The impact of a 9-month sedentary behaviour reduction intervention on frailty and brachial artery health: A feasibility study

by

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Dalhousie University is located in Mi'kma'ki, the
ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

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Abstract

Many adults engage in excessive amounts of sedentary time (ST; sitting/lying while awake), which increases frailty and cardiovascular disease risk. However, there is limited evidence evaluating whether long-term sedentary behavior reduction interventions are effective at decreasing ST and improving these health outcomes. This study tested the feasibility of a 9-month intervention and hypothesized that it would reduce daily ST in adults who do not achieve national ST recommendations (i.e., >8-hours/day), as well as improve frailty index scores and brachial flow-mediated dilation (FMD) responses. Following 2 participant dropouts, 18 sedentary adults were randomly allocated to a Control (3 older females, 84±8 years; and 6 younger adults, 3♀, 23±3 years) and Intervention (5 older adults, 4♀, 75±15 years; and 4 younger adults, 3♀, 24±3 years) group. The Intervention group watched an educational video that highlighted the negative health consequences of excessive ST and received 2-4 messages/week via text or email prompting them to decrease their ST. At Baseline, 3 months, 6 months, and 9 months, a thigh-worn activPAL inclinometer recorded habitual physical and sedentary activities for 7-days and assessments of frailty and brachial FMD were conducted. No Group × Time effects were observed for ST, sedentary breaks, light-intensity physical activity, moderate-to-vigorous intensity physical activity, sleep time or standing time (all, p>0.122). There were also no interaction effects for frailty (p=0.667) or brachial FMD (p=0.502). Based on monthly follow-up phone calls with the Intervention group, there were several life factors that may have acted as barriers to changes in habitual behaviour including: mental health, work/school schedule, weather changes, and/or willingness to change. This intervention was feasible based on low drop out (10%) and high acceptability among participants. However, it was not effective at decreasing ST in adults. Future interventions may need to include more frequent prompt/phone calls and/or a better individualized approach to reducing ST in adults.

List of Abbreviations and Symbols

BH_4 = tetrahydrobiopterin

COM-B = capability, opportunity, and motivation as three key factors capable of behaviour change

CVD = cardiovascular disease

DBP = diastolic blood pressure

eNOS = endothelial nitric oxide synthase

ET-1 = endothelin-1

FI = frailty index

FMD = flow-mediated dilation

HR = heart rate

LPA = light-intensity physical activity

MAP = mean arterial pressure

MPA = moderate-intensity physical activity

MVPA = moderate-to-vigorous physical activity

NMD = nitroglycerin-mediated dilation

NO = nitric oxide

PAD = peripheral artery disease

RBCv = red blood cell velocity

SBP = systolic blood pressure

SR = shear rate

SR_{AUC} = shear rate area under the curve

ST = sedentary time

VPA = vigorous-intensity physical activity

VSMCs = vascular smooth muscle cells

Acknowledgements

I would like to thank my supervisor, Dr. Derek Kimmerly, for his hard work and dedication to his field that inspired me to pursue research. His consistent support and guidance have greatly contributed to my success and fostered a positive learning environment for his students to thrive. I would also like to thank my thesis committee, Dr. Olga Theou and Dr. Scott Kehler, and my external examiner, Dr. Travis Saunders, for challenging me and providing their valuable expertise and contributions to this project. Special thanks to Beverly Schwartz and Molly Courish for dedicating their time to analyzing the ultrasound files for this project, and everyone in the ACCE lab who pitched in to help with data collection sessions. Lastly, I would like to thank all my past and present lab mates for their friendships and support throughout this experience, and my family for their constant love and encouragement.

Chapter 1: INTRODUCTION

Sedentary behaviour can be defined as any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents while in a sitting, reclining or lying posture (141). Current 24-hour movement guidelines from the Canadian Society for Exercise Physiology recommends that adults accumulate ≤8 hours of total sedentary time (ST) per day and break up long periods of sitting as much as possible (116). Additionally, the World Health Organization recommends adults limit their total ST and replace it with physical activity whenever possible (17). However, the average Canadian adult exceeds these guidelines and accumulates ~9.6 hours of ST per day (126, 128). In addition, older adults residing in retirement communities accumulate >10 hours of daily ST (8). By engaging in excessive ST, Canadians put themselves at risk for chronic conditions associated with adverse health effects. For example, sedentary behaviour may contribute to all-cause mortality, cardiovascular disease (CVD), diabetes, cancer, hypertension, and depression (62). The development of these chronic health conditions negatively impacts quality of life and contributes to increased frailty levels (66).

Frailty can be characterized as a diversity in aging. People with higher frailty levels experience increased vulnerability and susceptibility to poor health outcomes as a result of declining function across multiple physiologic systems at varying rates (145). Frailty level (or biological age) may be more informative than chronological age and has been implemented as a routine measurement in some health care settings (e.g., geriatrics) (35). Frailty levels are typically higher in females versus males across the lifespan, despite mortality being lower in females at any frailty level (48). A multicenter clinical trial demonstrated that a health deficit-based measure of frailty level is a key risk factor

for cardiovascular morbidity and mortality (40). Frailty levels can be quantified using questionnaires that provide a frailty index score (FI), among other methods (81, 118). Excessive sedentary behaviours are associated with increased frailty, independent of habitual physical activity levels (66). In a study of community-dwelling older adults, the frailest of the population accumulated 9.5 hours of ST per day, while those who were deemed non-frail accumulated 8.2 hours (12). In addition, prolonged, uninterrupted sedentary bouts (e.g., >30 minutes) have a greater negative association with frailty (65). Therefore, reducing ST may be a key component to managing frailty among other chronic conditions in the aging population.

In Canada, CVD is the second leading cause of death (110), and was responsible for 25% of deaths in 2019 (125). A predominant risk factor for CVD is engagement in excessive amounts of sedentary behaviour (33), independent of physical activity and aerobic fitness levels (136). Specifically, peripheral artery disease (PAD) is directly linked with ST (99) and preceded by atherosclerosis (plaque build-up in arteries) (4). An early indication of increased atherosclerosis and PAD risk is dysfunction of the vascular endothelium (i.e., the innermost cell layer in blood vessels) (38), which can occur as a result of reduced peripheral blood flow during periods of ST (147). Arterial endothelial function can be assessed via the flow-mediated dilation (FMD) test. Importantly, a greater brachial artery FMD response is indicative of healthier endothelial function (15) and decreased risk of adverse cardiovascular events (58, 112). A previously conducted 16-week intervention in adults with increased CVD risk utilized a mobile health device with vibrotactile feedback. Following the intervention, they observed a decrease in ST and an associated increase in superficial femoral artery FMD (54). Furthermore, for the

purposes of this study, prolonged ST bouts that are associated with attenuated artery FMD responses can be defined as >1 hour (88, 137) and a greater number of daily prolonged sedentary bouts (i.e., >1 hour/bout) have been negatively correlated with popliteal artery FMD. This emphasizes the importance of habitual sedentary patterns on peripheral vascular health (120). However, there is limited evidence to support the impact on upper limb vessels (e.g., brachial artery FMD) and whether a sedentary behaviour reduction intervention can improve endothelial function and/or frailty levels.

A previous 12 day intervention that incorporated the Behaviour Change Wheel framework (21, 80) via a single one-on-one session, together with 4 automated text messages per day observed a reduction in total daily ST (21, 80). In addition, Koltyn et al. (2019) conducted a 4 week randomized control trial in 56 older adults that consisted of 4 weekly small-group educational workshops and reduced daily ST by ~1 hour (28). However, these studies were limited by relatively short intervention periods, homogenous populations (i.e., young healthy university students or older adults), and the majority lacked a randomized control trial design. Therefore, the purpose of this feasibility study was to: 1) assess the feasibility of a 9-month sedentary behaviour reduction, 2) determine the effectiveness of a 9-month sedentary behaviour reduction intervention to reduce total ST and the number of prolonged sedentary bouts in a population of sedentary adults, and 3) evaluate if adults who successfully reduce these sedentary metrics also improve their frailty, and brachial FMD outcomes. It was hypothesized that this intervention would feasible (i.e., low attrition, high acceptance, low cost and easily deliverable) and effectively decrease ST and the number of prolonged sedentary bouts, as well as increase the number of sedentary breaks, which would be positively associated with improved

frailty. Based on the previous literature, it is unclear if brachial FMD would be attenuated with reductions to habitual sedentary activity (113, 120). Therefore, the impact of total ST and/or sedentary patterns on brachial FMD was exploratory.

Chapter 2: LITERATURE REVIEW

2.1 Negative Health Impacts Associated with Excessive Sedentary Time

2.1.1 Quantifying Sedentary Time and Patterns

While physical inactivity refers to a lack of engagement in physical activity, sedentary behaviour is an independent construct. Specifically, sedentary behaviour can be defined as any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents (i.e., resting metabolic rate) while in a sitting, reclining, or lying posture (141). Canadians spend the majority of their day in sedentary postures (128) and most commonly accumulate their ST at work (108), on a screen (e.g., computers, tablets, phones, etc.) (107), or in passive transportation (24). The Canadian Society for Exercise Physiology recommends that adults (≥18 years) limit their ST to ≤8 hours per day (116). However, this guideline is based on very low quality evidence and there is limited research to suggest that meeting this guideline is associated with improved health outcomes (116). Furthermore, the World Health Organization suggests limiting total ST as much as possible (17). However, in 2020, the Canadians accumulated ~9.6 hours of ST per day (Figure 2.1) (24). During the global COVID-19 pandemic, there was a further increase in ST brought about by lock-downs and staying at home for health and safety reasons (132). This excessive accumulation of ST presents in both sexes and is exaggerated in older adults (Figure 2.1) (127). Therefore, Canadians exceed national ST recommendations and put themselves at an increased risk for associated adverse health effects.

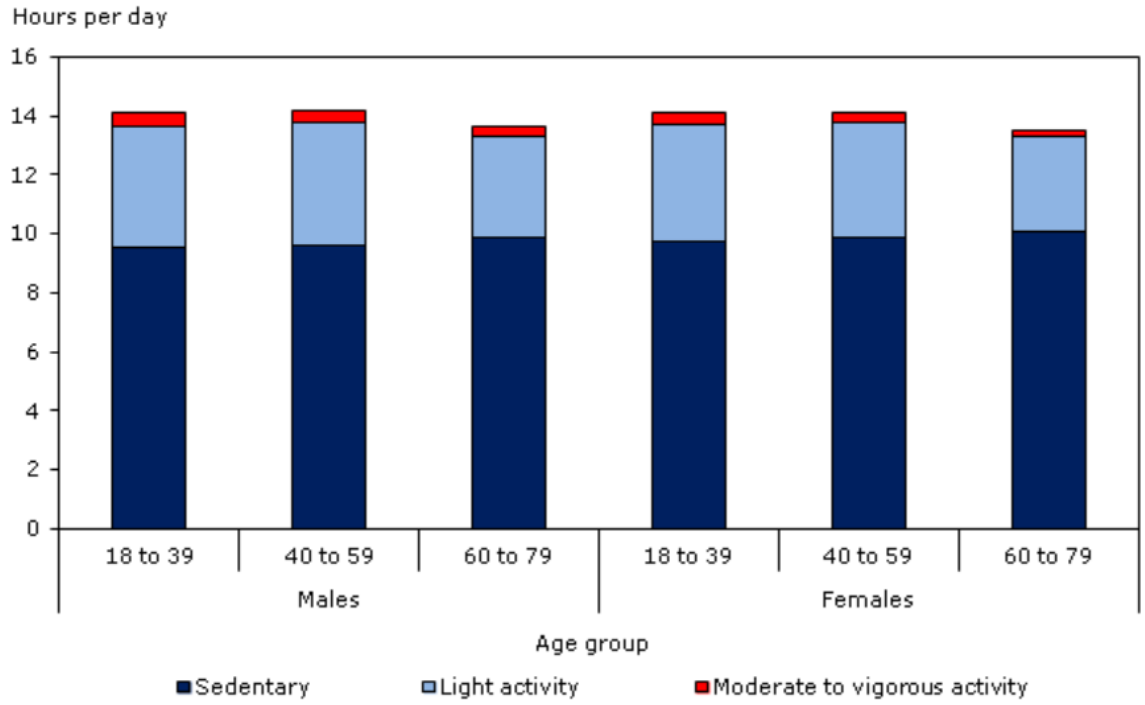

Figure 2.1. Total sedentary time (dark blue bars) accumulated across varying age categories of Canadian adults. Males 18-39 years, 40-59 years, and 60-79 years accumulated 9.5, 9.6, and 9.9 hours, respectively. Females 18-39 years, 40-59 years, and 60-79 years accumulated 9.7, 9.9, and 10.1 hours, respectively (127).

Total ST can be accumulated via several different patterns. For example, while two people could engage in the same amount of total ST, the length of sedentary bouts, which accumulate to make up this total, may differ. The Canadian Society for Exercise Physiology guidelines also recommend that adults should break up prolonged bouts of ST as often as possible (116). Previous literature has shown that prolonged sedentary bouts (i.e., ≥1 hour) are associated with negative health effects (34, 120, 137), but can be interrupted by periods of non-sedentary activity (i.e., sedentary breaks) (141)**.** Non-sedentary activity may include physical activity, characterized by bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level (e.g., light-, moderate-, or vigorous-intensity physical activity) (106) or standing (i.e., a stationary activity) (Figure 2.2). Similar to total ST, engagement in

excessive prolonged sedentary bouts and few sedentary breaks may contribute to diminished health outcomes and associated mortality (134, 137).

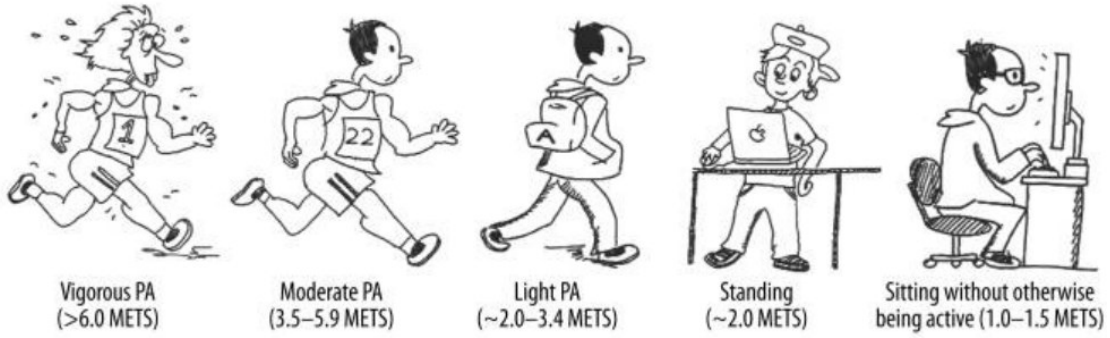

Figure 2.2. The movement continuum. As exercise intensity decreases, there is an associated decline in energy expenditure, measured in metabolic equivalents of task (METS). Sitting or sedentary time requires the smallest energy expenditure but other activities including standing or physical activity (PA) can be used to break up sedentary time (139).

2.1.2 Sedentary Behaviour and Frailty

People accumulate health problems at different rates and people who accumulate health problems at a higher rate experience increased frailty. The concept of frailty seeks to capture increased vulnerability and susceptibility to poor health outcomes as a result of declining function over multiple physiological systems (145). This puts frail people at increased risk for adverse health outcomes and mortality (119). While two individuals may have the same chronological age (i.e., in years), they may differ drastically from each other in health status (115). Furthermore, frailty can occur across the life course, but is more prevalent with advancing age (64). Therefore, the concept of frailty provides a unique perspective on aging by proxy of severity of illness and proximity to death.

There are a number of risk factors that increase frailty including age, sex, physical activity habits, and ST (65). Specifically, there is a positive association between high

levels of ST and increased frailty levels (12, 65). This puts older adults, particularly those who reside in retirement communities, at risk for frailty as they accumulate the most excessive amounts of ST (8) and simultaneously have diminishing physiological age. Furthermore, living in a private institution (e.g., retirement home, nursing home) has a strong association with poor physical frailty among older adults (72). This is particularly concerning when considering the global aging population. Importantly, the positive association between ST and frailty (i.e., increased ST associated with worse frailty) is independent of habitual physical activity levels (57). Blodgett et al. (2015) found that frailer adults (>50 years) were more likely to be sedentary. Specifically, the frailest community-dwelling older adults spent 9.5 hours per day sedentary compared to 8.2 hours amongst those who were non-frail (12) (Figure 2.3). Similarly, it has been reported that adults who spent larger percentages of their waking hours sedentary were more frail (66). In addition, those with increased frailty levels also accumulated more prolonged sedentary bouts lasting ≥30 minutes (66). In fact, prolonged sedentary bout accumulation may be more detrimental to frailty levels than total ST accumulation (65).

A study conducted in older adults (i.e., >65 years) assessed ST and sedentary patterns using hip-worn, triaxial accelerometry, and reported that both total ST and the proportion of that time spent in prolonged sedentary bouts lasting >10 minutes were positively associated with frailty, independent of age, sex, and comorbidities (32). Interestingly, the relationship between frailty and prolonged sedentary bouts was stronger than versus total ST (β, 95% CI = 0.079, 0.234 to 0.195 versus 0.015, 0.004 to 0.027). Furthermore, breaks in ST were also negatively related to frailty in the same cohort (β, 95% CI = -0.031, -0.048 to -0.014) (32). Another study, conducted in adults ≥50 years,

investigated sex-differences in the association between sedentary patterns with frailty and found that prolonged sedentary bouts were associated with worse frailty levels in females (63). However, sedentary break intensity (e.g., standing versus walking versus running) and duration were associated with attenuated frailty in both sexes (63). This emphasizes the importance of breaking up prolonged bouts of ST to improve frailty levels, particularly in older females. However, both studies were limited by their hip-worn monitor-based objective measures of ST and patterns, which cannot truly distinguish between sitting (sedentary) and standing (non-sedentary) postures. There was also no interventional evidence to suggest that decreasing ST or improving sedentary patterns was associated with better health outcomes.

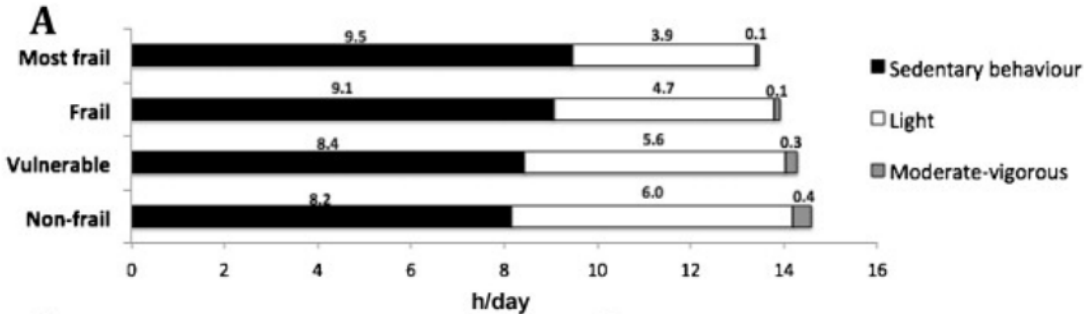

Figure 2.3. Total daily time (hours) spent in sedentary behaviours, light, or moderate-to-vigorous physical activity. The most frail older adults accumulated the highest amount of sedentary time (12).

2.1.3 Sedentary Behaviour and Peripheral Artery Health

Peripheral artery disease is directly linked with ST (99) and characterized by atherosclerosis development (4). One of the early indications of PAD is vascular endothelial dysfunction (38). This dysfunction promotes further pathology and may progress asymptomatically long before a cardiovascular event occurs (2). Healthy endothelial function is important for optimal tissue blood flow and blood pressure

regulation. Therefore, endothelial dysfunction contributes to the development of atherosclerosis and hypertension, which are risk factors for CVD and PAD (38).

In a community of Hispanic/Latino adults, ST was associated with a higher odds of PAD, independent of physical activity levels (144). Furthermore, Fullwood et al. (2019) conducted a cross-sectional study that established that older adults with symptomatic PAD accumulated more total ST compared to their asymptomatic peers (43). In an epidemiological study of 3.3 million patients in the United States, Berger et al. (2013) discovered that those who lived a more sedentary lifestyle had an odds ratio for PAD of 1.34 (CI%: 1.32-1.36) after adjustment for age, sex, race/ethnicity, body mass index, and family history of CVD (10). This means that those who lived a sedentary lifestyle were 34% more likely to develop PAD. Of note, they defined "sedentary lifestyle" as a lack of physical activity, which does not necessarily constitute being sedentary and represents a limitation of their study. This is because it is the reduced metabolic activity during ST that contributes specifically to pathology.

As previously mentioned, being sedentary is considered as any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents while in a sitting, reclining, or lying posture (141). The reduction in energy expenditure of these postures contributes to increased blood pooling in the lower leg due to gravitational forces (98), increased mean arterial pressure (122), and most importantly low blood flow and shear stress (148). Shear stress can be characterized as the tangential force of laminar blood flow on the endothelial surface of the blood vessel (101). Specifically, reductions in blood flow and shear stress contribute to established physiological mechanisms, which

have been proposed to contribute to atherosclerotic vascular disease (details provided below) (139), and increase the risk of experiencing a cardiovascular events.

2.2 Frailty as a Metric of Predicting Adverse Health Outcomes

2.2.1 Linking Frailty and Cardiovascular Health

Considering that frailty is impacted by a wide range of health deficits, sedentary activity may contribute to frailty in a wide variety of ways. For example, increased sedentary activity is linked with poor mental health and depression (133). Physiologically, sedentary activity is also associated with higher cancer rates (74), impaired lipid metabolism (i.e., increased metabolic disease incidence) (100), impaired glucose metabolism (i.e., elevated risk for diabetes) (51), and dysregulation of hemodynamics that may contribute to vascular dysfunction (142). Each of these conditions is related to pathology in multiple physiological systems that is fundamental to the development of frailty. Specifically, frailty is a marker of poor prognosis for cardiovascular and geriatric outcomes across different populations including severe aortic valve disease, ischemic heart disease, or peripheral vascular disease (29). Across both sexes, carotid intima-media thickness (an index of central cardiovascular health) is positively associated with frailty in both older and middle-aged adults (89). Furthermore, frailty is more common in individuals with CVD compared to those without (1), and those who live with frailty have an increased risk of CVD-related morbidity and mortality (146). This demonstrates the interconnected relationship between frailty and cardiovascular health and how risk factors, such as ST, may mediate this relationship.

There is a bidirectional relationship between frailty and cardiovascular health whereby diminished cardiovascular health can accelerate frailty and frailty can increase the risk of adverse health outcomes in people with diminished cardiovascular health (131). This relationship may be explained by their common underlying pathophysiology between frailty and cardiovascular health. Cardiovascular health and frailty are both influenced by the cumulative burden of risk factors. Specifically, increased biomarkers of inflammation, such as C-reactive protein, interleukin, fibrinogen, and white blood cell count are present in both chronic conditions (124). In addition, markers of oxidative stress including lipoprotein phospholipase or derivatives of reactive oxygen metabolites are directly associated with frailty (124). As such, frail individuals have diminished antioxidant parameters, which contribute to poor arterial health (124). Furthermore, higher levels of frailty are directly associated with arterial stiffness (as assessed using carotid-femoral pulse wave velocity) (95). Even those classified as 'prefrail' have augmented arterial stiffness compared to those who are non-frail (95). Habitual activity patterns also act as a risk factor that contributes to both frailty and cardiovascular health. Although not the population of interest for this study, individuals with CVD are susceptible to reduced physical activity and increased sedentary behaviour. If their condition goes untreated, decreased functional mobility may occur over time. Therefore, timely and/or prevention treatment of cardiovascular conditions is essential for delaying frailty (131). Together, this emphasizes the interconnected relevance of frailty and cardiovascular health to this project (Figure 2.4).

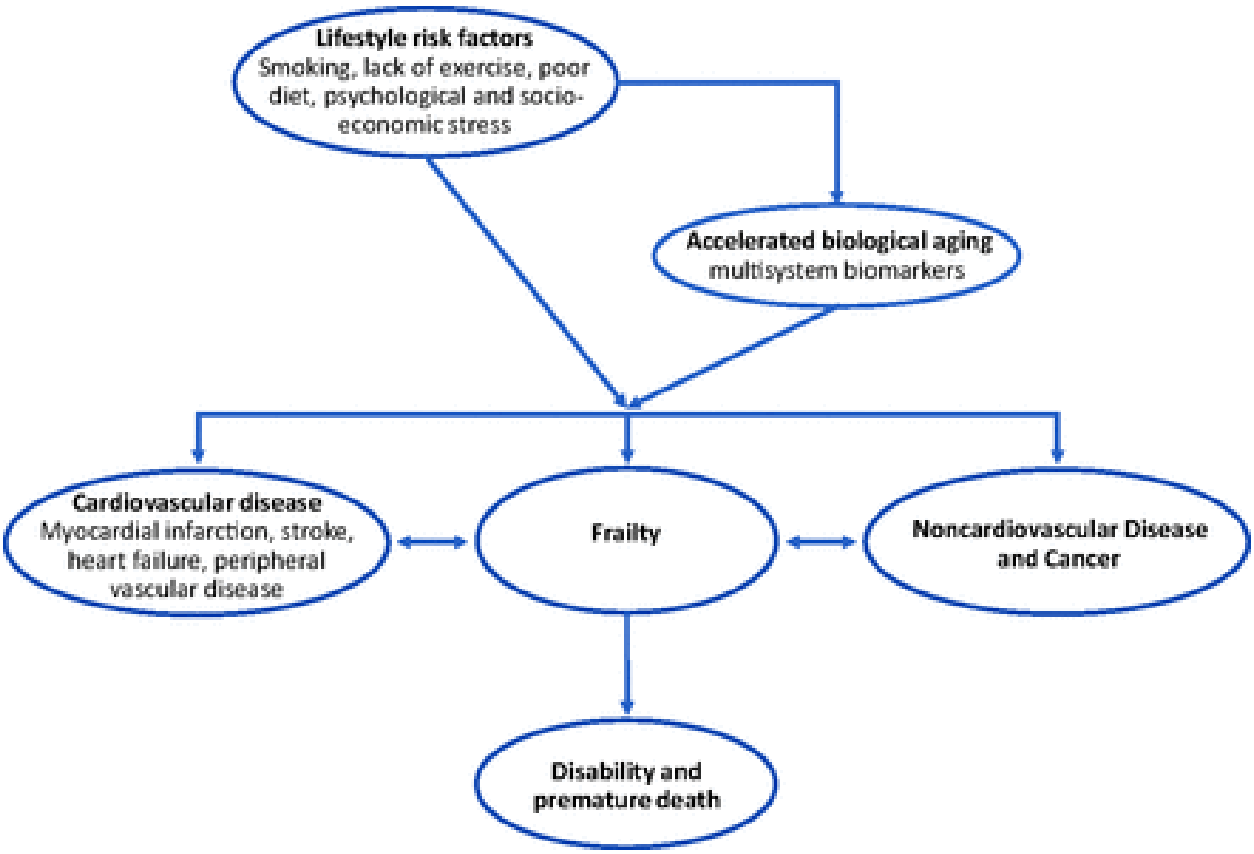

Figure 2.4. Proposed mechanistic links between cardiovascular disease and frailty. Lifestyle risk factors and pathophysiological pathways involving multiple body systems are associated with an increased risk of both frailty and cardiovascular disease. In addition, cardiac and cerebrovascular diseases increase the risk of frailty, and frailty increases the risk of disability and death (131).

2.2.2 Quantifying Frailty

Currently, there are >75 different assessment tools used to quantify frailty. The two most dominant paradigms to assess frailty are the evaluation of deficits (81) and the perspective of frailty as a biological syndrome resulting from cumulative declines across multiple physiologic systems (42). There is no general consensus on how to best measure frailty, but there are a few outstanding tools derived from these concepts including the frailty phenotype (42), and the frailty index [FI, (81)]. Specifically, the FRAIL scale considers someone frail if they experience ≥3 of the following: 1) fatigue, 2) resistance

(i.e., diminished muscular strength), 3) ambulation problems, 4) illness, and 5) loss of weight. Similarly, the frailty phenotype considers someone frail if they experience ≥3 of the following characteristics: 1) weight loss, 2) weakness, 3) exhaustion, 4) poor walking speed/gait characteristics, and 5) physical inactivity. Conversely, the FI aims to count deficits in health (i.e., signs, symptoms, functional impairments, and laboratory abnormalities), as the more deficits a person has, the more likely they are to be frail. The FI is expressed as a ratio of the number of deficits present to the number of deficits considered (118). Therefore, a higher FI (i.e., a value closer to '1') is associated with poorer health outcomes.

There are both advantages and disadvantages to the use of each scale. The frailty phenotype categorically defines the presence/absence of a condition and provides a clinically friendly variable to guide decisions regarding the possible need of adapted care and/or interventions. However, specific conditions, particularly disabling conditions, may affect the predictive value of the phenotype for negative health-related events (25). Specifically, due to the simplistic nature of this assessment, a ceiling effect may be encountered once one or more chronic conditions are present in an individual whereby further decreases in frailty are difficult to detect. In contrast, the FI consists of a long checklist of clinical conditions and/or diseases where ~50 items have been shown to be the most robust, but versions that include as few as 20 deficits have been explored (25). This relatively more extensive tool is more sensitive to health modifications compared to the phenotype and may be an alternative tool to ascertain the effectiveness of any intervention and describe health trajectories over time (25). Therefore, the phenotype may be more suitable for an immediate identification of non-disabled older adults at risk

of negative events, but the FI may be more appropriate for use in an intervention setting. For this reason, this study will implement the FI to assess frailty in addition to ultrasound-based measures to evaluate the regulation of arterial diameter and blood flow.

2.3 Regulation of Arterial Diameter and Blood Flow

2.3.1 Functional Anatomy of the Vascular Endothelium

Arteries can be divided into three distinct layers (Figure 2.5) (59). The outermost layer [*tunica adventitia* (or *externa*)] is composed of perivascular adipose tissue, fibroblast cells, collagen fibers, and sympathetic nerve endings; the middle layer (*tunica media*) is comprised mainly of vascular smooth muscle cells (VMSCs); and the innermost layer (*tunica intima*) consists of a monolayer of endothelial cells known as the endothelium. The primary regulatory functions of a healthy endothelium are to minimize thrombosis and inflammatory processes within blood vessels, and maintain vascular tone (71). Vascular tone can be defined as the degree of vasoconstriction (i.e., contraction of VSMCs) relative to the maximally dilated state (46). The endothelium achieves this through processes of vasodilation (i.e., relaxation of VSMCs) and vasoconstriction via the production of vasoactive substances (69). Specifically, endothelial cells sense hemodynamic changes (e.g., increases/decreases in blood flow and shear stress) and blood borne chemical signals (e.g., bradykinin, acetylcholine, etc.) to trigger the release of these vasoactive substances from the *tunica intima* for diffusion into the *tunica media* where they act upon the VSMCs (69). Vasodilation is impacted by key substances such as nitric oxide (NO), prostaglandins, and endothelial-derived hyperpolarizing factors that are produced by the vascular endothelium (117).

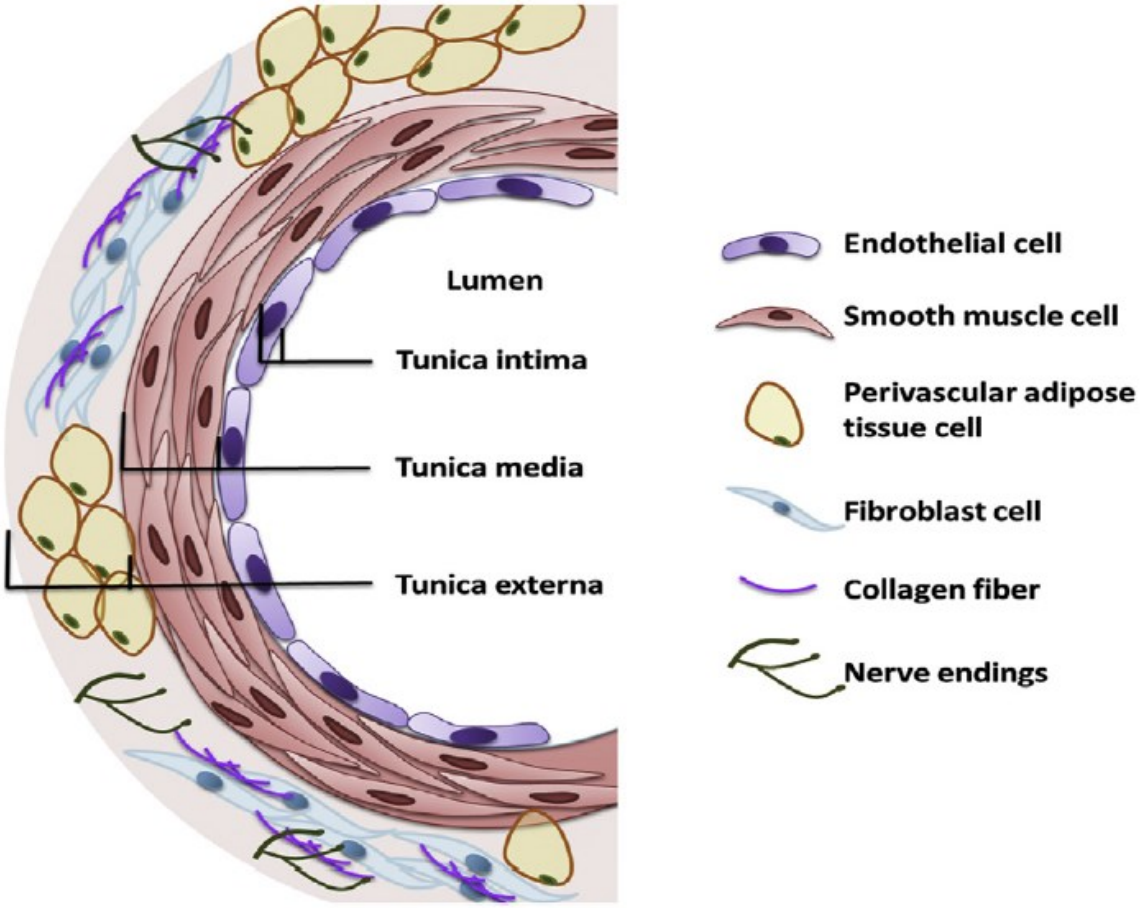

Figure 2.5. Cross sectional view of a peripheral artery. The outermost layer [*tunica externa* (or *adventitia*)] is composed of perivascular adipose tissue, fibroblast cells, collagen fiber, and sympathetic nerve endings. The middle layer (*tunica media*) contains the vascular smooth muscle cells. The innermost layer (*tunica intima*) lines the lumen and is composed of a monolayer of endothelial cells (155).

Nitric oxide is the most predominant vasodilator and is synthesized in the endothelium by endothelial nitric oxide synthase (eNOS) from the amino acid L-arginine via two main mechanisms (117) (Figure 2.6). Firstly, when agonistic molecules (e.g., bradykinin, acetylcholine, and/or thrombin) bind to endothelial membrane receptors, or when shear stress activates Ca^{2+}/K^{+} channels, there is an influx of calcium into the endothelial cells. This calcium binds with the cytosolic protein Calmodulin, while previously inactive eNOS detaches from the integral membrane protein, caveolin (117).

The newly formed Ca^{2+}-Calmodulin complexes bind to eNOS causing it to convert L-arginine to NO using cofactors including nicotinamide adenine dinucleotide phosphate and tetrahydrobiopterin. Secondly, eNOS activation via phosphorylation is a calcium-independent mechanism that regulates NO production (111). Shear stress initiates eNOS phosphorylation through Protein Kinase-A and Protein Kinase-B (Figure 2.6) (91). There is evidence to suggest that laminar shear stress is detected by hair-like protrusions on the lumen-facing surface of the endothelial cell known as the glycocalyx (82). Several studies have reported that the majority of NO produced in endothelial cells is via calcium-independent mechanism caused primarily by increases in shear stress (6, 30). Regardless of the mechanism, NO then diffuses from the endothelial cells to the VSMCs.

As previously mentioned, NO is not the only vasodilator produced by the vascular endothelium. However, it has been demonstrated that vasodilation still occurs when NO production is blocked, via the eNOS inhibitor L-NMMA, indicating the presence of other endothelial-derived vasodilatory substances (11). Two other predominant vasodilators are endothelium-derived hyperpolarizing factors and prostaglandins (e.g., prostacyclin). Similar to NO, the production of endothelium-derived hyperpolarizing factors are initiated when either agonistic molecules (e.g., acetylcholine, bradykinin) or elevated shear stress act upon the endothelial cells to increase intracellular calcium concentration (18). This leads to the activation of the enzyme phospholipase, which converts membrane phospholipids to arachidonic acid. Newly formed arachidonic acid activates cytochrome p450 epoxygenase that results in the production of epoxyeicosatrienoic acids. This activates Ca^{2+}-dependent K^{+} channels and the generation of cyclic adenosine monophosphate in the endothelial and VSMCs to elicit hyperpolarization.

Hyperpolarization across the endothelium occurs via the enhancement of electrotonic spread of hyperpolarization through the vessel wall (18, 50). Furthermore, arachidonic acid can also activate the enzyme cyclooxygenase that is responsible for the production of prostaglandin H_2 (7), which is converted to prostacyclin (via prostacyclin synthase) and diffuses to the VSMCs to elicit vasodilation (Figure 2.7).

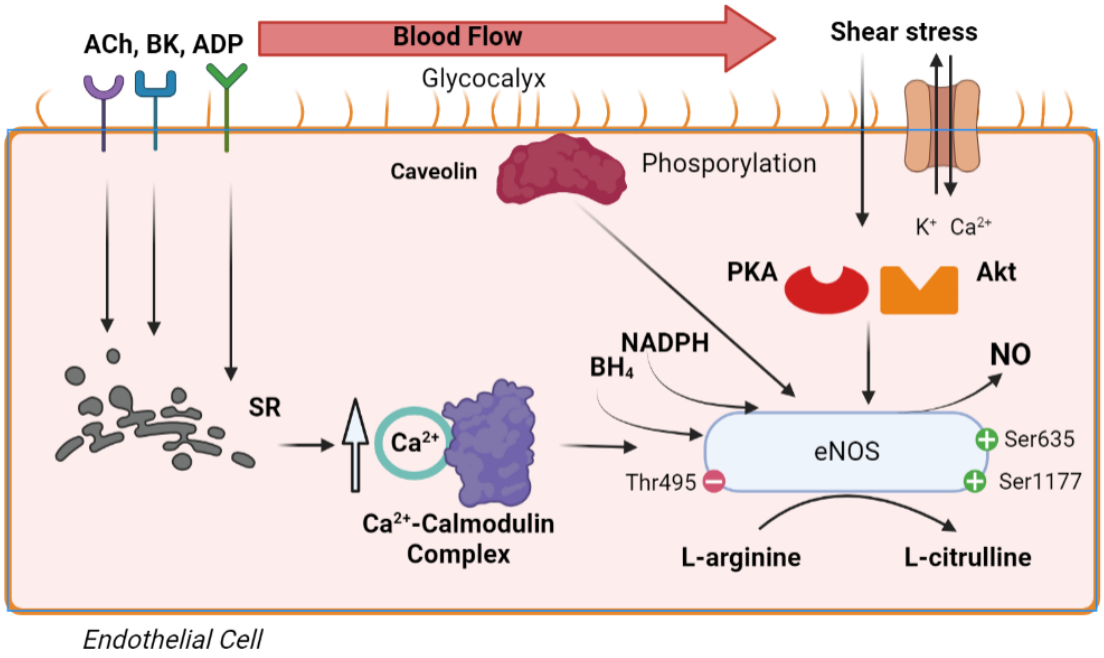

Figure 2.6. Visual depiction of two methods of nitric oxide (NO) production within endothelial cells (30). Shear stress or blood borne agonists such as acetylcholine (ACh), bradykinin (BK), or adenosine diphosphate (ADP) trigger an increase in intracellular Ca^{2+} from the sarcoplasmic reticulum (SR) or receptor operated calcium channels. This Ca^{2+} binds with Calmodulin, which elicits the activation and detachment of endothelial nitric oxide synthase (eNOS) from caveolin. Alternatively, shear stress activates Protein Kinase A (PKA) and Protein Kinase B (Akt). PKA phosphorylates Ser1188 and Ser635, while Akt only phosphorylates Ser177 to activate eNOS and cause the subsequent activation of eNOS. Conversely, Thr495 is an inhibitory site that can be dephosphorylated by agonists such as bradykinin to further promote NO production. The cofactors tetrahydrobiopterin (BH_4) and nicotinamide adenine dinucleotide phosphate (NADPH) aid in the production of NO as L-arginine is degraded to L-citrulline. Figure created with BioRender.com.

In contrast to these endothelium-derived vasodilators, vasoactive peptides such as endothelin-1 (ET-1) and angiotensin II have a vasoconstrictor function (140). Specifically, ET-1 is an endothelial-dependent vasoconstrictor that is augmented with endothelial dysfunction and plays a role in the development of PAD (143). Endothelin converting enzyme, located in the endothelial cell membrane, converts Big ET-1, the inactive polypeptide, to ET-1 when it is stimulated by factors such as low shear stress, thrombin, angiotensin II, vasopressin, or reactive oxygen species (68). Endothelin-1 binds to two receptor subtypes: ET_A or ET_B (104). However, ET_A receptors are more predominant on the VSMCs and regulate vasoconstriction, whereas ET_B are less dominant and mediate vasodilation via the activation of eNOS.

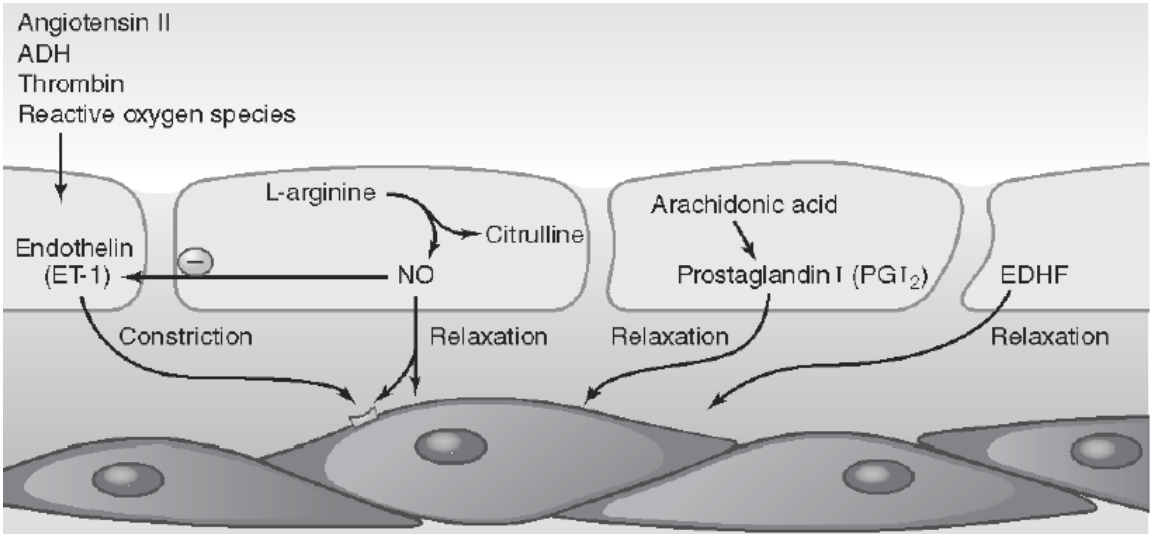

Figure 2.7. Visual summary of pathways impacting vascular tone of the arterial vascular smooth muscle cells. In response to angiotensin II, antidiuretic hormones (ADH), thrombin, or reactive oxygen species, endothelin-1 (ET-1) elicits vasoconstriction. In contrast, nitric oxide (NO), prostacyclin (PGI_2), and endothelial-derived hyperpolarizing factors (EDHF) elicit vasodilation via relaxation of vascular smooth muscle cells (123).

2.3.2 Functional Anatomy of Vascular Smooth Muscle Cells

Vascular smooth muscle cells are fusiform in shape, which contributes to dynamic changes to the lumen diameter of blood vessels (152). The actin and myosin filaments are

arranged in an array pattern that allows for multidirectional contraction of these cells (Figure 2.8) (152). During cross-bridge formation, tension is concentrated at the dense bodies where the actin filaments are anchored to the sarcolemma of the VMSCs. These structural features cause the muscle fibers to contract in a way where the ends of the fusiform cell are pulled toward the centre to create a 'bulging' effect and a decrease in luminal diameter (Figure 2.8) (152). The contraction of VSMCs is elicited by an influx of calcium from either the extracellular space or the sarcoplasmic reticulum. As in endothelial cells, calcium binds to Calmodulin to form a calcium-Calmodulin complex, which activates the enzyme myosin light chain kinase. The role of myosin light chain kinase is to phosphorylate the myosin light chains, which causes myosin heads to bind with actin for cross-bridge formation (and hence contraction).

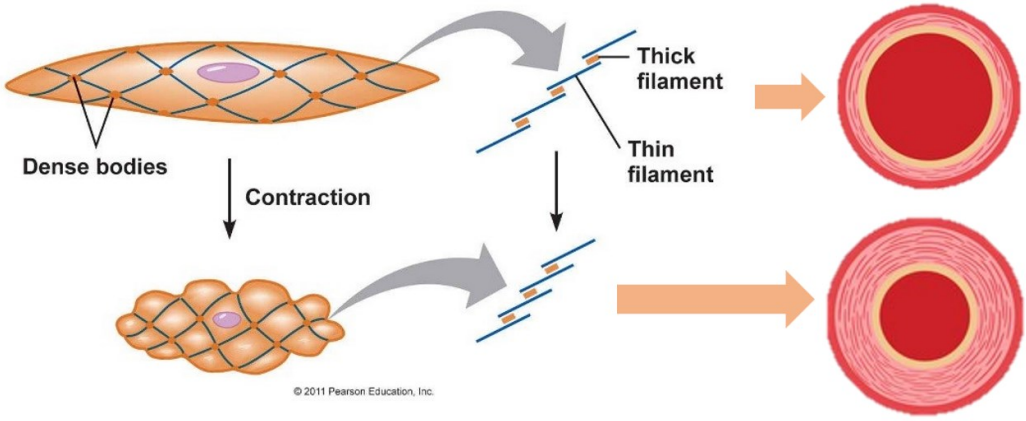

Figure 2.8. Thick and thin filaments are arranged in an array formation within the vascular smooth muscle cells. This arrangement allows the relaxed vascular smooth muscle cells to be flat and elongated. When contraction is elicited, the arrayed filaments shorten causing the vascular smooth muscle cells to enlarge in circumference. The right images provide a cross-sectional view of an artery during vasodilation (top) and vasoconstriction (bottom) where the arterial lumen increases and decreases in size, respectively (16).

When a vasoconstricting agonist (e.g., ET-1, norepinephrine, angiotensin II) binds to its respective receptors on the surface of the VSMCs, it causes an influx of calcium.

Specifically, when ET-1 binds to ET_A receptors in the *tunica media*, calcium enters the VSMCs through receptor-operated channels. The influx of calcium causes the depolarization of the VSMCs and the subsequent activation of a G_q-protein coupled receptor (104). This initiates a second messenger signaling cascade where the G_q-protein coupled receptor activates phospholipase-C that produces inositol trisphosphate and diacylglycerol. Inositol trisphosphate binds to calcium channel receptors on the sarcoplasmic reticulum to induce calcium release into the cell. Additionally, diacylglycerol activates protein kinase-C and upregulates VSMC surface calcium channels to further increase intracellular calcium concentrations and elicit vasoconstriction via the phosphorylation of the myosin light chains (via myosin light chain kinase) (140).

2.3.3 Cell-Signaling Pathways of Nitric Oxide-Mediated Vasodilation

Due to a consistent stimulus (e.g., sympathetic activity) acting on the VSMCs to promote vasoconstriction, vasodilating and vasoconstricting substances are constantly in competition with each other to achieve vascular tone. Although there are multiple endothelial-derived vasodilators, NO is the most prominent vasodilator that strives to offset the vasoconstricting capacity of ET-1, as well as sympathetic nerve activity that contributes to basal tone of the systemic vasculature. Once NO crosses the basal lamina and reaches the VSMCs, it binds to and activates the protein receptor, soluble guanylyl cyclase (117). Soluble guanylyl cyclase increases the conversion rate of guanosine 5'-triphosphate to cyclic guanosine monophosphate. Cyclic guanosine monophosphate activates protein kinase G, which prevents calcium influx via voltage-gated calcium channels, inositol triphosphate-derived release of calcium from the sarcoplasmic

reticulum, promotes the reuptake of cytosolic calcium into the sarcoplasmic reticulum via calcium pumps and activates calcium pumps on the plasma membrane to increase calcium expulsion (155). As intracellular calcium and calcium-Calmodulin complex concentrations decrease, there is less activation of myosin light chain kinase. Simultaneously, intracellular calcium depletion also increases the activity of myosin light chain phosphatase, which removes the phosphate groups from the myosin light chains, decreasing cross-bridge formation and promoting vasodilation (Figure 2.9) (155).

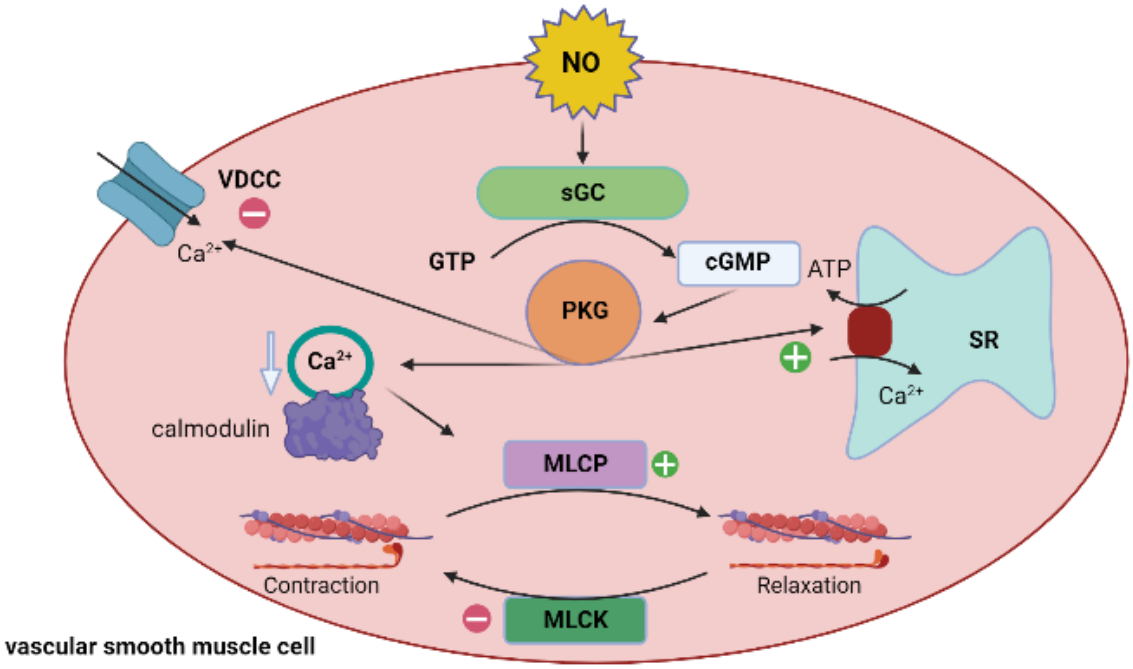

Figure 2.9. Nitric oxide (NO) diffuses into the vascular smooth muscle and activates soluble guanylyl cyclase (sGC), which increases guanosine triphosphate (GTP) conversion to cyclic guanosine monophosphate (cGMP). The second messenger cGMP then activates Protein Kinase G (PKG), which closes voltage-dependent calcium (Ca^{2+}) channels (VDCC) and upregulates calcium-pumps on the sarcoplasmic reticulum (SR) to decrease intracellular calcium concentrations. The net result is a reduction in the number of calcium-Calmodulin complexes. Myosin light chain phosphatase (MLCP) is activated while myosin light chain kinase (MLCK) is inhibited, which results in the net removal of phosphate groups from the myosin light chains, decreasing cross-bridge formation and causing vasodilation. ATP, adenosine triphosphate. Figure created using BioRender.com.

2.3.4 Roles and Functions of Endothelial-Derived Nitric Oxide

Once NO is produced, it serves several different functions. Specific to this project, the primary regulatory function of NO is to induce vasodilation. However, for completeness, NO also regulates the processes of thrombosis and inflammation. Specifically, NO plays a role in maintaining blood flow through conduit arteries by modulating platelet-endothelial interactions (73). When platelet coagulation is not regulated it leads to vascular occlusion and possible cardiovascular events. In the circulation, platelets are usually in an inactive form due to inhibition from substances including NO (73). Nitric oxide inhibits platelet activation in the vasculature via cyclic guanosine monophosphate production and the subsequent reduction in cytosolic calcium concentrations as highlighted above. Furthermore, diminished calcium concentrations reduce the activation of platelets and aggregation-related mechanisms (73). Activation of platelets may be harmful to arterial health as they play a key role in the development of atherosclerosis and coagulation that can occlude the lumen (77). Specifically, NO is involved in preventing adherence of circulating monocytes to the vascular endothelium, which contributes to dysfunction (77). In addition, NO may inhibit the activation of nuclear kappa B, a transcription factor that is responsible for proinflammatory and proatherosclerotic responses of endothelial cells and VMSCs (77). This emphasizes that NO is an important substance for overall vascular health.

2.3.5 Ultrasound Assessment of Peripheral Artery Health

The magnitude of endothelial function can be quantified using the clinically relevant FMD test (135). Flow-mediated dilation refers to an endothelium-dependent and NO-mediated dilation of conduit arteries in response to a distal ischemia-induced reactive

hyperemia (i.e., an increase in blood flow and shear stress) (135). The test consists of a 2-minute baseline measurement of lumen diameter and blood flow, followed by inflation of a distal cuff to supra-systolic levels for a period of 5-minutes (135). Once the cuff is released there is an increase in blood flow, which increases anterograde (forward moving) shear stress on the endothelial cells (30, 135). This acts as the stimulus for the production and release of NO, therefore causing a vasodilatory response (increase in lumen diameter). A larger vasodilatory response is indicative of a healthier endothelium and greater NO bioavailability. The current study will measure FMD responses in the brachial artery as it is inversely associated with future CVD events (112). Furthermore, Ras et al. (2013) found that for each 1% increase in relative brachial artery FMD there was an associated ~13% relative risk reduction in experiencing an adverse cardiovascular event (112). The brachial FMD assessment provides early detection of CVD, where FMD responses are lower in patients with coronary artery dysfunction (15).

2.4 Impact of Sedentary Behaviours on Peripheral Vascular Function

2.4.1 Dysfunction of the Vascular Endothelium

Endothelial dysfunction is a key contributor to the development of atherosclerosis, a defining feature of PAD (16). As previously mentioned, maintaining an appropriate balance between vasodilation and vasoconstriction is essential in the regulation of vascular tone and endothelial health (30). Atherosclerosis can be caused by pathophysiological stimuli such as hypertension, aging, environmental toxins (e.g., tobacco), and hemodynamic forces such as disturbed/decreased blood flow, all of which promote lesions of the endothelial cells (1). Atherosclerosis manifests at the site of these lesions and promotes permeation, entrapment, and modification of circulating

lipoproteins within the subendothelial space (16). Due to lesions, the endothelium experiences increased permeability of circulating plasma lipoproteins, mainly low-density lipoproteins, which are recruited into the intimal wall (77). They are then oxidized by existing free radicals from macrophages within endothelial cells or VSMCs. Oxidized low-density lipoproteins cause endothelial surface expression of vascular cell adhesion molecules, such as vascular cell adhesion molecule-1 and P-selectin, which bind to monocytes in the circulation (77). Meanwhile, oxidized low-density lipoproteins also stimulate the release of chemokines, such as monocyte chemoattractant protein-1. Together, the vascular cell adhesion molecules and the chemokines recruit these monocytes into the *tunica intima*. Within the intima, the monocytes differentiate into lipid-laden macrophages, which internalize the oxidized low-density lipoproteins to form foam cells. In addition, macrophages release proinflammatory cytokines that increase the expression of low-density lipoprotein receptors on the endothelial surface. This initiates a vicious cycle where more low-density lipoproteins are recruited into the intimal layer to proliferate the atherosclerotic process (77) (Figure 2.10). This process is further intensified by growth factors (e.g., platelet-derived growth factor, fibroblast growth factor, transforming growth factor) that elicit migration of VSMCs from the *tunica media* into the *tunica intima* where they undergo proliferation before they deposit extracellular matrix components onto pre-existing foam cells (77). This solidifies the formation of a thick fibrous plaque within the intimal wall (16).

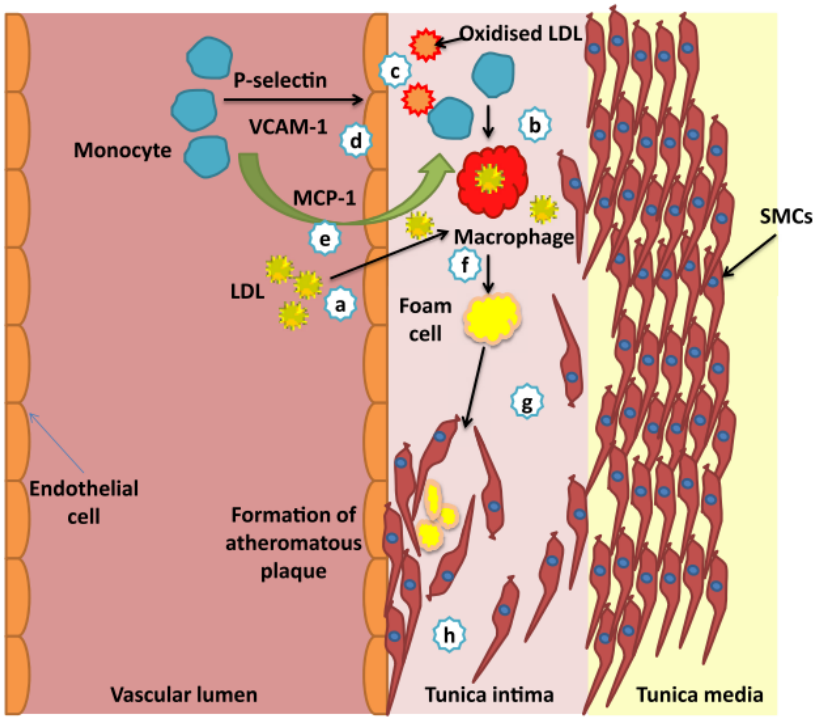

Figure 2.10. Process depicting how endothelial dysfunction contributes to the development of peripheral artery disease via the pathogenesis of atherosclerosis: (a) when a lesion is present, low-density lipoprotein (LDL) accumulates within the intima, (b) LDLs becomes oxidized by free radicals, (c) oxidized LDLs cause increased expression of cell adhesion molecules on the endothelial surface, (d) vascular cell adhesion molecules [vascular cell adhesion molecule-1 (VCAM-1 and P-selectin)] recruit monocytes from the circulation to the endothelium, (e) monocyte chemoattractant protein-1 (MCP-1) brings monocytes into the intima, (f) monocytes differentiate into macrophages that engulf oxidized LDLs to form foam cells, (g) vascular smooth muscle cells (SMCs) migrate from the *tunica media* to the intima due to growth factors, (h) vascular smooth muscle cells undergo proliferation and deposit extracellular matrix components around the foam cells to form an atherosclerotic plaque within the vessel wall (77).

Over time, the population of inflammatory cells surrounding these plaques can encourage proteases to act on the extracellular matrix of the plaque and create structural instability. Furthermore, unstable plaques are more susceptible to rupturing into the arterial lumen and to cause an atherothrombotic occlusion that could potentially be life threatening. Conversely, even if the lesion remains stable, the plaque build-up can encroach on the lumen space to disturb blood flow and cause ischemic symptoms (i.e., pain in limbs and/or chest) that are associated with CVD (46) (Figure 2.11).

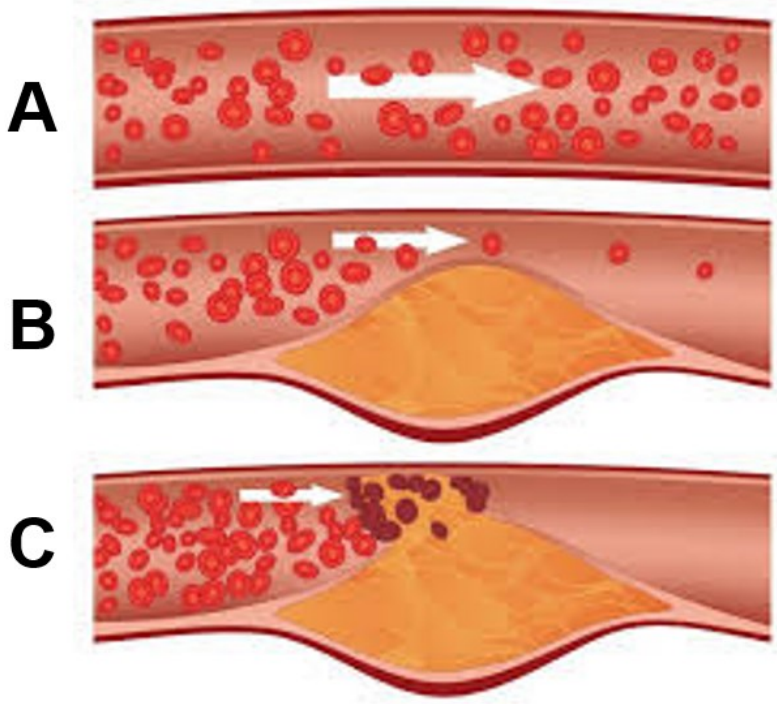

Figure 2.11. Progression of atherosclerosis in a conduit artery depicted in three stages *(46)*. (A) healthy blood vessel with laminar (streamlined) flow. (B) atherosclerotic lesion encroaching on the arterial lumen causing decreased blood flow to downstream tissues. (C) atherosclerotic rupture into the lumen causes full occlusion and distal ischemia.

Over time, these responses lead to atherosclerosis (117) and a decrease in the bioavailability of NO (26). Nitric oxide production can be further diminished in the presence of reactive oxygen species (e.g. superoxide) that reduces the cofactor tetrahydrobiopterin (BH_4) to BH_3-, which results in the uncoupling of eNOS (117). Additionally, existing NO can be degraded into inactive forms (i.e., peroxynitrite) by these reactive oxygen species (117). While NO bioavailability is defined by both production and utilization of NO, the current literature emphasizes that a decrease in production is more pertinent to endothelial dysfunction (155). Without NO as an inhibitor, there is an increased production of ET-1, causing a chronic vasoconstrictor response an increase in platelet aggregation (26). Progressively, endothelial dysfunction and atherosclerosis will have serious vascular consequences (26) (Figure 2.11).

Due to the build-up of atherosclerosis in the peripheral arteries, the arterial lumen becomes partially occluded, causing a disruption in blood flow to distal tissues (77). Following the development of atherosclerosis, the blood is protected from exposure to the plaque via the fibrous cap (96). However, when the fibrous cap is thin, or inflammation inhibits the synthesis of extracellular matrix components from the VSMCs, the atherosclerotic lesion is vulnerable to rupture. Once the lesion becomes unstable (i.e. when there is a pronounced hemodynamic stressor applied), the encapsulated contents of the lesion rupture into the arterial lumen and cause further occlusion (96). The rupture of plaque into the arterial lumen exposes the contents of the atherosclerotic lesion to platelets and other proteins associated with the coagulation pathway (77). Platelets undergo adhesion, aggregation, and activation to release vasospastic substances such as thromboxane-A2, serotonin, platelets 3 and 4, and coagulation factors that initiate the coagulation cascade. A complicated matrix of the platelets and the fibrin molecules then form a platelet 'clump'. In some cases, when the thrombotic clump is firmly anchored to the arterial wall, it continues to grow until the entire arterial lumen is occluded (96). Alternatively, when the clump is insecure, prominent increases in blood flow can dislodge and embolize to potentially cause clinical cardiovascular events such as stroke, amaurosis fugax, or digital ischemia (77). Lifestyle behaviours (e.g., excessive ST, physical activity, etc.) contribute to this development of atherosclerosis (70) and interventions may be needed to reduce the risk of adverse health effects.

2.4.2 Acute Impacts of Sedentary Time on Endothelial Function

Several studies have been conducted in a laboratory setting to investigate the effects of acute prolonged sedentary bouts on peripheral artery endothelial-dependent

vasodilation. For example, Restaino et al. (2015) recruited 11 healthy young males (27±1 years) to participate in a 6-hour bout of prolonged sitting (113). Flow-mediated dilation was assessed in the popliteal and brachial arteries at baseline, following 6 hours, and then following a 10-minute walk at a self-selected pace. They observed that popliteal, but not brachial FMD, was blunted after sitting, but returned to baseline levels after walking. Similar findings have been observed in other acute lab-based prolonged sitting studies (61, 113, 138). Importantly, Thosar et al. (2015) conducted two prolonged sitting trials in 12 healthy young males (137). In the first trial, participants engaged in uninterrupted sitting for the entire 3-hour duration. However, the second trial had participants engage in a similar prolonged sedentary bout, but were required to walk on a treadmill for 5-minutes at a speed of 2-miles per hour after 0.5, 1.5, and 2.5 hours of sitting. Measures of superficial femoral artery FMD were assessed at baseline, 1, 2, and 3 hours of sitting. They reported declines in FMD and shear rate after only 1-hour of sitting, which persisted after 3 hours (Figure 2.12). Importantly, superficial femoral FMD outcomes were protected when participants engaged in intermittent activity breaks, highlighting the potentially beneficial role of sedentary breaks in protecting endothelial function (Figure 2.12).

Carter et al. (2019) sought to investigate how the duration and frequency of breaks in ST impacted lower-limb artery endothelial dysfunction (20). Using a 4-hour uninterrupted bout of sitting in 15 adults (5 females, 36 ± 10 years), they examined the impact of no breaks, 2-minute walking breaks every 30 minutes, and 8-minute walking breaks every 120 minutes on superficial femoral artery blood flow, shear stress and FMD responses. They found that following the sitting bout, reductions in superficial femoral

artery blood flow were only prevented with 8-minute walking breaks every 120 minutes (20). However, neither the longer (i.e. 8-minute) or shorter (i.e. 2-minute) duration walking bouts where effective at reducing sitting-induced impairments in FMD (20). They attributed this discrepancy to permitted leg movements during sitting time (i.e., leg shaking and bathroom breaks).

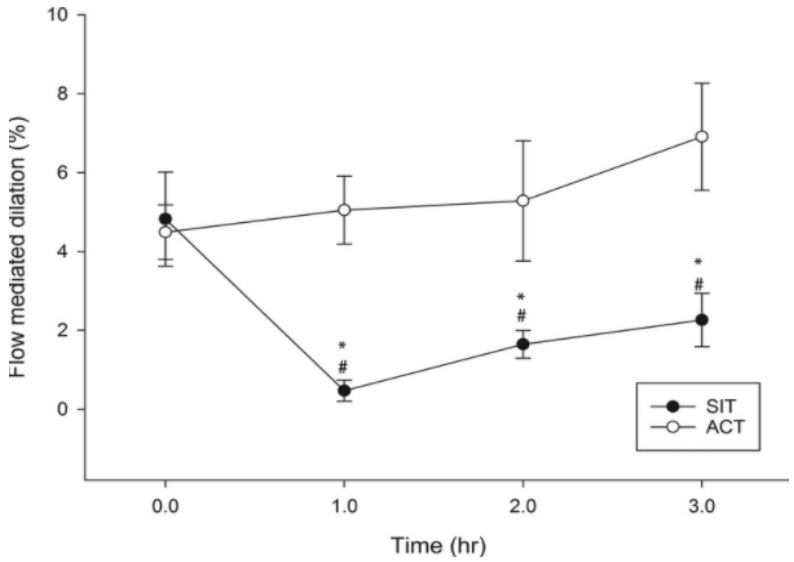

Figure 2.12. Superficial femoral artery flow-mediated dilation responses before (0.0 hours) and during an uninterrupted 3-hour bout of sitting without (SIT) versus with active breaks (ACT). #, P<0.05 versus baseline; *, P<0.05 between SIT versus ACT (137).

2.4.3 Chronic Impacts of Sedentary Time and Patterns on Endothelial Function

Boyle et al. (2013) investigated the impact of reduced physical activity with brachial artery FMD (14). In a sample of 11 recreationally active males (25 ± 2 years), brachial and popliteal artery FMD were assessed before and after instructing participants to accumulate <5,000 steps/day and refraining from planned exercise. In some cases, subjects were pushed in a wheel chair to reduce physical activity and increase sedentary activity. Popliteal artery FMD decreased with reduced activity, whereas brachial artery FMD was unchanged. Of note, physical inactivity does not equate with sedentary behaviour. In the lower-limb alone, Shivgulam et al. (2022) investigated the cross-

sectional relationship between conduit artery endothelium function and objectively recorded habitual ST and patterns (120). Specifically, in a sample of 98 healthy adults (16-77 years, 53♀) there was an independent, inverse relationship between popliteal FMD and total time spent in prolonged sedentary bouts >1 hour, as well as a positive relationship between popliteal FMD with the number of sedentary breaks. Interestingly, total accumulated ST was unrelated to popliteal FMD, suggesting that the pattern by which ST is accumulated may be more important than total ST on arterial health. Overall, Wilmot et al. (2012) suggested that high levels of ST was associated with an 147% increased risk of CVD (151). Furthermore, Pandey et al. (2016) reported a similar relationship with high levels of habitual ST (>10 hours/day) (99). However, there is no evidence that longitudinally decreasing ST (i.e., via an intervention) improves brachial artery FMD.

2.5 Sedentary Behaviour Reduction Interventions

2.5.1 Feasibility and Success of Existing Sedentary Behaviour Reduction Interventions

Based on the negative health effects that sedentary behaviours have in adults, developing sedentary behaviour reduction interventions to help combat this problem is important. Sedentary behaviour reduction interventions are a relatively new phenomenon compared to other lifestyle interventions (e.g., physical activity programs) and therefore, the feasibility of these interventions is still under review. Nguyen et al. (2020) conducted a systematic review of 11 studies that investigated sedentary behaviour reduction interventions in adults (85). The length of the interventions ranged from 1 week to 3 years and the interventional components included induced motivation, physical environmental changes, and policy changes (27, 121). Among studies included in the

review, the average reduction in ST was 42 minutes per day (85). Meta-analyses indicated sedentary behaviour interventions were superior to physical activity interventions alone or combined physical activity and sedentary behaviour interventions in reducing sitting time (85). Among working adults, motivation approaches (e.g., counselling sessions, goal setting, mass media advertising, etc.) had higher success rates, as well as environmental changes (i.e., sit-to-stand desks). Among general young to middle-aged adults, technologies to reduce sedentary behaviour (e.g., computer prompts and reminder emails) were also common intervention strategies (85). For example, Castro et al. (2021) provided prompting at frequent intervals (e.g., 4 times per day) (21) in additional to face-to-face motivational interviewing strategies in young undergraduate students to elicit reductions in total daily ST on weekend days (67). Vibrotactile feedback, another form of prompting using vibration technology, has been demonstrated to reduce prolonged ST, rather than total daily ST (86), Furthermore, another review by Gardner et al. (2016) found that 39% of the interventional studies they reviewed had '*very promising'* feasibility and 21% had '*quite promising'* feasibility based on the observed magnitude of changes in sedentary patterns (45). Those interventions that were '*very promising'* targeted sedentary behaviour instead of physical activity were educational based. However, this review also highlighted that there is a need for future sedentary behaviour reduction interventions to include randomized control trials with a no-treatment control group, as well as objective measures of ST and/or patterns (45).

Several sedentary behaviour reduction interventions have been developed for older adults. Hartman et al. (2021) conducted a prospective study with 24 older adults (65 ± 5 years) with increased CVD risk (54). This 16-week intervention was designed to

decrease total ST and prevent prolonged sitting (i.e., >30 minutes) using a mobile health device with vibrotactile feedback. Before and after the intervention, superficial femoral arterial health was evaluated in the context of a 3-hour prolonged sitting bout in a laboratory setting with and without light-intensity activity breaks every 30 minutes. Following the intervention, they observed a decrease in ST (10.2 ± 0.4 to 9.2 ± 0.3 hours/day) and an associated increase in superficial femoral artery FMD (more details below) (54). In addition, the intervention acutely attenuated the prolonged sitting-induced arterial dysfunction (54). This suggests that this intervention design may be effective at promoting peripheral vascular health in a sample with chronic disease (i.e., increased CVD risk), but may not be applicable to healthy adults.

Matei et al. (2015) conducted an 8-week uncontrolled trial intervention using healthy older adults (age: 60-75 years) from a retirement community, as well as community-dwelling older adults (78). Participants were provided with an information leaflet that contained tips for displacing sitting with light-intensity physical activity, forming activity habits, and self-monitors for habitual activity. In addition, participants were given a 'tick sheet' to record their adherence to information provided in the leaflet. Habitual activity was monitored using self-reported information and additional qualitative data were collected to assess the feasibility of the intervention. They found that only community-dwelling older adults experienced a decrease in ST, improved sedentary habits, and increased physical activity, while those participants from the retirement community were unchanged. This may be attributed to varying needs across the populations as those in retirement communities may be less independent and require more encouragement. Similarly, Crombie et al. (2022) (28) and Koltyn et al. (2019) (67)

implemented a 4 week sedentary behaviour reduction intervention in community-dwelling older adults. However, only Crombie et al. (2022) used a randomized controlled trial (28). Both intervention protocols consisted of 4 weekly, 1.5-hour information sessions presented in a small group workshop format. Workshops were formatted to provide participants with information regarding how they could decrease ST, set practical goals, develop action plans to reach them, and refine existing goals during follow-up workshops. Both studies reported >60 minute reductions in ST following 4 weeks and increased self-reported, health-related quality of life (Figure 2.15) (28, 67). However, it is unknown if this intervention would be applicable to a population of younger adults.

Sedentary behaviour reduction interventions have also been targeted toward students – another highly sedentary population of adults (22). Castro et al. (2021) conducted a 1-day intervention in university students that aimed to reduce ST using a framework known as the Behaviour Change Wheel (see more below) (21). All participants underwent a 6-day baseline to establish sedentary patterns using a triaxial thigh-worn inclinometer. Then, on the seventh day, participants attended a one-on-one intervention session that involved discussions of key concepts/health effects of sedentary behaviour, review of accelerometer-assessed ST from the 6-day baseline assessment, guided reflection on the idea of changing their sedentary behaviour; and suggested strategies to reduce and break up ST. Subsequently, participants underwent 6 additional days of habitual sedentary activity assessment post-intervention. During this time, participants also received a total of 24 messages (i.e., 4 per day) at fixed intervals throughout the day to act as prompts/reminders for the participants to reduce and break up their ST, and to reinforce the key messages delivered during the interventional

session. From baseline to post-intervention, there was a reduction in total and prolonged ST during weekend days. However, there was no difference in total ST across the 6-day period or during weekdays. This study was limited by a lack of a control group, small homogenous sample size, and a short intervention duration. It also draws attention to the importance of targeting ST accumulated during weekdays in working young adults and the potential value the Behaviour Change Wheel may have for future sedentary behaviour reduction interventions.

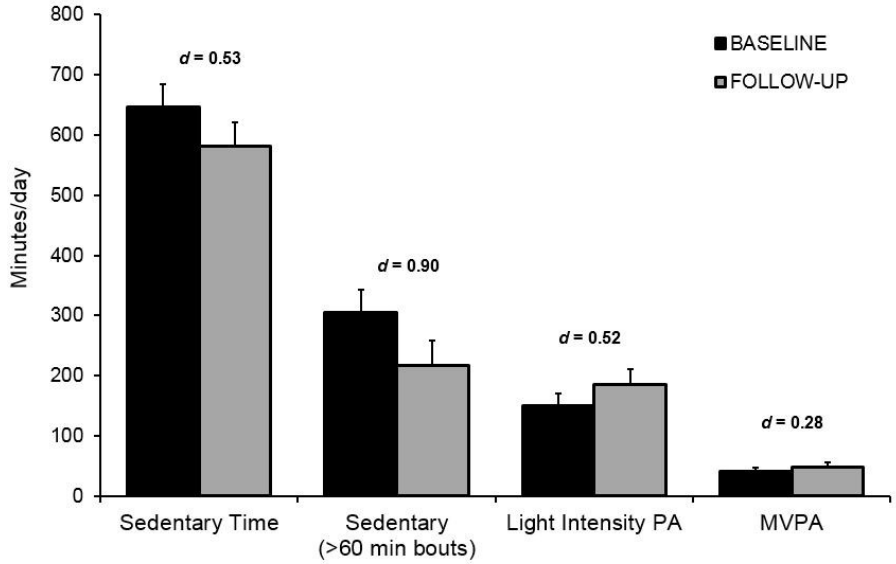

Figure 2.13. Koltyn et al. (2019) conducted a 4-week sedentary behaviour reduction intervention designed to break up sedentary behaviour by standing up multiple times throughout the day. The intervention was delivered using one small group workshop to educate older adults (≥65 years) on the harmful effect of sedentary activity and strategies on how to break up their sedentary time. Bar graph depicts objectively measured sedentary time, light-intensity physical activity (PA), and moderate-to-vigorous physical activity (MVPA) at baseline and post-intervention. The reduction in total sedentary time experienced a moderate effect size (*d*=0.53) and reductions in prolonged sedentary bouts (>60 minutes) was strong (*d*=0.90). Error bars depict standard error (67).

2.5.2 Intervention Guided by The Behaviour Change Wheel

The Behaviour Change Wheel is a theory-driven framework that provides a systematic way of developing interventions (80). It particularly focuses on a model that aims to integrate methods of promoting capability, opportunity, and motivation to promote behaviour change (i.e., the COM-B model, see Figure 2.14) (80). *Capability* is characterized as the psychological and physical capacity of an individual to engage in the behaviour of interest and focuses on the necessary knowledge and skills needed to do so. *Opportunity* is considered to encompass factors outside the control of the individual, which contribute to making the behaviour accessible. Lastly, *motivation* is defined as the brain processes that promote the desire to engage in the behaviour aside from conscious decision-making. Each of these factors may influence behaviour in their own unique way. However, behaviour also has the ability to reciprocally influence them (80). Furthermore, these 3 factors also exist within the Behaviour Change Wheel itself (Figure 2.15). This framework is not a linear model, but instead functions under the theory that each layer of the wheel interacts with each other. Specifically, the outermost layer (policy categories) impacts behaviour through the middle layer (intervention functions) that then elicit 'sources of behaviour' change at the center of the wheel (80). This is known as the Theoretical Domains Framework. When applied to function within an intervention, this framework was considered a reliable source of behaviour change within varying demographics (e.g., tobacco control and obesity) (80).

The Behaviour Change Wheel has been applied within the context of identifying potential intervention strategies in university students (22). Castro et al. (2020) conducted semi-structured, one-on-one interviews with 18 undergraduate students (23 ± 3 years) using the COM-B and Theoretical Domains Framework. Each interview sought to

uncover the beliefs about the role of each theoretical domain framework modality in influencing the targeting behaviour of breaking up sitting time during academic activities every 30 minutes. Results revealed that most participants required and/or desired more information regarding the adverse health risks of prolonged ST. In addition, they highlighted that sedentary breaks are usually automatic responses as opposed to conscious decisions, and that external reminders such as timers or alarms may be helpful to enable their capacity. Furthermore, they reported that a lack of motivation was a key contributor to their relatively fewer movement breaks, and that known health improvements may be an important motivator for them. Sedentary breaks may be impeded by physical opportunities (e.g., lack of access to standing desk), while social opportunity may facilitate breaks in ST through social influence and interaction (e.g., getting up to chat with someone). The Behaviour Change Wheel has also been implemented into the development of a number of office-based sedentary behaviour reduction interventions [e.g., (83, 92, 93, 129)]. These interventions often included the implementation of strategies including the introduction of environmental changes (e.g., sit-to-stand desk), changes to organizational policies, and individual components (e.g., face-to-face coaching).

These results support that the components of the Behaviour Change Wheel may be a particularly useful framework for conducting sedentary behaviour reduction interventions that may elicit frailty- and/or vascular-related health benefits. Using interventions to promote improved ST and patterns may play a particularly beneficial role in regulating vascular health and endothelial function.

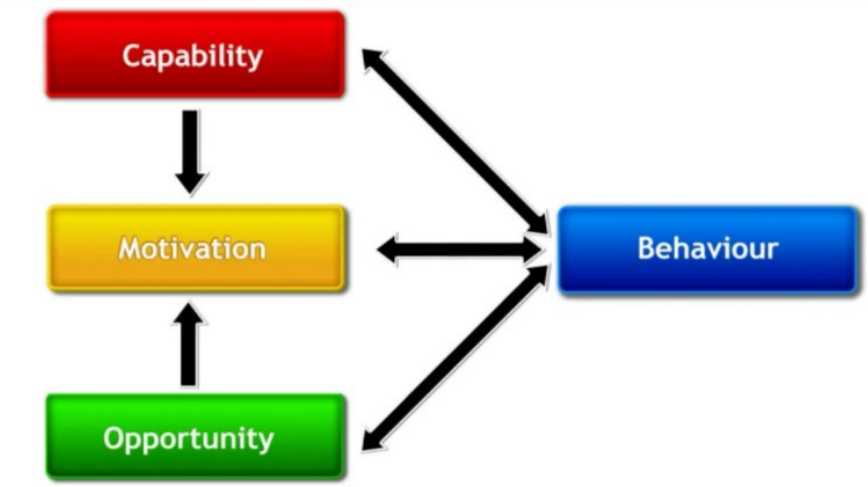

Figure 2.14. Visual representation of the Capability, Opportunity, and Motivation driven methods of Behaviour change (COM-B model). Capability, opportunity, and motivation impact behaviour, while behaviour also reciprocally impacts each factor. In addition, capability and opportunity have the ability to influence motivation (80).

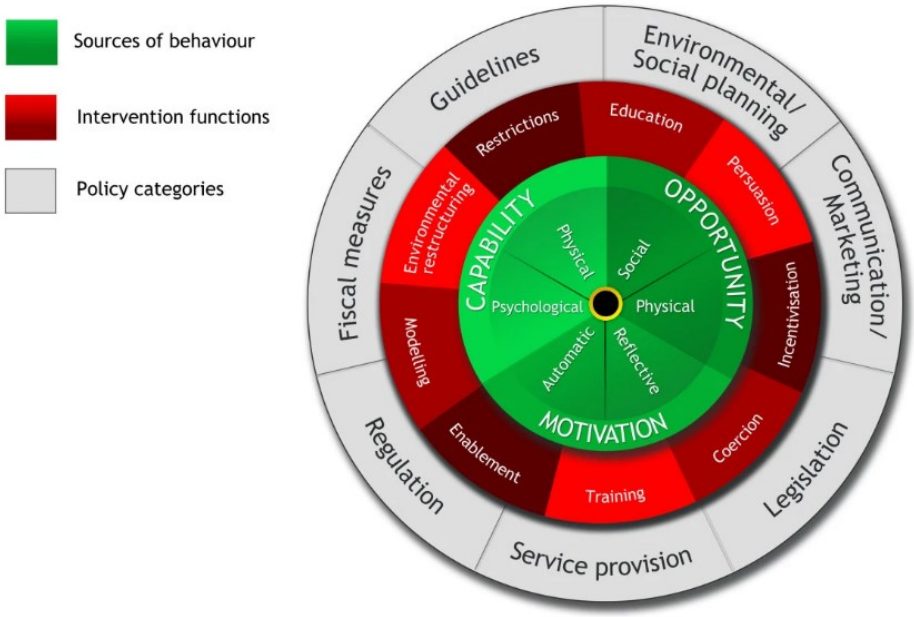

Figure 2.15. Visual depiction of the Behaviour Change Wheel. There are 3 distinct layers of the wheel that interrelate with each other. Policy changes give rise to intervention functions, and intervention functions are able to elicit sources of behaviour (80). Sources of behaviour include capability (both physical and mental), Opportunity (both physical and social), and motivation (both automatic and reflective). Once sources of behaviour have been identified, they can be implemented via intervention functions, which has numerous modes of delivery (e.g., education, training, enablement, etc.). Then, the outer layer identifies seven policy categories that can support the delivery of these intervention functions (e.g., regulation, guidelines, marketing, etc.) to elicit behaviour change.

2.6 Purpose and Hypotheses

To this end, a feasibility study is needed to assess the practicality and effectiveness of a novel long term, randomized control sedentary behaviour reduction intervention to determine if such an intervention would be appropriate. Therefore, the purpose of this study was to: 1) assess the feasibility of a 9-month sedentary behaviour reduction, 2) determine the effectiveness of a 9-month sedentary behaviour reduction intervention to reduce total ST and the number of prolonged sedentary bouts in a population of sedentary adults, and 3) evaluate if adults who successfully reduce these sedentary metrics also improve their frailty, and brachial FMD outcomes. It was hypothesized that this intervention would feasible (i.e., low attrition, high acceptance, low cost and easily deliverable) and effectively decrease ST and the number of prolonged sedentary bouts, as well as increase the number of sedentary breaks, which would be positively associated with improved frailty. Based on the previous literature, it is unclear if brachial FMD would be attenuated with reductions to habitual sedentary activity (113, 120). Therefore, the impact of total ST and/or sedentary patterns on brachial FMD was exploratory.

Chapter 3: METHODS

3.1 Participants

Participants were recruited for this randomized control trial through word of mouth, recruitment posters, and directly from a Shannex retirement community. Specifically, at the Shannex Dartmouth Location (Parkland at the Lakes), recruitment posters were displayed promoting study participation and advertising an in-person information session. This presentation provided an overview of the research project and what participation entailed. Following the presentation, the audience had the opportunity to have their questions or concerns addressed by research staff members. Interested individuals then provided their name and contact information for determination of study eligibility.

Participants were eligible if they were ≥18 years old, did not meet national ST guidelines (116) (i.e., if they accumulated >8 hours/day of objectively measured ST), and had access to a phone or email account. Premenopausal females were excluded if pregnant, breastfeeding or planned on becoming pregnant within 9 months of entry into the study. Individuals were excluded if they were using or planning on starting hormone replacement therapy within the first 9 months of the study due to known impacts on artery function (31, 79). In addition, potential participants were not admitted into the study if they had a known allergy to the clear medical adhesive dressing (i.e., Tegaderm^{TM}) used to secure the activity monitors used in the project.

Participants were informed of the methods and procedures verbally and in writing before providing written informed consent. All protocols and procedures conformed to the Declaration of Helsinki, except for registry in a public database, and were approved

by the Dalhousie Health Sciences Research Ethics Board (REB# 2021-5792; Appendix A).

All eligible participants were randomly assigned to either the Intervention or Control group. Group assignment for females was stratified based on the phase of their natural menstrual or oral contraceptive pill phase cycle during baseline vascular testing, method of contraception (premenopausal females), or menopausal status (postmenopausal females) to ensure the effects that females sex hormones have on arterial function is similar between groups. Premenopausal females were tested during the same phase of their menstrual or oral contraceptive pill cycle for all assessments to control for the potential confounding impact of female sex hormone fluctuations on FMD responses (56, 149, 150). All participants were stratified based on age (younger: 18-54 years, older: ≥55 years), presence of chronic conditions, body mass index (i.e., category matched based on underweight, healthy weight, overweight, obese), and menstrual cycle (i.e., pre/post menopausal, menstrual cycle phase, method of contraceptive) (23). Specifically, participants were randomly allocated to either the Control or Intervention group by MES while trying to maintain homogenous groups.

3.2 Experimental Procedures and Analyses

3.2.1 Anthropometrics, and Objective Physical and Sedentary Activity Monitoring

Height and body mass were measured using a calibrated stadiometer (Health-O-Meter, McCook IL, USA) to the nearest 0.5 cm and 0.1 kg, respectively. Body mass index was then calculated (kg/m^2).

To objectively measure physical and sedentary activities, participants wore an activPAL accelerometer and inclinometer (activPAL3 or activPAL4, Pal Technologies

Ltd.®, Glasgow, UK) 24 hours per day for ~7 days. The activPAL is a valid and reliable measure of both habitual physical activity (e.g., activity intensity, step counts) (49, 60, 87, 153) and stationary time (i.e., sedentary and standing times) (49). The activPAL was waterproofed using a nitrile finger cot and secured to the midline of the right thigh, one-third of the way between the hip and knee (36) using transparent medical dressing (Tegaderm^{TM}, 3M, London, ON, Canada). Participants completed a log to self-report their waking hours to supplement activPAL analysis (Appendix B). Specifically, this information was considered to ensure the analysis software program accurately categorized epochs into the appropriate category (e.g., sleeping versus ST).

Consistent with recommendations for valid habitual activity data (36, 52), only participants with a minimum 5 days (i.e., 24 hour wear) of activPAL data (including ≥1 weekend day) were included for analysis. These recommendations were derived from a sample of 52 older adults (69.3 ± 7.4 years) that wore an Actigraph accelerometer for 21 consecutive days (53). This study determined that 3-4 days of complete data were needed to accurately predict physical activity behaviours. However, ≥5 days of complete data are needed to provide reliable estimates of sedentary behaviours (3,6). If the activPAL was removed for any reason, the time was recorded on their sleep-wear time log and omitted from analysis if the participant had already accumulated enough valid days (i.e., ≥5 days). However, no participants prematurely removed their activPAL.

The activPAL data were analyzed using a customized MATLAB program (MATLAB 2020, MathWorks, USA) that confirmed their waking hours, summarized daily averages of time spent in sedentary postures, as well as reported: total daily ST, the number of sedentary breaks (i.e., transitions from lying/sitting to standing), number of

(and time spent engaged in) prolonged sedentary bouts (e.g., >1 hour), standing time, and steps per day. This analysis program has previously demonstrated excellent inter-rater reliability (91). Habitual light- (LPA), moderate- (MPA), and vigorous-intensity physical activity (VPA) were determined from a customized LabVIEW program (LabVIEW 2020, National Instruments, Austin, TX, USA) using height-adjusted step rate thresholds, or step rate thresholds of 110-130 steps per minute for healthy younger (87) and older adults (90), respectively. Due to the very low accumulation of VPA amongst older adults in this study (range: 0-3 minutes/week), MPA and VPA were summed and presented as moderate to vigorous-intensity physical activity (MVPA). All habitual sedentary and physical activity data were analyzed by a researcher blinded to participant brachial ultrasound outcomes.

3.2.2 Frailty Index Questionnaire

The FI implemented in the present study was based on the deficit accumulation model and developed using the Canadian Longitudinal Study on Aging dataset (102). Specifically, the FI was based on 52 items, most being coded as 0 (no deficit) or 1 (deficit). Details of the items included on this FI can be found in Appendix D, but include activities of daily living, and chronic conditions. Interval or ordinal variables were coded as a proportion of complete deficit (e.g., self-rated health has 5 options: excellent = 0, very good = 0.25, good = 0.5, fair = 0.75, poor = 1). The FI was then calculated as the number of deficits identified divided by the number of total possible deficits (e.g., 15/52 = 0.29), with a value closer to 1.00 indicating a higher degree of frailty. Questionnaires were reviewed during ultrasound assessments to ensure no missing data.

3.2.3 Ultrasound-Based Assessment of Brachial Flow-Mediated Dilation

Ultrasound assessments were performed in a thermoneutral environment (~21°C). All participants abstained from MVPA for 24 hours, avoided foods high in saturated fats, caffeine (e.g., coffee), chocolate, citrus fruits, nicotine, alcohol, and any antioxidant supplements for 12 hours, and were at least 6 hours post-prandial before assessments in accordance with recommended guidelines (135). Adherence to these instructions is pertinent for the assessment of accurate FMD responses as these factors are either known to directly impact NO bioavailability (e.g., antioxidant supplements, citrus fruits, etc.), while others impact resting vasomotor tone (e.g., exercise, caffeine, etc..), and therefore, baseline diameter (135). Prior to the brachial artery assessments (Figure 3.1), participants rested in the supine position (i.e., lying on their back) for ~10 minutes. All hemodynamic data were recorded directly following this resting period. Three consistent serial measures of brachial systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were recorded using an automated vital signs monitor (Carescape v100, General Electric Healthcare, Mississauga, ON, Canada) and averaged to represent resting hemodynamics.

The brachial artery was imaged 3-5 cm proximal to the antecubital fossa. Ultrasound images were obtained using a 12-MHz multi-frequency linear array probe attached to a high-resolution duplex ultrasonography machine (Vivid I, General Electric Healthcare, Mississauga, ON, Canada). The brightness-mode depth and frequency were adjusted to optimize image quality. Red blood cell velocity (RBCv) was continuously recorded simultaneously using a pulsed frequency of 5-MHz and an insonation angle corrected to 60 degrees, which was maintained across all participants. The sample volume for RBCv recording was adjusted to ensure the superior and inferior edges of the

lumen were included, as recommended in published guidelines (135). A pressure cuff attached to a rapid inflation system (E20 and AG101, Hokanson®, Bellevue, WA) was secured around the widest circumference of the forearm (~3 cm distal to the antecubital fossa).

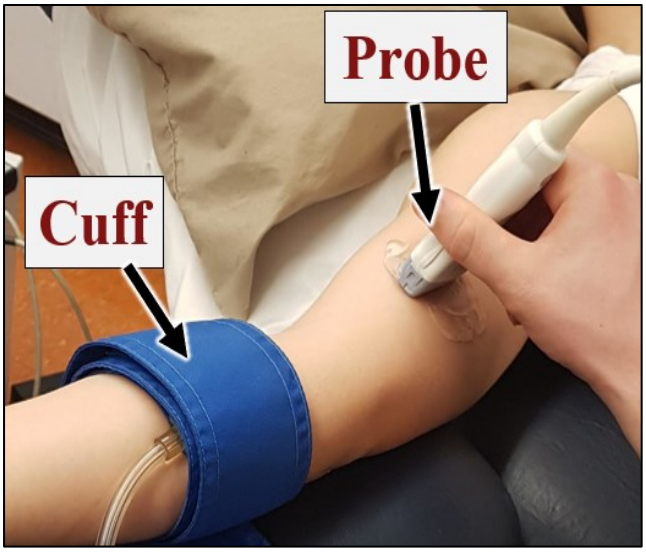

Figure 3.1. Ultrasound probe and distal pressure cuff set-up for the brachial flow-mediated dilation (FMD) assessment of endothelial-dependent vasodilation. The probe was connected to a duplex ultrasonography machine and the rapid-inflation pressure cuff secured around the widest circumference of the forearm. After 2 minutes of baseline recordings, the cuff was inflated to suprasystolic levels to induce distal ischemic. After 5 minutes, the cuff pressure was released to elicit a reactive hyperemia (increase in blood flow), the stimulus for the FMD response.

Resting artery diameter and RBCv were measured for 2 minutes to establish baseline levels. The pressure cuff was then inflated to 250 mmHg for 5 minutes while arterial lumen diameter and RBCv were continuously recorded until rapid deflation of the cuff. Lumen diameter and RBCv were also recorded for an additional 5 minutes following cuff deflation. Video recordings from the ultrasound system were exported onto a laptop via a video graphics array converter (Epiphan Systems Inc., VGA 2 USB, Ottawa, Canada) and exported for offline analysis. Brachial lumen diameter, RBCv, and

shear rate (SR) were calculated using commercial edge detection and wall-tracking software (FMD Studio, Cardiovascular Suite; Quipu, Pisa, Italy). Resting diameter and RBCv were averaged from the 2-minute baseline period prior to cuff inflation. Brachial blood flow (mL/min) was calculated as [$\pi \times$ lumen radius^2 (cm^2) $\times$ RBCv (cm/s) $\times$ 60 (s/min)] and SR (/s) as [(8 $\times$ RBCv (cm/s) / arterial diameter (cm)].

Absolute FMD (Δmm) was defined as [(peak diameter) – (baseline diameter)], relative FMD (%) as [(peak diameter – baseline diameter) / baseline diameter $\times$ 100%]. The SR area under the curve (SR_{AUC}) stimulus for the FMD response was calculated between the start of cuff deflation to the time that peak dilation occurred. The time (s) required to reach peak dilation was also recorded.

To minimize the interindividual vasodilatory response to reactive hyperemia, SR_{AUC} normalized FMD is recommended (97) if the following statistical assumptions were met: 1) the relationship (β) between FMD and SR_{AUC} was linear (i.e., $p<0.05$), and 2) the intercept for the regression slope of this relationship was zero (y-intercept) (6, 111). However, these assumptions were not met for the relationship between FMD and SR_{AUC} ($\rho=0.219$, $p=0.064$) or for intercept for the regression slope ($\beta=2.843^{-6}$, 95% CI: -1.558^{-6}, 7.245^{-6}, y-intercept: 0.165). As such, brachial FMD responses were not normalized to SR_{AUC}.

Interindividual differences in resting brachial artery diameter may also impact the magnitude of the FMD response (i.e., smaller baseline diameters produce larger shear stress and FMD responses) (5). If so, allometric scaling can be applied if the linear relationship between the logarithmically transformed peak and baseline diameters yields an unstandardized β-coefficient that deviates from 1 and has an upper 95% confidence

interval <1 (5). However, these assumptions were also not met (β=1.01, 95%CI: 0.971, 1.053) and allometric scaling was not applied to the FMD responses.

3.3 Experimental Design

Figure 3.2 displays a schematic of the study design involved with the 9 month sedentary behaviour reduction intervention. All participants completed 5 data collection sessions, which occurred at either the Shannex independent living retirement complex or the Autonomic Cardiovascular Control and Exercise Laboratory located within the Dalhousie University recreation complex. During the first visit, participants completed a Health History Questionnaire (Appendix C) and were equipped with the activPAL to confirm the habitual ST eligibility (i.e., averaged >8 hours of ST per day).

Participants underwent 4 subsequent visits at Baseline (June), 3 (September), 6 (December), and 9 (March) months for assessment of anthropometrics, completion of the FI Questionnaire (135) (Appendix D), and brachial FMD assessments. At the 3, 6, and 9 month follow-ups, Intervention and Control participants were again equipped with the activPAL inclinometer for ~7 days. Total activPAL wear times were 7.0 ± 0.0 days, (range: 7-7), 6.8 ± 0.4 days (range: 6-7 days), 6.6 ± 0.8 days (range: 5-8 days) and 6.8 ± 0.4 (range: 6-7) for the Baseline, 3, 6, and 9months time points, respectively.

Behaviour change was elicited through the COM-B model of the Behavior Change Wheel. Specifically, Capability was promoted through a single educational module within the first week of the intervention. Motivation was promoted through follow-up phone calls between the participant and MES every 1-3 months to discuss progress, goals, and action plans. Lastly, opportunity was elicited through prompts sent

via text message or email to motivate intervention participant to break up and reduce their sedentary time (Figure 3.2).

Participants in the Intervention group individually viewed the educational video about the negative health consequences of a sedentary lifestyle and were provided with effective strategies to help reduce ST and increase the frequency of sedentary breaks (Appendix E). Participants were not given explicit instructions as to what they should replace their sedentary time with, but were educated on the possible options (i.e., physical activity or standing). Specifically, MES developed this ~9 minute video as a Microsoft PowerPoint presentation that provided an understanding of what ST is, the impacts that excessive ST has on arterial health and frailty levels, and how participants could make changes to reduce this ST and improve sedentary patterns.

Intermittently throughout the 9 months, those in the Intervention group received standardized information and tips to help reduce their sedentary behaviours via email (n=4), text and/or voice messages (n=6). These messages were both motivational (e.g., 'don't forget to try to decrease your sedentary time today') and educational [e.g., 'physical activity can cause tiredness but standing can promote recovery and decrease feeling fatigue') and were delivered at predetermined times. However, based on preliminary analysis participants did not demonstrate reductions in their ST after 6 months. Therefore, sedentary prompts increased in frequency (see Table 3.1 for details regarding the original and revised prompt schedules). At Baseline, 3, 6, 7, 8, and 9 months, those in the Intervention group received phone calls to discuss their progress. These calls were initially scheduled to review activity data (i.e., every 3 months), but due to a lack of improvement, the frequency of calls was increased follow month 6 to

monthly. During these calls, feedback from participants was documented regarding how they thought they were progressing, and any barriers/facilitators to behaviour change they were encountering. Based on this feedback, individualized action plans were formulated to help improve their habitual activity patterns. The Control group did not receive these interventional modalities.

Figure 3.2 displays a schematic of the study design involved with the 9-month sedentary behaviour reduction intervention. All participants completed 5 data collection sessions, which occurred at either the Shannex independent living retirement complex or the Autonomic Cardiovascular Control and Exercise Laboratory located within the Dalhousie University recreation complex. During the first visit, participants completed a Health History Questionnaire (Appendix C) and were equipped with the activPAL to confirm the habitual ST eligibility (i.e., averaged >8 hours of ST per day).

Participants underwent 4 subsequent visits at Baseline (June), 3- (September), 6- (December), and 9 months (March) for assessment of anthropometrics, completion of the FI Questionnaire (135) (Appendix D), and brachial FMD assessments. At the 3-, 6-, and 9-month follow-ups, Intervention and Control participants were again equipped with the activPAL inclinometer for ~7 days. Total activPAL wear times were 7.0 ± 0.0 days, (range: 7-7), 6.8 ± 0.4 days (range: 6-7 days), 6.6 ± 0.8 days (range: 5-8 days) and 6.8 ± 0.4 (range: 6-7) for the Baseline, 3-, 6-, and 9-month time points, respectively.

Behaviour change was elicited through the COM-B model of the Behavior Change Wheel (80). Specifically, ‘capability’ was promoted through a single educational module within the first week of the intervention. ‘Motivation’ was promoted through follow-up phone calls every 1-3 months to discuss progress, goals, and action plans.

Lastly, ‘opportunity’ was elicited through prompts sent via text message or email to motivate intervention participant to break up and reduce their ST (Figure 3.2).

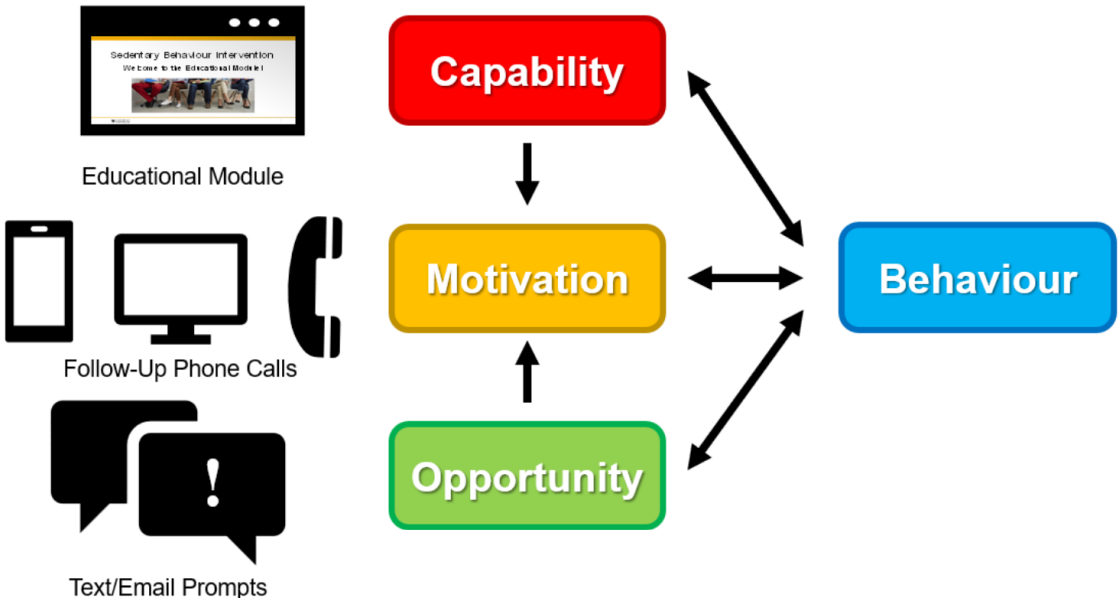

Figure 3. 2. Schematic depicting the intervention strategies used through sedentary behaviour reduction intervention based on the Capability, Opportunity, and Motivation Behaviour (COM-B) model of the Behaviour Change Wheel. To elicit behaviour change, ‘capability’ was promoted through a single educational module within the first week of the intervention. ‘Motivation’ was promoted through follow-up phone calls every 1-3 months to discuss progress, goals, and action plans, and ‘opportunity’ was elicited through prompts sent via text message or email to motivate intervention participant to break up and reduce their sedentary time.

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Table 3. 1. Sedentary prompt schedule for the 9 month sedentary behaviour reduction intervention.

Time Point	week 0 – week 2	week 2 – month 3	month 3 – month 6	month 6 – month 9
Original Frequency of Messages	Every other day	Twice a week	Once a week	Every other week
Updated Frequency of Messages	Every other day	Twice a week	Once a week	Every other day

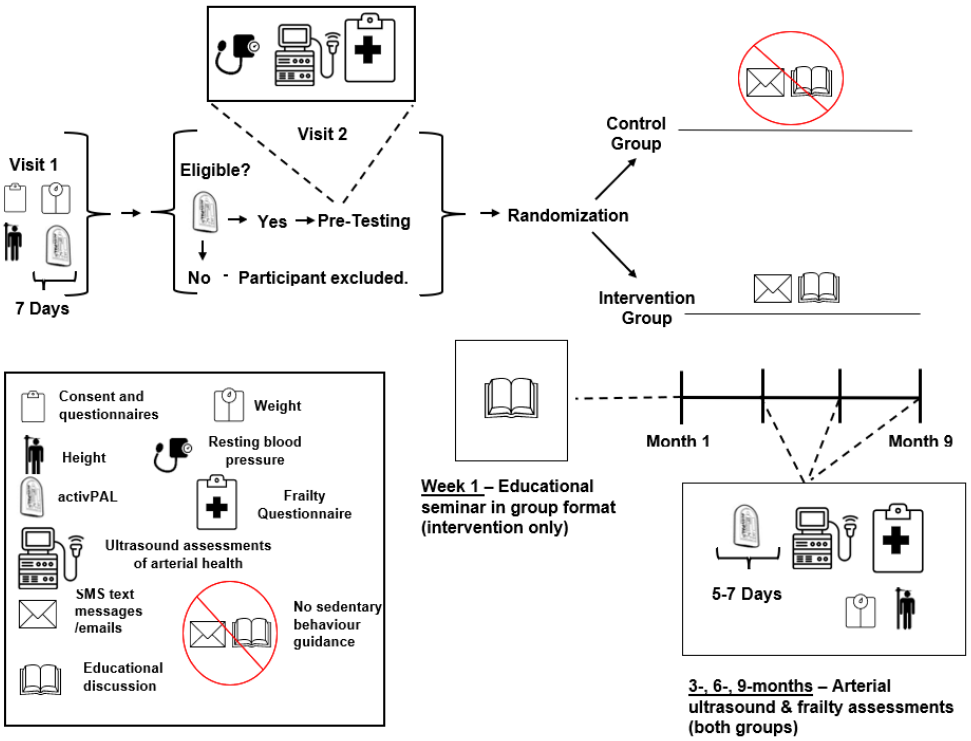

Figure 3. 3. Nine-month sedentary behaviour reduction intervention research protocol schematic. This project involved a total of 5 laboratory visits over the course of 9 months. Visit 1 was used to obtain informed consent and confirm eligibility via 7 days of activPAL inclinometer wear. If they were eligible (i.e., accumulated >8 hours daily sedentary time) participants attended the subsequent visits (Baseline, 3, 6, and 9 months) that were dedicated to the assessments of brachial artery health using the flow-mediated dilation protocol and completion of the Frailty Index Questionnaire. Additionally, at 3, 6, and 9 months, participants were equipped with an activPAL monitor on their upper thigh that they wore for 7 additional days. In addition to laboratory visits, those in the Intervention Group also viewed an educational video within the first week of the intervention and receive standardized information and tips regarding improving sedentary behaviours via email or text throughout the duration of the intervention.

3.4 Statistical Analyses

All dependent variables were assessed for normality using a Shapiro Wilk test (normal data, $p>0.05$). All non-normalized data were either log-transformed (i.e., SBP, ST, daily step count, resting brachial diameter, resting SR, all $p>0.055$), square root-transformed (FI, total time spent in prolonged sedentary bouts, number of prolonged sedentary bouts, resting brachial blood flow, absolute FMD, time-to-peak dilation, all $p>0.102$), cube root-transformed (i.e., resting RBCv, $p=0.163$), or inverse-transformed (i.e., body mass, peak brachial diameter, all $p>0.061$) and confirmed normally distributed.

Participant characteristics, habitual activity outcomes, systemic hemodynamics, FI scores, and brachial FMD outcomes were compared using a 2-way [Group (Control, Intervention) × Time (Baseline, 3-, 6-, and 9-month)] repeated measures analysis of variance (RM-ANOVA). For all RM-ANOVAs, the variance of differences was assessed using Mauchly's test of sphericity and the Greenhouse-Geisser correction factor to the degrees of freedom was used if assumptions of sphericity were violated. Bonferroni *post-hoc* testing was used for pairwise comparisons if significant interactions were identified. Sensitivity analysis was conducted in the older and younger Intervention Group participants via separate 1-way (Baseline, 3-, 6-, and 9-month) RM-ANOVAs to investigate potentially unique responses to the intervention. The specific outcome variables included in this sensitivity analysis included: ST, sedentary breaks, total time/number of prolonged sedentary bouts, FI, and brachial artery relative FMD. Partial eta squared (η_p^2) was calculated as an effect size for all comparisons and represented the

proportion of the variance in the dependent variable explained by the variance in groups (Control versus Intervention) between timepoints. Strength of effect sizes were determined as small (0.01- 0.05), medium (>0.05-0.14) or large (≥0.14). All statistical analyses were conducted in SPSS Version 28 (IBM, NY). Data are presented as means ± SD. Statistical significance was accepted as $p<0.05$.

Chapter 4: RESULTS

4.1 Participants

Approximately 40 adults were approached to participate in the current study (~18 older adults). Twenty-three adults (16♀, 12 older adults) consented to participate and agreed to be assessed for eligibility. Prior to randomization, 3 participants were excluded or removed from the study because they: accumulated <8 hours/day of ST (n=1), experienced an adverse reaction to the medical adhesive used to secure the activPAL monitor (n=1), or refused to wear the activPAL for the required amount of time (n=1). Therefore, 20 participants remained in this study.

The Control group consisted of 10 participants, 4 older (3♀; age: 85 ± 7 years) and 6 younger adults (3♀; age: 23 ± 3 years). The younger participants were all healthy (i.e., free of chronic disease), while the older adults reported having hypertension (n=1), chronic obstructive pulmonary disease (n=2), or type 2 diabetes mellitus (n=1). The participant with hypertension was prescribed amlodipine besylate (i.e., a calcium channel blocker) and perindopril erbumine (i.e., an angiotensin converting enzyme inhibitor). The younger females used oral contraceptives (n=2) or an intra-uterine device (n=1), whereas the 3 older females self reported being post-menopausal.

The Intervention group consisted of 10 participants, 6 older (5♀; age: 77 ± 14 years) and 4 younger adults (3♀; age: 24 ± 3 years). All younger adults and 1 older adult were healthy, while the other 5 older adults reported having hypertension (n=3), a neuropathy (n=1) or type 2 diabetes mellitus (n=1). Those with hypertension were taking amlodipine besylate (i.e., a calcium channel blocker, n=1), quinapril (i.e., an angiotensin converting enzyme inhibitor, n=1), angiotensin II receptor blockers [irbesartan (n=1) or

candesartan (n=1)], hydrochlorothiazide (i.e., a diuretic, n=1), and/or bisoprolol (i.e., a selective β_1-receptor blocker, n=1). Younger females were using oral contraceptives (n=2), or an intrauterine device (n=1), while the 5 older females were post-menopausal.

After random stratification, 1 older female in the Intervention group dropped-out of the study following Baseline assessments, and 1 older male in the Control group removed himself from the study due to poor health. This resulted in a final sample of 9 individuals included in both the Control (3 older females, 84 ± 8 years; and 6 younger adults, 3♀, 23 ± 3 years) and Intervention (5 older adults, 4♀, 75 ± 15 years; and 4 younger adults, 3♀, 24 ± 3 years) groups (Table 4.1)

No differences in height, weight, or body mass index were observed between groups (all, $p>0.119$; $\eta_p^2<0.153$) or across timepoints (all, $p>0.608$; $\eta_p^2<0.027$; Table 4.1). In addition, the Intervention and Control groups had similar resting SBP, DBP, MAP, and HR that were unchanged at all follow-up timepoints (all, $p>0.088$).

4.2 Habitual Activity

Habitual activity outcomes are presented in Table 4.2. No Group × Time interaction effects were observed for any habitual activity outcomes (all, $p>0.122$) (Table 4.1). Based on sensitivity analyses, there were no changes in total ST (both, $p>0.231$, $\eta^2<0.291$), sedentary breaks (both, $p>0.374$, $\eta^2<0.172$), total time spent in prolonged sedentary bouts (both, $p>0.665$, $\eta^2<0.119$), number of prolonged sedentary bouts (both, $p>0.313$, $\eta^2<0.248$) in either older or younger Intervention group participants over time (Figure 4.1). However, 5/9 participants (2 younger adults, 3 older adults) in the Intervention group reduced their ST between Baseline and the 9-month follow-up (9.9 ± 1.6 to 9.2 ± 2.1 hours/day) with an average difference of 0.8 ± 0.8 hours/day (range: 0.1-

2.1 hours/day). Of these 5 participants, 1 younger adult reduced their ST to achieve national recommendations (9.0 to 7.0 hours/day). In the Control group, 4/9 participants (2 younger adults, 2 older adults) also decreased their ST (11.2 ± 1.4 to 9.5 ± 2.0 hours/day) between Baseline and 9 months, with an average difference of 1.7 ± 0.7 hours/day (range: 0.7-2.4 hours/day). Two younger adults achieving the ST guidelines (10.0 ± 0.1 to 7.7 ± 0.4 hours/day). Regardless of group designation, 9/18 participants reduced their ST between Baseline and 9 months (Appendix F).

4.3 Frailty Index

Frailty Index outcomes are presented in Table 4.3. No Group × Time interaction effect was observed for FI (p=0.667; η_p^2=0.030) (Table 4.3; Figure 4.2). Based on sensitivity analysis, there were also no changes in FI for either the older or younger Intervention group participants (both, p>0.893; η^2<0.114).

Table 4.1. Participant demographic and descriptive characteristics

	Baseline	3 Months	6 Months	9 Months	Interaction p-value	Effect Size (η_p^2)
Descriptive Characteristics						
Height (m)						
Intervention	1.69±0.15 (1.51-1.95)	1.69±0.14 (1.52-1.94)	1.68±0.15 (1.52-1.94)	1.68±0.14 (1.52-1.96)	0.703	0.015
Control	1.67±0.92 (1.51-1.82)	1.67±0.88 (1.51-1.82)	1.67±0.92 (1.51-1.82)	1.67±0.89 (1.51-1.82)		
Weight (kg)						
Intervention	82.3±22.9 (65.0-136.8)	80.7±23.5 (58.5-136.0)	81.0±22.6 (64.4-136.0)	81.5±22.8 (65.1-137.0)	0.608	0.027
Control	67.6±12.7 (43.5-85.3)	66.8±12.1 (42.0-84.5)	68.0±12.2 (43.5-85.0)	68.0±12.2 (43.2-83.8)		
Body Mass Index (kg/m^2)						
Intervention	28.4±4.7 (22.2-36.0)	28.0±4.5 (23.2-36.0)	28.3±4.3 (23.4-35.3)	28.4±4.2 (23.7-35.7)	0.716	0.017
Control	24.3±5.5 (17.0-35.5)	23.9±4.89 (16.4-31.8)	24.5±5.4 (17.0-35.5)	24.6±5.5 (16.7-36.2)		
Resting Systemic Hemodynamics						
Heart Rate (beats/min)						
Intervention	65±8 (51-84)	68±8 (55-82)	65±10 (51-86)	69±9 (55-86)	0.233	0.084
Control	64±10 (44-80)	70±11 (47-88)	71±12 (45-87)	67±10 (44-81)		
Systolic Blood Pressure (mmHg)						
Intervention	136±20 (113-167)	123±16 (100-146)	132±22 (110-183)	126±17 (109-155)	0.702	0.029
Control	131±23 (101-172)	127±25 (104-174)	131±21 (106-169)	127±16 (107-155)		
Diastolic Blood Pressure (mmHg)						
Intervention	71±11 (57-94)	68±9 (56-86)	71±12 (57-91)	71±10 (57-89)	0.383	0.061
Control	66±7 (56-77)	67±9 (56-82)	65±8 (54-79)	64±8 (56-76)		
Mean Arterial Pressure (mmHg)						
Intervention	93±13 (78-109)	87±12 (71-103)	91±14 (77-122)	89±11 (74-108)	0.608	0.037
Control	88±12 (74-107)	87±13 (73-113)	87±11 (76-109)	85±10 (73-102)		

Sample size: Intervention (n=9, 3 females) and Control (n=9, 4 females). Data are presented as means ± standard deviations (minimum-maximum). Group × Time interaction effects were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post hoc* pairwise comparisons to determine within- and between-group differences (interaction effects). Effect sizes reported as Partial Eta Squared.

Table 4.2. Comparison of habitual activity metrics between the Intervention and Control groups across timepoints.

	Baseline	3 Months	6 Months	9 Months	Interaction p-value	Effect Size (η_p^2)
Total Sedentary Time (hours/day)						
Intervention	10.0±1.2 (9.0-12.7)	11.0±1.5 (8.9-13.6)	10.0±1.3 (7.9-12.1)	9.9±1.8 (7.0-12.6)	0.322	0.068
Control	10.7±2.1 (8.5-15.1)	10.7±2.0 (7.4-14.9)	10.8±2.0 (7.4-14.6)	10.7±2.5 (7.4-16.1)		
Sedentary Breaks (breaks/hour)						
Intervention	2.7±0.9 (1.1-4.0)	2.5±0.6 (1.3-3.1)	2.9±1.0 (1.2-4.3)	2.8±0.9 (1.5-2.7)	0.122	0.113
Control	3.5±1.0 (2.5-5.7)	3.1±0.9 (2.1-4.8)	3.1±0.8 (1.9-4.5)	3.2±1.0 (2.0-5.3)		
Total Time Spent in Prolonged Sedentary Bouts (minutes/day)						
Intervention	316±198 (68-592)	384±90 (256-498)	338±180 (49-696)	300±131 (127-497)	0.275	0.077
Control	227±146 (69-544)	243±137 (22-434)	278±91 (161-423)	272±160 (108-646)		
Number of Prolonged Sedentary Bouts (bouts/day)						
Intervention	2.5±1.1 (1.0-4.4)	2.8±0.7 (1.9-3.8)	2.6±1.0 (0.7-4.0)	2.3±0.9 (1.3-4.0)	0.282	0.076
Control	2.1±1.3 (0.7-5.0)	2.0±1.2 (0.3-4.5)	2.3±1.0 (1.1-4.4)	2.3±1.5 (0.8-6.0)		
Light-Intensity Physical Activity (minutes/day)						
Intervention	72±34 (23-123)	69±25 (42-122)	60±2 (22-91)	65±25 (28-92)	0.887	0.013
Control	66±23 (31.2-95)	67±18 (39-100)	52±15 (32-70)	57±20 (31-970		
Moderate-Vigorous-Intensity Physical Activity (minutes/week)						
Intervention	152±154 (3-368)	140±143 (2-423)	97±105 (3-269)	118±110 (1-280)	0.573	0.040
Control	203±175 (3-441)	211±215 (3-625)	202±231 (2-672)	181±212 (2-667)		
Daily Step Count (steps/day)						
Intervention	7993±4496 (2619-14642)	7801±3822 (3701-14097)	6126±2955 (2522-10694)	6893±3153 (2351-12581)	0.725	0.027
Control	8332±4299 (2248-13511)	8812±4705 (3338-18079)	7562±4751 (2251-16704)	7209±4858 (2273-18444)		

	Baseline	3 Months	6 Months	9 Months	Interaction p-value	Effect Size (η_p^2)
Standing Time (minutes/day)						
Intervention	299±104 (164-445)	306±78 (189-445)	318±106 (139-468)	329±101 (181-470)	0.545	0.043
Control	296±113 (117-419)	286±108 (128-451)	272±112 (106-451)	280±123 (115-500)		
Sleeping Time (hours/day)						
Intervention	7.6±2.0 (4.7-10.8)	6.4±1.1 (4.7-8.4)	7.4±1.5 (5.7-10.4)	7.2±0.9 (5.8-8.4)	0.285	0.075
Control	6.7±1.1 (5.3-8.3)	6.8±1.3 (5.1-9.4)	7.2±1.3 (4.5-9.1)	7.2±1.6 (4.3-9.4)		

Sample size: Intervention (n=9, 3 females) and Control (n=9, 4 females). Data are presented as means ± standard deviations (minimum-maximum). Group × Time interaction effects were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post hoc* pairwise comparisons to determine within- and between-group differences (interaction effects). Effect sizes reported as Partial Eta Squared.

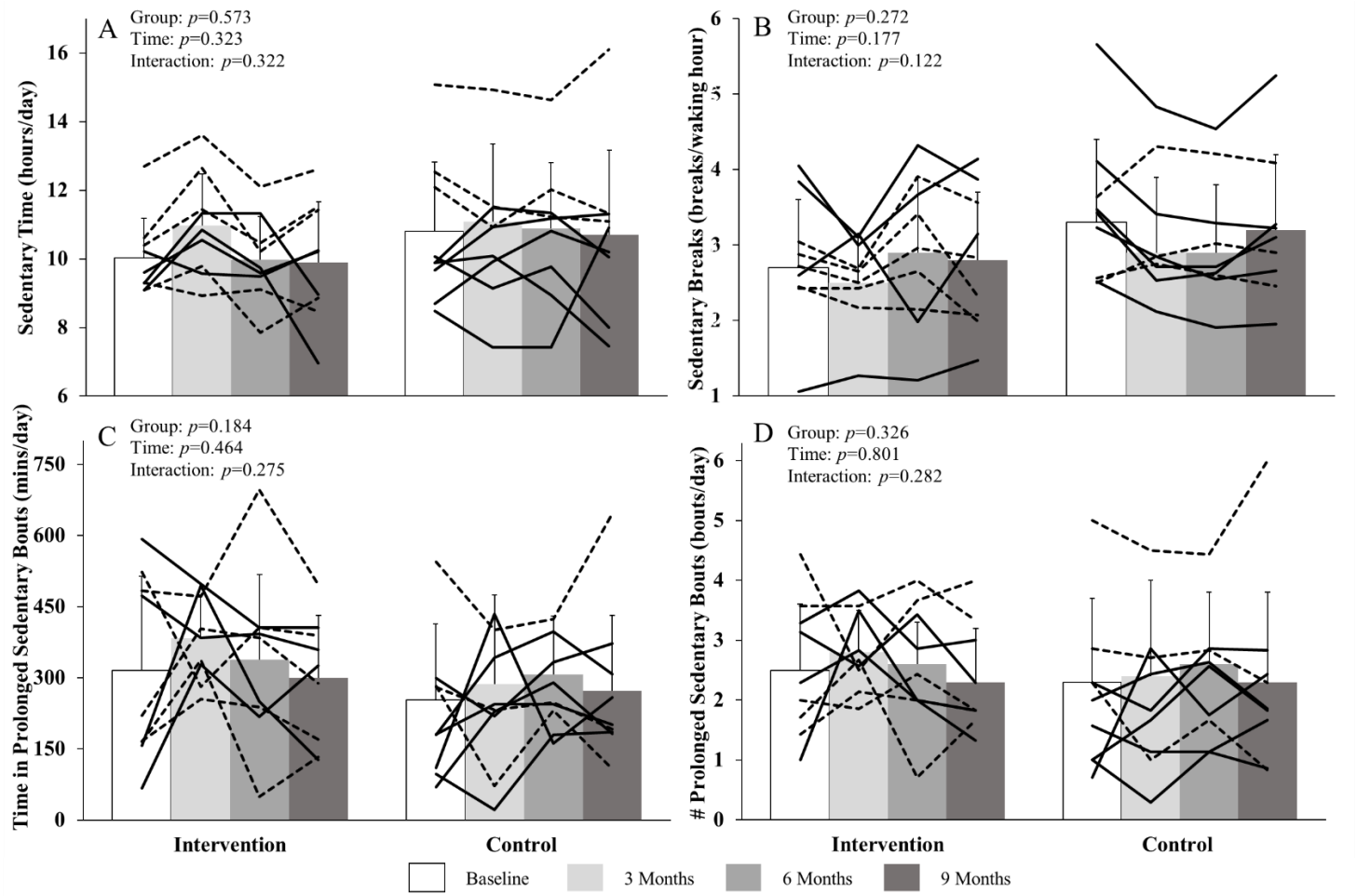

Figure 4.1. Total sedentary time (A), sedentary breaks (B), total time spent in prolonged sedentary bouts >1-hour (C), and number of prolonged sedentary bouts (D) for both the Intervention (left) and Control (right) groups between Baseline, 3-month, 6-month, and 9-month follow-ups. Individual data for both older (n=8, 5 Intervention and 3 Control) and younger (n=8, 4 Intervention and 6 Control) adults are presented as dotted and solid lines, respectively. Group × Time interactions were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post hoc* pairwise comparisons. No significant main or interaction effects were observed.

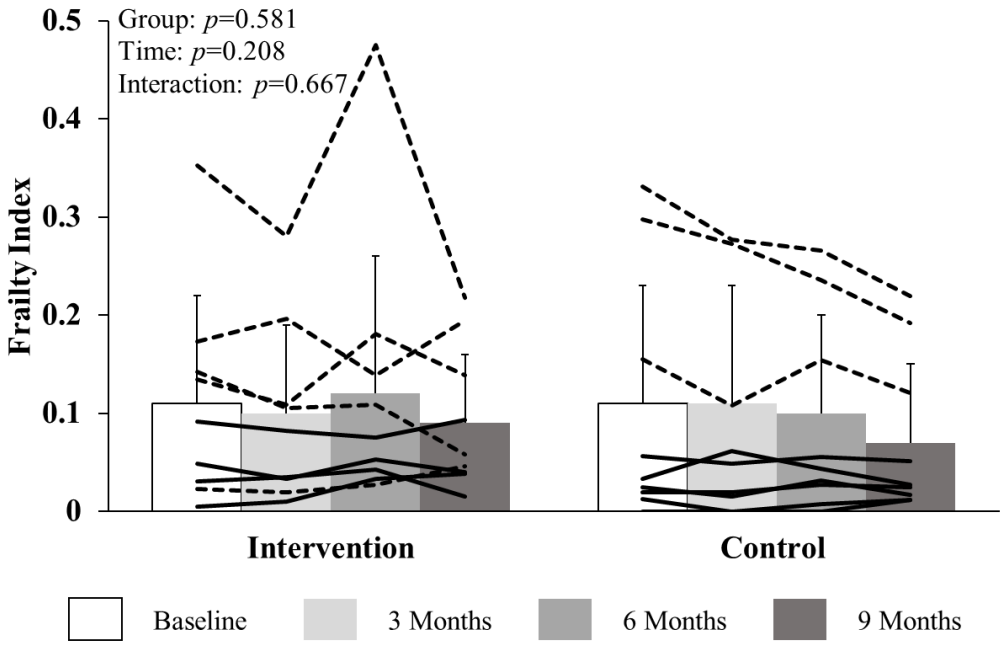

Figure 4.2. Frailty Index (0-1) scores for both the Intervention and Control groups between Baseline, 3-month, 6-month, and 9-month follow-ups. Individual data for both older (n=8, 5 Intervention and 3 Control) and younger (n=8, 3 Intervention and 6 Control) adults are presented as dotted and solid lines, respectively. Group × Time interactions were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post hoc* pairwise comparisons. No significant main or interaction effects were observed.

4.4 Brachial Artery Function

A Group × Time interaction effect was observed for resting SR (p=0.040, η_p^2=0.157), whereby both 3-month (p=0.012) and 6-month (p=0.010) timepoints were higher than at 9-month in the Control group. Furthermore, the Control group had a larger resting SR than the Intervention at Baseline (p=0.037). A Group × Time interaction effect was also observed for RBCv (p=0.022, η_p^2=0.179), whereby it was higher at 9- versus 6 months in the Intervention group (p=0.009). Furthermore, baseline RBCv was higher in the Control group (p=0.020). No Group × Time interaction effects were uncovered for any other brachial artery function outcome variables (all, p>0.069, η_p^2>0.136) (Table 4.3;

Figure 4.3). Based on sensitivity analysis, there were also no changes in relative FMD in either older or younger Intervention group participants over time (both, $p>0.149$; $\eta^2<0.277$).

Table 4.3. Comparison of frailty index and brachial artery outcomes between the Intervention and Control groups across timepoints of the sedentary behaviour reduction intervention.

	Baseline	3 Months	6 Months	9 Months	Interaction P-value	Effect Size (η_p^2)
Frailty Index						
Intervention	0.11±0.11 (0.01-0.35)	0.10±0.09 (0.01-0.28)	0.13±0.14 (0.03-0.48)	0.09±0.07 (0.02-0.22)	0.667	0.030
Control	0.10±0.12 (0.00-0.33)	0.09±0.11 (0.00-0.28)	0.09±0.10 (0.00-0.27)	0.07±0.08 (0.01-0.22)		
Brachial Resting Hemodynamics						
Resting Diameter (mm)						
Intervention	4.03±0.98 (3.09-6.38)	3.83±0.66 (3.00-4.89)	3.95±0.69 (3.05-5.41)	3.83±0.75 (2.76-5.03)	0.088	0.138
Control	3.86±0.50 (3.12-4.63)	3.78±0.58 (3.14-4.85)	3.65±0.59 (2.98-4.48)	4.10±0.57 (2.93-4.82)		
Red Blood Cell Velocity (cm/s)						
Intervention	8.1±4.1† (2.7-15.1)	10.4±8.7 (0.5-21.6)	9.0±7.6* (0.4-33.3)	15.3±12.0 (4.9-45.4)	**0.022**	0.179
Control	16.5±9.1 (4.1-35.4)	15.9±9.2 (3.3-32.7)	14.1±7.2 (5.8-28.0)	10.9±5.8 (3.7-23.2)		
Blood Flow (mL/min)						
Intervention	76±58 (21-199)	80±86 (4-257)	75±84 (5-272)	85±75 (2.0-245)	0.858	0.016
Control	91±61 (36-225)	104±65 (18-235)	98±74 (29-270)	89±58 (19-200)		
Shear Rate (/s)						
Intervention	99±41 (54-189)	141±66 (42-218)	133±51 (64-243)	133±52 (66-239)	**0.040**	0.157
Control	161±72† (73-204)	202±89* (112-405)	176±70* (92-277)	119±52 (55-215)		
Brachial Flow-Mediated Dilation						
Peak Diameter (mm)						
Intervention	4.20±1.00 (3.18-6.52)	4.02±0.69 (3.26-5.15)	4.16±0.75 (3.15-5.78)	4.05±0.73 (3.12-5.27)	0.069	0.136
Control	4.05±0.51 (3.34-4.84)	3.97±0.69 (3.35-5.28)	3.82±0.55 (3.18-4.59)	4.27±0.54 (3.18-4.97)		

	Baseline	3 Months	6 Months	9 Months	Interaction p-value	Effect Size (η_p^2)
Absolute FMD (mm)						
Intervention	0.18±0.08 (0.09-0.34)	0.19±0.14 (0.04-0.48)	0.21±0.08 (0.10-0.37)	0.23±0.11 (0.06-0.37)	0.535	0.044
Control	0.20±0.12 (0.07-0.46)	0.22±0.12 (0.04-0.43)	0.17±0.09 (0.02-0.30)	0.17±0.09 (0.07-0.30)		
Relative FMD (%)						
Intervention	4.45±2.06 (2.29-8.39)	5.15±3.72 (1.03-11.26)	5.16±1.61 (3.28-8.25)	6.32±3.67 (1.62-13.24)	0.502	0.047
Control	5.14±3.07 (1.57-11.82)	5.52±2.41 (1.18-8.80)	5.07±3.00 (0.47-10.20)	4.45±2.61 (1.60-8.42)		
Shear Rate Area Under the Curve (a.u.)						
Intervention	10370±4514 (3886-16594)	9279±3202 (3026-14552)	11898±3633 (6510-18240)	12720±8413 (1474-29217)	0.365	0.061
Control	10901±3146 (6211-15570)	11313±7826 (1236-24108)	11030±7392 (4001-27959)	93301±4533 (2271-16990)		
Time-to-Peak Dilation (s)						
Intervention	59±34 (28-145)	53±8 (41-65)	35±9 (15-47)	47±13 (34-71)	0.561	0.056
Control	44±13 (24-57)	51±31 (17-115)	39±15 (21-75)	44±18 (25-76)		

Sample size: Intervention (n=9, 3 females) and Control (n=9, 4 females). Data are presented as means ± standard deviations (minimum-maximum). Group × Time interaction effects were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post hoc* pairwise comparisons to determine within- and between-group differences (interaction effects). Effect sizes reported as Partial Eta Squared. *, $p<0.05$ versus 9-month timepoint in same group. †, $p<0.05$ versus Control group at the same timepoint.

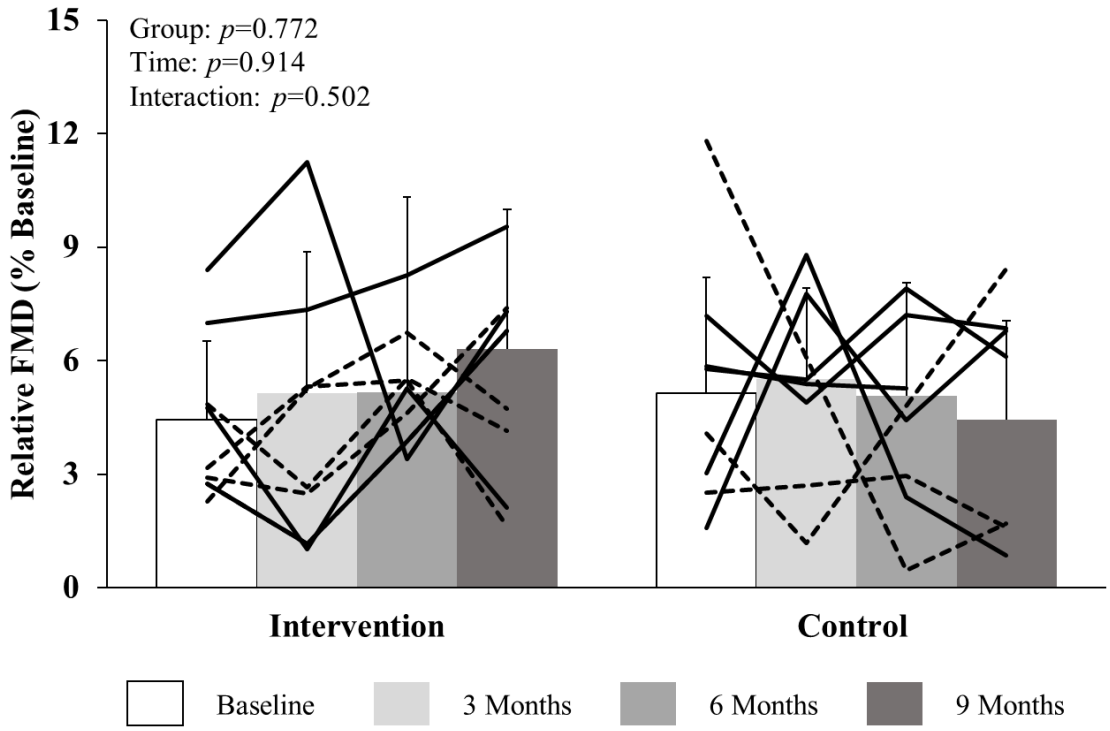

Figure 4.3. Relative brachial flow-mediated dilation (FMD) responses for the Intervention and Control groups between Baseline, 3-Month, 6-Month, and 9-Month follow-ups. Individual data for both older (n=8, 5 Intervention and 3 Control) and younger (n=8, 3 Intervention and 6 Control) adults are presented as dotted and solid lines, respectively. Group × Time interactions were assessed using a 2-way repeated measures analysis of variance with Bonferroni *post hoc* pairwise comparisons. No significant interaction effects were observed.

4.5 Intervention Feasibility

Of the ~40 people approached to participant in the current study, 23 agreed (~18 older adults, ~22 younger adults (i.e., ~58% uptake). As previously mentioned, 20/23 were eligible (~87%) and over the 9-month intervention, 2/20 participants dropped out (i.e., 10% attrition or 90% completion). Based on phone calls with Intervention group participants, common barriers to sedentary behaviour change were identified including work/school responsibilities (n=6), habitual exercise patterns (n=1), physical constraints (e.g., low energy levels, body/joint pain, functional instability; n=4), being unmotivated

to change (n=4) and lack of social support (i.e., habitual activity patterns alone; n=1) (Figure 4.4). Of note, work/school responsibilities were primarily identified in young adults (n=4), while physical constraints and lack of social supports were primarily presented in older adults (n=5). For example, younger adults noted that during exam periods, ST was difficult to avoid, and 1 working older adult remarked that online meetings were a barrier to movement throughout the day. Furthermore, older adults specifically complained of joint pain as a limitation to breaking out of sedentary postures, a lack of desire to walk alone, and poor weather conditions. Conversely, in some instances (i.e., 4 younger adults) job/school responsibilities were a facilitator to an activity routine where participants felt their job allowed them to be less sedentary (e.g., security guard, lifeguard, coach). These barriers and facilitators were consistently identified throughout the duration of the intervention. However, younger adults identified heightened school responsibilities at the 6-month timepoint (December 2022) due to end of year exams (n=4). At this same timepoint, mental health/motivation to be active was identified as a barrier in younger adults (n=3), while older adults identified the colder weather as a barrier to behaviour change (n=4). These barriers were alleviated at the 9-month follow-up. Of note, over the course of the intervention, older adults experienced adverse health events including knee replacement surgery (3 months, n=1), lower-limb vascular surgery (6 months, n=1), and foot injury (9 months, n=1) that they felt impeded their ability to improve habitual activity/sedentary patterns and decrease ST.

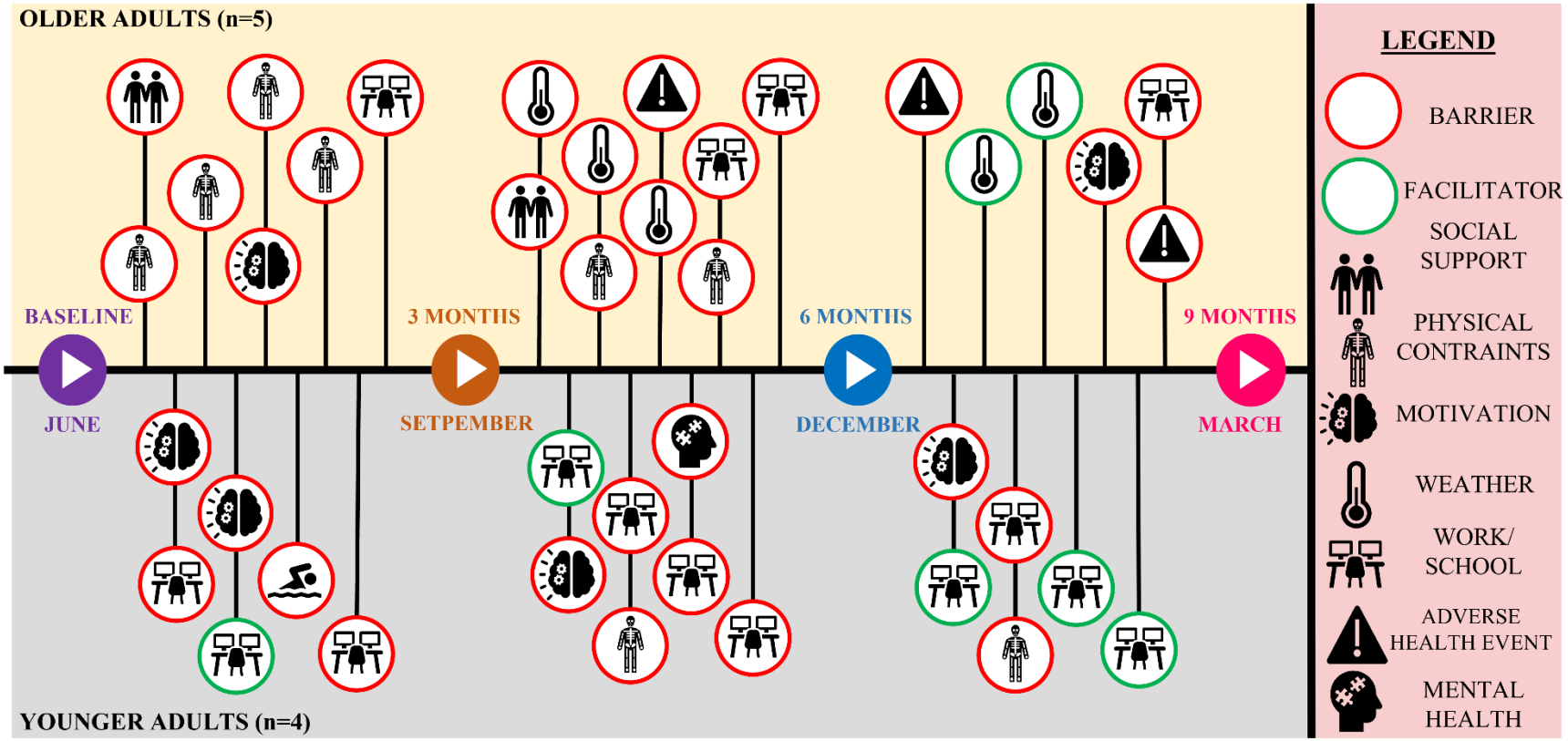

Figure 4.4. Visual representation of barriers and/or facilitators identified from phone calls with Intervention participants at 3 months, 6 months, and 9 months. Each line represents a single participant and their individual barriers and facilitators. Older adults (above) and younger adults (below) are depicted separately.

Chapter 5: DISCUSSION

The purpose of this study was to, 1) assess the feasibility of a 9-month sedentary behaviour reduction, 2) determine the effectiveness of a 9-month sedentary behaviour reduction intervention to reduce total ST and the number of prolonged sedentary bouts in a population of sedentary adults, and 3) evaluate if adults who successfully reduce these sedentary metrics also improve their frailty, and brachial FMD outcomes. In contrast to the hypotheses, there were no changes in habitual activity patterns, the FI or brachial FMD outcomes at follow-up in the Intervention group. Although this intervention was not effective, as a feasibility study it was successful, and valuable insights were gained to contribute to future research in the field. `

The current study implemented interventional strategies that included an educational module, sedentary prompts via text messages/email, and phone calls to address barriers and create individualized action plans. Other studies have implemented similar educational components including information sessions (28, 44, 67), and prompting (via text message or email) (130) within their interventions. However, these previous interventions were deemed successful as they observed >60 minute reductions in daily total ST. Specifically, while Koltyn et al. (2019) did not use prompting, they reported that 4 weekly, 1.5-hour in-person, small group sessions, which provided participants with information (i.e., how participants could decrease ST, set practical goals and develop action plans to reach them) successfully reduced sedentary time by ~1 hour/day (67). This intervention strategy decreased ST by ~60 minutes in 21 older adults (i.e., >65 years). Similarly, in younger adults, the use of text message prompts and one-on-one, in-person discussions with research personnel proved effective at reducing ST on

weekend days only (10.7 to 8.8 hours/day) over a 2 week intervention period (21). However, the effectiveness of prompting adults to take sedentary breaks and reduce total ST has been reported to be highest in the short-term (i.e., <3 months), but lessens over time (130). In addition, successful interventions have been more intensive, with a face-to-face component. For example, Castro et al. (2021) provided prompting at more frequent intervals (e.g., 4 times per day) (21) and used face-to-face motivational interviewing strategies in their very short-term (i.e., 7 day) intervention in young undergraduate students (67). Similarly, Hartman et al. (2021) consistently promoted participants to break up sedentary time every 30-minutes using a pocket-worn vibrotactile device (54). This highlights that although the present study is novel by implementing a long-term randomized control trial in sedentary older and younger adults, it may have been too long in length and/or lacked a more personal and intensive approach required to elicit behaviour change. Specifically, the phone calls involved in the present study may need to be replaced with one-on-one or small group, in-person sessions with greater frequency. Future interventions should consider a combination of in-person and phone call meetings with participants to increase personal connection (i.e., via more in-person meetings), but maintain the accessibility of conversation (i.e., via phone calls). This is particularly important as 4/10 Intervention participants reported feeling unmotivated to make changes to their habitual behaviour. While the results of this study demonstrate the present intervention to be ineffective at altering habitual activity patterns (Figure 4.1), the feasibility data provides valuable information to inform future interventions.

The feasibility of this study is emphasized by a high completion rate (90%) over a 9-month duration. Attention to these key implementation outcomes is critical as sedentary

behaviour reduction interventions are relatively new and rapidly expanding. Based on uptake, eligibility, and attrition rates, the current study can be deemed as a feasible intervention. Based on commonly recommended outcomes for implementation research (109), the acceptability, appropriateness, and feasibility of this intervention should be considered. Acceptability, or the perception among implementation stakeholders that the given intervention was agreeable or satisfactory was high based on verbal feedback and participant retention (i.e.,18/23 or 78%) over the 9-month intervention. Furthermore, while the concepts of the intervention may be appropriate, how they were implemented, particularly to those of varying ages may not have been. Although the overarching components were similar (i.e., education, prompting, motivational interviewing), older and younger adults may require different structures and/or approaches to a sedentary intervention (109). Specifically, while younger adults highlighted school/work responsibilities as a main barrier to decreasing ST, implementing environmental changes [e.g., standing-desks (75)] along with messaging/prompting may be more effective. For example, the use of prompting via vibrotactile feedback may be effective at reducing ST in adults (37), although the evidence is conflicting (86). Vibrotactile feedback is implemented using a body-worn monitor whereby it omits a small vibration when the wearer exceeds ST over a certain threshold (e.g., >30 uninterrupted minutes) (37, 86). Therefore, this tactic may be more suited towards decreasing prolonged ST, rather than total daily ST (86). Previous reports also suggested that environmental changes (e.g., standing desks), particularly in working-aged adults, may also be effective at reducing ST (19, 27). Conversely, older adults may require more one-on-one support and/or motivational interviewing to overcome barriers and keep them consistently on track

(105). One-on-one support may take many forms, but increased frequency of in-person meetings may be beneficial based on the null findings of the current study. Therefore, altering the appropriateness of the intervention to the population may be crucial to increase effectiveness. Guided by the current randomized control trial, future interventions should also focus on alternative implementation outcomes including sustainability and penetration.

Sustainability, or the extent to which a newly implemented treatment/intervention is maintained or institutionalized should be evaluated using longer follow-up periods. While this study failed to implement a follow-up period to assess this outcome, Crombie et al. (2019) demonstrated that an 8-week follow-up period after a 4-week randomized control trial yielded poor retention of ST reductions among older adults (28). Specifically, those in the Intervention group reduced their total daily ST by ~1.1 hours/day, but upon follow-up had returned to baseline levels (10.3 hours/day). Targeting not only long-term, but long-lasting interventions is critical to sustain desirable activity patterns and healthier populations. Similarly, penetration, defined as the integration of the intervention into practice (109) should be explored within a variety of settings and its subsystems. The current study focused solely on community-dwelling (n=2) and retirement home-dwelling (n=6) older and younger sedentary (n=10) adults. However, future interventions should explore a variety of populations (e.g., differing occupations, health status, socioeconomic status, sex, age, etc.) to reveal the ideal strategies for various populations. For example, an intervention that used motivational wrist-worn activity monitors was effective in stroke patients to provide real time feedback based on customized goals (39), while one-on-one coaching sessions elicited small reductions in

ST in those with multiple sclerosis (76). While these are both sedentary adults, the strategies needed to elicit behaviour change may vary, particularly within a clinical setting. Overall, based on the learned insights from the current intervention, future studies may explore the impact of changes in sedentary patterns on varying health conditions. With these considerations, future interventions can be developed to elicit impactful changes to the field that develop and form the foundation of health policy agendas that may lead to systemic changes (e.g., guidelines, 'exercise' prescription, community programs, etc.)

Congruent with the lack of change in habitual activity outcomes, the current intervention did not evoke changes in frailty levels. In contrast, a previous 14-week randomized controlled trial conducted in 23 older adults (>65 years) that implemented 3 face-to-face motivational sessions in combination with vibrotactile feedback successfully increased sedentary breaks by vibrating during prolonged sedentary bouts to prompt posture change and improved functional capacity (assessed using a combination of Chair Sit-and-Reach, Sit-to-Stand, Timed Up and Go, and a Balance Screening Tool) (55). This study noted that unpredicted health issues led to high attrition within the intervention, which is in accordance with the current study whereby the long-term nature of the intervention (i.e., 9 months) may have been a substantial barrier for consistent behaviour change. However, Harvey et al. (2018) may have observed reductions despite this attrition due to their implementation of face-to-face and vibrotactile prompting interventional components (55). Furthermore, intervention fatigue has been reported to be prevalent in older adults after only 4 weeks (55), which may provide reason as to why the current study was ineffective to change both habitual activity patterns and frailty. Of

note, only 3/18 participants included in the present intervention were considered frail [i.e., FI=>0.25 (114)] and 12/18 participants had very low frailty level (i.e., <0.10), which suggests that a 'floor effect' may have been observed in the current cohort. To this extent, when targeting frailty in the general adult population, centering interventions around symptoms such as pain, fatigue and breathlessness may be important for effectiveness and eliciting changes to frailty in a relatively healthy population (154). Although frailty was unchanged in the present study, corresponding to the lack of change in habitual activity, intervention strategies should be highlighted and tailored in accordance with the frailty and physical function levels of individuals. For example, if someone had a higher frailty level at baseline, they may need more environmental changes (walking aid) or social support to enable them to change. Alternatively, someone with lower frailty level may benefit more from sufficient prompting to develop improved day-to-day routines. Cross-sectional work has demonstrated that replacing 1 hour of ST with MVPA was associated with a lower FI in community-based adults aged 50 years and older (47). Therefore, developing sedentary interventions that specifically promote decreasing ST and increasing physical activity may be an important segue into exercising and the associated health benefits. However, decreasing ST and altering sedentary patterns may be a useful adjunct approach for those that lack the capacity/motivation to undertake physical activity and/or exercise programs.

There were also no changes in brachial FMD following the intervention. In a laboratory setting, brachial FMD was unaffected by an acute bout of prolonged sitting (113, 138) and the impact of habitual activity patterns is unknown. Although Hartman et al. (2021) observed significant reductions in superficial femoral artery FMD

corresponding to a reduction of ~1 hour/day of sedentary time using their intervention, this may not translate to the brachial artery investigated in the current study. Of note, Boyle et al. (2013) observed a reduction in baseline and peak brachial diameter following 5 days of reduced daily physical activity and increase total ST (14). However, increased physical inactivity should not be confused for increased sedentary behaviour. It is well-established that ST is independently associated with CVD risk (33), with each 1% increase in relative brachial FMD associated with a ~ 13% relative risk reduction in experiencing an adverse cardiovascular event (112). However, as an upper-limb vessel, it is likely that the brachial artery does not experience a large enough reduction in shear stress during sedentary postures to elicit attenuation of endothelial function (113). Conversely, habitual prolonged sedentary bouts and sedentary breaks are predictors of lower-limb (e.g. popliteal artery) endothelial-dependent vasodilatory function (120). While the popliteal artery may be particularly difficult to image clearly in older and frail adults due to intolerance to the pressure cuff and prone lying/recumbent position, which elicits limb movement (41), alternative markers of vascular health may be considered in the future (e.g., carotid-intima media thickness, pulse wave velocity, etc.). However, a 4-month intervention conducted in adults (age: 56 ± 7 years) using behaviour change techniques through health education and counselling, also did not alter habitual activity patterns or arterial stiffness (via carotid-femoral pulse wave velocity) (13). Therefore, longer, and varying types of sedentary interventions should be explored to improve vascular function and reduce cardiovascular risk in sedentary adults.

Interestingly, there were changes in SR and RBCv observed in the Control and Intervention groups, respectively. Specifically, SR was decreased in the Control group

from 3- and 6- to 9 months and RBCv increased in the Intervention group from 6- to 9 months. Since there were no changes in habitual activity patterns or frailty, these brachial artery hemodynamic responses may be attributed to confounding factors beyond the control of this study. Although participants were instructed to follow strict guidelines prior to FMD testing (e.g., avoid foods high in saturated fats), it was beyond the scope of this study to be able to monitor the factors known to effect SR and RBCv other than gaining verbal confirmation (e.g., we did not conduct blood testing). Specifically, hydration and levels of dietary saturated fat and antioxidants may have altered RBCv and SR (84). For example, increased hydration, decrease saturated fats, and increased antioxidants are associated with increased RBCv and more favorable vascular outcomes (84). In addition, medication status may also have caused these changes, whereby if people did not take their medications prior to testing, it could have influenced the vascular outcomes. Specifically, if someone failed to take their blood pressure medication, it could have increased or decreased RBCv (103). For example, if someone failed to take their calcium channel blocker, they would experience increased vasoconstriction and thus reduced RBCv. Resting blood pressures were particularly high at some time points compared to others (e.g., maximum SBP of 146-mmHg at 3 months, but 183-mmHg at 6 months; Table 4.1). However, this study did not account for, or measure these factors.

5.1 Strengths and Limitations

There is currently high-quality evidence to suggest that physical activity interventions are effective at improving habitual activity outcomes and promoting associated health benefits [e.g., (91)], but less is known regarding our ability to reduce ST

and improve sedentary patterns. This study was the first long-term investigation determining whether a Behaviour Change Wheel-based framework could reduce ST in both younger and older adults. As such, the inclusion of a control group in this 9-month randomized controlled trial strengthens the quality of this evidence. Furthermore, the current study is a novel sedentary intervention by attempting to prompt the reduction of ST rather than increasing physical activity or replacing ST with physical activity. This is particularly important as a reduction in ST may have benefits independent of physical activity levels (136). To this extent, future interventions should consider the limitations of the current study to develop more effective sedentary behaviour reduction interventions.

Habitual physical activity patterns of the current older adult population may be difficult to detect using a thigh worn inclinometer. Specifically, older adults often reported engaging in activities such as chair yoga, stretching or stationary resistance training for physical activity. Due to the fundamental posture of these activities, they may have been categorized as ST by the activPAL inclinometer and were only accounted for based on self-reports. Although this self-reported information was accounted for during analysis, it is subject to human error. This may have contributed to an overestimation of ST and an underestimation of physical activity levels if not reported properly. Although this study was strengthened by the inclusion of both older and younger adult populations, it may be statistically underpowered. Based on the ST effect size (ηp^2=0.068), α=0.05, and β=0.70, 36 participants would be needed to observe an effect using a 2-way RM-ANOVA with 4 timepoints. Primarily, we were especially underpowered to run sufficient sensitivity analyses on the two age categories in the Intervention and Control groups. Therefore, future studies should focus on interventions that target larger populations, both

younger and older adults, so age-related differences in the responses to an intervention can be accurately explored. Although this study was also strengthened by the inclusion of both males (n=7) and females (n=16), the distribution was not equal, with the sample mainly consisting of females. This is particularly important as there is some evidence to suggest that certain behaviour change techniques may target a specific sex (94). For example, females may be more persuadable and more receptive to behaviour change strategies (94). Furthermore, evidence suggests there may be sex differences in sedentary patterns, whereby females break up prolonged ST more often compared to their male counterparts (9), which further substantiates the need to consider sex in intervention design.

The intervention included in this study was also not without limitations. Younger and older adults were recruited from the Dalhousie Sports Complex (Dalplex) and a Shannex retirement community (Parkland at the Lakes), respectively. To this extent, this may have caused a cross-over effect between the Intervention and Control participants. Specifically, many participants were acquaintances or even friends, therefore it is possible that those in the Intervention group shared their experiences with those in the Control group. Similarly, this study neglected to account for the potentially confounding effect of social interaction on habitual activity and overall health. Specifically, loneliness and greater social vulnerability is associated with increased frailty and mortality in older adults (3). As such, those in the Intervention group received regular phone calls and messages from the intervention team, while those in the Control group did not. If a positive effect had been observed, it would be difficult to ascertain whether this was

based on the structured sedentary behaviour reduction intervention, or the social interaction. Future interventions should consider this limitation in their design.

5.2 Perspectives and Future Directions

The current study is an important contribution to the development of interventions targeted at reducing ST in adults. Future research should continue to conduct randomized controlled trials in multiple settings with a variety of populations. Accumulating a battery of high-quality interventions to draw from, will contribute to implementing effective strategies to minimize ST and improve sedentary patterns in our increasingly sedentary population. Although the current study was not effective, there are valuable pieces of information to consider and learn from. As an increasingly prevalent field, the present research may advance our understanding of an emerging field and work towards future policy implementation alongside the pre-existing physical activity recommendations. To guide this process, additional qualitative research is warranted to explore perspectives from key stakeholders (i.e., sedentary adults). Importantly, to achieve the goal of designing effective interventions to elicit behaviour change and reduce ST, it will be critical to gather understanding of the most prevalent barriers in different populations (e.g., older versus younger adults) and desirable strategies (e.g., in-person versus online, environmental changes versus motivational approaches) to develop informed and attractive interventions.

As such, based on the findings of this feasibility study, future interventions should implement the following changes. In a large sample of older and younger adults (both sexes), the length of the intervention should be shortened to 6 months to avoid intervention fatigue and include the addition of a 3-month follow-up period to evaluate

behaviour change retention. In addition, while the interventional components applied in the current intervention (i.e., education, motivation, opportunity) are still relevant and have previously been deemed effective (22, 80, 83) they may need to be implemented in a different way. Specifically, the intervention should include in-person meetings to educate, create action plans, set goals, and conduct motivational interviewing. Brief in-person meetings should also be conducted in the Control group to control for social effects. Meetings and prompts should be standardized for participants for the first month (e.g., prompt via message once per day, meetings once every 2 weeks), but based on progress after 1-month, a decision tree should be implemented to accomplish a more individualized approach. For example, if a participant does not make any change after each month, their frequency of meetings and prompts should be increased. This strategy combined with increased meetings is particularly important to meet the needs of individuals with varying ages, sexes, frailty levels, and lifestyles to implement the strategies that work best for them. Lastly, researchers interested in conducting sedentary interventions should aim to do so in collaboration with community partners (e.g., community centers, health offices, etc.) to promote penetration and sustainability within the community to spark important conversation and awareness about sedentary behaviour as being equal in importance to habitual physical activity and exercise. Executing these changes, while maintaining the foundations set by the current intervention, may be successful at reducing ST in adults and promoting the associated health benefits.

5.3 Conclusion

In conclusion, this study demonstrated that a 9-month sedentary behaviour reduction intervention driven by techniques from the Behavior Change Wheel in

sedentary adults did not elicit changes in total ST, sedentary breaks, or prolonged sedentary bouts. In addition, there were no corresponding changes in frailty or brachial artery endothelial dependent vasodilatory function. Although this intervention was not effective, as a feasibility study, valuable insights were gained regarding the intervention format, delivery, and potential barriers to behaviour change. This feasibility study will inform the development and implementation of future randomized controlled trials targeted at decreasing ST and promoting the associated health benefits.

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Appendix A: Letter of REB Approval

DALHOUSIE UNIVERSITY
Research Services

Health Sciences Research Ethics Board
Letter of Approval

December 03, 2021

Derek Kimmerly
Health\School of Health and Human Performance

Dear Derek,

REB #: 2021-5792
Project Title: The impact of a 12-month sedentary behavior reduction intervention on cardiovascular health: a pilot study

Effective Date: December 03, 2021
Expiry Date: December 03, 2022

The Health Sciences Research Ethics Board has reviewed your application for research involving humans and found the proposed research to be in accordance with the Tri-Council Policy Statement on *Ethical Conduct for Research Involving Humans*. This approval will be in effect for 12 months as indicated above. This approval is subject to the conditions listed below which constitute your on-going responsibilities with respect to the ethical conduct of this research.

Effective March 16, 2020: Notwithstanding this approval, any research conducted during the COVID-19 public health emergency must comply with federal and provincial public health advice as well as directives from Dalhousie University (and/or other facilities or jurisdictions where the research will occur) regarding preventing the spread of COVID-19.

Sincerely,

[redacted]

Dr. Lori Weeks, Chair

Appendix B: Sleep Log

Date	Time you woke up	Time you fell asleep	Non-Stepping Activities (Start/End Times)
Example: July 23rd, 2021	*7:30 am*	*11:30*	*Bicycled (8:00-8:20am)*
July 24th, 2021	*7:00 am*	*10:00*	Swimming (5:00-6:00 pm)
July 25th, 2021	*8:00 am*	*1:30 AM*	*Nap (3:00-4:00PM)*
Day 1:			
Day 2:			
Day 3:			
Day 4:			
Day 5:			
Day 6:			
Day 7:			
Day 8:	Return Monitor		

Appendix C: Health History Questionnaire

Age: _____ years

PARTICIPANT I.D. (Completed by Research Team): _____

The following questions in Section 1 will determine your eligibility for the study. If you answer 'Yes' to questions 1-4 you will <u>not</u> be able to participate in the study. If you answer 'No' to these questions, please proceed to Section 2.

<u>Section 1</u>

1. Are you younger than 18 years old?
   ☐YES ☐ NO
2. Are you allergic to Tegaderm™ (3M) medical adhesive dressing? ☐YES ☐ NO
3. Are you pregnant, breastfeeding or intending to become pregnant in the next 12 months (females only)? ☐YES ☐ NO
4. Do you <u>lack access</u> to a mobile phone, home phone and email? ☐YES ☐ NO
5. Are you taking any phosphodiesterase 5 inhibitors (e.g., Viagra®) or Soluble Guanylate Cyclase Stimulators (e.g., Verquvo®)? ☐YES ☐ NO
6. Are you planning on starting, hormone replacement therapy in the next 12 months? ☐YES ☐ NO

<u>Section 2</u>

7. Do you smoke or consume any nicotine/marijuana-containing products daily?
   ☐YES ☐ NO
8. Have you been prescribed medications for high blood pressure? ☐YES ☐ NO

   If yes, please indicate medications here: _____
   _____

9. Do you have a cardiovascular, neural (e.g., Raynaud's disease), respiratory or a metabolic disorder (e.g., diabetes)? ☐YES ☐ NO

   If yes, please indicate health disorder(s) here: _____
   _____

<u>For females only:</u>

10. Are you menopausal?
    ☐YES ☐ NO
11. Are you using contraceptives?
    ☐YES ☐ NO

    If yes, please specify type:_____

Appendix D: Frailty Index Questionnaire

CLSA-Frailty Index Questionnaire

The following questions ask about some basic activities of daily living. Remember, these are activities that can be done without help, with some help, or which you are unable to do.

Can you ...	*Yes, without help*	*Yes, with some help*	*No, unable to do*
... dress and undress yourself (including picking out clothes and putting on socks & shoes)?	☐	☐	☐
... take care of your own appearance, for example, combing your hair, shaving (if male)?	☐	☐	☐
... walk?	☐	☐	☐
... get in and out of bed?	☐	☐	☐
... take a bath or shower (including getting in or out of the tub)?	☐	☐	☐

The following questions ask about some other activities of daily living, activities that can be done without help, with some help or which you are unable to do. You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone.

Can you ...	*Yes, without help*	*Yes, with some help*	*No, unable to do*
... use the telephone, including looking up numbers and dialing?	☐	☐	☐
... get to places out of walking distance (i.e., you drive your own car, or travel alone on buses, or taxis)?	☐	☐	☐
... go shopping for groceries or clothes (taking care of all shopping needs yourself)?	☐	☐	☐
... prepare your own meals (i.e., you plan and cook full meals yourself)?	☐	☐	☐
... do your housework (i.e., you can clean floors, etc.)?	☐	☐	☐
... take your own medicine (in the right doses at the right time)?	☐	☐	☐
... handle your own money (i.e., you write cheques, pay bills, etc.)?	☐	☐	☐

Do you have difficulty with any of the following?	*No*	*Yes, a little difficult*	*Yes, somewhat difficult*	*Yes, very difficult*	*Unable to do*	*Don't do on doctor's orders*
Reaching or extending your arms above your shoulders	☐	☐	☐	☐	☐	☐
Stooping, crouching, or kneeling down	☐	☐	☐	☐	☐	☐
Pushing or pulling large objects like a living room chair	☐	☐	☐	☐	☐	☐
Lifting 10 pounds (or 4.5 kg) from the floor, like a heavy bag of groceries	☐	☐	☐	☐	☐	☐
Handling small objects, like picking up a coin from a table	☐	☐	☐	☐	☐	☐
Standing for a long period, around 15 minutes	☐	☐	☐	☐	☐	☐
Standing up after sitting in a chair	☐	☐	☐	☐	☐	☐
Walking alone up and down a flight of stairs	☐	☐	☐	☐	☐	☐
Walking 2 to 3 neighbourhood blocks	☐	☐	☐	☐	☐	☐
Making a bed	☐	☐	☐	☐	☐	☐
Washing your back	☐	☐	☐	☐	☐	☐
Using a knife to cut food	☐	☐	☐	☐	☐	☐
Recreational or work activities in which you take some force or impact through your arm, shoulder, or hand (e.g., golf, hammering, tennis, typing, etc.)	☐	☐	☐	☐	☐	☐

In general, would you say your health is...

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

Is your eyesight, using glasses or corrective lens if you use them...

Excellent	Very good	Good	Fair	Poor or non-existent (non-existent=blind)
☐	☐	☐	☐	☐

Is your hearing, using a hearing aid if you use one...

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

Do you consider yourself...

Overweight	Underweight	Just about right
☐	☐	☐

How many times have you had a fall in the past 12 months that was serious enough to limit some of your normal activities? For example, the fall resulted in a broken bone, bad cut, or sprain.

None	Once	Twice or more
☐	☐	☐

In the past week, how often did you feel ...	*All of the time (5-7 days)*	*Occasionally (3-4 days)*	*Some of the time (1-2 days)*	*Rarely or never (less than 1 day)*
... that everything you did was an effort?	☐	☐	☐	☐
... lonely?	☐	☐	☐	☐
... that you could not "get going"?	☐	☐	☐	☐

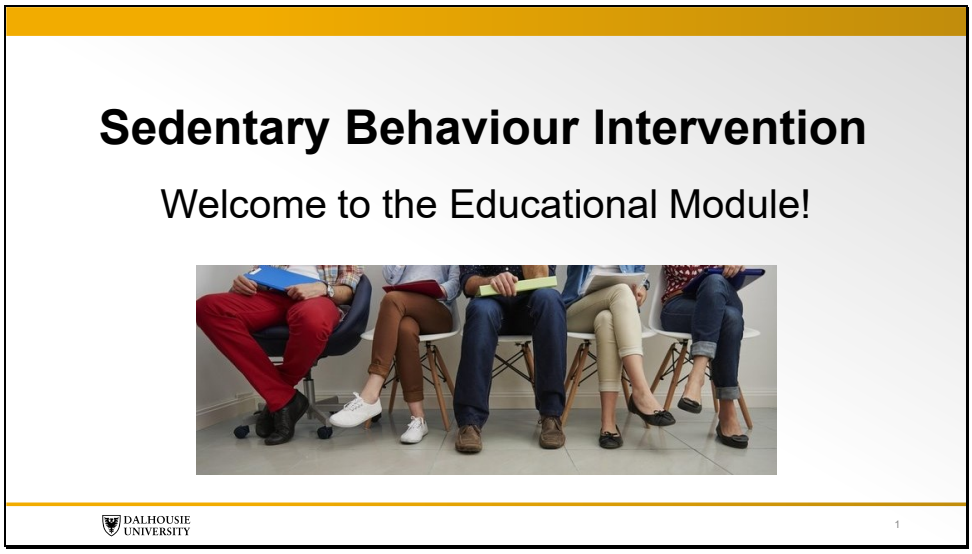
In the past 12 months, have you seen a doctor for any of the following reasons?	*Yes*	*No*
Pneumonia	☐	☐
Urinary tract infection (UTI)	☐	☐

The following questions ask about chronic health conditions. We are interested in "long-term conditions" which are expected to last, or have already lasted 6 months or more and that have been diagnosed by a health professional.

Has a doctor ever told you that you ...	*Yes*	*No*
... have osteoarthritis in the knee?	☐	☐
... have osteoarthritis in the hip?	☐	☐
... have osteoarthritis in one or both hands?	☐	☐
... have rheumatoid arthritis?	☐	☐
... have any other type of arthritis?	☐	☐
... have/had any of the following: emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or chronic changes in lungs due to smoking?	☐	☐
... have high blood pressure or hypertension?	☐	☐
... have diabetes, borderline diabetes or that your blood sugar is high?	☐	☐
... have heart disease (including congestive heart failure or CHF)?	☐	☐
... have angina (or chest pain due to heart disease)?	☐	☐
... have had a heart attack or myocardial infarction?	☐	☐
... have peripheral vascular disease or poor circulation in your limbs?	☐	☐
... have experienced a stroke or CVA (cerebrovascular accident)?	☐	☐
... have experienced a mini-stroke or TIA (transient ischemic attack)?	☐	☐
... have a memory problem?	☐	☐
... have dementia or Alzheimer's disease?	☐	☐
... had Parkinsonism or Parkinson's disease?	☐	☐
... have intestinal or stomach ulcers?	☐	☐
... have a bowel disorder such as Crohn's Disease, ulcerative colitis, or Irritable Bowel Syndrome?	☐	☐
... experience bowel incontinence?	☐	☐
... experience urinary incontinence?	☐	☐
... have cataracts?	☐	☐
... have glaucoma?	☐	☐
... have macular degeneration?	☐	☐
... had cancer?	☐	☐
... have osteoporosis, sometimes called low bone mineral density, or thin, brittle or weak bones?	☐	☐
... have back problems, excluding fibromyalgia and arthritis?	☐	☐
... have an UNDER-active thyroid gland (sometimes called hypothyroidism or myxedema)?	☐	☐
... have an OVER-active thyroid gland (sometimes called hyperthyroidism or Graves' disease)?	☐	☐
... have kidney disease or kidney failure?	☐	☐

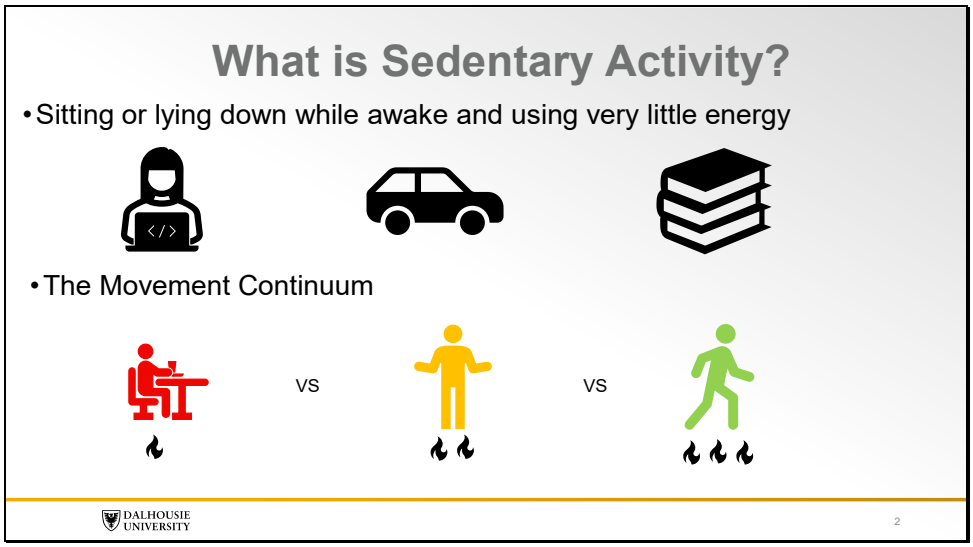
Adapted from the baseline Canadian Longitudinal Study on Aging questionnaires

Appendix E: Education Video Slide Deck, Script, Link, and Quiz



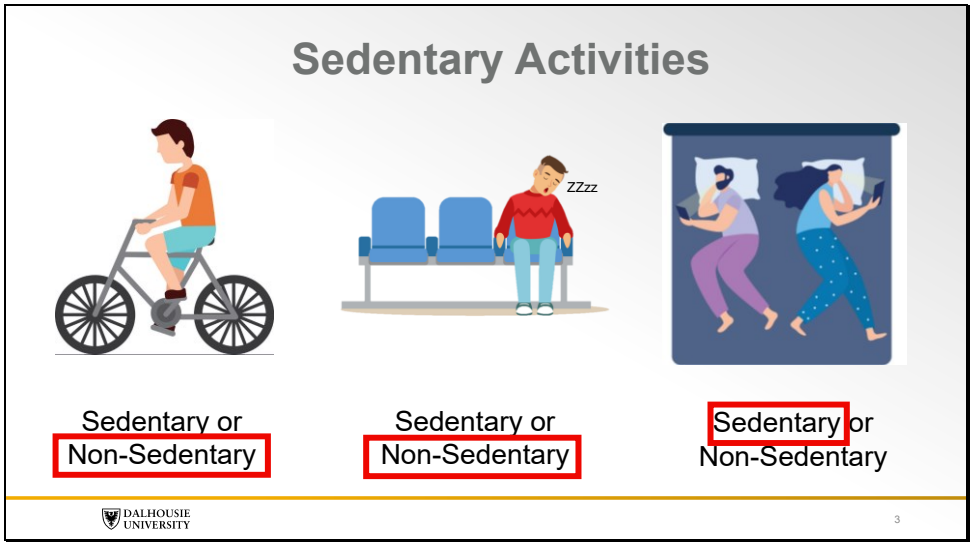
Welcome to the educational module highlighting the negative impact of sedentary behaviour on your cardiovascular health. This video is part of the research project entitled 'The impact of a 12-month sedentary behavior intervention on cardiovascular health: a pilot study' being conducted by researchers in the Faculty of Health at Dalhousie University. If you are watching this video, it is because you were randomly selected to be a part of the habitual sedentary behaviour reduction intervention group for the duration of this study. Let's begin!

Slide 2



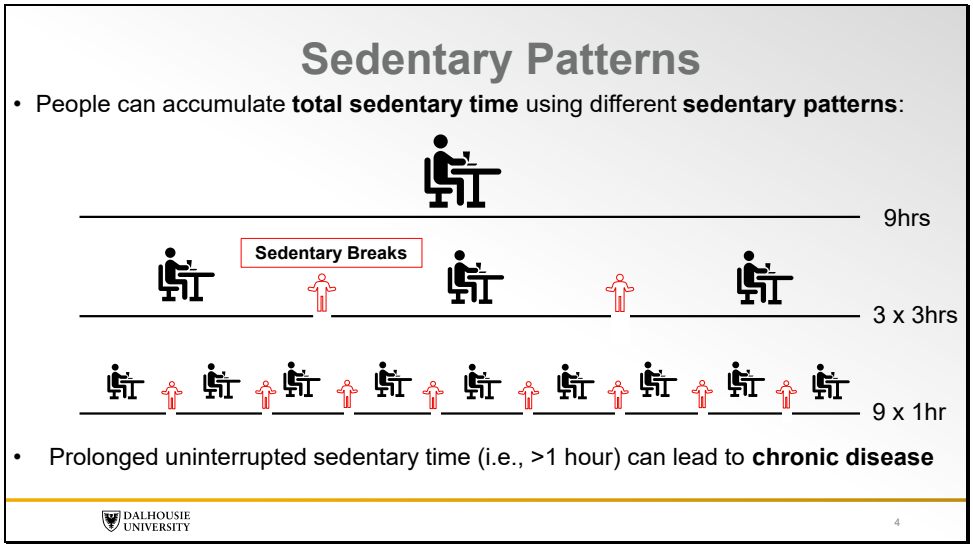
Right now, you are probably engaging in sedentary activity watching this video. But what does that mean? Sedentary activity can be described as time spent using little energy while sitting, reclining, or lying down while awake. Some common examples of daily sedentary activities include, using a computer while sitting, driving a vehicle, or reading. Now, let's get one thing clear: movement behaviours exist on a continuum. This means that your classification of activity depends on how much energy you are using. For example, sedentary behaviors, such as sitting down, require very little energy. Something as simple as standing up can increase your energy use and so, this is no longer considered a sedentary behaviour. Furthermore, activities such as walking and running use up the most energy and are deemed "physical activity".

Slide 3



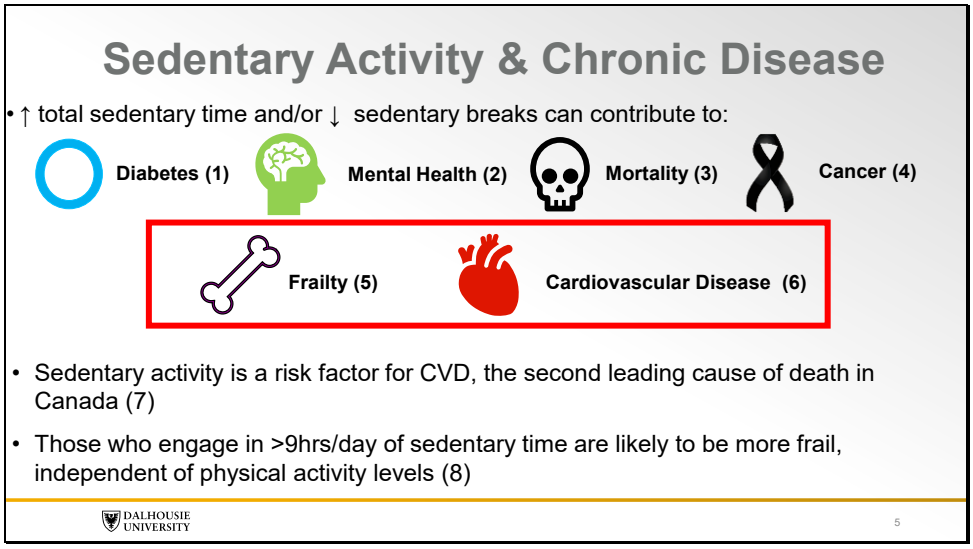
Let's check your understanding. If you are riding your bike while sitting down is this considered sedentary or non-sedentary activity? *pause* This is considered non-sedentary activity. Even though you are in a sitting posture, the act of riding your bike takes up lots of energy so it is not deemed sedentary. What about if you are sitting on the couch watching TV and fall asleep? *pause* This too is considered non-sedentary. Sedentary activity only occurs while you are awake. Only the time spent sitting or lying before you fell asleep would be deemed sedentary behaviour. Lastly, would lying in bed on your phone before going to sleep be sedentary? *pause* This is considered sedentary! Screen time in a lying postures fall under the definition of sedentary behaviour. Understanding what is considered sedentary is important for developing an awareness of your own ST.

Slide 4



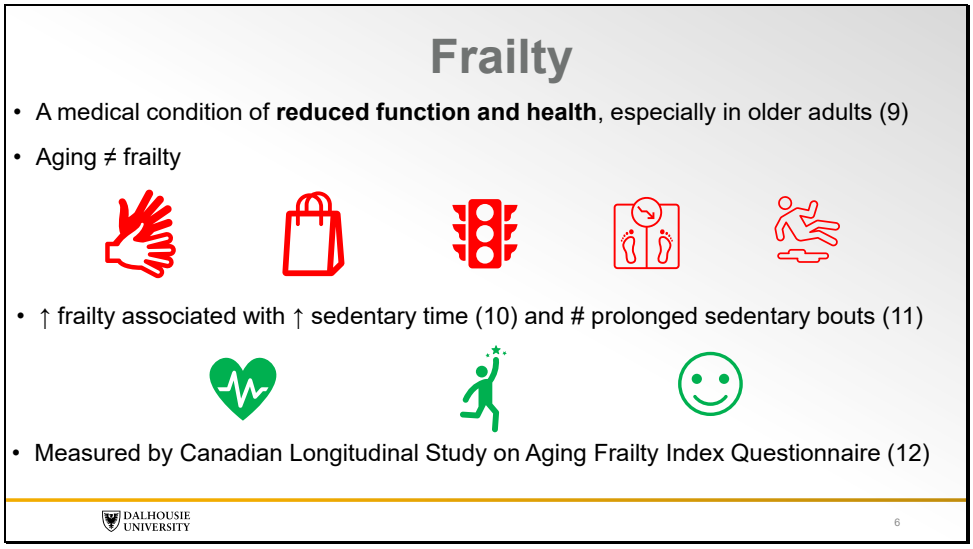
In addition, total ST, we are also interested in documenting your "sedentary patterns". These patterns can be described as the way someone accumulates their total ST. For example, someone could sit down all day without any breaks and accumulate 9 hours of ST. Meanwhile, someone else could also accumulate 9 hours of ST but may have broken up their ST by standing up or engaging in physical activity every 3 hours. Even better, someone could take a sedentary break every hour and still accumulate 9 hours of total ST. These sedentary breaks are really important because without them, prolonged bouts of ST can contribute negatively to the development of many chronic diseases.

Slide 5



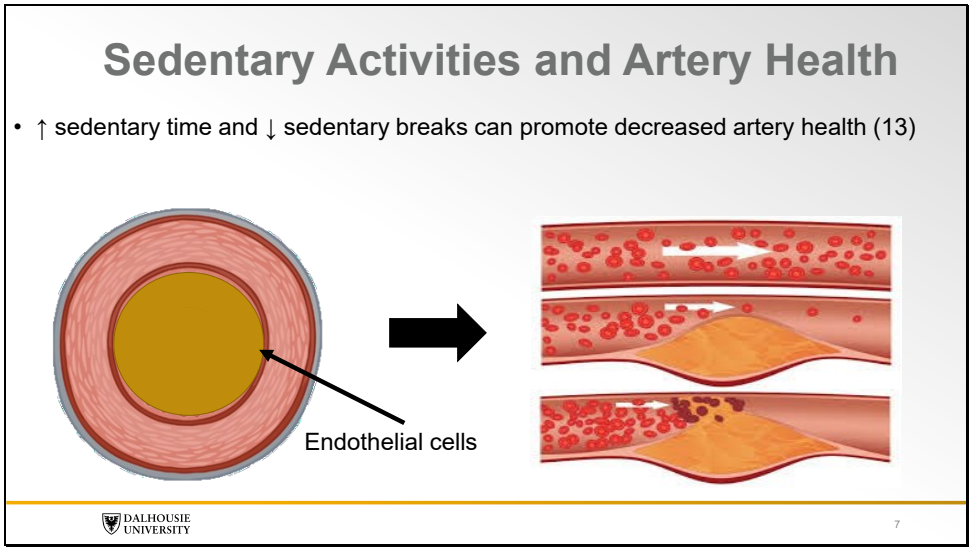
Specifically, increased total daily ST, more frequent prolonged (>1 hr), uninterrupted sedentary bouts and fewer sedentary breaks contribute to a greater risk of diabetes, poor mental health, premature death, and cancer, as well as frailty and cardiovascular disease risk, which we are interested in for this study. Sedentary activity is a prominent risk factor for cardiovascular disease, which is the second leading cause of death in Canada. Additionally, those who engage in >9 hours per day of ST are more likely to develop higher frailty levels, independent of their habitual physical activity level. This means that even if you go for a run every morning, but you sit on the couch for more than 9 hours the rest of the day, you are still at risk for the negative health effects that excessive sedentary activities can impose.

Slide 6



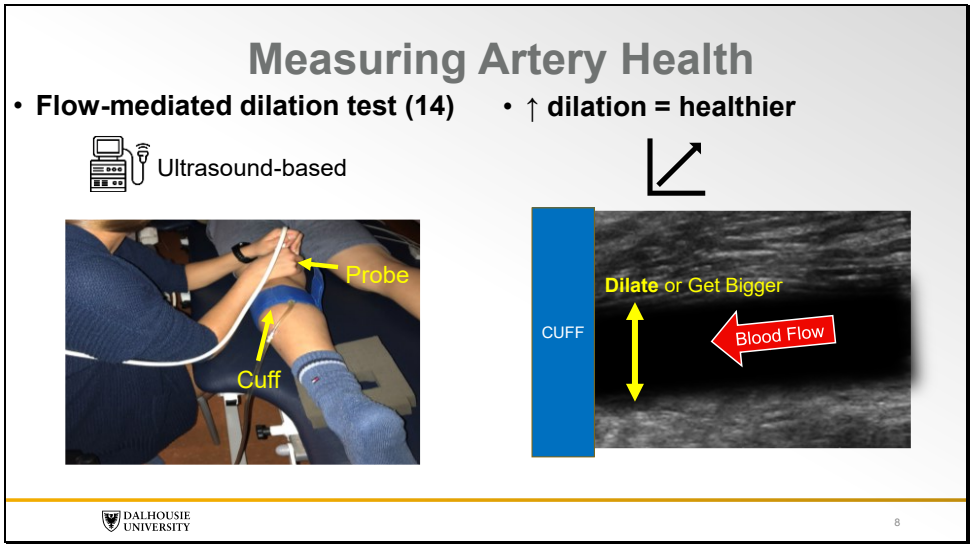
Frailty can be described as a medical condition of reduced function and overall health, especially found in older adults. However, frailty is not an inevitable part of aging. Even younger people can experience frailty if they don't take proper care of their health. Some common signs of frailty include struggling to open a jar, carry groceries, or crossing the street in a timely manner, losing weight unexpectedly, or having stability problems. Studies have shown that people who are frailer often engage in more sedentary activity and more prolonged sedentary bouts. However, each of us can make smart decisions about our sedentary behaviour to delay the onset of frailty and promote healthy living, maintain independence, and increase our quality of life. We will be able to track your frailty levels throughout this study using the Canadian Longitudinal Study on Aging frailty index questionnaire.

Slide 7



Aside from frailty, increased ST and fewer sedentary breaks can contribute to cardiovascular disease through detrimental effects on artery health. On the inside of an artery, like this one here, there is a layer of cells on the innermost surface called the endothelium. Usually, the endothelium is happy and healthy when blood is flowing through the artery. In a healthy artery, greater blood flow allows the endothelium to make helpful chemicals that cause it to stay relaxed or bigger. However, during prolonged sedentary bouts like sitting, the endothelium can become very unhappy and not work as well. Overtime, this can cause plaque buildup within the artery wall that will eventually lead to the artery becoming partially or completed blocked.

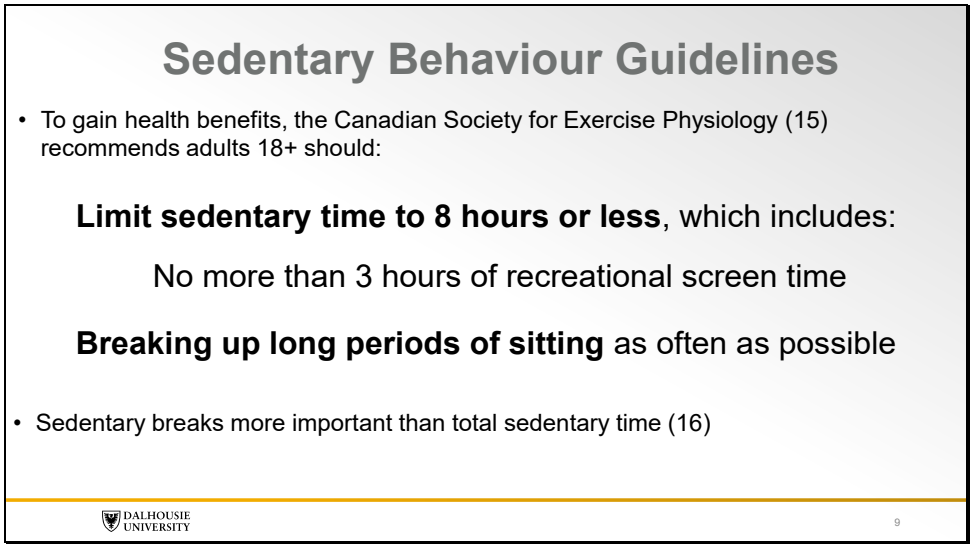
Slide 8



As you may remember from your baseline testing visit to the lab, we will use an ultrasound machine and a flow-mediated dilation test to measure the ability of your endothelium to produce these relaxing chemicals. As you can see in this picture, we use the ultrasound probe to image your artery, and an inflatable pressure cuff to alter your blood flow.

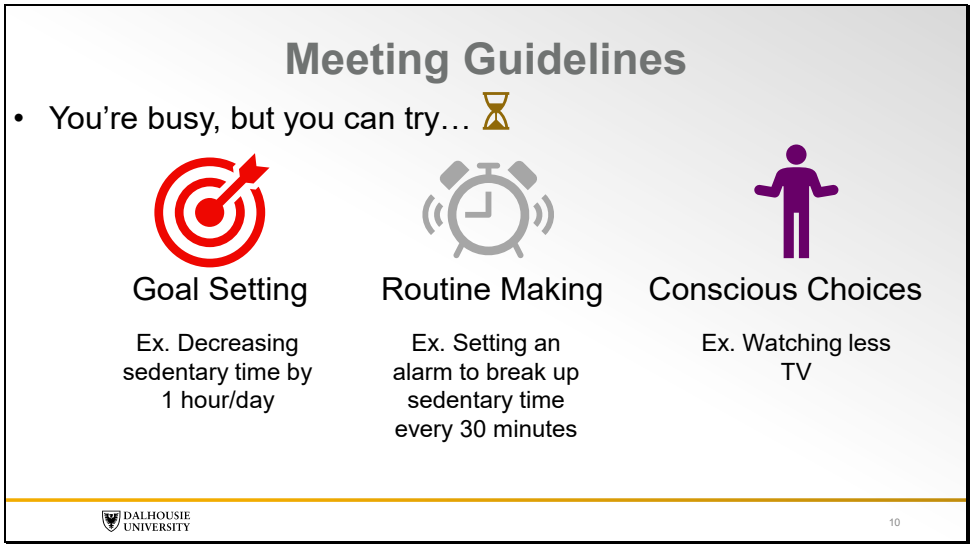
During the test, when the pressure-cuff is inflated, blood flow through your artery is decreased. However, when the cuff is deflated, blood flow increases and goes rushing through the arteries in your arm or leg. This increase in blood flow stimulates the endothelium to produce these relaxing chemicals and allows your artery to get bigger. The bigger it gets, the healthier your artery is! However, prolonged bouts of sitting can reduce the ability of your artery bigger during this flow-mediated dilation test. With that being said, the more you reduce your ST and increase sedentary breaks can contribute to healthier vascular function.

Slide 9



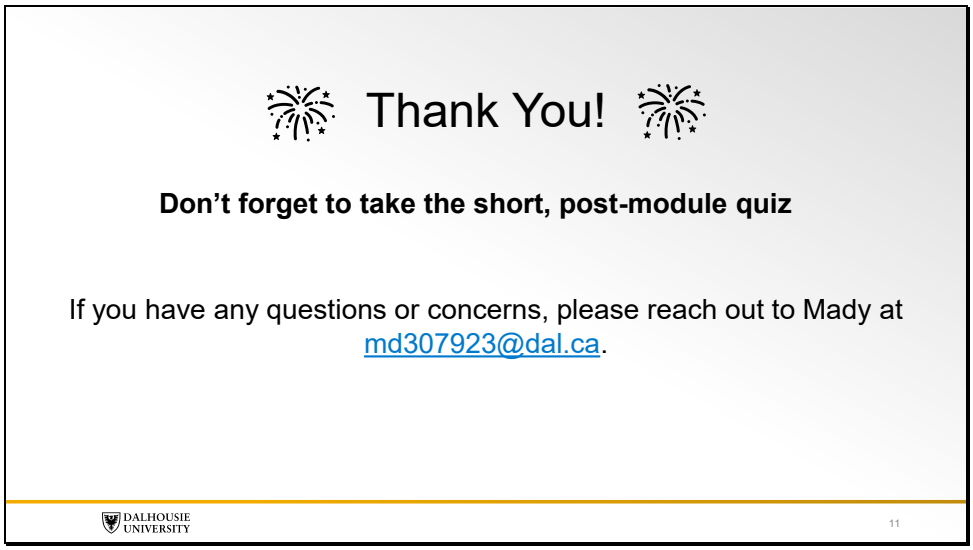
So, how much is too much when it comes to ST? To promote overall health, including cardiovascular health and decreased frailty, the Canadian Society for Exercise Physiology recommends that adults limit their ST to 8 hours or less each day. This includes no more than 3 hours of recreational screen time such as watching television, scrolling through your phone, or watching YouTube videos. However, recreational screen time does not include the time you spend on screen for school or work. Additionally, during the ST that you do accumulate throughout the day, you should break up prolonged bouts as often as you can! Some studies suggest that sedentary breaks can be even more important to your health than total ST!

Slide 10



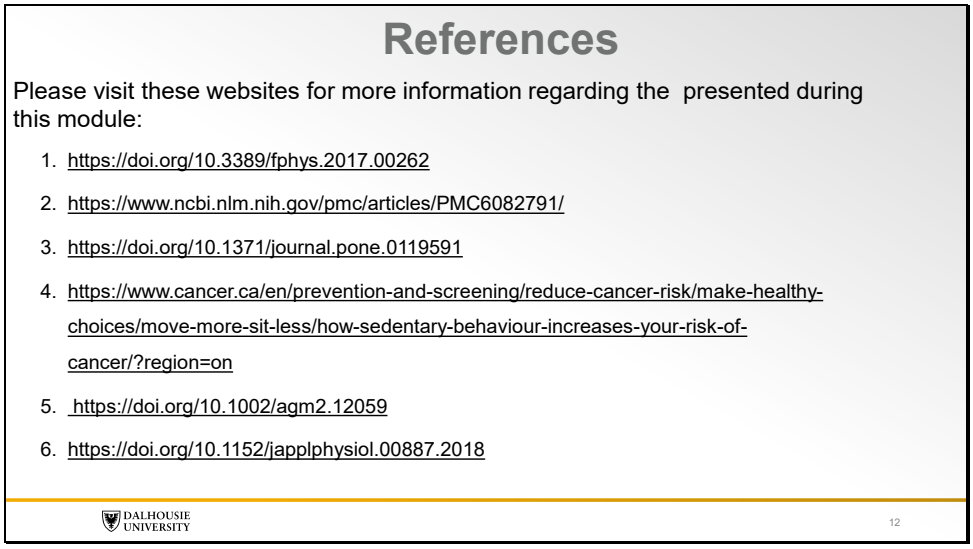
So how are you going to do this? There are lot of easy and accessible ways you can change your routine to meet these sedentary guidelines. Goal setting can be helpful to give you something to work towards and motivate you to accomplish something. For example, you could set a goal that you want to decrease you ST by 1 hour per day. Alternatively, you can get into a routine where you are able to meet your sedentary goals and guidelines. This could mean setting a schedule for yourself to break up your ST every 30 minutes to increase your sedentary breaks. What's important is that you're making conscious choices. Understand the guidelines and make changes to achieve them. It may sound daunting, but simple, small changes like these can go a long way and it's within your reach!

Slide 11



Thank-you for listening and don’t forget to take our short quiz. Please do not hesitate to reach out with any question or concern you have! See you in lab!

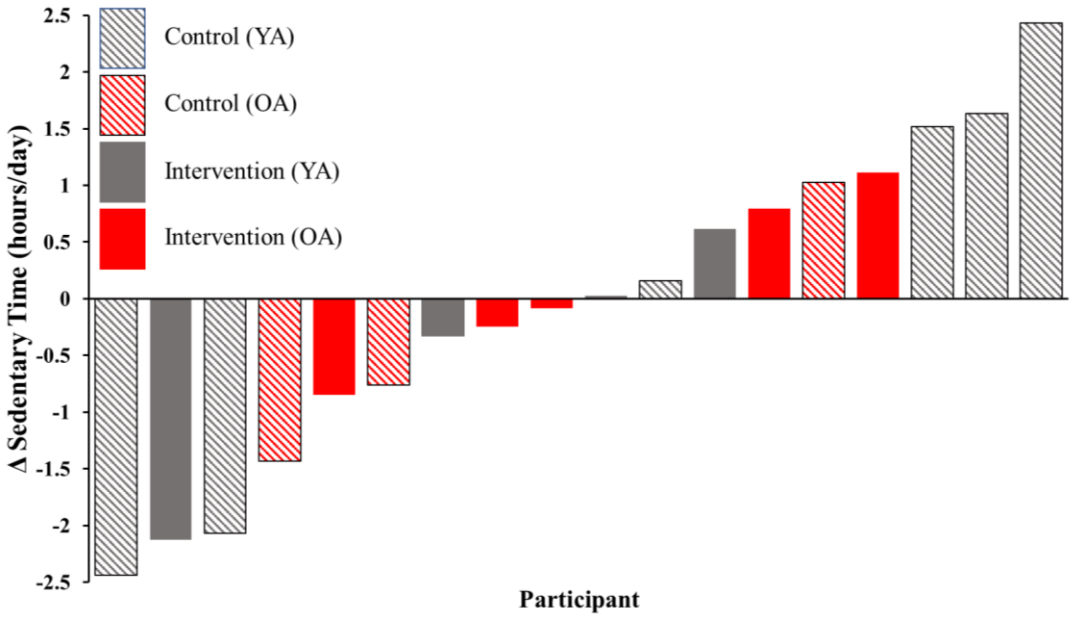
Slide 12



Slide 13

Link to Educational Module: https://dalu-my.sharepoint.com/:v:/g/personal/md307923_dal_ca/ETAL-EZPMiZHpwCkSHcoM6cBkRNaAeF86UBFIy1xiL0Y7Q?email=md307923%40dal.ca

Appendix F: Supplemental Figure 1



Supplemental Figure 1. Changes in total daily sedentary time (ST) across all participants (n=18) regardless of group (Intervention versus Control) assignment from Baseline to 9 months. Each bar represents an individual participant. A negative Δ value represents a reduction in ST. YA, younger adults (i.e., <55 years); OA, older adult (i.e., >55 years).

Appendix G: Curriculum Vitae

Madeline E. Shivgulam, BSc, MSc (Cand.)

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EDUCATION HISTORY

Bachelor of Kinesiology (Honours)
2017-2021
Dalhousie University, Halifax, Nova Scotia, Canada
Supervisor: Dr. Derek Kimmerly
Thesis Title: "Impact of ST and patterns on popliteal artery endothelial function in healthy adults

- GPA: 4.05/4.30

Master of Science in Kinesiology 2021-Present
Dalhousie University, Halifax, Nova Scotia, Canada
Supervisor: Dr. Derek Kimmerly
Thesis Committee: Dr. Olga Theou, Dr. Scott Kehler
Thesis Title: "The impact of a 12-month sedentary behaviour reduction intervention on frailty and arterial health: a pilot study"

- GPA: 4.23/4.30

PEER-REVIEWED JOURNAL ARTICLES

Published Articles (Total: *n*=22; *n*=7 first author)

1) **Shivgulam ME** & O'Brien MW. Applying Average-Real Variability to Quantifying Day-Day Physical Activity and Sedentary Postures Variability: A Comparison with Standard Deviation. (2023) *Journal for the Measurement of Physical Behaviour.* In Print.

2) Courish MK, **Shivgulam ME**, MacLeod JR, Kimmerly DS, O'Brien MW. (2023) Impact of a Unilateral Bifurcation on Brachial Artery Endothelial Function and Vascular Smooth Muscle Cell Sensitivity. *Applied Physiology, Nutrition & Metabolism.* In Print.

3) Patterson C, So S, Shipley K, **Shivgulam ME**, Avitzur Y, Ng VL. (2023). Physical function in children and adolescents pre- and 1-year post-liver transplant. *Pediatric Transplantation.* In Print.

4) **Shivgulam ME**, Schwartz BD, Wu Y, Daley SW, Kimmerly DS, Frayne RJ, O'Brien MW. (2023). Validity of ActivPAL CREA Software Detection of Sitting and Lying During Free-Living Conditions. *Physiological Measurement*. 44(7), 075003.

5) O'Brien MW, Schwartz BD, Shivgulam ME, Daley SW, Frayne RJ, Kimmerly DS. (2023). Higher Habitual Lying Time is Inversely Associated with Vagal-Related Heart Rate Variability Outcomes in Younger Adults. *Applied Physiology, Nutrition & Metabolism.* In Print.

6) MacLeod JR, Kivell MJ, **Shivgulam ME**, Liu H, O'Brien MW. (2023). The Effectiveness of Duplex Ultrasound for Detecting Renal Artery Stenosis Compared to Angiography in Children and Adults: A Systematic Review. Journal for Vascular Ultrasound. Accepted.

7) **Shivgulam ME**, Liu H, Schwartz BD, Langley JE, Bray NW, Kimmerly DS, O'Brien MW. (2023). Impact of Exercise Training Interventions on Flow-Mediated Dilation in Adults: An Umbrella Review. Sports Medicine. 53, 1161–1174.

8) O'Brien MW, Daley WS, Schwartz BD, **Shivgulam ME**, Wu Y, Kimmerly DS, Frayne RJ. (2023). Characterization of Detailed Sedentary Postures Using a Tri-Monitor ActivPAL Configuration in Free-Living Conditions. *Sensors.* 23(2), 587.

9) O'Brien MW, Pellerine LP, **Shivgulam ME**, Kimmerly DS. (2023). Disagreements in Physical Activity Monitor Validation Study Guidelines Create Challenges in Conducting Validity Studies. *Frontiers in Digital Health.* 4: 278.

10) O'Brien MW, Petterson JL, Pellerine LP, **Shivgulam ME**, Kimmerly DS, Frayne RJ, Hettiarachchi P, Johansson P. (2023). Moving Beyond the Characterization of Activity Intensity Bouts as Square-Waves Signals. *Journal for the Measurement of Physical Behaviour*. 6(8):1-6.

11) Pellerine LP, Petterson JL, **Shivgulam ME**, Johansson PJ, Hettiarachchi P, Kimmerly DS, Frayne RJ, O'Brien MW. (2023). Step Length, But Not Stepping Cadence, Strongly Predicts Physical Activity Intensity During Jogging and Running. *Measurement in Physical Education and Exercise Science.* 1-10.

12) Schwartz BD, **Shivgulam ME**, Petterson JL, Wu Y, Frayne RJ, Kimmerly DS, O'Brien MW. (2023). Higher Moderate-Intensity Physical Activity and Less Prolonged ST are Associated with Better Systolic Blood Pressure Variability in Healthy Adults. *Journal of Human Hypertension.* In Press.

13) Palmer KL, **Shivgulam ME**, Champod AS, Wilson BC, O'Brien MW, Bray NW. (2023). Exercise Interventions Augment Brain Activity and Reduce Pain Perceptions in Adults with Chronic Pain: A Systematic Review. 13, 100129.

14) **Shivgulam ME***, O'Brien MW*, Johns, JA, Petterson JL, Wu Y, Frayne RJ, Kimmerly DS. (2022). Impact of Habitual Sedentary Patterns on Popliteal Artery Endothelial-Dependent Vasodilation in Healthy Adults. *Vascular Medicine*. 27(2): 120-126. *Co-First Authors.

15) **Shivgulam ME**, Petterson JL, O'Brien MW. (2022). Viewpoint: Habitual Activity and Aerobic Fitness May Complement Iron Status When Conducting Sex Comparisons. *Journal of Applied Physiology*. 132(3): 703-709.

16) O'Brien MW, Liu H, **Shivgulam ME**, Langley JE, Bray NW, Kimmerly DS. (2022). The Impact of Exercise Training Interventions on Flow-Mediated Dilation: An Umbrella Review Protocol. *Healthy Populations Journal.* 2(1): 106-115.

17) O'Brien MW, **Shivgulam ME**, Petterson JL, Wu Y, Johns JA, Frayne RJ, Kimmerly DS. (2022). Substituting Stationary Time with Moderate-Intensity Activity May Improve Flow-Mediated Dilation. *Journal of Cardiopulmonary Rehabilitation and Prevention.* 42(6): 105-107.

18) **Shivgulam ME**, Landau M, Steiner K, Lee V, Harvey M. (2022). Understanding the Use of Patient Rooms to Inform Family Zone Implementation: A Qualitative Study. *Healthcare Quarterly*. 25(3): 49-53.

19) O'Brien MW, **Shivgulam ME**, Jojcik WR, Barron BA, Seaman RE, Fowles JR. (2022). 30 Year Trends of Reduced Physical Fitness in Undergraduate Students Studying Human Movement. *International Journal of Research and Public Health.* 19(21): 14099.

20) O'Brien MW, **Shivgulam ME**, Petterson JL, Wu Y, Frayne FJ, Mekari S, Kimmerly DS (2022). Habitual ST and stationary time are inversely related to aerobic fitness. *Sports Medicine and Health Science*. 4(4): 260-266.

21) **Shivgulam ME**, Petterson JL, Pellerine LP, Kimmerly DS, O'Brien MW. (2022). The Stryd Foot Pod is a Valid Measure of Stepping Cadence During Treadmill Walking and Running. *Journal for the Measurement of Physical Behaviour.* 6(1): 73-78.

22) O'Brien MW, Al-Hinnawi A, Wu Y, Petterson JL, **Shivgulam ME**, Johns JA, Frayne RJ, Kimmerly DS. (2021). The Influence of Habitual Breaks in ST on Cardiovagal Baroreflex Function. *Applied Physiology, Nutrition and Metabolism*. 46(9): 1143-1146.

KNOWLEDGE TRANSLATION ACTIVITIES

1) **Shivgulam ME,** O'Brien MW, Johns JA, Petterson JL, Wu Y, Frayne RJ, Kimmerly DS. (2022) Impact of habitual sedentary patterns on popliteal artery endothelial-dependent vasodilation in healthy adults. Sedentary Behaviour Research Network.

2) O'Brien MW, Schwartz DS, **Shivgulam ME**, Wu Y, Kimmerly DS, Frayne RJ. Characterization of detailed sedentary postures using a tri-monitor activPAL configuration in free-living conditions. (2023). Sedentary Behaviour Research Network.

3) Shivgulam ME, O'Brien MW. Exercise Training Recommendations for Adults With and Without Chronic Disease to Improve Endothelial Health (Infographic). (2023). Healthy Populations Journal.

ACADEMIC CONFERENCE PRESENTATIONS

Published Conference Presentations

1) **Shivgulam ME**, O'Brien MW, Johns JA, Petterson JL, Wu Y, Frayne RJ, Kimmerly DS. (2021). Impact of habitual sedentary patterns on popliteal artery endothelial dependent vasodilation in healthy adults. *Applied Physiology, Nutrition and Metabolism*. 46(10): S75.

2) **Shivgulam ME**, Liu H, Schwartz BD, Langley JE, Bray NW, Kimmerly DS, O'Brien MW. (2022) An Umbrella Review of the Impact of Exercise Training Intervention on Flow-Mediated Dilation in Adults. *Applied Physiology, Nutrition and Metabolism*. *In Press.*

3) Schwartz BD, **Shivgulam ME**, Petterson JL, Wu Y, Frayne RJ, Kimmerly DS, O'Brien MW. (2022). Impact of Habitual ST and Physical Activity on Beat-by-Beat Blood Pressure Variability in Healthy Adults. *Applied Physiology, Nutrition and Metabolism. In Press.*

4) O'Brien MW, **Shivgulam ME**, Petterson JL, Wu Y, Johns JA, Frayne RJ, Kimmerly DS. (2022). Substituting Stationary Time with Moderate-Intensity Activity May Improve Brachial Flow-Mediated Dilation: An Isotemporal Substitution Approach. *Medicine & Science in Sport & Exercise.* In Press.

5) Patterson C, So S, **Shivgulam ME**, Ng V. (2022). Clinical factors impacting physical function in older children one year post liver transplant. *Pediatric Transplantation.* 26.

6) **Shivgulam ME**, Schwartz BD, Kehler S, Theou O, O'Brien MW, Kimmerly DS. (2023) Feasibility and Effectiveness of a 3-Month Sedentary Behaviour Reduction Intervention in Sedentary Adults. *Medicine & Science in Sports & Exercise.* Accepted.

7) Courish MK, **Shivgulam ME**, MacLeod JR, Kimmerly DS, O'Brien MW. (2023) Impact of Unilateral Bifurcation on Brachial Artery Endothelial Function and Vascular Smooth Muscle Cell Sensitivity. *Medicine & Science in Sports & Exercise.* Accepted.

Professional Meetings and Other Academic Conferences

1) **Shivgulam ME**, O'Brien MW, Johns JA, Petterson JL, Kimmerly DS. (2021). Impact of Habitual Sedentary Patterns on Popliteal Artery Endothelial-Dependent Vasodilation in Healthy Adults. Atlantic Provinces Exercise Science Conference. University of New Brunswick, Fredericton, New Brunswick, Canada.

2) **Shivgulam ME**, Landau M, Steiner K, Verweel L, Harvey M. (2022) Understanding the use of patient rooms to inform family zone implementation: A qualitative study. Best Practices Day 2022. GTA Rehab Network, Toronto, Ontario, Canada.

3) Courish M, **Shivgulam ME**, MacLeod J, Kimmerly DS, O'Brien MW. (2023) Impact of Brachial Bifurcation on Endothelial-dependent And Independent Vasodilation: A Case Study. Atlantic Provinces Exercise Science Conference. University of New Brunswick, Moncton, New Brunswick, Canada.

4) **Shivgulam ME**, Schwartz BD, Kehler DS, Theou O, O'Brien MW, Kimmerly DS. (2023). Feasibility and Effectiveness of a 6-Month Sedentary Behaviour Reduction Intervention in Sedentary Adults. Atlantic Provinces Exercise Science Conference. University of New Brunswick, Fredericton, New Brunswick, Canada.

RESEARCH EMPLOYMENT

Research Assistant

SickKids Hospital, Department of Physiotherapy, Toronto, ON — May 2019-August 2019
"Physical function in children pre and post liver transplant"
Mrs. Catherine Patterson & Mrs. Stephanie So

West Park Healthcare Center, Toronto, ON — May 2021-August 2021
"Use of Patient Rooms to Inform Family Zone Implementation"
Mr. Lee Verweel

Nova Scotia Health Authority, Halifax, NS — September 2022-Present
"The Breaking "Bad Rest" Study: Interrupting ST to Reverse Frailty Levels in Acute Care"
Dr. Olga Theou

Nova Scotia Health Authority, Halifax, NS — January 2022- Present
"*The Personalized Approach for Healthy Aging (PAHA) program"*
Dr. Olga Theou

TEACHING EXPERIENCE

Physiology of Exercise (KINE 2310) — 2021/2022
2022/2023

Philosophy and Ethics of Kinesiology (KINE 1106) 2021/2022

Application of Physiological Principles to Human Performance (KINE3419) 2022/2023

Teaching Assistant: Dalhousie University

Guest Lecturer

Physical Activity & Chronic Disease (KINE 4709) Sept. 2022
"Sedentary Behaviour and Peripheral Vascular Health"
Dalhousie University

FUNDING, DISTINCATIONS, & AWARDS

Dalhousie University M.Sc Level

Nova Scotia Graduate Scholarship 2021-2023
$20 000

Heart & Stroke: BrightRed Award 2022
$5 000

Dalhousie University BSc Level

Dalhousie Entrance Scholarship 2017
$2 000

Dalhousie In-Course Scholarship 2018-2021
$2 000

Academic All-Canadian 2017-2021
GPA of 3.5 or higher while being a varsity athlete

Dalhousie University 3-Minute Thesis Finalist 2022
One of five finalists competing

Grant: Dalhousie Workplace Wellness Grants Program 2023
Primary: Myles O'Brien; *2 000 over 1 year*
Role: Co-Applicant
Project: Implementing the development of the Stand Up for Your Health Initiative
Status: Successful

PROFESSIONAL AFFILIATIONS & SERVICE

Journal Review

JMIR Rehabilitation and Assistive Technologies	2023; n=1
Interactive Journal of Medical Research	2023; n=1

Certifications

Swimming Canada - Fundamentals and Age Group Coaching	2017-Present

Memberships

Canadian Society for Exercise Physiology (CSEP)	2022-Present
Sedentary Behaviour Research Network (SBRN)	2022-Present
American College of Sports Medicine (ACSM)	2023-Present

Volunteer experience

Special Tigers – Varsity Athletics 2017-2021
Worked with special needs children to promote physical activity through sport and play

Extracurricular Associations

Assistant Coach – Dalhousie Men's & Women's Varity Swim Team 2022-Present