistics for each group and site, which included: GCF, domain specific function (four), single and dual-task gait, mood and behaviour, and balance, in addition to attendance and recruitment. The observed values at V0 and V1 were summarized descriptively for each site and group. We used an ANCOVA to examine differences between groups at V1, controlling for V0. For ordinal measures, ordinal logistic regression and chi-square tests were utilized.

A number of sensitivity analyses were considered, including adjusting for age, sex, and years of education as covariates. Exploratory analyses were conducted, whereby we analyzed the data looking at level of care as a factor as well as within group and within sex. Statistical significance was set at $p < 0.05$; however, since this was a feasibility study we also interpreted effect size, reported as partial eta squared (η_p^2 , where 0.1 is small, 0.25 is medium, and 0.4 is large)[56].

Results

Recruitment for the study began on 16 May 2016 and was completed on 30 June 2016. Outcome data collection (V1) was completed on 4 October 2016 and the wait-list control group completed the intervention in February 2017. We recruited 71 participants out of a total of 1128 residents across the four sites, which is 6.3% recruitment (i.e., site 1, $n=15$; site 2, $n=15$; site 3, $n=17$; and site 4, $n=24$; see Table 2). Participants were [mean

(SD; range)]: 81.7 (11.4; 38-100) years old with a Charlson Co-morbidity Index of 2.9 (1.6) (See Table 3a and 3b) and an additional 19 residents tried the SSE program even though they were not enrolled in the study.

Feasibility of the intervention

The average attendance across all enrolled participants at all sites was 40.5 % (n=71). The average attendance rate excluding participants who attended zero sessions was 52.3% (n=55). The average attendance rate of participants with >50% attendance was 77.7% (n=30) (See Table 4).

For the SSE group only, the average attendance of all participants enrolled was 33.1% (n=30). The average attendance rate excluding participants who attended zero sessions was 43.2% (n=23). The average attendance rate of participants with >50% attendance, was 71.0% (n=10).

In wait-list control group, the average attendance of all participants enrolled was 45.9% (n=41). The average attendance rate excluding participants who attended zero sessions was 58.8% (n=31). The average attendance rate of participants with >50% attendance, was 81.3% (n=20).

Program Fidelity: Feedback from Kinesiologists

Sites 1 and 2 completed the 12-week SSE program first (July – September 2016), which was the first-time SSE was implemented in LTC or CC environments, and thus feedback from these sites prompted changes for SSE implementation in the wait-list sites, sites 3 and 4 (November 2016 – January 2017).

Site 1: Long-term care home in SSE group

Site 1 was a LTC home with one kinesiologist employed in addition to a kinesiology student assisting throughout the duration of the SSE program. The

kinesiologist decreased the duration of each session from 60 minutes to 45 minutes to maintain engagement of participants, and altered the program progression; the kinesiologist reported:

“We will often bounce around throughout the beginner series within a class if we are seeing loss of interest (not complete them in sequential order) and we know the [patterns that the participants] always do well on and so we will go back and complete one of those [patterns] if the group is struggling” (source of information: email).

The kinesiologist at site 1 found SSE increased physical activity and social engagement, and conveyed:

“... we are seeing some great improvement in a few residents that are participating with us, both socially and physically... some residents that will simply join for some extra walking as they were not picking up the patterns at all. The residents that could follow did amazingly well and they were great at coaching the others” (source of information: email).

Site 2: Continuum care in SSE group

Site 2 had two kinesiologists working there, one assigned to RL and one assigned to LTC. Site 2 kinesiologists found that repeating each pattern four times, as per the SSE protocol, was too much because of the range of cognitive abilities, and therefore reduced the number of repetitions to two. Participants with higher cognitive function provided peer support by becoming SSE coaches to support the participants with cognitive impairments (source of information: phone call discussion).

The wait-list control sites, 3 and 4, began the program with the changes that sites 1 and 2 implemented, i.e. 45 minutes' duration, and encouraging participants to become peer coaches.

Site 3: Long-term care home in wait-list control group

At site 3, there were two kinesiologists working at this LTC home. At 4-weeks into the program the kinesiologist reported on the positive social aspects of the program: "...They like being in this group and they are very supportive of each other. The [participants with higher cognitive function] are stepping up and helping to coach the [participants] that are finding it challenging... everyone cheers for them" (source of information: email).

Site 3 found that participants continued to be engaged despite declining function and increased use of the hand SSE mat; the kinesiologist relayed:

"...we noticed several [participants] declined, their dementia progressed, one fractured a hip, another became more unsteady on her feet. This resulted in 4-5 [participants] using the finger board. They work well together and are very encouraging to each other, so socially it has been a good experience for the residents" (source of information: email).

Site 4: Continuum care in wait-list control group

Similar to site 2, site 4 had two kinesiologists, where one kinesiologist was assigned to RL and one kinesiologist was assigned to LTC. At this site, the kinesiologists chose to separate the residents into two SSE groups based on their level of care.

In the LTC group, a volunteer assisted the kinesiologist at all of the sessions. The kinesiologist did not follow the patterns in sequential order, but rather chose patterns that the participants could do and enjoyed. The residents adopted peer coaching on their own, which fostered a supportive group dynamic (source of information: in person).

A kinesiologist and volunteer completed the SSE program in the retirement living side of site 4; they reported that the participants enjoyed the social aspect of the program, and they found it to be an encouraging group dynamic and the participants' circle of

friends was widened by meeting new people in the program. Anecdotally, several participants reported they felt that their balance improved and one resident began using walking poles instead of a walker (source of information: in person).

Feasibility of the outcome measurements

There was vast variability in cognitive and mobility impairments and thus, participants completed assessments as they were able, regardless of their diagnoses (see Table 5). This created variability in the number of participants who completed each assessment.

Mood and Behaviour Questionnaire

The participants with dementia in the SSE group improved in the NPIQ total, ($F(23)=7.3$, $p=0.01$, $\eta_p^2=0.25$); frequency, ($F(23)=9.4$, $p=0.01$, $\eta_p^2=0.30$) and severity, ($F(23)=7.0$, $p=0.02$, $\eta_p^2=0.24$), scores at V1 compared to the control group (with dementia), controlling for V0 (See Figure 1). Exploratory chi-square analyses were conducted to identify which of the 12 questions were improved. It was found that the SSE group demonstrated reduced delusions, [$X^2=4.2$, $p=0.04$ (SSE group 0%; Control group 33%)], dysphoria/depression, [$X^2=5.2$, $p=0.03$ (SSE group 20%; Control group 67%)] and disinhibition, [$X^2=3.7$, $p=0.05$ (SSE group 10%; Control group 47%)] compared to the control group at V1.

Cognition

No between group differences were seen at V1 controlling for baseline in GCF, memory, planning, reasoning, or concentration (all $F<1$, $p>0.05$; SSE group, $n=11$, Control group, $n=10$) (See Figure 2).

In exploratory analyses, level of care was added as a factor in our model, that is, a 2 (group) x 2 (level of care) model; however, no differences were found in level of care at V1, when controlling for baseline.

In further exploratory analyses, sex was added as a factor in our model, that is, a 2 (group) x 2 (sex) model, controlling for baseline score, age, and years of education. In the planning domain model an interaction was found ($F=7.7$, $p=0.02$, $\eta_p^2=0.35$), with main effects of group ($F=6.6$, $p=0.02$, $\eta_p^2=0.32$) and sex, ($F=13.4$, $p<0.01$, $\eta_p^2=0.49$), favouring the SSE group and females respectively. In the concentration domain model an interaction was also found ($F=5.6$, $p=0.03$, $\eta_p^2=0.29$); however, no main effects were significant. Descriptively, males had lower mean z-scores for all domains and GCF at all time points. Within sex analyses did not reveal between group differences in GCF (see Figure 3). Regardless of group assignment, females had higher planning domain z-scores at V1 compared to males, controlling for V0 ($F=5.1$, $p=0.04$ and $\eta_p^2=0.22$); however, no other domains were significant.

The mean scores of CBS are reported with population norms for adults 75-90 years of age as reference population (See Table 6). Results remained similar in sensitivity analyses.

Gait

We observed that the control group demonstrated higher single task gait velocity at V1, when controlling for baseline, compared to the SSE group ($F(54)=5.6$, $p=0.02$, $\eta_p^2=0.10$). No other between group gait characteristics were significant at V1, when controlling for V0 ($p>0.05$). The number of participants completing single task gait was:

SSE group, n= 22 (73%); Control group, n=32 (78%), and dual task gait: SSE group, n= 16 (53%); Control group, n=20 (49%).

In exploratory analyses, we conducted a group x level of care model, controlling for baseline for all gait characteristics. In single task gait velocity, a significant interaction ($F(54)=7.0$, $p=0.01$) with a significant main effect of group ($F(54)=6.0$, $p=0.02$) was found. Site 1 had a lower usual gait velocity at V1 compared to the other sites, thereby lowering the SSE group mean usual velocity, resulting in the control group having significantly higher usual gait velocity. There was also an interaction for usual gait step length ($F(54)=4.1$, $p=0.05$), with a main effect of level of care ($F(54)=5.2$, $p=0.03$), favouring retirement living. Once again, site 1 had the lowest mean step length at V1. Lastly, there was a significant interaction in dual task step length ($F(35)=9.5$, $p<0.01$) and a main effect of group ($F(35)=6.3$, $p=0.02$), again favouring the control group. Descriptively, site 1 had the slowest gait velocity, shortest step length and highest stride time variability means in single and dual task gait at V1 (see Figure 4).

Balance

Ordinal logistic regression was performed to assess between group differences in total balance score (0, 1, 2, 3, 4); however, no association was found.

In exploratory analyses, an ordinal logistic regression was performed, whereby level of care was used as the grouping variable, RL versus LTC. It was found that participants living in RL were 3.4 [95% CI, 1.1- 10.0] times more likely to have a higher balance score at 12-weeks (V1), controlling for baseline, than residents living in LTC, a statistically significant finding, Wald $X^2=4.8$, $p=0.03$ (see Figure 5).

In further analyses of RL only participants, a between groups ordinal logistic regression was performed and there was no significant difference between groups.

Adverse Events

There were no adverse events reported.

Discussion

Feasibility of SSE

Across all of the sites, the average attendance was 40%, and there was 30 out of 71 (42.5%) participants who achieved greater than 50% attendance rates, which averaged 78% attendance at sessions. Further, 16 participants (22.5%) attended zero sessions, and another 25 (35%) attended less than 50% of sessions. This cohort included participants with mobility impairments (e.g., wheelchair bound) as well as cognitive impairments (e.g., dementia).

It is not surprising that the participants did not have perfect attendance because many of the residents have co-morbid chronic diseases with cognitive and mobility impairments, which generally worsen with increasing age. This was demonstrated through the Charlson Co-morbidity Index score, which indicated the participants had a chronic disease burden of nearly three, which would be expected for adults living in CC and LTC homes. However, the number of participants attending the SSE sessions was similar to residents who attended other programs at the sites by the kinesiologists, which may indicate the feasibility of SSE is on par with other offered programs. Lastly, the Schlegel Villages and RIA anecdotally acknowledged that participants for this study were easy to recruit for compared to other research studies conducted at their homes because of the interest represented at the information sessions in addition to the number of participants who enrolled and continued to participate throughout the program duration.

It was noted in the attendance records that participants with low attendance rates generally came to a few sessions at the beginning of the program, lost interest and

discontinued participation in the sessions. This allowed the participants with higher attendance rates to foster good relationships and engage socially with one another throughout the 12-weeks, as demonstrated through the feedback from the kinesiologists on social engagement during the program. There is little research that measures social interaction as a part of an intervention; however, it is known that low social contacts and loneliness are related to increased risk of dementia and AD [5,6]. Therefore, maintaining good social networks is important for maintained cognition, which SSE provides. Square-stepping exercise is unique in its social interactions compared to other group programs because it specifically encourages peer coaching, support, and peer problem solving to achieve the correct stepping patterns.

Our 12-week study of SSE in CC and LTC homes demonstrated it was not feasible in older adults with diverse cognitive and mobility impairments due to a recruitment rate of 6.3% and average attendance rate of 40%. However, we did find integrating individuals with a variety of cognitive and mobility impairments to be successful. Recommended modifications by the kinesiologists for diverse populations included: 1) 45 minutes per session, 2) instruction with at least one kinesiologist in RL and two kinesiologists in LTC, 3) peer coaching should be fostered, 4) volunteers should be recruited, and 5) pattern progression should be tailored to individuals participating.

Outcome Assessments

A 12-week SSE program can improve mood and behaviours symptom scores in participants living with dementia, specifically questions relating to delusions, depression, and disinhibition. Mood and behaviours in people living with dementia are associated with quality of life [59] and thus, improving these symptoms may increase quality of life through the SSE program. We cannot identify a specific mechanism for this change as it

is likely multifactorial; nonetheless, this evidence provides support for the benefits and importance of group programs that provide cognitive stimulation and social interaction for people living with dementia in LTC with high chronic disease burden.

We did not see any differences between groups in cognition (GCF, memory, planning, concentration, or reasoning) following the 12-week SSE as measured by the CBS games. This may be due to several factors related to feasibility, which may include the SSE program, the CBS games and/or the population recruited. Additionally, we must not negate the fact that SSE may not impart cognitive benefits and/or the small sample size resulted in high natural variation and therefore, did not show any cognitive benefits. In administering the CBS games, we found limited feasibility in the current population, which resulted from: cognitive fatigue, lack of familiarity with computers and visual fatigue from the computer monitor. The SSE program was only 12-weeks in duration, which may not have been long enough duration to elicit cognitive changes in a population with diverse cognitive function. Previous literature has indicated that a longer intervention, of at least 20 hours, is required in cognitive training programs to elicit cognitive change [16]; however, we felt 12-weeks was an appropriate length for a pilot feasibility study in LTC and CC homes. It is likely a combination of factors that led to our null result.

We found there is limited feasibility using a GAITRite walkway due the variability of cognitive and mobility disability. The control group had significantly higher single task gait than the SSE group at V1. This may be explained by lower mean single gait velocity at V1 at site 1 compared to the other three sites, [site 1: 54.6 cm/s (SD 28.7); site 2: 71.9 cm/s (SD 26.5), site 3: 77.3 cm/s (SD 23.6) and site 4: 78.8 cm/s (SD 23.5)], although site 1 was not significant different from other sites. However, a similar result

was found in a previous research study by our group using SSE. The multiple modality exercise active-control group improved on gait characteristics compared to the multiple modality exercise plus SSE group [60]. We suspect that the SSE program may be focused on taking short, thoughtful steps (i.e., correct) foot placement, that are not natural to a single task gait velocity assessment; thus, we may be training the participants to be more accurate in their steps, rather than improve their gait speed. Although speculative, this may result in participants to be more cognizant and careful in their stepping patterns outside of the program and contribute to reduced falls risk over time. Further studies of the effects of SSE on gait characteristics should be explored.

We found limited feasibility in the balance outcome we chose because there was a ceiling effect observed; 60% of participants in RL had the highest possible score at V0. In previous studies, SSE has improved balance and lower extremity functional fitness in community-dwelling older adults [24,25]. Anecdotally, some participants expressed they felt their balance had improved, which was not demonstrated by the test. We chose the test because it was administered quickly and catered to a wide range of balance abilities. In future, we would recommend a more challenging balance task for participants in RL and one similar for adults in LTC.

Overall, there was large variability in the number of participants who completed each assessment. It is likely related to high disease burden and therefore, we conclude that the feasibility of the assessments is limited in this setting (LTC and CC homes) because they were individualized to each participant's cognitive and mobility abilities. In future implementation, utilizing outcomes already assessed within the homes would be more pragmatic.

Limitations

A limitation in assessing the feasibility of the SSE program in LTC and CC homes was that we did not conduct formal recorded interviews with the kinesiologists and thus, we were unable to conduct qualitative theme-based analyses, in the future this would allow more objective measures of program fidelity. Formal interviews and analyses may have led to a better understanding of the social relationships formed between residents and themes related to program modifications for diverse groups and environments. In analyzing the results of this pilot study, we found that there was much variability in our study population; the mean age was 81.7 years but the range was 38 -100 years, which encompassed a large combination of chronic disease and mobility impairments, as noted in the Charlson Co-morbidity Index scores. This heterogeneous population made it very difficult to choose appropriate outcome assessments and this was noted in the lack of feasibility. Therefore, a second limitation of the study was the variability in our study sample; there was a vast range of participant age and health status, while this is likely a representative sample of individuals in LTC and CC homes, the literature suggests that the level of cognitive decline may predict response to interventions (i.e., those with dementia may not be able to improve their cognitive function [61,62]). However, our goal was to assess the feasibility of the SSE program in a wide sample and therefore we will be able to alter for future implementation trials. A potential third limitation would be bias at site 1; we conducted initial pilot work in August 2014 and a few residents had brief exposure to SSE. This initial pilot work led to the current Mind-fun Study that we are reporting on.

The variability described above would be seen in many LTC and CC homes in Ontario and thus was likely a representative sample. Without an exclusion criteria, we

have little way of controlling for cognitive and/or mobility abilities. If we had a larger sample, more sites or larger capacity to implement the program, we may have been able to control more variables in our analyses and thus see trends in our outcomes. This would help to determine if SSE is efficacious in adults in assisted living.

Future directions

To improve the recruitment and attendance of SSE (i.e., feasibility) in LTC and CC homes in the future, there are several strategies that could be employed. For example, a longer recruitment period and/or rolling recruitment would allow for more exposure of SSE to the residents. This could be individual rolling recruitment and/or rolling site recruitment. To improve exposure and/or understanding of the program, trial SSE sessions could be made available. To improve attendance, it would be beneficial to have multiple SSE sessions during each week at varying levels of difficulty (e.g., Mondays are beginner patterns for LTC participants and new participants; Wednesdays and Fridays are intermediate and advanced patterns for RL participants). This would allow for rolling recruitment of individuals. However, it was expressed to us that separating LTC and RL residents is not the wish of the CC homes, which prefer integration of LTC and RL residents. Lastly, in the future, it would be advantageous to develop *a priori* criteria to determine recruitment and attendance feasibility. For example, determine the average regular attendance of a comparable program already offered within the homes to make a direct comparison, or set a criteria, for example: 70% attendance rate and 10% recruitment of eligible residents [30].

Conclusions

SSE is not feasible in LTC and CC homes due to low average attendance and recruitment rates across all participants and sites. However, the kinesiologists were able

to make modifications and tailor SSE to groups with diverse cognitive and mobility impairments. They have expressed interest in continuing SSE as a part of their regular programming. Additionally, SSE improved mood and behaviours symptom scores in residents living with dementia. The efficacy on cognition, gait, and balance remain equivocal. Efficacy of SSE should be further explored in LTC and CC homes.

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Table 1: Descriptions of Cambridge Brain Sciences cognitive battery games.

Game Name and Domain	Brief description of game
Memory	
Monkey Ladder	Sets of numbered squares are displayed all at the same time at random locations within an invisible 5*5 grid. After a variable interval, the numbers are removed leaving just the blank squares visible and a tone cues the participant to respond by clicking on the squares in ascending numerical sequence. After 3 errors the test ends.
Digit Span	Participants view a sequence of digits that appear on the screen one after another. Subsequently, they repeat the sequence of numbers by entering them on the keyboard. After 3 errors the test ends.
Planning	
Hampshire tree task	Numbered beads are positioned on a tree shaped frame. The participant repositions the beads so that they are configured in ascending numerical order running from left to right and top to bottom of the tree, solving as many problems as possible in 3 minutes.
Spatial Search	Sets of boxes are displayed on the screen in random locations within an invisible 5*5 grid. The participant must find a hidden “token” by clicking on the boxes one at a time to reveal their contents. When the token is found, it is hidden within another box. After 3 errors the test ends.
Reasoning	
Double Trouble	A coloured word is displayed at the top of the screen, for example the word RED drawn in blue ink. The participants must indicate which of two coloured words at the bottom of the screen describes the colour that the word at the top of the screen is drawn in. The colour word mappings may be congruent, incongruent, or doubly incongruent, depending on whether or not the colour that a given word describes matches the colour that it is drawn in, solving as many problems as possible within 90 seconds.
Odd One Out	A 3* 3 grid of cells is displayed on the screen. Each cell contains a variable number of copies of a coloured shape. The features that make up the objects in each cell (color, shape, number of copies) are related to each other according to a set of rules. The participant must deduce the rules that relate the object features and select the one cell whose contents do not correspond to those rules, solving as many problems as possible in 3 minutes.

Concentration	
Polygon Task	A pair of overlapping polygons is displayed on one side of the screen. To gain maximum points, the participant must indicate whether a polygon displayed on the other side of the screen is identical to one of the interlocking polygons, solving as many problems as possible within 90 seconds.
Rotations Task	In this variant, two grids of coloured squares are displayed to either side of the screen with one of the grids rotated by a multiple of 90 degrees. When rotated, the grids are either identical or differ by the position of just one square. To gain maximum points, the participant must indicate whether the grids are identical, solving as many problems as possible within 90 seconds.

Table 2: Study site characteristics by cluster group.

	Site 1	Site 2	Site 3	Site 4
Level of Care	Long term care	Continuum care	Long term care	Continuum care
Total No. of beds	192	369	256	311
Group Allocation	SSE group	SSE group	Wait-list control	Wait-list control
Residents enrolled	15	15	17	24
Residents who completed final assessments	13	15	17	23

Table 3a: Participant characteristics by study site.

	Site 1 (n=15)	Site 2 (n=15)	Site 3 (n=17)	Site 4 (n=24)
Age, years, mean (SD)	76.5 (14.8)	84.5 (10.4)	78.9 (13.9)	85.2 (4.7)
Female sex, No. (%)	10 (66.7)	13 (86.7)	11 (64.7)	19 (79.2)
Married, No. (%)	4 (46.7)	7 (46.7)	4 (23.5)	9 (37.5)
Caucasian, No. (%)	15(100)	14 (93.3)	16 (94.1)	22 (91.7)
Height, cm, mean (SD)	159.0 (11.6)	159.5 (9.8)	160.7 (10.2)	160.9 (8.8)
Weight, kg, mean (SD)	76.9 (27.1)	65.7 (15.2)	80.2 (21.3)	69.2 (13.1)
Education, years, mean (SD)	10.6 (3.6)	13.3 (2.5)	12.4 (4.2)	13.2 (4.0)
Blood pressure mmHg (sBP/dBP), mean (SD)	139.6/74.7 (22.4/12.3)	132.1/73.5 (26.2/10.6)	131.7/72.1 (20.0/10.2)	125.5/67.0 (14.9/10.1)
Presence of depression, No. (%)	9 (60.0)	3 (20.0)	10 (58.8)	9 (37.5)
Use of Walking aid, No. (%)	14 (93.3)	10 (66.7)	9 (52.9)	11 (45.8)
Independent transfer status, No. (%)	13 (86.7)	15 (100)	13 (76.5)	23 (95.8)
Memory/Thinking Worse^{a,e} No. (%)	-	9 (81.2)	-	13 (86.7)
Memory Worse^{b,e} No. (%)	-	2 (13.3)	-	7 (29.2)
Concern about cognition^{c,e}, No. (%)	-	6 (54.5)	-	7 (46.7)
MoCA^{d,e}, /30, mean (SD)	-	23.3 (3.1)	-	21.9 (3.0)
Disease diagnoses				
Charlson Index Score^f, mean (SD)	3.7 (1.8)	2.1 (1.2)	3.2 (1.5)	2.5 (1.6)
Total number of diagnoses, mean (SD)	5.9 (3.0)	5.5 (2.6)	5.6 (1.8)	5.4 (3.1)
Cardiac Condition, No. (%)	10 (66.7)	13 (86.7)	13 (76.5)	17 (70.8)
Dementia, No. (%)	10 (66.7)	1 (6.7)	11 (64.7)	7 (29.2)
Medications				
Total number of medications, mean (SD)	12.6 (5.7)	10.6 (5.8)	11.1 (3.7)	8.0 (3.9)
Cardiac condition, No. (%)	2 (13.3)	7 (46.7)	8 (47.1)	9 (37.5)
Mood, No. (%)	9 (60.0)	5 (33.3)	10 (58.8)	11 (45.8)
Dementia, No. (%)	8 (53.3)	2 (13.3)	11 (64.7)	7 (29.2)

^a Do you feel your memory and/or thinking skills has gotten worse recently? (yes or no)

^b What do you think has gotten worse? Memory, thinking or both

^c Are you worried/concerned about worsening memory and/or thinking skills? (yes or no)

^d MoCA = Montreal Cognitive Assessment

^e Questions and tests were only completed on those without cognitive impairments (i.e. all participants in sites 1 and 3 did not complete cognitive assessments due to pre-diagnosed impairments).

^f Charlson Co-morbidity Index Score [37]

Table 3b: Participant baseline characteristics, by randomization group.

	Control Group (n=41)	SSE Group (n=30)
Age, years, mean (SD)	82.6 (10.0)	80.5 (12.2)
Female sex, No. (%)	30 (73.2)	23 (76.7)
Married, No. (%)	13 (31.7)	11 (36.7)
White Race, No. (%)	38 (92.7)	29 (96.7)
Height, cm, mean (SD)	160.8 (9.3)	159.3 (10.5)
Weight, kg, mean (SD)	73.8 (17.9)	71.3 (22.4)
Education, years, mean (SD)	12.9 (4.0)	12.2 (3.2)
Blood pressure mmHg, mean (SD)	128.0/69.1 (17.2/10.3)	135.9/74.1 (24.3/11.3)
Presence of depression, No. (%)	19 (46.3)	12 (40.0)
Use of Walking aid, No. (%)	20 (48.8)	24 (80.0)
Independent transfer status, No. (%)	36 (87.8)	28 (93.3)
Memory/Thinking Worse^a No. (%)	13 (86.7)	9 (81.2)
Memory Worse^b No. (%)	7 (29.2)	2 (13.3)
Concern about cognition^c, No. (%)	7 (46.7)	6 (54.5)
MoCA^d, /30, mean (SD)	21.9 (3.0)	23.3 (3.1)
Charlson Index Score^e, Mean (SD)	2.9 (1.7)	2.8 (1.6)
Total number of diagnoses, mean (SD)	5.5 (2.6)	5.7 (2.7)
Total number of medications, mean (SD)	9.3 (4.1)	11.6 (5.7)

^a Do you feel your memory and/or thinking skills has gotten worse recently? (yes or no)

^b What do you think has gotten worse? Memory, thinking or both; memory only reported

^c Are you worried/concerned about worsening memory and/or thinking skills? (yes or no)

^d MoCA = Montreal Cognitive Assessment

^eCharlson Comorbidity Index Score [37]

Table 4: Attendance rates of Square-stepping exercise program at each study site, and attendance rates of other offered exercise programs at each of the sites.

	Site 1	Site 2	Site 3	Site 4 CC ^a	Site 4 LTC ^a
SSE sessions offered, No.	19	24	23	24	24
Residents at sessions, No. mean (SD)	5.5 (1.3)	7.8 (2.7)	6.4 (2.2)	9.9 (1.6)	4.0 (1.3)
Participants with >50% attendance, No.	5	6	7	10	3
Attendance Rate %^b, mean (SD)	77.9 (2.3)	66.0 (7.6)	73.3 (17.8)	87.9 (7.2)	77.8 (15.3)
Participants with 1- 50% attendance, No.	6	6	5	3	4
Dropouts or 0% attendance, No.	4	3	5	4	0
Residents who tried SSE but not enrolled, No.	2	13	0	2	2
Attendance rate of physical activity programs at sites^c	7.8 (2.0)	6.7 (1.9)	12.0 (6.3)	6.1 (3.8)	-

^a Continuum care (CC) and long-term care (LTC) at site 4 completed the square-stepping program as separate groups and are reported as such.

^b Attendance rates based on participants with >50% attendance

^c Data provided by Schlegel Villages; values represent the average attendance rates of physical activity programs that are normally offered at each of the sites by kinesiologists during the intervention period (July-September 2017).

Table 5: The number of participants that completed each outcome assessment at baseline (V0) and post-intervention (V1).

	Time point	Site 1 (n=15)	Site 2 (n=15)	Site 3 (n=17)	Site 4 (n=24)	Total (n=71)
Global Cognitive Functioning^a	V0	4	10	2	13	29
	V1	1	10	1	11	23
Monkey Ladder	V0	4	10	7	15	36
	V1	1	10	5	13	29
Digit Span	V0	4	10	7	15	36
	V1	1	10	5	13	29
Hampshire Tree Task	V0	4	10	5	15	34
	V1	1	10	5	12	28
Double Trouble	V0	4	10	2	15	31
	V1	1	10	2	12	25
Interlocking Polygons	V0	4	10	2	15	31
	V1	1	10	1	12	24
Token Search	V0	4	10	2	13	29
	V1	1	10	1	11	23
Odd One Out	V0	4	10	2	13	29
	V1	1	10	1	11	23
Rotations Task	V0	4	10	2	13	30
	V1	1	10	1	11	23
Normal (Single task) gait	V0	14	14	13	23	64
	V1	8	14	11	21	54
Dual task gait^b	V0	5	12	2	14	33
	V1	0	11	1	11	23
Counting backwards	V0	6	12	6	18	42
	V1	4	12	5	15	34
Semantic fluency	V0	6	12	6	18	42
	V1	3	13	3	15	31
Serial sevens	V0	5	12	2	14	33
	V1	0	11	1	11	23
Balance test	V0	8	14	10	21	53
	V1	8	14	10	21	53
NPIQ^c	V0	10	2	9	6	27
	V1	8	2	9	6	25

^a Global cognitive functioning is created through a composite of the 8 games

^b Dual Task gait is a composite of conditions (Counting backwards, Semantic Fluency and Serial Sevens)

^c NPIQ is the Neuropsychiatric Inventory Questionnaire.

Table 6: Randomization group mean scores of Cambridge Brain Sciences games at baseline and normative population values for older adults.

Game, mean (SD)	Control Group	SSE Group	Population norms^a
Memory: Monkey Ladder	4.5 (1.9) n=22	5.0 (1.5) n=14	6.1 (1.7) n=243
Memory: Digit Span	3.9 (1.7) n=22	4.4 (1.5) n=14	6.5 (1.7) n=246
Planning: Hampshire Tree task	8.8 (5.0) n=20	8.7 (5.7) n=14	13.8 (9.7) n=215
Reasoning: Double Trouble	4.6 (6.6) n=17	4.0 (7.4) n=14	15.5 (14.8) n=249
Concentration: Interlocking polygons	11.6 (13.6) n=17	15.9 (17.5) n=14	30.6 (21.6) n=248
Planning: Token Search	4.5 (1.7) n=15	4.7 (0.9) n=14	5.8 (2.2) n=241
Reasoning: Odd one out	7.3 (4.2) n=15	6.7 (4.2) n=14	8.9 (4.2) n=243
Concentration: Rotations task	37.9 (37.6) n=15	40.8 (34.0) n=14	62.2 (32.8) n=246

^aPopulation norms for adults 75-90 years old from www.cambridgebrainsciences.com.

Figure 1: Neuropsychiatric Inventory Questionnaire (NPIQ) mean scores with standard deviations for total score, frequency score and severity score, separated by randomization group (Circles = control group; squares = Square-stepping exercise group (SSE) group). Lower scores represent less affliction of mood and behaviours. SSE group, n=10; Control group, n=15. * Represents statistically significant difference between groups at V1, controlling for baseline.

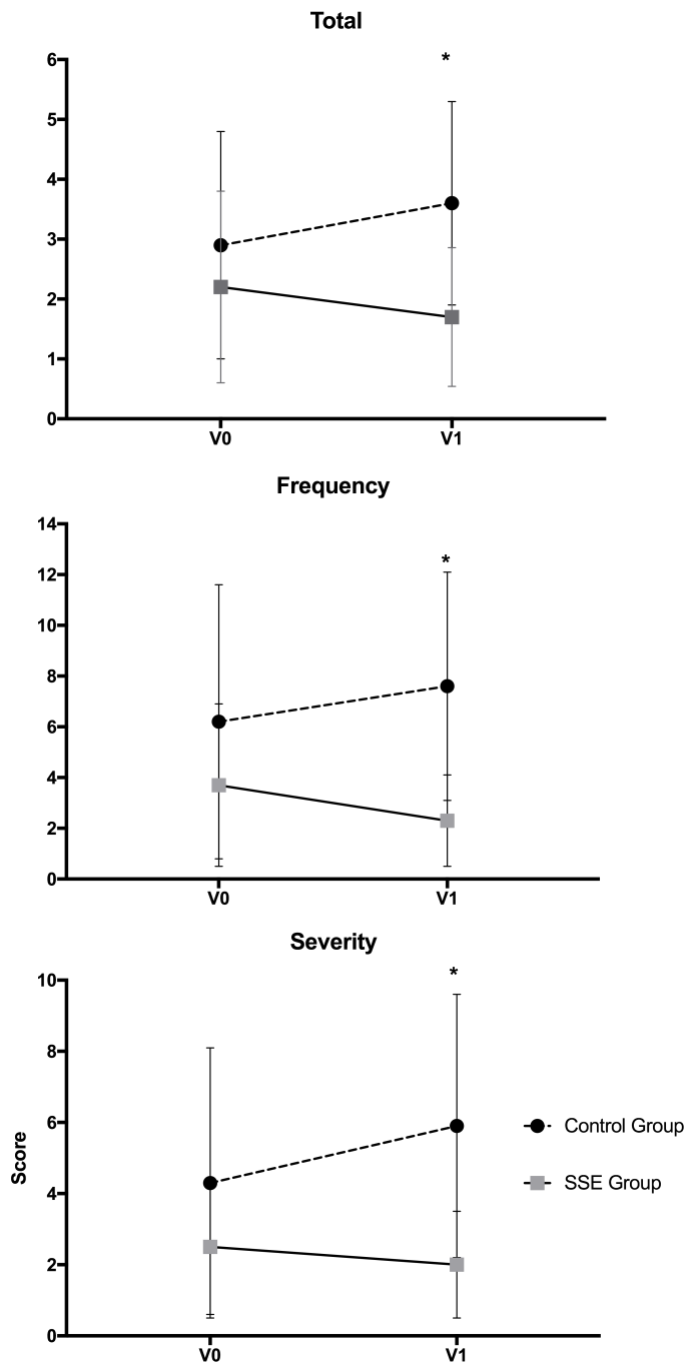


Figure 2: Boxes with error bars represent mean change in cognitive outcomes (standardized z-scores) by randomization group; circles represent individual change score in Square-stepping exercise (SSE) group and squares represent individual change scores in control group for each cognitive domain, V0-V1.

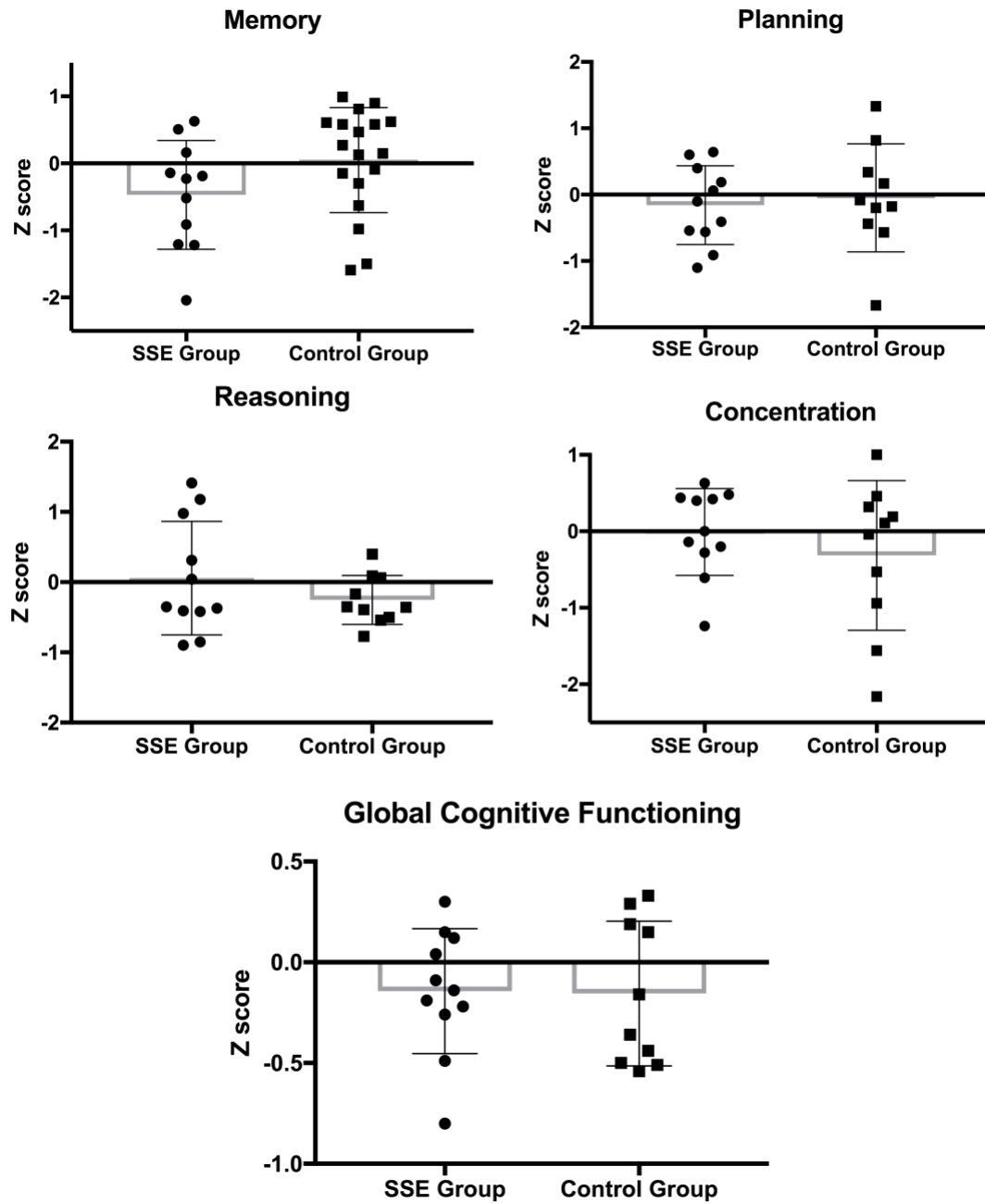


Figure 3: Boxes with error bars represent mean change in cognitive outcomes (standardized z-scores) by sex and randomization group. Each symbol represent change in cognitive domain from V0-V1 for individual participants. Squares represent females in the control group, circles represent males in the control group, upward triangles represent females in the Square-stepping exercise (SSE) group and downward triangles represents males in the SSE group.

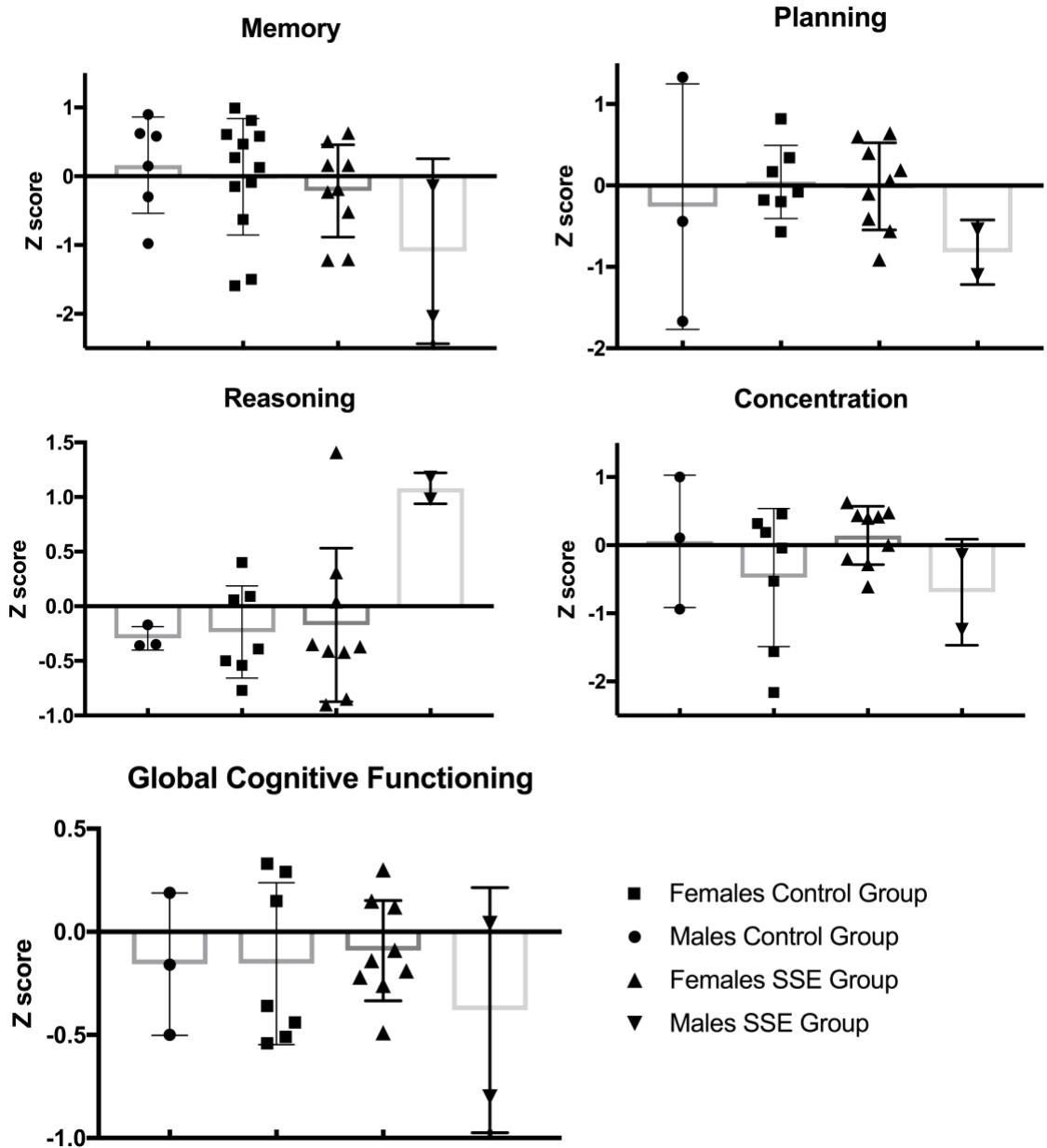


Figure 4: Usual and dual task gait characteristics [velocity (cm/s), step length (cm) and stride time variability (coefficient of variation %)], represented as means and standard deviations, separated by randomization group [Square-stepping exercise (SSE) group and control group] and level of care [Long-term care (LTC) and Retirement living (RL)].

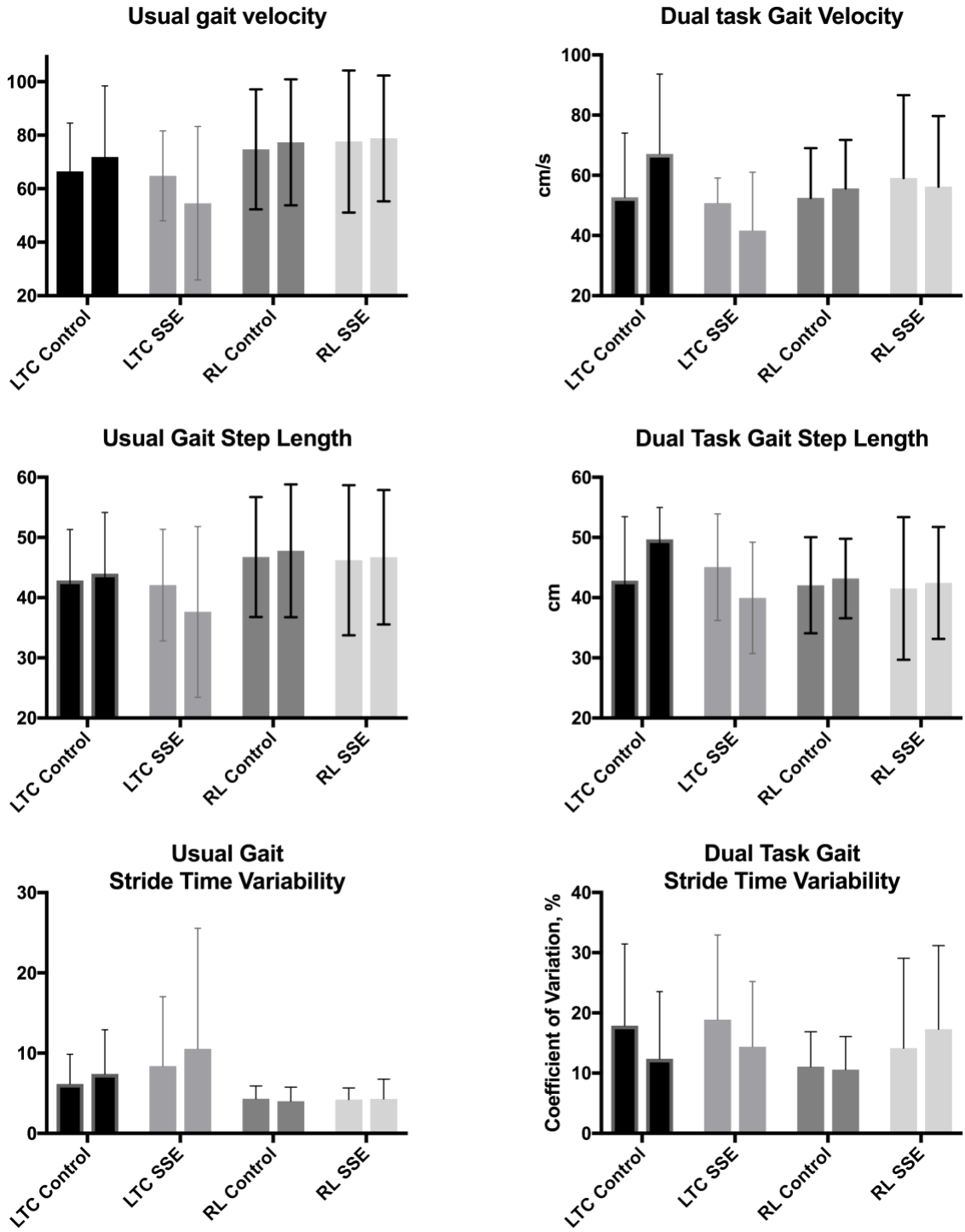
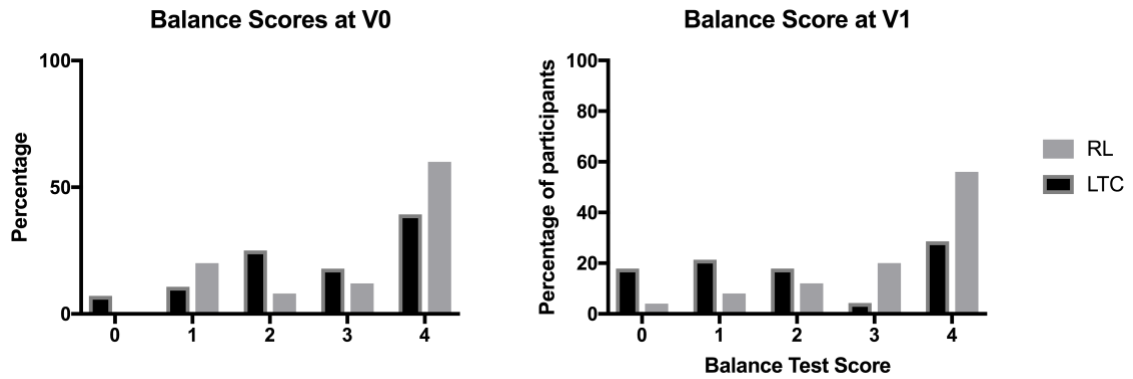


Figure 5: Short Performance Physical Battery balance test total scores, depicted as percentage of participants in each score category (0,1,2,3,4) at baseline (V0; left panel) and 12-weeks (V1; right panel), separated by level of care; Retirement Living (RL, n=25) and Long-term Care (LTC, n=28).



A six-month study of antisaccade reaction time in elderly adults with cognitive impairment in a retirement living home: a Mind Fun sub-study.

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Abstract

Seven adults, mean age of 85.4 years old (SD 3.2) with a mean Montreal Cognitive Assessment score of 22.6 (SD 3.5), participated in a 12-week Square-stepping exercise (SSE) program over a 6-month period. Executive-related oculomotor control task (antisaccades) were assessed at baseline (V0) and post-intervention (6-months, V1). Results showed no reliable change in antisaccade reaction time (RT) from V0 (360 ms, SD 37) to V1 (361 ms, SD 36). Results suggest SSE may maintain executive control in an elderly population with objective cognitive impairment.

Background

Elderly adults with objective cognitive impairment in retirement living (RL) homes are at high risk of further cognitive decline [1,2]¹. Evidence has shown that interventions, such as exercise, can improve cognitive function and brain health in adults with and without objective cognitive impairment [3–7], including those living in RL homes [8,9].

The antisaccade task represents an objective, non-invasive, and sensitive task that requires top-down inhibitory control, making it an ideal tool to detect changes in executive control [10]. For further reading, see a review on the antisaccade task by Everling and Fischer 1998 [11]. Extensive neuroimaging and neuropsychological work from humans and electrophysiology work from non-human primates has shown that the control of directional correct antisaccades is mediated via increased activation of the prefrontal cortex – an area associated with impairment in Alzheimer’s disease (AD) [12,13].

Antisaccade reaction time (RT) increases in duration with increasing age [14], and thus, demonstrate reduced executive control with advancing age. Further, our group has previously shown that a six-month moderate-intensity aerobic exercise or multi-modality exercise program improves antisaccade RT in community-dwelling older adults with subjective or objective cognitive impairment; that is, results show that a long duration exercise program improves executive-related oculomotor cognitive control in persons at increased risk of cognitive decline [15,16].

¹ In this chapter, elderly refers to octogenarians, as opposed to older adults.

The present study was a sub-study of a larger pilot cluster randomized controlled trial (RCT) in RL and long-term care homes in Ontario Canada. We proposed that the use of a cognitive training program, called Square-stepping exercise (SSE), can improve cognition and executive control in older adults in RL. The SSE program is a visuospatial working memory task with a cued stepping response. It has demonstrated improved memory, executive function, and global cognitive functioning in community-dwelling older adults [17–19]. The program is progressive and increases in complexity as a visuospatial task. Additionally, it is performed in a group setting which promotes social interaction.

To our knowledge, there are no known reports of antisaccade RT in elderly adults with objective cognitive impairment, nor have there been reports of the effects of SSE on executive control in this population. We have conducted a 12-week cognitive training intervention to assess whether we could change antisaccade RT over time, and thus this report adds a unique population (i.e., adults over 80 years) of executive-related oculomotor functioning to the literature to further advance our knowledge on cognition and aging.

The aim of the current investigation was to assess whether executive-related oculomotor control improved in elderly adults in RL over a six-month period, including a 12-week SSE intervention.

Methods

Participants

The participants of the larger cluster RCT (n=71) were recruited to participate in this sub-study. In the current study, the participants were in a RL home in Kitchener

Canada, which was randomized as a wait-list control site (n=24)². Participants were pre-screened and excluded if they had known eye-related issues associated with older age, such as macular degeneration and glaucoma – eye diseases that preclude accurate eye-tracking. A total of ten participants were eligible and agreed to participate; seven completed both baseline (V0) and post-intervention (V1) assessments (1 refused, 1 moved and 1 had deteriorated vision which could not be tracked). Data presented in this paper are for the seven participants who completed both assessments. Participants were assessed at baseline, V0 (21 July 2016, 11 August 2016) and post-intervention, V1 (9 or 10 February 2017) (Figure 1).

All participants had previously provided written informed consent, as approved by the Western Health Sciences Research Ethics Board (No.107891) and this study complies with the Declaration of Helsinki.

Intervention

The SSE intervention was conducted twice weekly for 45 minutes over 12-weeks (November 2016 to February 2017). An instructor demonstrated a stepping pattern across a gridded mat; the mat is 250 cm x 100 cm and it is divided into four columns of 10 rows, totaling 40 squares. The participants were required to memorize and repeat the patterns correctly two times. There are over 200 patterns that are progressive; the SSE program begins with beginner patterns and gradually progresses to intermediate and advanced patterns. The number of steps in a pattern range from two to 16 steps, and includes stepping forward, backward, horizontal, or diagonal in direction to challenge and potentially improve visuospatial, and executive function skills. Each pattern has a right

² Chapter 4a includes participants from all levels of care in continuum care homes, while Chapter 4b only includes residents in retirement living within the continuum care home.

and left foot start. SSE is a group-based program and participants are encouraged to provide peer support and coaching, therefore SSE increases social engagement.

Oculomotor Assessment

Participants sat at a table with their head in a head/chin rest with a 30-inch LCD monitor (1280 x 960 pixels, DELL 3007WFP, Round Rock, TX, USA) located at their midline and 550 mm from the edge of the table. The gaze position of the participants' left eye was assessed using a video-based eye-tracking system, sampling 360Hz (Eye-Trac6; Applied Sciences Laboratories, Bedford, MA, USA). Oral and written instructions were provided for the participants before each block of pro- and antisaccades (see details below). Computer and experimental trials were controlled via MATLAB (MathWorks, Natick, MA) and the Psychophysics ToolBox [20].

For the oculomotor assessment, participants completed both pro- and antisaccades. In both pro- and antisaccade tasks, a trial was initiated with a midline and eye-level central fixation cross (1-degree diameter) presented on the computer monitor. Following the attainment of a stable fixation (+1.5 degrees for 450 ms), a 1000-2000 ms interval for initiation of a target stimulus (50 ms duration) appeared left or right of the fixation cross at a proximal or distal eccentricity. The onset of the target serves as the movement imperative to pro- or antisaccade as quickly as possible. A prosaccade required a rapid response to the target's veridical location. An antisaccade required suppressing the stimulus-driven prosaccades (i.e. response suppression) and completing a response mirror-symmetrical to the target's location (i.e., 180-degree spatial transformation). Pro- and antisaccades were completed in separate and randomly ordered blocks (two blocks of 40 trials), the location (i.e., left or right of fixation), and eccentricity (proximal or distal) of a target was also ordered randomly and presented on 10 occasions during a block.

Statistical Analysis

Data reduction and statistical analyses were completed in Microsoft Excel, MATLAB, and SPSS (version 24). We examined pro- and antisaccade RT via 2 (time: baseline, post-intervention) by 2 (task: pro-, anti-saccade) Analysis of Variances (ANOVAs).

Results

Participants were 86% female, mean age 85.4 years (SD 3.2; range 79-89) with subjective and objective cognitive impairment, mean Montreal Cognitive Assessment (MoCA) score 22.6 (SD 2.5; range 18-25) out of 30 with an average of 14.4 (SD 2.8) years of education (See Table 1).

Baseline and post-intervention oculomotor assessment

Results revealed a main effect of task ($F=37.2$, $p<0.01$); however, neither the effect of time ($F<1$, $p>0.05$), nor the time by task interaction was significant ($F<1$, $P>0.05$). As such, prosaccade RTs (254 ms, SD 36) were shorter than antisaccade RTs (362 ms, SD 37) (see Figure 2).

Discussion

In the current report, we demonstrated maintenance of executive control in antisaccade RT over the six-month period, including 12-weeks of SSE, in an elderly population with objective cognitive impairment. We did not see an improvement; this is likely because of the high disease burden, objective cognitive impairment, in addition to a longer duration intervention may be required to elicit benefit [21], which logistically we were unable to do because of time constraints and some of participants were frail. However, there is some evidence to support maintenance of executive control as a positive outcome in this elderly population with objective cognitive impairment. Previous

reports have shown that a lack of intervention (i.e., control group) in adults aged 68.7 (SD 8.5) years old with subjective or objective cognitive impairment is associated with a decline in cognition over 24-weeks [22].

We have previously shown that adults with subjective and/or objective cognitive impairments improved their antisaccade RT following a six-month aerobic or multi-modality exercise program by a large magnitude of effect (i.e., 25 and 30 ms) [15,16]. These improvements were shown to be maintained up to six months after the intervention ended [23]. We also know that antisaccade RT remains stable over short periods of time (4-weeks) in adults without known cognitive impairment, demonstrating there is not a learning effect associated with the task [24]. Thus, our previous work provides a framework to demonstrate that executive-related improvements are exercise-specific, and therefore, SSE alone may not be enough to elicit cognitive benefit in elderly adults in RL [15,16]. The interventions in our previous studies were moderate-intensity exercise [15,16] and it is thought that aerobic exercise increases cerebral blood flow to improve structure and function [4,25,26]. In this study, we did not have aerobic exercise as a component of our intervention, which may be related to the lack of improvements seen in antisaccade RT, further supporting the notion that antisaccade RT improvements may be exercise-specific. Square-stepping exercise is a cognitive training program and thus, has a distinctly different mechanism. Although speculative in relation to SSE, the mechanism for cognitive training is related to increased activation in the brain, which results in increased region-specific resting state activation, cerebral blood flow, and metabolism [27]. Overall, SSE twice per week for 45 minutes for 12-weeks may not be enough to elicit improvements in elderly individuals with objective impairment, but rather it may provide maintenance of executive-related oculomotor control.

To our knowledge, this is the first report of a six-month investigation of antisaccade RT in elderly adults with objective cognitive impairment, following 12-weeks of cognitive training. The main challenge associated with completing eye-tracking in elderly adults was eligibility. There were many participants in the larger RCT who were willing to participate; however, due to severe macular degeneration and/or glaucoma, many were excluded in this sub-study, resulting in a final sample of seven. Based on the current findings, to conduct a randomized controlled trial we would require a sample size of 30 to find a 20 ms improvement in antisaccade RT [28].

Limitations and future directions

Our major limitation was a lack of a control group in this investigation; antisaccade RT was a tertiary outcome of a larger RCT and thus, this was a sub-study. Additionally, it was difficult to recruit eligible participants and follow them up for 6 months due to relocation, and deteriorating eye-function. This sub-study was in a population which had not previously been studied to assess antisaccade RT.

In the future, it would be advantageous to have a control group and assess individuals directly before and after an intervention. Further, it may be beneficial to utilize an aerobic training intervention, rather than cognitive training to determine if improvements can be made in this population similar to what we have shown in previous studies.

Conclusions

This novel application of antisaccade RT adds to our understanding of executive-related oculomotor control in elderly adults and examines how they respond over a six-month period. We did not see improvement, but rather maintenance of antisaccade RT in elderly adults with cognitive impairment. We speculate that engaging in cognitive

training, such as SSE, which requires working memory, and visuospatial acuity, in late life has potential to preserve executive control; however, robust evidence is required. Lastly, aerobic-based exercise may be required for improvements in executive-related oculomotor control for elderly adults with cognitive impairment.

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Table 1: Participants baseline characteristics, n=7.

Female sex, No. (%)	6 (86)
Age, years, mean(SD)	85.4 (3.2)
Caucasian, No. (%)	7 (100)
Years of education, mean (SD)	14.4 (2.8)
Height (cm), mean (SD)	161.8 (9.6)
Weight (kg), mean (SD)	68.7 (10.1)
Blood pressure, mmHg, mean (SD)	128.9/69.7 (5.4/7.6)
Number of medications, mean (SD)	8.3 (2.9)
Number of diagnoses, mean (SD)	4.9 (4.5)
Montreal Cognitive Assessment /30, mean (SD)	22.6 (2.5)
Do you feel your memory and/or thinking skills have gotten worse recently? (yes or no), No. (%)	7 (100)
Are you concerned/worried about your worsening memory and/or thinking skills (yes or no), No. (%)	4 (57)

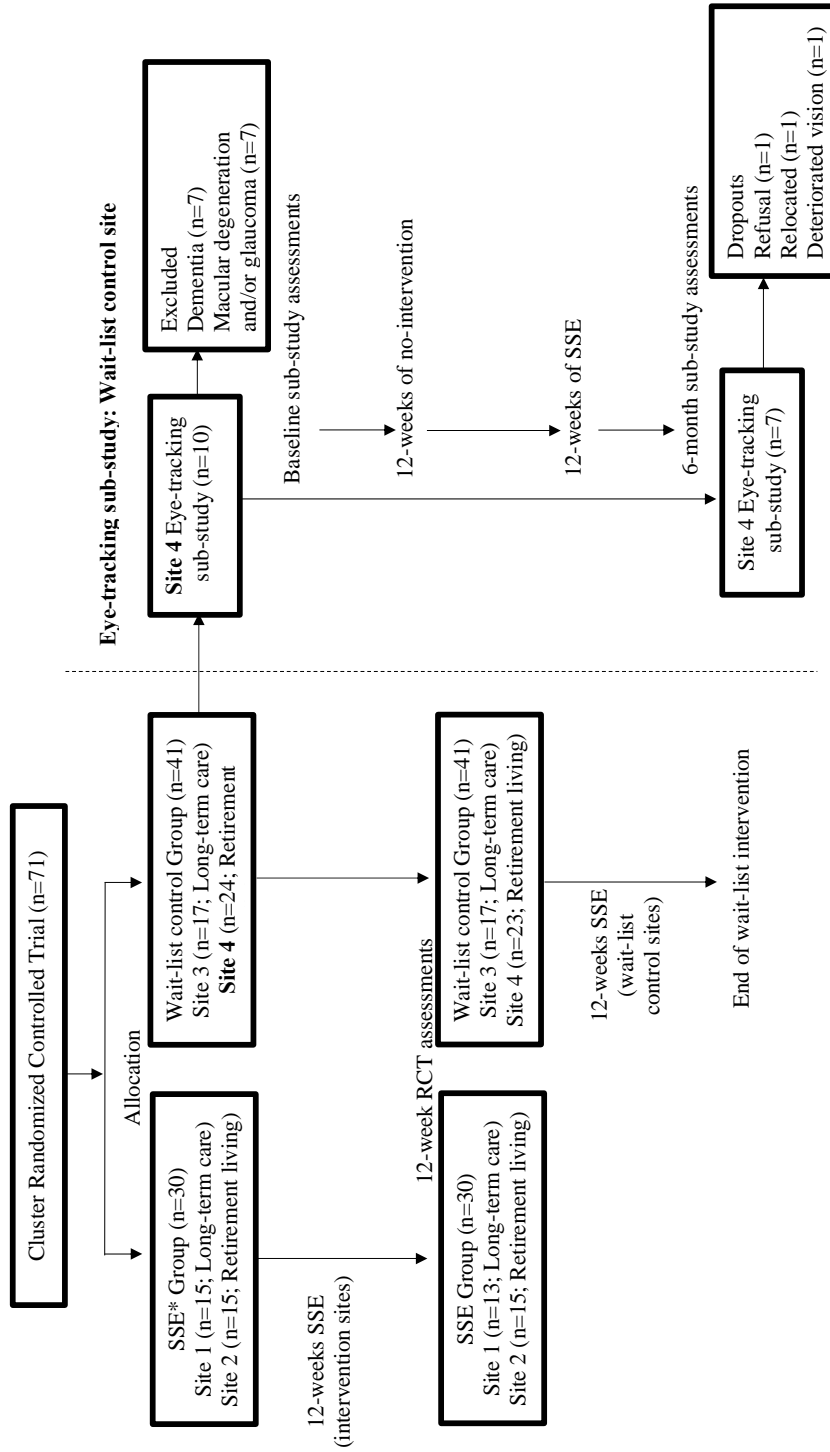


Figure 1: Study flow diagram for eye-tracking sub-study
 *SSE = Square-stepping exercise

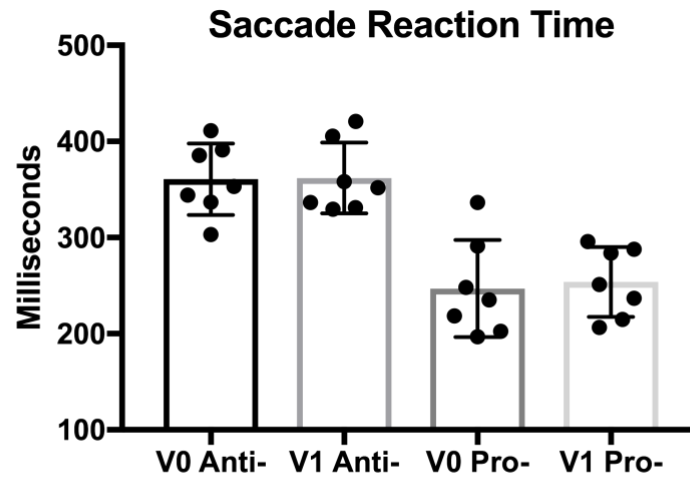


Figure 2: Pro-saccade and anti-saccade reaction times at baseline (V0) and post-intervention (V1). Bars represent means with standard deviation error bars, circles represent individual values, $n=7$.

Discussion

This thesis aimed to investigate the feasibility of Square-stepping exercise (SSE) as a universal program to improve cognition and mobility in older adults with chronic disease, specifically older adults with: 1) knee osteoarthritis (OA), 2) type 2 diabetes mellitus (T2DM) and self-reported cognitive complaints (sCC), and 3) adults living in continuum care (CC) and long-term care (LTC) homes, as example populations. In sum, our key findings were: 1) SSE is not feasible in adults with chronic disease, 2) the efficacy of SSE on mobility in adults with knee OA is equivocal, 3) SSE may improve executive control in adults with T2DM and sCC, 4) SSE can improve mood and behaviour symptom scores in adults with dementia, and 5) SSE may maintain executive control in elderly individuals with objective cognitive impairment.

Feasibility

We introduced feasibility at the beginning of this document using Bowen et al.'s definition: "meeting intended behavioural outcomes under ideal circumstances"[1]. We measured feasibility with recruitment and attendance to a program as our primary aims in all three trials conducted [2]. Overall, we found that the attendance of our SSE programs were lower than those reported in previous studies [3–9]. Our average attendance rates ranged from 34-49% across the studies (when including all enrolled participants), which demonstrated the limited feasibility of SSE as a cognitive training program for adults with chronic disease and therefore may not be suitable. We did find that chronic diseases imparted a higher burden, which influenced the recruitment, and attendance of participants when comparing these metrics to studies in healthy community-dwelling older adults [10]. Recruitment and dropout rates in studies with healthy community-dwelling older adults are generally better, and therefore are more feasible compared to

chronic disease populations. As an example, in a 24-week exercise intervention with a 28-week follow up period, we recruited 127 community-dwelling older adults, which had attendance rates of 71% and a dropout rate of 19% [11]. We found recruitment and adherence difficult in adults with T2DM and sCC; over a 10-month recruitment period, we were only successfully able to recruit 25 participants, and 41% of the intervention group did not complete the intervention. The disease burden of T2DM was likely a deterrent to participate in a 24-week cognitive training program. Conversely, we found it was easier to recruit adults living in CC or LTC because the intervention was in their living community in addition to designated program staff kinesiologists, resources, facilities, and relevant workflows in place. Even though this group still had disease burden, we found that the convenience of location and time of program were important factors for implementation of the SSE program. In the future, it will be important to carefully consider the location, time of day, and duration of the SSE intervention to improve recruitment and limit dropouts.

Adverse events

Few adverse events were reported that resulted from participation in the studies. Adverse events included headaches due to looking down at the SSE mat and falls. In the SSE groups, there was a 4% adverse events rate (or 2 out of 52 participants) over 60 intervention weeks. Some participants may need more focus on stretching and resting their necks to prevent or aggravate ongoing issues with headaches, in addition to encouragement that balance is more important to maintain than completing challenging patterns correctly.

Efficacy of SSE on cognition and mobility

SSE has previously been investigated for its use as a fall prevention program in community-dwelling older adults in studies of varying methodological quality (i.e., non-randomized and randomized trials). As previously described in this thesis, SSE has shown some benefits to balance, lower extremity functional fitness and strength, global cognition, executive function, and memory [3–9]. We sought to determine if SSE showed similar benefit in adults with chronic disease.

In doing so, our findings were equivocal on SSE's efficacy for mobility in older adults with knee OA. Therefore, SSE may not be a suitable alternative program to Tai Chi, which has demonstrated reduced pain and improved physical function in adults with knee OA, through improved neuromuscular function and proprioception [12,13].

In older adults with T2DM and sCC, we demonstrated that SSE may improve executive function demonstrated by improved planning domain scores and non-significantly in antisaccade reaction time in the SSE group. If we speculate that SSE imparts cognitive benefits similarly to other cognitive training programs, a potential mechanism may be through increased activation of the prefrontal cortex during SSE, which in turn results in higher levels of regional cerebral blood and synaptic connectivity [14]. However, we cannot negate the possible benefits of increased social interactions that SSE provided, which may have contributed to cognitive benefits [6]. Lastly, because of our small sample size, the improvements demonstrated may be due to natural variation and SSE may not provide cognitive benefit. Older adults with T2DM are at an increased risk for cognitive decline, and this can be detrimental to their diabetes self-management and therefore, maintenance of cognition is crucial to sustain their independence [15,16].

In older adults living with dementia we found SSE to benefit mood and behaviour symptom scores, which is related to quality of life; specific improvements were seen in questions relating to depression, disinhibition, and delusions [17]. This evidence provides support that SSE has a positive benefit in adults with severe cognitive impairments and can potentially improve quality of life in this population.

In our sub-study of the antisaccade task in elderly individuals, we found that the SSE program may maintain executive control in a group of octogenarians with objective cognitive impairment. However, a major limitation of this sub-study is the lack of a control group. This was an exploratory study of the antisaccade task and reaction time measurement in this population, which we found to be successful and adds to the literature on oculomotor function in elderly individuals with cognitive impairment.

Our group's previous work has demonstrated that multi-modality exercise plus SSE or balance and range-of-motion exercise [18] improves cognitive function in adults with sCC [19]. At this time, we speculate the improvements resulted from the aerobic exercise component (i.e., improvements in cerebral blood flow [20]) in addition to the complementary cognitive training benefits provided by SSE. This may help explain why the cognitive benefits were less robust in the current studies. Additionally, the previous study was in healthy older adults with sCC and thus, we cannot extrapolate these findings to adults with chronic disease. Future work should focus on determining the best combination of intervention(s) (i.e., most efficacious) for adults with chronic disease, while balancing the intervention with feasibility.

Overall, the evidence for SSE as an intervention for adults with chronic disease is weak, though some evidence is supportive of cognitive benefit in adults with T2DM and sCC. Results for mobility remain equivocal in adults with knee OA. These populations

may need a longer duration intervention, or higher dose (i.e., more sessions per week) to improve intervention efficacy on mobility and cognition. However, the low attendance remains to be the prominent barrier to feasibility in adults with chronic disease.

SSE and social engagement

We describe SSE as an intervention that increases social engagement because it is a group based program where peer coaching and support is encouraged. Chapter 4a describes the positive feedback we received on the social impacts of SSE on adults living in LTC and CC homes, while there is potential for social interactions to be negative, this was not our experience. Although we did not have a formal method of assessing social engagement, the kinesiologists reported that the participants were very supportive of each other, regardless of cognitive or mobility impairments and the participants became peer coaches on their own. Additionally, the kinesiologists reported that the participants met new people and widened their circle of friends within the homes. Thus, this evidence supports the positive social benefits of SSE in diverse groups.

Scalability and future directions

Square-stepping exercise has the potential to be an easily scalable intervention. It is a low-cost program, that is easy to implement as it requires limited training and resources (i.e. SSE mat). Further, an alternative way to scale SSE is through mobile health (mHealth). We have developed a smartphone app, called HealthzBrain, which has the SSE patterns on it to improve the scalability of the program [21]. We demonstrated that SSE can be modified to suit the participants' capabilities. Square-stepping exercise can be implemented on its own, in addition to a seniors' fitness program, or as a supplemental intervention. SSE provides improved adherence to other programs and provides superior exercise pleasure scores [22,23].

As demonstrated in this thesis, adults with chronic disease have high disease burden, which impacts their participation in interventions, such as SSE. Future work should focus on minimizing barriers to participation for adults with chronic disease. For example, focus groups with target populations should be conducted during a study design period to understand potential issues with recruitment and attendance. Incorporating interventions into pre-existing programs, such as senior's community centres, physiotherapy clinics, and doctor's or specialist's offices. In LTC and CC settings, it would be beneficial to have outcome measurements suited to the population. For example, if global cognitive functioning is an outcome, using paper-based tests may be more suitable than computer-based tests in older adults who are unaccustomed to using computers. Lastly, it would be appropriate to incorporate aerobic exercise into future trials as an additional arm and/or aerobic plus cognitive training arm in order to maximize potential cognitive benefits.

Limitations

A limitation associated with this thesis is that we chose specific populations with inclusion and exclusion criteria and thus we are not able to generalize to all community-dwelling chronic disease populations. However, we had a broad scope of individuals in LTC and CC, which may represent a more diverse population. Nevertheless, we chose these populations because of the variety of symptoms, associated risk factors, and varied disease severity, to try and simulate a real-world setting (i.e., an array of cognitive and mobility impairments). A second limitation is the small sample sizes in these feasibility studies, which limited our ability to obtain statistical significance and determine efficacy of the program. A third limitation was the decision to use the Cambridge Brain Sciences online computer battery as an cognitive outcome in two of the studies. The CBS games

are based on well-established neuropsychology paradigms; however, they have not been well used in intervention studies (e.g., cognitive training studies [28]), and therefore are not validated to use as an outcome assessment. Additionally, these games are computer based and several participants did not have experience using computers. This led to an added challenge of learning to use a computer, combined with the cognitive task of completing the games. Further, the games required a familiarization session and many of the older adults found it cognitively fatiguing to complete the games twice in a row. These limitations likely influenced the results of the games. The fifth limitation is that SSE is a social program and therefore, it is plausible that the social engagement provided cognitive benefit and not SSE. However, we are not able to separate the benefits of SSE on cognition from those of social interaction. Overall, our randomized controlled study designs allowed us to have confidence in the outcomes we have demonstrated here.

Conclusions

Overall, we conclude that SSE is not a feasible intervention for older adults with diverse cognitive and mobility impairments because of low attendance and poor recruitment. However, we did find that it can be easily modified to suit a variety of cognitive and mobility impairments. The benefits for SSE on mobility remain equivocal in older adults with knee OA. SSE may benefit executive control (planning domain) in older adults with T2DM and sCC. Additionally, we have demonstrated it improves mood and behaviours symptom scores in adults with dementia.

In the future, SSE should be investigated to determine if it is feasible when implemented differently, for example, in a senior's fitness centre. Additionally, *a priori* criteria should be identified for feasibility and formal qualitative assessments should be

conducted to better understand social relationships developed by the program. Further, SSE may be best suited when combined with aerobic exercise.

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**Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice**

Principal Investigator: [Redacted]
Department & Institution: Schulich School of Medicine and Dentistry/Geriatric Medicine, Parkwood Institute

HSREB File Number: 106537
Study Title: An innovative mind-motor exercise approach to osteoarthritis treatment
Sponsor:

HSREB Initial Approval Date: May 15, 2015
HSREB Expiry Date: May 15, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Letter of Information & Consent	Revised LOI - clean	2015/04/21
Recruitment Items	revised telephone script- clean copy	2015/04/21
Western University Protocol	Western Protocol Clean copy (received April 28, 2015)	
Instruments	Leisure Activities Questionnaire	2015/03/18
Instruments	WOMAC Scale	2015/03/08
Data Collection Form/Case Report Form	CRF- 26 weeks	2015/03/18
Instruments	FAB Scale	2015/03/18
Data Collection Form/Case Report Form	CRF - 13 weeks	2015/03/18
Other	Participant Contact Info	2015/03/18
Data Collection Form/Case Report Form	CRF- baseline	2015/03/18

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[Redacted]

Ethics Officer to Contact for Further Information

[Redacted]

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[Redacted]



Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice

Principal Investigator: [Redacted]
Department & Institution: Schulich School of Medicine and Dentistry/Geriatric Medicine, Parkwood Hospital

HSREB File Number: 105883
Study Title: Mind-motor exercise in older adults with type 2 diabetes and self-reported cognitive complaints
Sponsor:

HSREB Initial Approval Date: December 22, 2014
HSREB Expiry Date: December 22, 2015

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	MoCA - clean	2014/09/30
Instruments	Leisure activities- clean	2014/09/30
Instruments	MMSE- clean	2014/09/30
Instruments	CES-D- clean	2014/09/30
Other	NEW** Clinical trials.gov approval receipt- NCT #02292511	2014/11/14
Instruments	NEW** Clock Drawing Test collection assessment form	2014/11/18
Other	NEW** - Email script for Cambridge Brain Sciences outcome measure	2014/11/18
Data Collection Form/Case Report Form	Participant contact info - clean	2014/11/18
Data Collection Form/Case Report Form	CRF post intervention - clean	2014/11/18
Data Collection Form/Case Report Form	CRF interim - clean	2014/11/18
Data Collection Form/Case Report Form	CRF baseline - clean	2014/11/18
Data Collection Form/Case Report Form	CRF screen - clean	2014/11/18
Other	New** HealtheBrain screen shots	2014/12/16
Western University Protocol	Western protocol clean	2014/12/16
Letter of Information & Consent	LOI/Consent - clean with final recommendation #5 (email)	2014/12/19
Instruments	Activities-specific Balance Scale	2014/09/30
Instruments	Fullerton Balance Scale	2014/09/30
Other	Telephone Script - recruitment	2014/09/30

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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**Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice**

Principal Investigator: [REDACTED]
Department & Institution: Schulich School of Medicine and Dentistry/Geriatric Medicine, Western University

Review Type: Full Board
HSREB File Number: 107891
Study Title: The MIND-FUN Research Study: Mind-motor exercise to improve cognition and functional fitness

HSREB Initial Approval Date: May 09, 2016
HSREB Expiry Date: May 09, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Recruitment Items	Slide for screens and village newsletter to recruit residents within the Schlegel Villages.	2016/03/16
Recruitment Items	Recruitment items for Schlegel Villages Page 1 - for residents Page 2 and 3 - for Schlegel staff	2016/03/11
Data Collection Form/Case Report Form	Case Report Form	2016/03/11
Data Collection Form/Case Report Form	Case Report Form - for participant contact information	2016/03/14
Data Collection Form/Case Report Form	Case report form - minor admin edits - tracked changes	2016/03/11
Data Collection Form/Case Report Form	case report form - clean	2016/04/18
Recruitment Items	Advertisement for Schlegel Villages newsletters - for recruitment.	2016/04/15
Letter of Information & Consent	photo LOI	2016/04/08
Letter of Information & Consent	dementia subpopulation	2016/04/08
Western University Protocol		2016/04/08
Letter of Information & Consent	Main	2016/04/08

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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Publications

1. **E.M. Shellington**, T. Felfeli, R. Shigematsu, D.P. Gill and R.J. Petrella. HealthBrain: An innovative smartphone application to improve cognitive function in older adults. *mHealth*. 2017. 3(17). doi: 10.21037/mhealth.2017.04.05
<http://mhealth.amegroups.com/article/view/14719/14901>

2. **E.M. Shellington**, M. Heath, D.P. Gill and R.J. Petrella. Long-term maintenance of executive-related oculomotor improvements in older adults with self-reported cognitive complaints following a 24-week multiple modality exercise program. *JAD*. 2017. 58(1): 17-22. doi: 10.3233/JAD-161190
<http://content.iospress.com/articles/journal-of-alzheimers-disease/jad161190>
3. M. Heath, **E.M Shellington**, S. Titheridge, D.P. Gill and R.J. Petrella. A 24-Week Multi-Modality Exercise Program Improves Executive Control in Older Adults with a Self-Reported Cognitive Complaint: Evidence from the Antisaccade Task. *JAD*. 2017; 56(1): 167-183. doi: 10.3233/JAD-160627
<http://content.iospress.com/articles/journal-of-alzheimers-disease/jad160627>
4. D.P. Gill, M.A. Gregory, **E.M. Shellington**, T. Liu-Ambrose, R. Shigematsu, G.Y. Zou, K. Shoemaker, A.M. Owen, V. Hachinski, M. Stuckey, and R.J. Petrella. Group-based exercise and cognitive-physical training in older adults with self-reported cognitive complaints: The Multiple-Modality, Mind-Motor (M4) study protocol. *BMC Geriatrics*. 2016; 16(17): doi:10.1186/s12877-016-0190-9
<https://bmccgeriatr.biomedcentral.com/articles/10.1186/s12877-016-0190-9>

Under review:

5. **E.M. Shellington**, M. Heath, A. Petrella, D.P. Gill, R.J. Petrella. A six-month study of antisaccade reaction time in elderly adults with cognitive impairment in a retirement living home: A Mind Fun sub-study. *JAD Reports*, September 2017.
6. **E.M Shellington**, S. Reichert, M. Heath, D.P. Gill, R. Shigematsu, R.J. Petrella. Results from a feasibility study of Square-stepping exercise in older adults with type 2 diabetes and a self-reported cognitive complaint to improve global cognitive functioning. *CJD*, October 2017.

Submitted:

7. **E.M. Shellington**, D.P. Gill, R. Shigematsu, R.J. Petrella. Square-stepping exercise as an innovative intervention for older adults with knee osteoarthritis: results from a pilot feasibility study. *CJA*, September 2017

Conference Abstracts

1. **Erin M. Shellington**, Dawn P. Gill, Sonja M. Reichert, Matthew Heath, Robert J. Petrella. Square-stepping Exercise For Older Adults With Chronic Disease To Improve Cognition and Mobility. Submitted to ACSM Annual Meeting. Minneapolis USA. 29 May – 2 June 2018.

2. M. Heath, **E. Shellington**, D. Gill, R. Petrella. A Six-Month Exercise Program Improves Executive Control in Persons in the Prodromal Stages of Alzheimer's Disease: Short- and Long-Term Benefits. SCAPPS Conference 2017. *Journal of Exercise, Movement, and Sport* 2017; 49(1).
3. A. Petrella, M. Heath, **E.M. Shellington**. The antisaccade task in long term care and retirement setting. Canadian Frailty Network Conference. *Canadian Geriatrics Journal* 2017; 20 (3):157.
4. N.C. Boa Sorte Silva, D.P. Gill, **E.M. Shellington** and R.J. Petrella. Multiple-Modality Exercise and Mind-Motor Training to Improve Cognition in Older Adults: Results from the M4 Study. Alzheimer's Association International Conference. London England July 2017. Accepted.
5. **E.M. Shellington**, D.P. Gill, N.C. Boa Sorte Silva, A. Petrella, P.K. Simmavong, K. Pfisterer, A. Matharu, S. Brown, J. Killingbeck, R. Shigematsu and R.J. Petrella. Feasibility Of Square-stepping Exercise To Improve Mobility And Cognition In Long-term Care and Retirement Living. *MSSE*. 2017; 49(5S): 216-17. doi: 10.1249/01.mss.0000517438.43007.1d
6. M. Heath, **E.M. Shellington**, S. Titheridge, D.P. Gill, R.J. Petrella. Older adults with self-reported cognitive complaint show improved executive control following 24-week multi-modality exercise training program. SCAPPS Conference 2016. *Journal of Exercise, Movement, and Sport* 2016; 48(1)
7. **E.M. Shellington**, C.E. Riley, D.P. Gill, S. Reichert and R.J. Petrella. Older adults with type 2 diabetes and self-reported cognitive complaints show sex-specific differences. *Applied Physiology, Nutrition and Metabolism*. 2016; 41(999): S337-S398.
8. **E.M. Shellington**, D.P. Gill and R.J. Petrella. Square-stepping exercise improves lower limb strength in older adults with knee osteoarthritis. *Applied Physiology, Nutrition and Metabolism*. 2016; 41(999): S337-S398.
9. **E.M. Shellington**, M. Heath, S. Titheridge, D.P. Gill and R.J. Petrella. Multiple Modality Exercise Improves Executive Control in Older Adults with Subjective Cognitive Complaints. *Alzheimer's & Dementia*. 2016; 12(7): Supplement P592. P1-411.
10. **E.M. Shellington**, M.A. Gregory, D.P. Gill, R.J. Petrella. Dual task gait training and aerobic exercise improves information processing, memory and gait in older adults with cognitive impairment. Abstracts from the 2015 CSEP General Meeting. *Applied Physiology, Nutrition, and Metabolism*, 2015, 40(S1): S1-S69

11. **E.M. Shellington**, T. Felfeli, R. Shigematsu, D.P. Gill, R.J. Petrella. A User Experience Survey for a Mind-Motor Exercise Intervention Smartphone Application - HealtheBrain. F-14 Thematic Poster - Physical Activity Interventions: Novel Strategies. *Medicine and Science in Sports and Exercise*. 2015. 47(5S): 707–708.
12. T. Felfeli, **E.M. Shellington**, D.P. Gill, R.J. Petrella. Feasibility of a Smartphone Delivered Aerobic and Cognitive Exercise Program for Community-Dwelling Older Adults. *Technology Evaluation in the Elderly Abstracts from the meeting held in Toronto, September 21-23, 2014. Canadian Geriatrics Journal*. 2015; 18(2): 108-133.

Unpublished:

1. **E.M. Shellington**, D.P. Gill, R. Shigematsu, C.E. Riley, A. De Cruz, N.C. Boa Sorte Silva, S. Reichert, M. Heath, and R.J. Petrella. Square-stepping exercise as a universal intervention for older adults to improve cognitive and physical function. *Exercise is Medicine on Campus: 1st National Student Conference*. University of Western Ontario, London Canada. 23-24 June 2017.
2. N.C.B.S. Silva, D.P. Gill, **E.M. Shellington**, P.K. Simmavong, R.J. Petrella. A Research Proposal: The MIND-FUN Research Study: mind-motor exercise to improve cognition and functional fitness. *Exercise is Medicine on Campus (EIMC) at Western University: Research Conference*, University of Western Ontario, London Ontario, 23-24 June 2016.
3. **E.M. Shellington**, D.P. Gill, R.J. Petrella. Walking speed is associated with standard cognitive assessments in older adults with type 2 diabetes and self-reported cognitive complaints: a preliminary sub-analysis of a randomized controlled trial. *2nd Annual Kinesiology Graduate Student Symposium*, University of Western Ontario, 26 April 2016.
4. **E.M. Shellington** and R.J. Petrella. Mind-motor exercise in older adults with type 2 diabetes and self-reported cognitive complaints: a project proposal. *Bodies of Knowledge Conference*. University of Toronto. 8 May 2015.
5. **E.M. Shellington**, T. Felfeli, R. Shigematsu, D.P. Gill, R.J. Petrella. A User Experience Survey for a Mind-Motor Exercise Intervention Smartphone Application - HealtheBrain. *1st Annual Kinesiology Graduate Student Symposium*, University of Western Ontario, 24 April 2015

Funding

Scholarships and Awards

Active:**Title: Post-Doctoral Fellowship**

Organization: Mitacs Elevate in partnership with Health and Fitness Society of British Columbia

Supervisors: Drs. Shannon Bredin and Darren Warburton, University of British Columbia

Amount: \$100 000 stipend; \$10 000 research allowance

Dates: February 2018 – January 2020

Status: Approved

Completed:**Title: Award in Aging (Travel)**

Organization: Northwater Capital Management

Amount: \$2000

Date: Spring 2017

Title: Travel Awards – Institute Community Support in Partnership with Institute of Aging

Organization: Canadian Institutes of Health Research

Notes: American College of Sport Medicine Annual Meeting, Denver Colorado

Amount: \$1000

Date: Winter 2017

Title: Travel Awards – Institute Community Support in Partnership with Institute of Aging

Organization: Canadian Institutes of Health Research

Notes: Canadian Society for Exercise Physiology Annual Meeting, Victoria Canada

Amount: \$1000

Date: Summer 2016

Title: Ontario Graduate Scholarship

Notes: MIND-Fun Research Study

Amount: \$15000

Date: September 2016 – May 2017

Title: Internship Program

Organization: Mitacs Accelerate in partnership with Carbylan Therapeutics Inc.

Supervisor: Dr. Robert Petrella

Square-stepping exercise as an innovative intervention for adults with knee osteoarthritis.

Amount: \$36000

Date: February 2015 – January 2016

Research Funding

Completed:

Grant title: Department of Family Medicine Research Committee Trust Fund

Awarded by: Department of Family Medicine, Schulich School of Medicine and Dentistry.

Principal Investigator: Robert J. Petrella

Project title The MIND-Fun Research Study: Mind-motor exercise to improve cognitive and functional fitness.

Amount: \$4739.59

Date: 2016-2017

Grant title: Department of Family Medicine Research Committee Trust Fund

Awarded by: Department of Family Medicine, Schulich School of Medicine and Dentistry.

Principal Investigator: Dr. Robert J. Petrella

Co-Investigators: Drs. Sonja Reichert and Dawn P. Gill

Project title: Mind-motor exercise in older adults with type 2 diabetes and self-reported cognitive complaints

Amount: \$2491.75

Date: 2015-2016

Media

Square off with memory

Gradcast #143

Radio Western CHRW 94.9 FM

<https://gradcastradio.podbean.com/e/gradcast-143-square-off-with-memory/>

3 November 2017

Two research programs are looking at the effects of square-stepping in those with Type II Diabetes with Cognitive Complaints and those 40 and over with knee osteoarthritis

Audience: Community

Type: Newspaper Interview

Sentinel Review

Woodstock Canada

26 November 2015

Service

Co-Chair

Kinesiology Graduate Student Association

University of Western Ontario

May 2016 – December 2017

Logistics Planning Team Member

Exercise is Medicine on Campus: National Student Conference
 University of Western Ontario
 March 2017 – June 2017

Co-President

Kinesiology Graduate Student Association
 University of Western Ontario
 May 2015 – April 2016

Annual Exercise Stress Testing and ECG Monitoring

Canadian Centre for Activity and Aging, University of Western Ontario
 Retired Research Association, University of Western Ontario
 Ladies Retired Research Association, University of Western Ontario
 Supervisor: Dr. Robert J. Petrella
 January 2014 – December 2015

Awards and Accolades**PhD Poster Competition Finalist**

Canadian Society for Exercise Physiology Annual Meeting Victoria, B.C.
 12-15 October 2016.

Older adults with type 2 diabetes and self-reported cognitive complaints show sex-specific differences.

The MSc Cardiac Rehabilitation Prize 2013

Awarded for most outstanding overall performance
 College of Biological Sciences
 University of Essex
 50 GBP

Professional Memberships

Student Member 2015 – present
 American College of Sports Medicine

Student Member 2015 – present
 Canadian Society for Exercise Physiology

Student Member 2016 - 2017
 Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment and Subjective Cognitive Decline Professional Interest Group

Acknowledgements

D.P. Gill, W. Blunt, A. De Cruz, B. Riggin, K. Hunt, G.Y. Zou, S. Sibbald, K. Danylchuk, M. Zwarenstein, C.M. Gray, S. Wyke, C. Bunn, R.J. Petrella. Hockey Fans in Training (Hockey FIT) pilot study protocol: a gender-sensitized weight loss and healthy lifestyle program for overweight and obese male hockey fans. *BMC Public Health*. 2016;16:1096. doi:10.1186/s12889-016-3730-5.

E. Knight, M. Stuckey, H. Prapavessis, R. J. Petrella. Public Health Guidelines for Physical Activity: Is there an App for that? A review of Android and Apple App Stores. *JMIR Mhealth and Uhealth* 2015; 3(2):e43