Cardiometabolic-Health Related Risk Factors and Physical Function with Aging: Targets for Lifestyle Intervention

by

Jenna Marie Napoleone

BS, Wake Forest University, 2015

MPH, George Washington University, 2017

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This dissertation was presented

by

Jenna Marie Napoleone

It was defended on

April 21, 2021

and approved by

Robert M. Boudreau, PhD, Assistant Professor, Epidemiology, University of Pittsburgh Graduate School of Public Health

Rachel G. Miller, PhD, Research Assistant Professor, Epidemiology, University of Pittsburgh Graduate School of Public Health

Bonny Rockette-Wagner, PhD, Assistant Professor, Epidemiology, University of Pittsburgh Graduate School of Public Health

Jennifer S. Brach, PhD, PT, Associate Dean for Faculty Affairs and Development, Professor, Physical Therapy, University of Pittsburgh School of Health and Rehabilitation Sciences

Dissertation Co-Director: Elsa S. Strotmeyer, PhD, MPH, Associate Professor, Epidemiology, University of Pittsburgh Graduate School of Public Health

Dissertation Co-Director: Andrea M. Kriska, PhD, MS, Professor, Epidemiology, University of Pittsburgh Graduate School of Public Health

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Jenna Marie Napoleone, PhD

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Abstract

Maintaining optimal physical function with age is critical for quality of life and health. Modifiable risk factors (e.g., cardiometabolic, lifestyle and behavioral) have shown to contribute to declining physical function in late-life adults, yet less is known about how earlier midlife risk factors impact mid- and late-life functional performance.

This dissertation examined associations of (1) maintenance session attendance impact on weight loss (WL) success in a lifestyle intervention (DPP-GLB) in adults with prediabetes and/or metabolic syndrome (MetS; n=238; mean age=62 years; 76% women), (2) objective physical function changes among GLB Moves participants randomized to an intervention with physical activity (DPP-GLB) or sedentary behavior (GLB-SED) goals vs. 6-month control and 12-month pre-post (n=305; 79% women), and (3) changes in the number of components of MetS across midlife with objective physical performance in early late life women from the Study of Women's Health Across the Nation (SWAN; n=1722; age 65.4±2.7 years; 26.9% Black, 10.1% Chinese, 9.8% Japanese, 5.5% Hispanic). Regression analyses were applied (1: logistic and multinomial; 2: mixed models; and 3: linear and latent class modeling).

Attending maintenance sessions and meeting the 6-month WL goal was associated with meeting the 12-month 5% WL goal, with Medicare eligible adults being more successful (OR=3.03, 95%CI:1.58-5.81). DPP-GLB and GLB-SED were effective at improving function with clinically meaningful changes (GLB-DPP: +0.05±0.17, GLB-SED: +0.06±0.16 m/s faster gait;

GLB-DPP: -0.17±2.7, GLB-SED: -0.55±2.2 secs faster chair stands); those with lower initial function improved more (+0.09 faster gait in DPP-GLB, +0.07 in GLB-SED). Midlife MetS groups (≥3 components) were related to worse early late life 40-ft walk (β:-0.08; 95% CI:-0.13, -0.03), gait speed (β:-0.09; 95% CI:-0.15, -0.02), SPPB (β:-0.79; 95% CI: -1.15, -0.44), and chair stands (β:0.69; 95% CI: 0.09, 1.28), but no difference in stair climb.

This dissertation provides valuable information to Medicare-DPP providers and characterize clinical and behavioral modifiable risk factors for functional decline in mid-to-early late life, to tailor preventive strategies to compress years of morbidity related to the onset of disability in late-life. Thus, the goal is to help older adults maintain independence with aging and live longer, healthier lives by intervening earlier in midlife.

Table of Contents

List of Tables

List of Figures

Preface

This dissertation work highlights my accomplishments while pursuing a doctoral degree in the Department of Epidemiology in the Graduate School of Public Health. While the past four years were some of the most challenging, they were also some of the most rewarding. My ability to accomplish and finish my doctoral degree is in part due to my amazing support system both at Pitt and within my own community of friends and family.

This work would not have been possible without my two advisors, Dr. Andrea Kriska and Dr. Elsa Strotmeyer. I am forever grateful for their continued support, encouragement, and mentorship. I offer sincere thanks to my doctoral committee who added immensely to my education but also offered insightful feedback throughout the research process.

I feel so lucky to have grown up in such a loving, supportive family. My parents taught me from an early age the importance of hard work, a positive attitude, and the power of prayer. I owe all my success to them and I am proud to be their daughter. Nick and Michael, thanks for being the best brothers and always making me laugh and feel proud of my accomplishments. Finally, I would like to thank my boyfriend James who has been my source of motivation, happiness, and courage to help me make it through the finish line. You have been my rock through this process and your perpetual optimism and ambition inspire my own.

1.0 Introduction

1.1 Aging and Disability Epidemiology

The global population is expected to increase by 25% from 2020 to 2050 with 1 in 6 adults 65 years and older (16%).[1] Older adults 60 years and over all countries is projected to increase from 841 million in 2013 to more than 2 billion by 2050.[2] As a result of many scientific and societal advancements, the life expectancy of older Americans continues to rise increasing the proportion of older adults ($\geq$ 65 years) by 188%, the oldest old adults ($\geq$ 85 years) by over 300% and those over the age of 100 years by over two times more than the oldest old.[3] However, concerning health and mortality trends that exist among midlife adults threaten these improvements in longevity.[4] Therefore, in order to maintain healthy aging and longevity, an emphasis on the mid-to-early old age period should be the focus in which midlife modifiable factors (e.g., cardiometabolic-health related risk factors, physical activity, and sedentary behavior) are priorities as potential early preventative mechanisms to preserve the health among old and oldest old populations.

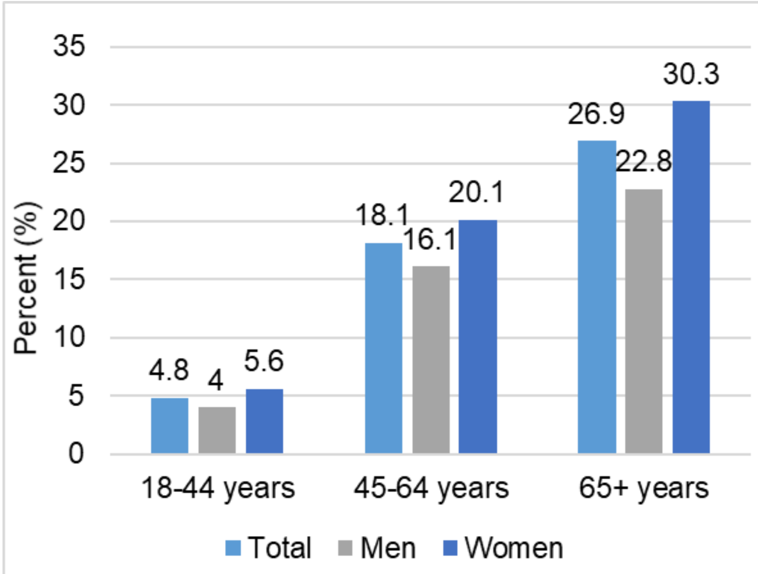

Figure 1. Prevalence of mobility disability among adults, by age and sex: BRFSS, 2016

Despite the reductions in mortality and advancements in healthy aging, disability remains a public health issue. Individuals with disability may experience several limitations including activities of daily living (e.g., eating, dressing, toileting, and walking from one room to another), instrumental activity of daily living (e.g., household chores, managing money, and food shopping), and social and leisure activities.[5] In the United States (US) in 2016, 1 in 4 adults reported having any type of disability (i.e., hearing, vision, cognition, mobility, self-care, and independent living).[6] The prevalence of total disability has increased since 2013, at which time 1 in 5 US adults reported any disability.[7] Mobility disability was the most prevalent type of disability among both midlife (18.1%; 45-64 years) and older adults (26.9%; 65+ years). Mobility disability prevalence is higher among women than among men for all age groups (18-44 years: 11.7% vs. 9.5%; 45-64 years: 20.1% vs. 16.1%; 65+ years: 30.3% vs. 22.8%) and increases with each age category as shown in Figure 1.[6] Additionally, disparities in prevalence of mobility disability exist by race/ethnicity with Black and American Indian/Alaska Native (AI/AN) adults experiencing the highest disability rates for younger, midlife and older adults compared to White counterparts (Figure 2).[6] The magnitude of the population living with disability and functional limitations is a serious public health concern. Disparities are apparent that need to be addressed among racial/ethnic minority populations.

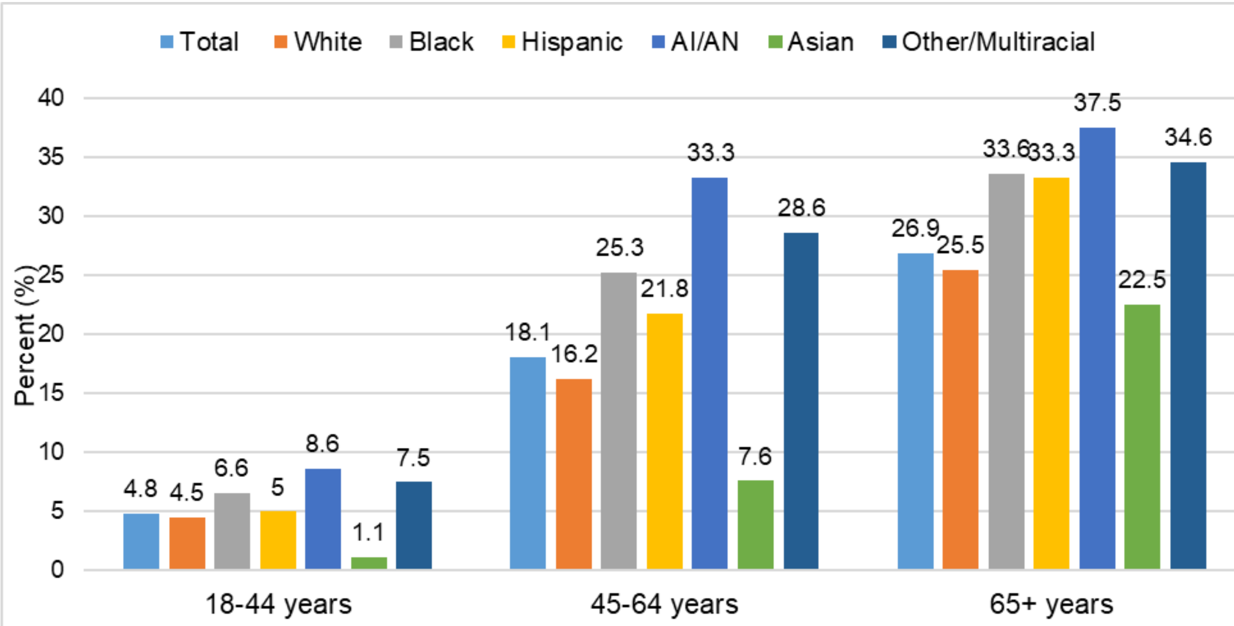

Figure 2. Prevalence of mobility disability among adults, by age and race/ethnicity: BRFSS, 2016

Functional limitations have been shown to significantly increase with age,[8] however, there is evidence to suggest that the disablement process begins earlier in midlife (i.e., approximately 45-60 years of age). Data from the National Health Interview Survey showed that 31%, 37% and 42% of persons aged 45-49, aged 50-54 and aged 55-59 reported functional difficulties, respectively. Participants reported having difficulty with at least one of the following functional tasks: standing two hours; sitting two hours; stooping; bending or kneeling; walking a quarter mile; climbing tens steps; reaching over one's head; grasping small objects; carrying ten pounds; and/or moving large objects.[9] Trends over time from 2000 to 2008 from five US national surveys demonstrated increased disability for midlife adults and stabilization or little improvement among older and oldest old adults.[10] Additionally, the multi-ethnic Study of Women's Health Across the Nation (SWAN) found that 30% of women aged 46-55 years reported some physical functional limitations and about 11% reported substantial limitations. Of those midlife SWAN women aged

56-66 years of age, 19% reported substantial limitations with over half of these women reporting at least some limitations (Figure 3).[11–13] Therefore, evidence suggests that the disablement process begins in midlife while adults still have decades of life for which remaining functionally independent is a priority.

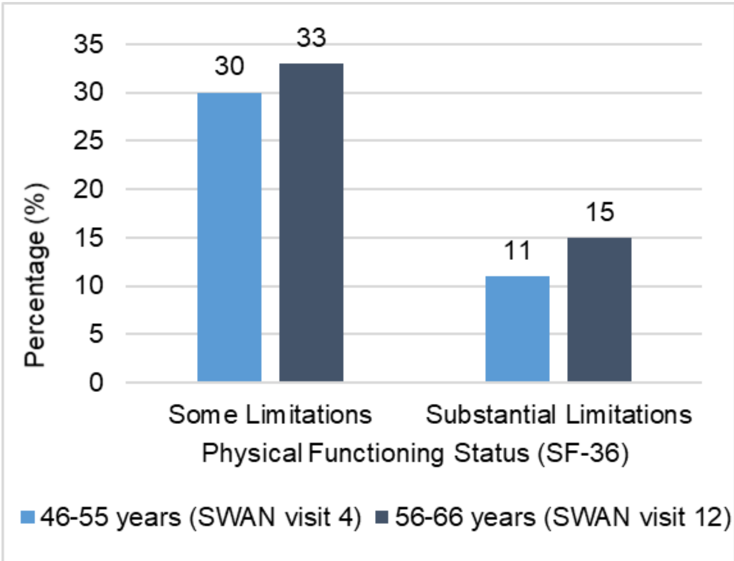

Figure 3. Self-reported physical functioning status by age group: SWAN

1.2 Physical Function and Health

Maintaining optimal physical function with age is critical for quality of life and health outcomes. People are living longer around the world and in the US, but functional and healthier, longer lives must be the focus.[14] The increasing prevalence of disability among older adults in the US is a public health problem because disability has been shown to be associated with increased utilization of health care, greater health care costs[15], increased mortality rates[16–19] and reduced quality of life.[20,21]

Functional dependence considerably impacts the US health care system. Adults 65 years and older who were functionally dependent on others for help due to physical limitations accrued approximately $10,000 higher health care expenditures over 2 years in 1993 compared to adults who remained functionally independent.[22] In addition, functionally dependent adults accounted for almost half of home health and nursing home expenditures (i.e., defined by Medicare-reimbursed or Medicaid-reimbursed health care expenditures) in this community-dwelling, older adult study cohort.[22] The most recent study over a decade ago in 2006 demonstrated that adults with physical disability have 4.3 times significantly higher total health care expenditures ($10,288/year) compared to adults without physical disability ($2,375/year).[23] These data suggest that health care expenditures among adults with physical disabilities are increasing over time; however, new analyses are needed to understand the implications disability has on the health system. Based on cost, people with functional disabilities are receiving health care services, but it is unclear if the care received is effective in preventing further functional decline.[23]

Disability (defined as any self-reported functional disability within the five domains of disability: activities of daily living (ADL), general physical activities (GPA), instrumental ADL (IADL), lower extremity mobility (LEM) and leisure and social activities (LSA)) have been associated with great than 2 fold increased risk of all-cause mortality (HR 2.23; 95% CI 1.29 to 3.85; p=0.004) among a national sample of older adults aged 60-84 years.[16] Additionally, among older adults from The Lifestyle Interventions and Independence for Elders (LIFE) study, faster 400-meter walk time at baseline was associated with higher health-related quality of life over 2.6 years (β=-0.001; p-value=0.0002) among older adults aged 70-89 years at risk for mobility disability.[24] Developing effective strategies to minimize disability and maintain functional status into old age are critical to reduce health care costs and sustain health outcomes and quality of life long-term.

1.3 The Disablement Process and Stages in the Process Amenable to Intervention

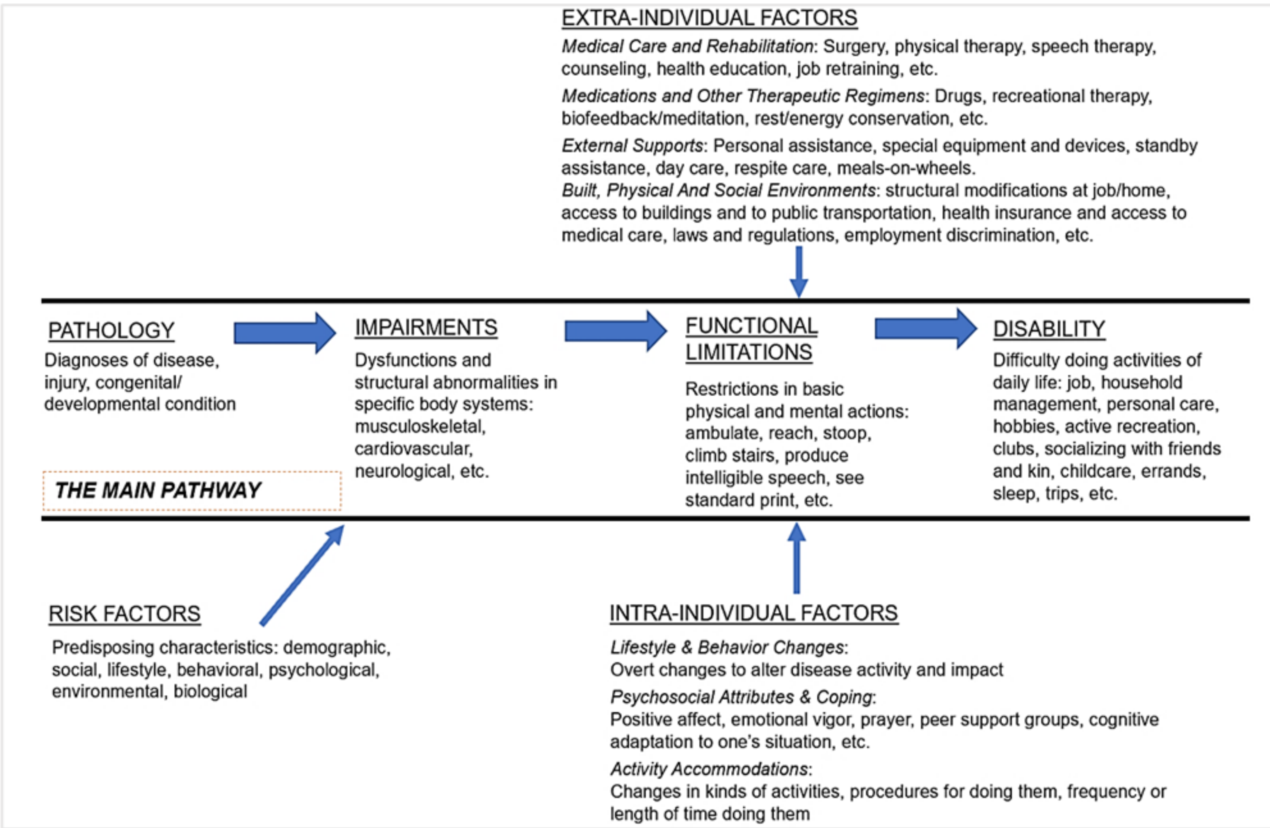

Figure 4. The disablement process adapted from Verbrugge and Jette

The disablement process is a complex, multi-stage process which involves risk factors, diseases and chronic conditions, and functional impairments and limitations. The fundamental disablement model was conceptualized by Saad Nagi and includes 4 levels: pathology, impairment, functional limitation and disability ("The Main Pathway" in Figure 4).[25] This initial disablement pathway was expanded by Verbrugge and Jette to include predisposing risk factors (demographic, lifestyle, social, environmental, etc.), intra-individual factors (e.g., lifestyle and behavior changes, psychosocial attributed and coping, and activity accommodations) and extra-individual factors (e.g., medical care and rehabilitation, medications and other therapeutic regimens, external supports, and built, physical and social environments) (Figure 4).[26] This model was constructed with prevention in mind and acknowledges that disability is both a sociological and medical condition (biophysical). The reasons that the additional predisposing factors in the Verbrugge and Jette model are critical for early prevention of disability is that these include early modifiable risk factors for physical functioning in older adults[27,28] such as weight loss/maintenance, physical activity, time spent sedentary, and cardiometabolic-related risk factors.

Maintenance of physical function is a substantial part of adults remaining independent into late life. Physical function represents a stage of the disablement process that is amenable to intervention and preventive efforts, particularly in early stages of decline.[29] Changes in physical function are likely the first stage on the path to disability which may continue from functional declines to disability, frailty and eventually death.[26] The goal should be to modify this decline at an early stage in the physical function changes. Midlife is likely a critical window for the onset of functional limitations, especially for women and minority populations with larger increases in functional declines compared to men and white populations, respectively.[6,8,30]

Due to the public health burden of age-related functional limitations and the importance of compressing years of morbidity for older adults, identifying earlier targets for intervention and preventing declines in physical function is a top priority. *This dissertation will fill several important gaps in knowledge to advance our understanding of preventing functional decline and maintaining physical function in older adults by focusing on implementing innovative interventions in midlife adults, which is likely a critical time period for the onset of functional* *limitations*. We will longitudinally assess how midlife cardiometabolic-related, modifiable risk factors impact early old age physical performance among a diverse population of racial/ethnic minority women in the SWAN cohort. In addition, we will examine how modifiable risk factors (e.g., weight, physical activity and changing sedentary time), that have been suggested to be important for functional outcomes, impact physical function in a clinical trial. In this community translated clinical trial, we have the opportunity to assess how a lifestyle intervention based on the Diabetes Prevention Program (DPP) that is being used nationally and reimbursed by Centers for Medicare and Medicaid Services affects physical function in a high-risk population of mid-to-early old age adults. Furthermore, one of the randomized arms of the clinical trial addresses whether an innovative sedentary behavior reduction intervention based on a DPP-based lifestyle intervention impacts physical function. Overall, this dissertation aims to examine how a combination of modifiable cardiometabolic-related risk factors and lifestyle interventions impact physical performance among mid-to-early old age adults.

1.4 Modifiable Risk Factors and Physical Function

Functional decline is not inevitable and is reversible**.** Physical function is a dynamic process and many factors are involved in the continuum from functional impairment to functional limitations.[31] Identifying modifiable risk factors that can halt, slow, or even reverse functional decline early in the disablement process is a significant public health concern. Little is known about "modifiable risk factors" in midlife adults and how this impacts later physical function changes including the extent to which these factors are similar and different from those in older adults. It is likely that the relationships between modifiable risk factors (e.g., health behaviors and treatable cardiometabolic-related risk factors) and physical functioning are bidirectional[32] which is not depicted in the fundamental disablement process depicted in Figure 4. This dissertation will help inform these complex relationships regarding risk factors and functional decline in mid-to-early old age adults using longitudinal studies with several adult populations. Understanding the epidemiology or clinical course of functional impairment in midlife is key to prevent further functional decline. If factors associated with functional loss in midlife are similar to those in older age, then existing interventions aimed at improving physical function may be appropriate for younger aged adults or changes for a different clinical approach will be better guided.[33] However, some modifications of relevant approaches to prevent disability are likely more effective for midlife versus older adults.

1.4.1 Conceptual Model of Modifiable Risk Factors with Functional Outcomes

Several cardiometabolic-related and behavioral modifiable risk factors may be associated with physical function outcomes**.** Figure 5 shows various behaviors (e.g., weight maintenance/loss, physical activity, and time spent sedentary) and cardiometabolic-related risk factors related to physical function that are of interest in this dissertation.

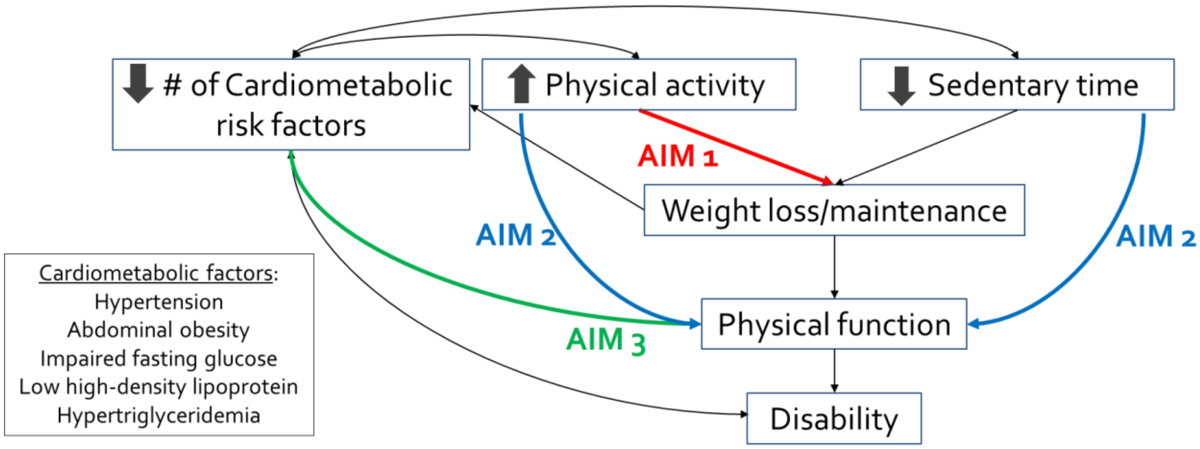

Figure 5. Conceptual model of modifiable risk factors impacting physical function

1.5 Targeted Interventions Aimed To Improve Physical Function Among Older Adults

1.5.1 Weight Loss and Weight Maintenance Interventions

Interventions to increase weight loss and encourage weight loss maintenance may be important for future functional outcomes. Increasing obesity prevalence among older adults is a public health issue in the US. In 2018 among adults ≥20 years, age-adjusted obesity and severe obesity prevalence rates were 11.9% higher and 4.5% higher compared to 1999, respectively (Figure 6).[34] About 35% of adults over the age of 65 are considered obese as defined by body mass index (BMI). Over 8 million adults aged 64-74 years and about 5 million adults over the age of 75 are considered obese.[35] Nationally-representative data demonstrate that midlife adults are as or more obese than older adults with 40% of 20-39 year old, 44.8% of 40-59 year old and 42.8% of ≥60 year old adults classified as being obese (Figure 7).[34] Both the increasing prevalence of adult obesity and high prevalence of young-to-midlife obesity is of particular concern since obesity negatively impacts physical disability and chronic conditions and diseases particularly as these adults transition from mid-to-early old age (i.e., functional limitations increase with increasing age as previously discussed).[36,37]

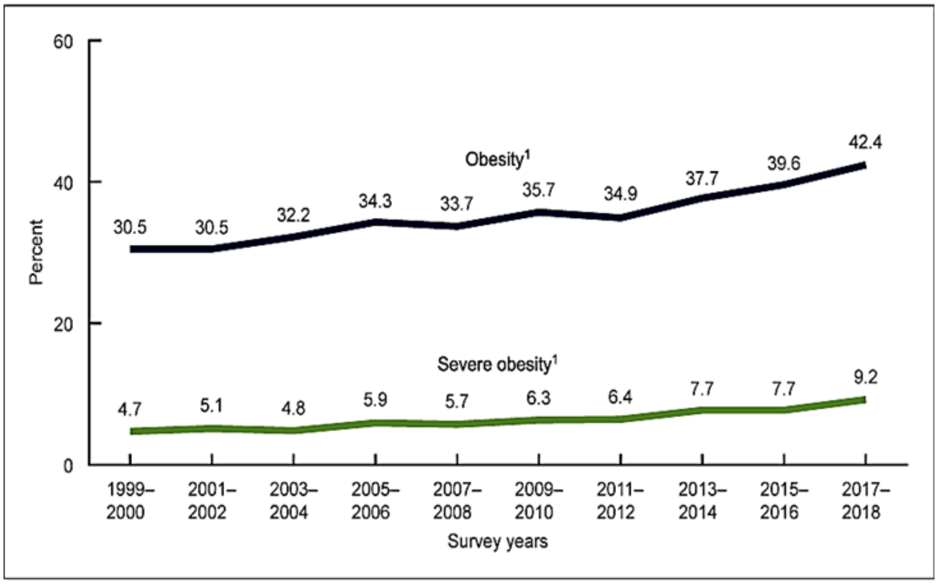

Figure 6. Trends in age-adjusted obesity and severe obesity prevalence among adults aged ≥20: National Health and Nutrition Examination Survey, 1999-2000 to 2017-2018.

[1]Significant linear trend. *Notes*: Estimates were age adults by the direct method to the 2000 US Census population using the age groups 20-39, 40-59, and 60 and over. Data from NCHS, 1999-2018.

In addition, there are geographic and racial/ethnic disparities in US obesity burden. Recent data showed that 31 states and the District of Columbia had an obesity prevalence of 35% or higher among non-Hispanic black adults, 8 states had an obesity prevalence of 35% of higher among Hispanic adults and only 1 state had an obesity prevalence of 35% or higher among non-Hispanic white adults.[38] In the US in 2017/2018, non-Hispanic black and Hispanic adults (44.8%) had higher prevalence of obesity (49.6%) compared to non-Hispanic white (42.2%) and non-Hispanic Asian (17.4%) adults aged 20 and over. The prevalence among non-Hispanic black women was the highest compared to all other groups (56.9%) (Figure 8).[39] We see the same patterns with obesity prevalence as described above among adults aged 65-74 years and 75 years and older (Figure 9)[40] indicating that preventative efforts should start before adults are classified as "old age". These strikingly high prevalence of obesity rates among all populations, but especially among non-Hispanic black and Hispanic women may have important functional implications in mid-to-early old age adults.

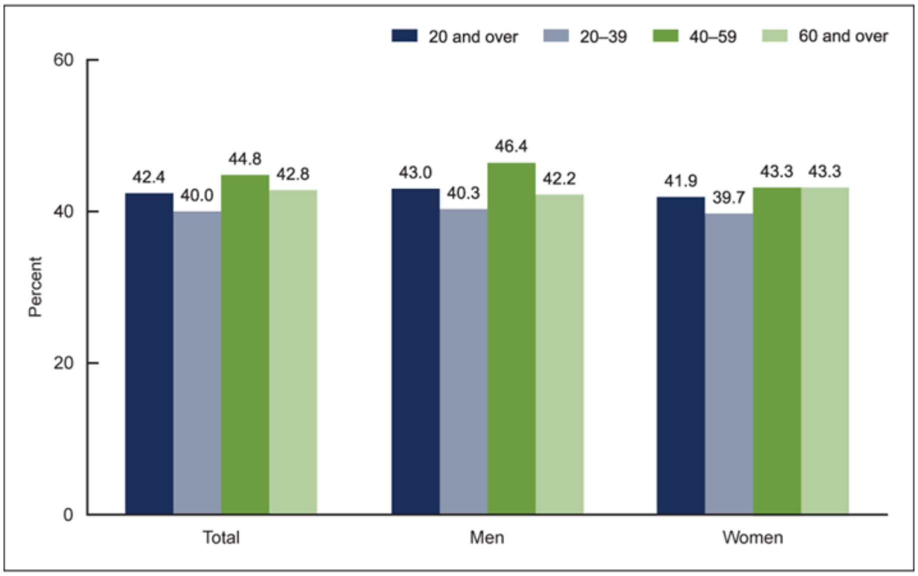

Figure 7. Prevalence of obesity among adults aged 20 years and older, by sex and age: National Health and Nutrition Examination Survey, 2017-2018

Notes: Estimates for adults aged 20 and over were age adjusted by the direct method to the 2000 US Census population using the age groups 20-39, 40-59, and 60 and over. Crude estimates are 42.5% for total, 43.0% for men, and 42.1% for women. Data source: NCHS, 2017-2018.

Obesity may worsen physical function declines in aging.[41] Among women 60 years and older from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004, after adjustment for major chronic conditions women in the highest quartile of waist circumference had 2.4 greater odds of reporting difficulties in activities of daily living, 2.3 for instrumental activities of daily living, 4.8 for lower extremity mobility and 2.9 for general physical activity compared to women in the lowest quartile. Among NHANES men from this study, the associations were more moderate compared to women.[42] Researchers estimate from the Behavioral Risk Factor Surveillance System that if obesity rates continue to increase among US adults, activity of daily living disability rates will increase by 1 percent each year among adults 50-69 years compared to was adults without additional weight gain.[43] Obesity has been specifically linked to mobility limitations (e.g., difficulty walking) due to increased risk for osteoarthritis which consequently increases mobility limitations.[44] Additionally, obesity is related to several other chronic conditions such as diabetes, metabolic syndrome and cardiovascular disease which in turn have each been shown to contribute to increased risk of disability.[45,46] Obesity and chronic conditions impact future disability proportionate to their severity[47]; therefore, it is critical to focus our efforts on preventing these health co-morbidities rather than treating them to have the largest effect on delaying the onset of disability among older adults.

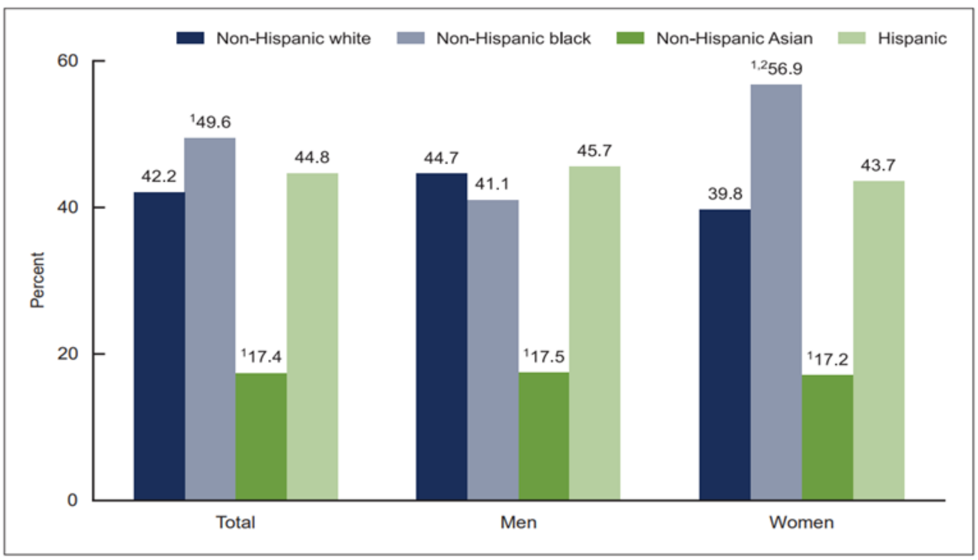

Figure 8. Age-adjusted prevalence of obesity among adults aged 20 and over, by sex and race and Hispanic origin: United States, 2017-2018

[1]Significantly different from all other race and Hispanic-origin groups. [2]Significantly different from men for same race and Hispanic-origin groups. Notes: Estimates for were age adjusted by the direct method to the 2000 US Census population using the age groups 20-39, 40-59, and 60 and over. Data source: NCHS, National Health and Nutrition Examination Survey, 2017-2018.

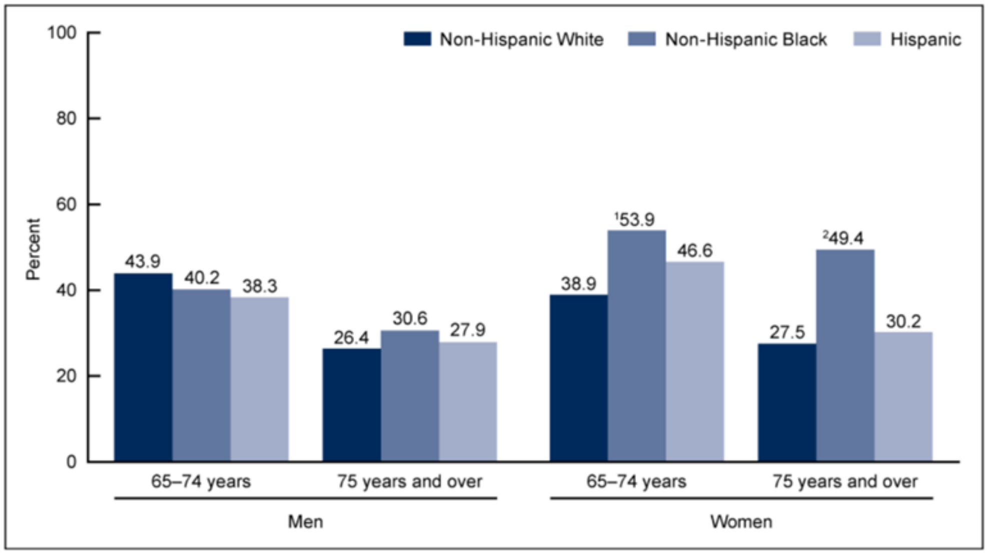

Figure 9. Prevalence of obesity among adults aged 65 and over, by sex and race and ethnicity: United States, 2007-2010

[1]Significantly different from non-Hispanic white. [2]Significantly different from non-Hispanic white and Hispanic. Data source: CDC/NCHS, National Health and Nutrition Examination Survey, 2017-2018.

Table 1 Weight Loss and/or Physical Activity Intervention Studies with Physical Function as an Outcome

Adapted from Starr et al 2014[48], Batsis et al 2017[49], Anton et al 2013[50], Miller et al 2013[51]

Study	Country	Study Population	Intervention	Outcomes	Findings	Limitations
Anton et al, 2011[52]	US	**N**= 34 **Age**: 63.7±4.5 yrs **Gender**: Women only **BMI**: Control: 35.8±6.8 kg/m^2, WL + EX: 37.8±5.5 kg/m^2 **Health**: Mild to moderate functional impairment	**Design:** RCT **Arms:** Control (n=17) WL+EX (n=17) **Duration:** 6 mo	Walking speed; SPPB; knee extension isokinetic; anthropometrics	**Weight loss:** Control: −0.23±4.08 kg; WL+EX: −5.95±4.08 kg **Function:** Walking speed increased more in WL+EX compared to control (0.16±0.03 m/s vs. 0.02±0.03 m/s); WL+EX and control increased in SPPB, with greater increases in WL+EX (1.82±1.24 vs 0.80±1.20)	Small sample, mean attendance was 70% (participants completed 2/3 of center-based exercise sessions), long-term maintenance of WL and function unknown; participants were mostly healthy, older obese women
Davidson et al, 2009[53]	Canada	**N**= 117 **Age**: Women: 67.4±5.1 yrs; Men: 67.7±5.1 yrs **Gender:** 58.0% women **BMI:** Women: 30.5±2.0 kg/m^2; Men: 30.4±2.7 kg/m^2 **Health**: Abdominal obesity, Sedentary	**Design:** RCT **Arms:** Control (n=28) Resistance EX (n= 36) Aerobic EX (n=37) Combined EX (n=35) **Duration:** 6 mo	Chair stands; 2-minute step; 8-ft-up-and-go; seated arm curl; VO_2 max; anthropometrics; body composition by MRI	**Weight loss:** Control; 0.28±0.37 kg; Resistance EX: −0.64±0.37 kg; Aerobic EX: −2.77±0.33 kg; Combined EX: −2.31±0.33 kg **Function:** Chair stands; 2-minute step; 8-ft-up-and-go; seated arm curl improved in all EX arms, with combined EX having greater improvements than Aerobic EX. VO_2 increased in Aerobic EX and Combined EX.	Ideal circumstances with motivated participants (supervised exercise, individualized diet plans); long-term maintenance of WL and function unknown; homogenous group of older white men and women *Note*: weight maintenance intervention via diet; WL via exercise only

Frimel et al, 2008[54]	US	**N=** 30 **Age:** WL: 70.3±4.8 yrs; WL+EX: 68.7±4.3 yrs **Gender:** 60% women **BMI:** WL: 36.9±4.9kg/m^2; WL+EX:36.7±5.1 kg/m^2 **Health**: Mild to moderate frailty; sedentary	**Design:** Rando mized, parallel groups **Arms:** WL (n=15) WL+EX (n=15) **Duration:** 6 mo	1-RM; body comp by DXA; anthropomet rics	**Weight loss:** WL: −10.7±4.5 kg, 10.6±4.6%; WL+EX: −9.7±4.0 kg, 100±3.9% **Function:** WL+ EX increased in upper and lower extremity strength (1-RM).	Small sample size; long-term maintenance of WL and function unknown; lacking physical function measures; results specific to 65+ older adults
Messier et al, 2004[55]	US	N= 252 **Age:** healthy lifestyle: 69±0.1 yrs; WL: 68±0.7 yrs; EX: 69±0.8 yrs; WL+EX: 69±0.8 yrs **Gender**: Control: 68% women; WL: 72% women; EX: 74% women; WL+EX: 74% women **BMI:** healthy lifestyle: 34.2±0.6 kg/m^2; WL: 34.5±0.6 kg/m^2; EX: 34.2±0.6 kg/m^2; WL+EX: 34.0±0.7 kg/m^2 **Health**: Knee pain, radiographic evidence of knee OA, sedentary, self-reported physical disability	**Design:** RCT **Arms:** Control (n=78) WL (n=82) EX (n=80) WL+EX (n=76) **Duration:** 18 mo	WOMAC; 6-minute walk; timed stair-climb; anthropomet rics	**Weight loss:** Control: 1.2% WL: 4.5%; EX: 3.7%; WL+EX: 5.7% **Function:** WL+ EX decreased in WOMAC score compared to control; WL+EX and WL decreased in WOMAC score compared to baseline scores. 6-minute walk distance increased in WL+EX and EX compared to control and stair-climb time decreased in WL+EX.	Results specific to knee OA older adults (~70 years old)
Miller et al, 2006[56]	US	**N=** 87 **Age:** Control: 69.3±0.9 yrs; WL+EX : 69.7±0.9 yrs **Gender:** WS: 60.5% women; WL+EX : 63.6% **BMI**: Control : 34.3±3.9 kg/m^2; WL: 34.9±4.9 kg/m^2 **Health**: Symptomatic knee OA; difficulty with 1 or more:	**Design:** RCT **Arms:** Control (n=43) WL+EX (n=44) **Duration:** 6 mo	WOMAC; 6-minute walk distance test; stair climb test; body comp by DXA; anthropomet rics	**Weight loss:** Control: −0.1±0.7 kg; WL+EX: −8.3 ±0.7 kg **Function:** Com pared to control WL+EX had improvements in WOMAC score in WL+EX; walking distance; faster stair climb in WL+EX.	long-term maintenance of WL unknown; disease specific cohort; highly selected population; very structured intervention with meal replacements/fac ility-based exercise

		lifting and carrying groceries, walking one-quarter mile, getting in and out of a chair, or going up and down stairs				
Rejeski et al 2011[57]	US	**N=**288 **Age:** Control: 67.2±4.8 yrs; EX: 67.2±5.1 yrs; WL+EX: 66.8±4.6 yrs **Gender:** both, 66% female **BMI: Control: 32.6** ±3.5; EX: 32.8±3.9; WL+EX: 33.1±4.1 **Health:** overweight or obese older adults in poor cardiovascular health	**Design:** translational RCT **Arms:** Control (n=84) EX (n=83) EX+WL (n=94) **Duration:** 18 mo	400 m walk in seconds	**Weight loss:** Control: -0.9 kg; EX: -0.8 kg; EX+WL: -7.1 kg **Function:** WL+EX group improved their 400 m walk time compared with both EX and control; participants with poorer mobility at baseline improved the most	Participants in control group (successful aging) attended a mean (SD) of 70.9% (26.5%) of the scheduled sessions, whereas for PA it was 79.8% (24.6%), and for WL+PA it was 88.2% (25.2%); not mentioned if differences in attendance was statistically different between control group and intervention arms
Rejeski et al 2012[58]	US	**N=**5016 **Age**: Control: 58.85 ± 6.86 yrs; WL+EX: 58.55 ± 6.77 yrs **Gender**: Both; 60% women **Health**: Type 2 diabetes; BMI >25 kg/m^2 (>27 kg/m^2 if currently taking insulin).	**Design:** RCT **Arms**: Control (n=2502) WL+EX (n=2514) **Duration:** 4 yrs	Self-reported limitation in mobility	**Weight loss:** Control: 0.88%; WL+PA: 6.15% **Function:** Compared to control, WL+EX reduced risk of loss of mobility	self-reported measure of mobility which is different from physical performance measures; intervention effects specific to older adults with type 2 diabetes
Santanasto et al 2010[59]	US	**N=**36 **Age:** 70.3 ± 5.9 years **Gender:** Both, 16.7% male **Health:** Overweight to moderately obese (BMI: 28.0 - 39.9 kg/m^2), sedentary (formal exercise less than 3x/week for a total of less than	**Design:** RCT **Arms:** Control (PA +SA) (n=15) PA+WL (n=21) **Duration:** 6 mo	SPPB; CHAMPS; anthropometric, body composition, bone mass, and muscle strength	**Weight loss:** PA+SA: -1.0±3.5 kg; PA+WL: -4.9±4.8kg **Function:** SPPB significantly increased in PA+WL (+0.7, p=0.04) but not PA+SA arm (+0.5, p=0.13)	SPPB was statistically significant between randomized arms at baseline (10.7 for PA+SA and 9.7 for PA+WL); lacks control groups for WL alone therefore difficult to distinguish

		90 min/week) older adults				effect of WL from PA on function; fairly healthy older adults; small sample size; short follow up time
Santanasto et al 2017[60]	US	**N=** 1635 **Age:** Control: 79.1±5.2yrs; EX: 78.7±5.2yrs **Gender:** Both **BMI:** Control: 30.3±6.2 kg/m^2; EX: 30.1±5.7 kg/m^2 **Health**: At-risk for mobility disability (SPPB < 10)	**Design:** RCT **Arms**: Control (n=817) EX (n=818) **Duration:** 36 mo	Grip strength; SPPB score and its components (balance, 4 m gait speed, and chair-stands); 400 m walking speed	**Function:** Total SPPB score and chair stand time were higher across all time points vs. control**;** EX had improvements in 400 m walking speed compared to control; no difference between arms for balance, grip strength or 4 m gait speed	No direct measure of lower extremity muscle strength or power, fitness or body composition; results generalizable to older adults at high risk for mobility disability
Villareal et al, 2006[61]	US	**N=** 27 **Age:** Control: 71.1±5.1 yrs; WL+EX : 69.4±4.6 yrs **Gender:** Both **BMI:** Control: 39.0±5.0 kg/m^2; EX+WL: 38.5±5.3 kg/m^2 **Health**: Mild to moderate frailty	**Design:** RCT **Arms:** Control (n=10) WL+EX (n=17) **Duration:** 6 mo	PPT; VO_2 max; FSQ score; 1-RM; knee extensor and flexor strength; dynamic balance (obstacle course); static balance (single limb leg stance time); gait speed; SF-36; body comp by DXA; anthropometric	**Weight loss:** Control: 0.7±2.7 kg; WL+EX: −8.2 ±5.7 kg **Function:** WL+EX increased in VO_2; FSQ score; knee extension and flexor strength; gait speed; physical function (SF-36); role limitations (SF-36); vitality (SF-36); and change in health (SF-36). WL+EX improved one leg limb stand and obstacle course time	long-term maintenance of WL unknown; small sample size; specific to older adults and results may not generalize to midlife adults
Villareal et al, 2011[62]	US	**N**= 93 **Age**: Control: 69±4; WL, EX, and WL+EX:70±4 yrs **Gende**r: Control:	**Design:** RCT **Arms:** Control (n=27) WL (n=26) EX (n=26) WL+EX (n=28)	PPT; VO_2 max; FSQ score; 1-RM; dynamic balance	**Weight loss:** Control: −0.1±3.5 kg,<1%; WL: −9.7±5.4 kg, 10%; EX:	Small sample size; Not powered to determine differences by sex; sample was

		67% women; WL: 65% women; EX: 62% women; WL+EX: 57% women **BMI:** control: 37.3±4.7; WL: 37.2±4.5; EX: 36.9±5.4; WL+EX: 37.2±5.4 kg/m^2 **Health**: Mild to moderate frailty Sedentary lifestyle	**Duration:** 12 mo	(obstacle course); static balance (single limb leg stance time); gait speed; SF-36; body comp by DXA; anthropometrics	−0.5±3.6 kg, 1%; WL+EX: −8.6±3.8 kg, 9% **Function:** WL+ EX and EX arms significantly improved in all functional measures compared to control. WL significantly improved compared to control in all functional measures except strength and gait speed. PPT and VO_2 improved more in WL+EX than WL or EX. Similar improvements seen between WL+EX and EX arms in FSQ, 1-RM and gait speed, and between WL+EX and WL in single limb leg stance time.	mostly women, white, well-educated, and older (70 yrs) with mild-to-moderate frailty which limits generalizability
Villareal et al, 2017[63]	US	**N=160** **Age:** Control, Ex + RT, and Both: 70±5; Ex: 70±4 yrs **Gender:** Control: 70% women, Ex: 65% women, RT: 62% women, Ex+RT: 60% **BMI**: control: 36.7±5, Ex: 35.9±4.4, RT: 36.7±5.8, Ex+RT:35.8±4.5 **Health**: Sedentary lifestyle, mild-to-moderate frailty	**Design:** RCT Arms: Control (n=40) Weight management program plus 1 of 3 exercise programs: EX (n=40) RT(n=40) EX+RT(n=40) **Duration**: 6 months	PPT; FSQ; Body Composition via DXA; strength, balance, 1-RM, static balance (single limb leg stance time), anthropometrics, gait speed	**Weight Loss:** Control: −0.9±0.5 kg, <1%; EX: −9.0±0.6 kg, 9%; RT: −8.5±0.5 kg, 9%; EX+RT: −8.5±0.5 kg, 9% **Function:** PPT increased more in ET+EX arm but significantly increase in all exercise groups vs. control; Strength significantly	Ideal circumstances (supervised exercise, individualized diet plans); not powered to determine differences by sex; white, well-educated women; long-term maintenance of WL unknown

					improved in RT and EX+ET	

Note: Adapted from Starr et al 2014[48], Batsis et al 2017[49], Anton et al 2013[50], Miller et al 2013[51]; RCT=Randomized Clinical Trial; RT=resistance training; BW = body weight; EX = exercise intervention; FSQ = functional status questionnaire; PPT =physical performance test; 1-RM = 1 repetition maximum; SF-36 = short form health survey; SPPB = short physical performance battery; VO_2 max= cardiorespiratory fitness; WC = waist circumference; WL = weight loss intervention; WL+EX = weight loss and exercise intervention; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; SA= Successful Aging; CHAMPS = Community Healthy Activities Model Program for Seniors questionnaire.

Prevention and management of chronic conditions among older adults is challenging due to the risks and benefits associated with intentional weight loss with aging.[64] As demonstrated in Table 1, intentional weight loss in older adults has positive benefits on physical function, as well as chronic diseases[65,66] and quality of life.[67] However, weight loss among older adults also poses potential risks such as increased nutritional deficiencies, loss of bone mineral density, and increase risk of fracture and sarcopenia.[35]

Lifestyle interventions in older adults have been shown to be effective for weight reduction and disease prevention. The landmark Diabetes Prevention Program (DPP) showed that 63% of older adults (≥ 65 years) achieved the 7% weight loss goal compared to only 27% younger adults (≤ 45 years) after 3-years (the DPP is described in detail later). Additionally, for each kilogram lost through the lifestyle intervention (i.e., diet and physical activity)[68], the incidence of type 2 diabetes was reduced by 16% over 3 years.[65,69] However, more research is needed to determine, 1) if weight maintenance is as beneficial as weight loss, 2) if differences for weight maintenance/loss exist for specific populations (e.g., younger vs. older adults), and 3) how both weight maintenance/loss impact geriatric-related health outcomes such as physical function.

Weight loss/maintenance in midlife may have important implications for late life physical function. However, there is a lack of studies examining the association between <u>weight loss/maintenance in midlife</u> and <u>physical function in older adults</u>. It is common among adults who lose weight to eventually regain the weight. *If individuals are not able to maintain weight* *loss/prevent weight gain, this may impact the ability to maintain physical function and ultimately prevent disability*. A cohort study followed 1418 men and women for 20 years and found that weight gain of 10-20% and over 20% from baseline (and not weight loss) was associated with significantly increased self-reported functional limitations (Odds Ratio (OR)=1.69 and OR=2.74, respectively), independent of baseline weight, physical activity, and other sociodemographic factors.[70] These findings indicate that both weight gain and maintenance of obesity may be related to higher risk of disability in later life. A lifestyle intervention called the Action for Health in Diabetes (Look AHEAD) trial in mid-to- early old age overweight or obese adults with type 2 diabetes found that the intensive lifestyle intervention arm had small but clinically meaningful changes in gait speed (0.05-0.08 m/s) between those who achieved and maintained the 7% weight loss goal versus those who did not.[71] This finding suggests that while the improvement in physical function may be modest on an individual scale, the potential impact of sustained weight loss on functional improvements at the population level could be substantial,[72] since a 0.01 m/s improvement in gait speed is associated with a 12% reduction in total mortality in late life.[73]

Gaps in the literature remain about understanding adults' ability to sustain weight loss and prevent weight gain through mid-to-early old age, which is important for determining how to maintain optimal physical functioning into late-life. Our specific aim 1 will address the first part of this research gap in knowledge.

1.5.2 Physical Activity Interventions

Physical activity has been shown to prevent or delay functional impairments in older adults. Regular physical activity has several health benefits; however, one of the most important health outcomes related to aging is maintaining or improving physical function. Being physically active can help prevent, delay or manage many chronic conditions of which older adults are at higher risk.[74] Table 2 shows the health benefits associated with participating in regular physical activity (only outcomes with moderate to strong scientific evidence were included in this table; adapted from 2018 Physical Activity Guidelines for Americans).

Table 2. Health Benefits Associated with Lifetime Regular Physical Activity for Adults/Older Adults and People with Chronic Health Conditions

Adults and Older Adults

- Lower risk of all-cause mortality
- Lower risk of cardiovascular disease mortality
- Lower risk of cardiovascular disease (including heart disease and stroke)
- Lower risk of hypertension
- Lower risk of type 2 diabetes
- Lower risk of adverse blood lipid profle
- Lower risk of cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach
- Improved cognition
- Reduced risk of dementia (including Alzheimer's disease)
- Improved quality of life
- Reduced anxiety
- Reduced risk of depression
- Improved sleep
- Slowed or reduced weight gain
- Weight loss, particularly when combined with reduced calorie intake
- Prevention of weight regain following initial weight loss
- Improved bone health
- Improved physical function
- Lower risk of falls (older adults)
- Lower risk of fall-related injuries (older adults)

People with Osteoarthritis (knee and hip)

- Decreased pain
- Improved physical function
- Improved health-related quality of life
- No effect on disease progression at recommended physical activity levels

People with Hypertension

- Lower risk of cardiovascular disease mortality
- Reduced cardiovascular disease progression
- Lower risk of increased blood pressure overtime

People with Type 2 Diabetes

- Lower risk of carediovascular disease mortality
- Reduced progression of disease indicators: hemoglobin A1c, blood pressure, body mass index, and lipids

The national physical activity guidelines encourage adults to engage in at least 150 minutes of moderate-to-vigorous physical activity (e.g., a brisk walk) or at least 75 minutes of vigorous intensity physical activity (e.g., jogging) per week. However, about 30% of the US adult population reports doing less than 10 minutes of moderate-to-vigorous physical activity each week which classifies them as "inactive".[75] Among adults 50 years or older, 31 million are inactive and 4 in 5 of the costliest chronic conditions among these adults can be prevented/managed by engaging in regular physical activity. More females are classified are inactive compared to males (29.4% compared to 25.5%). Additionally, midlife adults have similar amounts of inactivity compared to early old and oldest adults and have similar levels of chronic disease which impacts their ability to be active (Figure 10).[76] For adults who perform little-to-no moderate physical activity, replacing sedentary behaviors (e.g., sitting) with lower intensity physical activity can reduce health risks (e.g., reduced risk of cardiovascular disease and mortality[77]) even if small amounts of movement are incorporated daily.[75]

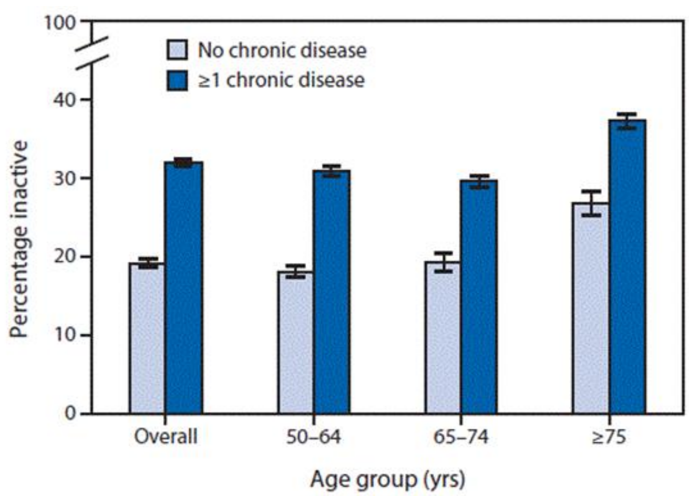

Figure 10. Percentage of self-reported physical inactivity among adults 50+ by chronic disease status and age group, BRFSS, 2014

Table 3. Lifestyle intervention characteristics of weight loss and/or physical activity studies with physical function as an outcome (continuation of studies from Table 2)

Study	Study Population	Intervention	Intervention Characteristics	Limitations
Anton et al, 2011[52]	**N**= 34 **Age**: 63.7±4.5 yrs **Gender**: Women only **BMI**: Control: 35.8±6.8 kg/m^2, WL + EX: 37.8±5.5 kg/m^2 **Health**: Mild to moderate functional impairment	**Design:** RCT **Arms:** Control (n=17) WL+EX (n=17) **Duration:** 6 mo **Goal**: ≥6% WL through moderate changes in energy intake (ie, a reduction of 500–1000 kcal/day) coupled with exercise sessions (both aerobic activities (ie, walking) and lower-body resistance training of moderate intensity)	**Control:** Asked to maintain normal eating/activity patterns, attended monthly educational sessions on topics relevant to older adults that were not related to weight loss, diet, or physical activity (eg, skin protection, sleep hygiene); given opportunity to have full WL+E intervention at end of 6 months **WL+EX:** weekly group-based weight management session held at church facility and 3 structured exercise sessions per week; WL sessions included nutrition education, behavioral strategies, and problem solving to reach goals; two 15-min walking bouts performed during EX session – after 1st bout, participants completed lower body exercises (wide leg squat, standing leg curl, knee extension, side hip raise, and toe stand)	Time intensive intervention with long-term sustainability unknown (clinic-based EX sessions used-participants may not have access to a gym following the intervention); attendance =70% for EX sessions
Davidson et al, 2009[53]	**N=** 117 **Age**: Women: 67.4±5.1 yrs; Men: 67.7±5.1 yrs **Gender:** 58.0% women **BMI:** Women: 30.5±2.0 kg/m^2; Men: 30.4±2.7 kg/m^2	**Design:** RCT **Arms:** Control (n=28) Resistance EX (n= 36) Aerobic EX (n=37) Combined EX (n=35) **Duration:** 6 mo	**Control:** none **Resistance EX:** set of 9 exercises: chest press, shoulder raise, shoulder flexion, leg extension, leg flexion, triceps	Control group protocol not described; resistance EX may not be feasible for the typical older adult and functional limitations with other

	Health: Abdominal obesity, Sedentary		extension, biceps curl, abdominal crunches, modified push-ups; ~20 min/session, 3 sessions/week **Aerobic EX:** 30 min of moderate-intensity treadmill **Combined:** Resistance EX and Aerobic EX combined	comorbidities; the intervention would need to be extensively modified to be translated in the community
Frimel et al, 2008[54]	**N=** 30 **Age:** WL: 70.3±4.8 yrs; WL+EX: 68.7±4.3 yrs **Gender:** 60% women **BMI:** WL: 36.9±4.9kg/m^2; WL+EX:36.7±5.1kg/m^2 **Health**: Mild to moderate frailty; sedentary	**Design:** Randomized, parallel groups **Arms:** WL (n=15) WL+EX (n=15) **Duration:** 6 mo	**WL:** WL goal of 10% with not more than 1.5% loss per week; met weekly with dietician for caloric intake adjustments and behavioral strategies **WL+EX:** WL program above plus an exercise program closely supervised by a physical therapist; 3 90-min sessions/week; session included 15 min of flexibility exercises, 30 min of low-impact aerobic exercise, 30 min of high-intensity progressive resistance training (squats, leg press, knee extension, knee flexion, seated row, upright row, seated chest press, biceps curl, and triceps extension) and 15 min of balance activities	Program sustainability will be an issue since the exercises should be supervised and require use of gym equipment
Messier et al, 2004[55]	N= 252 **Age:** healthy lifestyle: 69±0.1 yrs; WL: 68±0.7 yrs; EX: 69±0.8 yrs; WL+EX: 69±0.8 yrs **Gender**: Control: 68% women; WL: 72% women; EX: 74%	**Design:** RCT **Arms:** Control (n=78) WL (n=82) EX (n=80) WL+EX (n=76) **Duration:** 18 mo	**Control:** provided attention, social interaction and health education; monthly meeting for first 3 months; monthly phone contact months 4-6,	Generalizability may be specific to overweight and obese older adults (approximately 70 years old) with knee OA

	women; WL+EX: 74% women **BMI:** healthy lifestyle: 34.2±0.6 kg/m^2; WL: 34.5±0.6 kg/m^2; EX: 34.2±0.6 kg/m^2; WL+EX: 34.0±0.7 kg/m^2 **Health**: Knee pain, radiographic evidence of knee OA, sedentary, self-reported physical disability		contact every other month during months 7-18 **WL:** goal=lose and maintain a WL of 5%; intensive phase (mo 1-4), transition (biweekly sessions, mo 5-6), maintenance (mo 7-18, monthly meeting and phone contacts, alternated every 2 weeks, newsletters) **EX:** 3 day per week program included: aerobic phase (15 minutes), a resistance-training phase (15 minutes), a second aerobic phase (15 minutes), and a cool-down phase (15 minutes); 4 months facility based; participants could do a home-based program or a combined facility-home-based program **WL+EX:** combination of above descriptions	
Miller et al, 2006[56]	**N=** 87 **Age:** Control: 69.3±0.9 yrs; WL+EX : 69.7±0.9 yrs **Gender:** WS: 60.5% women; WL+EX : 63.6% **BMI**: Control : 34.3±3.9 kg/m^2; WL: 34.9±4.9 kg/m^2 **Health**: Symptomatic knee OA; difficulty with 1 or more: lifting and carrying groceries, walking one-quarter mile, getting in and out of a chair, or going up and down stairs	**Design:** RCT **Arms:** Control (n=43) WL+EX (n=44) **Duration:** 6 mo	**Control:** weight stable control group; bimonthly group meetings included info on general health (OA and exercise), weigh-ins (encouraged to maintain weight), bimonthly newsletters **WL+EX:** goal=10% WL during the first 6 months; partial meal replacements (max 2/day), nutrition education and lifestyle behavior modifications;	Generalizability specific to older obese adults with knee OA; highly motivated and specific population (highly educated and mostly white); meal replacements n realistic as a long-term mechanism for WL and weight maintenance; short-term intervention

			pedometers and self-monitoring logs used for physicl activity; instructed to reach 10,000 steps/day goal by end of 6-months	
Rejeski et al 2011[57]	**N=**288 **Age:** Control: 67.2±4.8 yrs; EX: 67.2±5.1 yrs; WL+EX: 66.8±4.6 yrs **Gender:** both, 66% female **BMI: Control: 32.6** ±3.5; EX: 32.8±3.9; WL+EX: 33.1±4.1 **Health:** overweight or obese older adults in poor cardiovascular health	**Design:** translational RCT **Arms:** Control (n=84) EX (n=83) EX+WL (n=94) **Duration:** 18 mo	**Control:** Successful aging education intervention; met weekly for 6 mo, bimonthly until end of study – 18 total sessions; taught how to actively "take charge" or health; did not receive a progressive, supervised program of PA or diet for WL **EX:** 48 total sessions; gradually increase or shape PA in a home-based environment to >30 min of moderately intense activity on most days/week; 6-mo of intensive phase (3 in person group sessions and 1 individual; each started with a 30-45 min walk); mo 7-18 maintenance phase with contact 2x/month **EX+WL:** EX program above plus dietary WL; goal = reduce caloric intake to lose 7-10% by first 6 mo; during maintenance participants were encouraged to continue to lose weight with a focus on weight maintenance	Overall, a well-designed intervention with a maintenance phase; specific to older adults rather than midlife adults
Rejeski et al 2012[58]	**N=**5016 **Age**: Control: 58.85 ± 6.86 yrs; WL+EX: 58.55 ± 6.77 yrs	**Design:** RCT **Arms**: Control (n=2502) WL+EX (n=2514)	**Control:** 3 diabetes support and education sessions each year for 4	*intervention details from Wadden et al[78]; specific to older

	Gender: Both; 60% women **Health**: Type 2 diabetes; BMI >25 kg/m^2 (>27 kg/m^2 if currently taking insulin).	**Duration:** 4 yrs	years; sessions cover PA and diet/nutrition; attendance is not required but encouraged **WL+EX:** goals= mean weight loss from baseline of more than 7% and to increase the duration of physical activity to more than 175 minutes a week; intervention modeled after the Diabetes Prevention Program; Phase 1 (months 1-12): weekly meetings (3 group and 1 individual); Phase II (months 13-48): minimum of 2 contacts per month, one in person, one by phone or email; refresher groups offered 3x/year; Phase III (months 49+) :at least 2 on-site contacts per year	adults with type 2 diabetes
Santanasto et al 2017[60]	**N=** 1635 **Age:** Control: 79.1±5.2yrs; EX: 78.7±5.2yrs **Gender:** Both **BMI:** Control: 30.3±6.2 kg/m^2; EX: 30.1±5.7 kg/m^2 **Health**: At-risk for mobility disability (SPPB < 10)	**Design:** RCT **Arms**: Control (n=817) EX (n=818) **Duration:** 36 mo	**Control:** health education group held weekly workshops for the first 26 weeks; then sessions held 2x/mo (required to attend 1); PA not discussed; 5-10 min light stretching at the end **EX:** PA sessions were group based and consisted mostly of walking (goal of 150 min/wk); strength and balance done at the center (2x/wk) using ankle weights	Clinic-based intervention study in older adults; unknown if effective on healthier midlife adults
Villareal et al, 2006[61]	**N=** 27 **Age:** Control: 71.1±5.1 yrs; WL+EX : 69.4±4.6 yrs	**Design:** RCT **Arms:** Control (n=10) WL+EX (n=17) **Duration:** 6 mo	**Control:** participants instructed to	PA intervention may not be feasible for all older adults; 90 minutes of exercise

	Gender: Both **BMI:** Control: 39.0±5.0 kg/m^2; EX+WL: 38.5±5.3 kg/m^2 **Health**: Mild to moderate frailty		maintain usual diet and activities **WL+EX:** diet prescribed to provide energy deficit of -750 kcal/d; goal=10% WL; curriculum based on Diabetes Prevention Program; meekly group meetings; group exercise sessions on 3 days each week supervised by physical therapist (15 min warm-up, 30 min endurance exercise, 30 min strength training, 15 min balance)	3x/week is a large commitment for most sedentary older adults with functional limitations and may not sustainable long-term; lack of detail on control group
Villareal et al, 2011[62]	**N**= 93 **Age**: Control: 69±4; WL, EX, and WL+EX:70±4 yrs **Gender**: Control: 67% women; WL: 65% women; EX: 62% women; WL+EX: 57% women **BMI:** control: 37.3±4.7; WL: 37.2±4.5; EX: 36.9±5.4; WL+EX: 37.2±5.4 kg/m^2 **Health**: Mild to moderate frailty Sedentary lifestyle	**Design:** RCT **Arms:** Control (n=27) WL (n=26) EX (n=26) WL+EX (n=28) **Duration:** 12 mo	**Control:** asked to not participate in external WL or EX program; attended group educational sessions about a healthful diet once a month **WL:** prescribed a balanced diet with energy deficit of 500-750 kcal/day;met weekly with dietician; attended weekly weigh-in sessions; recorded in food diaries; goal=10%WL at 6 months maintain WL for additional 6 mo **EX:**3 group sessions per week; 90 min in duration with aerobic exercises, resistance training and flexibility/balance exercises **WL+EX:** participated in both interventions above	Relatively small sample sizes in each group; Length of exercises sessions may not be feasible/sustainable for all older adults; lack of detail describing the control group

Villareal et al, 2017[63]	**N=**160 **Age:** Control, Ex + RT, and Both: 70±5; Ex: 70±4 yrs **Gender:** Control: 70% women, Ex: 65% women, RT: 62% women, Ex+RT: 60% **BMI**: control: 36.7±5, Ex: 35.9±4.4, RT: 36.7±5.8, Ex+RT:35.8±4.5 **Health**: Sedentary lifestyle, mild-to-moderate frailty	**Design:** RCT **Arms**: Control (n=40) Weight management program plus 1 of 3 exercise programs: EX (n=40) RT(n=40) EX+RT(n=40) **Duration**: 6 mo	**Control:** asked to not participate in external WL or EX program; attended group educational sessions about a healthful diet once a month Weight management program (met weekly with dietician; prescribed balanced diet with energy deficit of 500-750 kcal/day; goal=10% WL at 6 mo) plus 1 of 3 exercise programs: **EX:** 3x/week aerobic sessions; 60 min long (10 min flexibility, 40 min aerobic, 10 min balance); walking, stationary cycling and stair climbing exercises used **RT:** same resistance training exercises at aerobic group 3x/week; 10 min flexibility, 40 min resistance, 10 min balance; weight-lifting machines used **EX+RT:** combination of above interventions; sessions were 75-90 min (10 min flexibility, 30-40 min aerobic, 30-40 min resistance, 10 min balance)	Length of EX sessions may not be sustainable or feasible for most older adults; weight machines used for RT which could decreases sustainability of program at the end of the study if participants don't have access to a gym; long-term effects unknown due to intervention length

It has been shown that physical activity maintains or improves physical function which is especially important in order for older adults to maintain their independence and quality of life with aging. Lifestyle interventions in older adults have been shown to improve physical function. The Lifestyle Interventions and Independence for Elders (LIFE) study which included sedentary, older adults (mean age=78.9 ± 5.2 years) and involved a moderate physical activity intervention (i.e., center-based 2x per week and home-based 3-4x per week) compared to a health education arm. They showed significantly improved objective physical function and physical performance as well as reductions in major mobility disability over the course of 2.6 years vs. health education group.[60,79] Other lifestyle intervention studies conducted in middle aged and older adults who were overweight or obese lasting up to a year and a half showed improvements in physical performance outcomes (Table 2 and Table 3).[55,57,62,80–82] The control group protocol was not described in detail for many of the lifestyle interventions presented in Table 3. A thorough description of control groups in physical activity interventions are especially important because they inform the effectiveness of the intervention itself and allow us to know what caused a difference in the results between the groups. Control groups may have unintended increases (or decreases) in physical activity during the intervention which can lead to inadvertent decreases in sedentary time and improvements in health characteristics.

However, few of these lifestyle interventions were based on the Diabetes Prevention Program (DPP)[83] and the existing exercise interventions have limitations regarding the sustainability of the program long-term, feasibility of the intervention for the general older adult population and ability of the interventions to be translated into the community setting (Table 3).

1.5.2.1 The Diabetes Prevention Program Lifestyle Intervention

The US DPP demonstrated that behavioral lifestyle intervention with weight loss and physical activity goals, can prevent/delay the development of type 2 diabetes by 58% compared to placebo and reduce the risk of developing the metabolic syndrome (MetS) by 41% compared to placebo. [83–85] Physical activity in the DPP, in addition to weight, was found to play an important role in that participants who successfully achieved the activity goal of 150 minutes per week had better success at weight loss and those who were more active in follow-up had a lower incidence of diabetes.[86]

The DPP-GLB lifestyle intervention curriculum has been detailed elsewhere [87,88] and is available at no cost online (www.diabetesprevention.pitt.edu). Similar to other DPP-based CDC recognized lifestyle intervention programs, it is a 12-month in-person, group-based program with a total of 16 core sessions and 6 maintenance sessions taught by a trained lifestyle coach. In the first 6 months of *core sessions*, there are 12 weekly sessions followed by 4 bi-weekly sessions. Months 7-12 consist of 6 monthly *maintenance sessions* [89]. The main goals of the DPP-GLB lifestyle intervention are to encourage participants to increase physical activity levels to at least 150 minutes of moderate intensity physical activity per week and achieve and maintain a 7% weight loss in a safe and progressive manner. All lifestyle coaches involved complete a standardized 2-day training workshop provided by the Diabetes Prevention Support Center which is recognized by the CDC [88]. Group intervention sessions are held at senior/community centers and participants receive session handouts, self-monitoring logs, and a pedometer, and are weighed at each session.

Given the success of these DPP-based community lifestyle intervention programs, the Centers for Disease Control and Prevention (CDC) was appointed to monitor national delivery [90] and collect program data in six month intervals that includes participant weight loss and session attendance [89]. Since 2018, the Centers for Medicare and Medicaid Services (CMS) reimburses CDC-recognized programs for delivery to all fee-for-service beneficiaries with prediabetes on these parameters: session attendance (at 6 and 12 months) and 5% WL goal achievement at 12 months [91]. As of April 2019, over 324,000 participants across 3,000+ organizations have participated in these programs [92]. *Therefore, if DPP-based lifestyle interventions are effective at* *improving physical function, this intervention has the potential to positively impact the functional ability of thousands of adults at high-risk for functional decline and late-life disability.*

Preliminary data suggests that the DPP-based lifestyle intervention improves functional outcomes since the odds of frailty versus non-frailty (i.e., frailty defined as 3 to 5 abnormalities in the Fried Frailty Phenotype Criteria: slow walking speed, weak grip strength, unintentional weight loss, low physical activity, and exhaustion) were 37% lower in the physical activity lifestyle arm compared to placebo.[93] The DPP-based programs that are nationally delivered by CMS for adults diagnosed with prediabetes are currently reimbursed based on maintenance session attendance and 5% weight loss. If these programs demonstrate increases in physical function, this criterion could be another option for reimbursement in the future. *However, there is a current gap in knowledge regarding the effect of DPP-based lifestyle intervention programs on physical function; we will fill this gap in our specific aim 2.*

1.5.3 Interventions to Reduce Sedentary Time

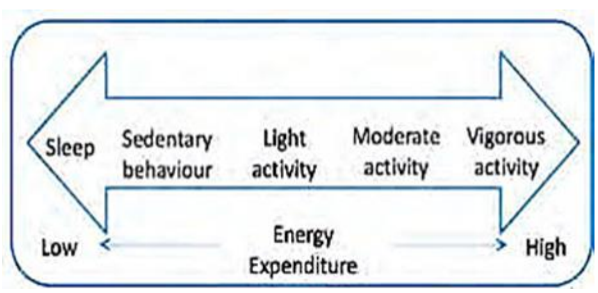

Figure 11. Human movement and energy expenditure continuum

Sedentary behavior may influence successful aging. During waking hours, one is either engaging in physical activity (of vigorous, moderate or light intensity) or spending time in sedentary behaviors (Figure 11).[94] Sedentary behavior has been used to refer to time during waking hours spent in activities with low energy expenditure (≤1.5 METs) that are performed while sitting or reclining and includes activities such as watching television, using the computer, and sitting during commuting or work.[95] It had previously been reported that most US adults spend approximately eight hours per day in sedentary activities, with older adults 60 years and older spending approximately 60% of their waking hours in these activities (Figure 12).[96,97] Levels of sedentary behavior are high among both males and females as well as midlife and older adults.[96] Additionally, high levels of mean total sitting time (hours/day) has remained stable among both midlife and older adults from 2007 to 2016 (Figure 13).[98]

However, while a considerable amount of research has been conducted to determine the cause of sedentary behavior in older adults[99], more research is needed to understand: 1) the association between sedentary time reduction and geriatric-relevant health outcomes (i.e., how does sedentary time affect healthy aging?), 2) the effectiveness of sedentary reduction interventions among older adults (with accurate measurement of sedentary time),[100] and 3) focus on prevention by including both midlife and older adults in sedentary behavior recommendations and interventions.

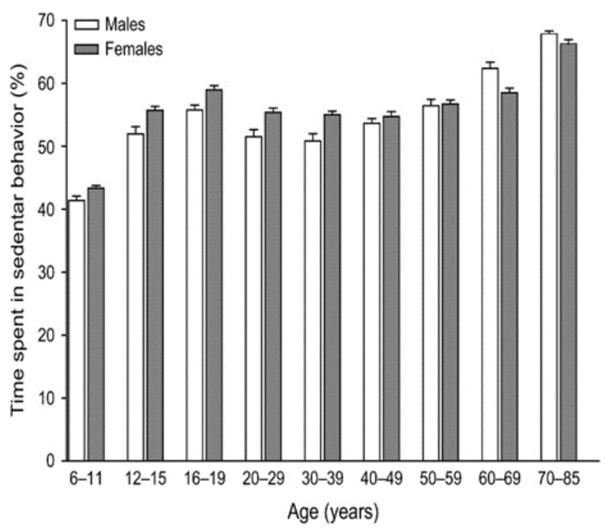

Figure 12. Percentage of time spent in sedentary behaviors, by age and gender, United States, 2003–2004

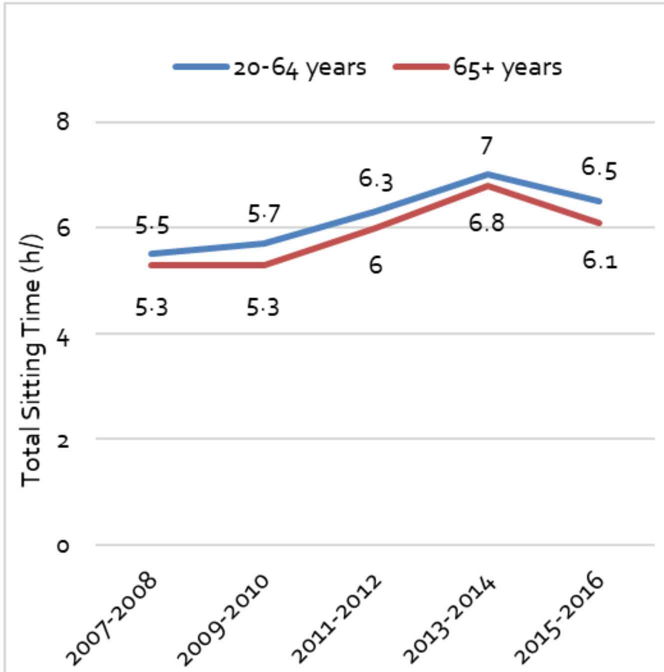

Figure 13. Crude Weighted Mean Trends in Total Sitting Time (hours/day) among US adults, NHANES 2007-2016

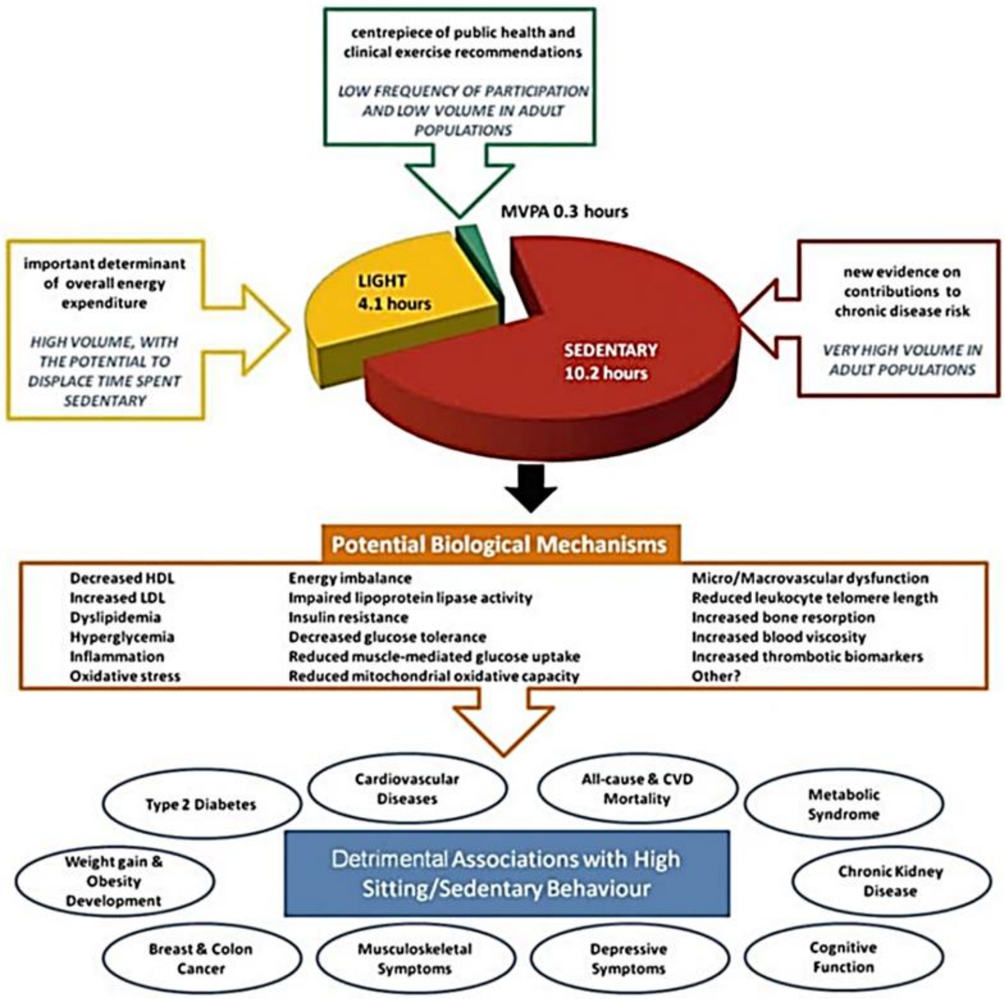

Figure 14. Illustration of sedentary time within total movement spectrum and potential biological mechanisms linking sedentary behavior to health outcomes

Note: Data in the pie chart was populated using objective activity monitoring from accelerometer measurements in a large population-based sample (NHANES). Data represent US adults who are in the top quartile of sedentary time (<100 counts per minute cut-point), associated levels of light-intensity activity (100-1951 cut-point) and moderate-to-vigorous intensity activity (>1952 cut-point).

Table 4. Overview of Sedentary Behavior and Health Outcomes

OUTCOMES	ADULTS
Mortality	
All-cause mortality	Strong Evidence[1,2,3]
CVD mortality	Strong Evidence[1,2,3]
Cancer Mortality	No Evidence[1,3,4]
Cardiovascular Diseases	Strong Evidence[1,2,3] Insufficient Evidence[4]
Cancer	
Breast	Insufficient Evidence[4]
Colorectal	Insufficient Evidence[4]
Colon	Moderate Evidence[6]
Endometrial	Moderate Evidence[6]
Ovarian	Moderate Evidence[6] Insufficient Evidence[4]
Prostate	Insufficient Evidence[6]
Type 2 Diabetes	Strong Evidence[1,2] Moderate Evidence[3] Insufficient Evidence[4]
Metabolic Syndrome	Strong Evidence[1,2,3,5]
Individual Cardiovascular Risk Factors	
Blood Pressure	Insufficient Evidence[1]
Total Cholesterol	Insufficient Evidence[1]
HbA1	Insufficient Evidence[1]
Fasting Insulin	Insufficient Evidence[2]
Insulin resistance	Insufficient Evidence[2]
Leptin	Insufficient Evidence[1]
Fibrinogen	Insufficient Evidence[1]
C-peptide	Insufficient Evidence[1]
Obesity	Insufficient Evidence[1,4]
Mental Health	
Self-Esteem	No Evidence
Depressive Symptoms	Insufficient Evidence[3]
Postnatal Depression	Insufficient Evidence[3,4]
Cognitive Aspects	No Evidence
Musculoskeletal	Insufficient Evidence[4]
Other Behaviors (PA, diet, alcohol consumption)	Insufficient Evidence[1]
Social Behavior Problems	No Evidence
Other Health Outcomes	
Bone Mass	No Evidence
Motor Dysfunction	No Evidence
Physical Fitness	No Evidence
Academic Achievement	No Evidence
Symptomatic gallstone disease	Insufficient Evidence[5]

1- Television viewing; 2- Screen-time; 3- Total Sitting time; 4- Occupational Sitting Time; 5- Objectively measured sedentary time; 6- Unspecified

Recent studies have shown that sedentary behavior is an important risk factor for diabetes, metabolic syndrome and type 2 diabetes, independent of moderate-to-vigorous physical activity.[95,101–104] A recent overview of systematic reviews detailed the current knowledge base for associations between sedentary behavior and various health outcomes (Table 4 adapted from de Rezende et al 2014).[105] One health outcome of particular concern for older adults are falls; however, as shown in table 4, falls was not listed as a potential health outcome associated with sedentary time. While physical activity has shown to be a protective factor against falls among older adults[106,107], high levels of sedentary behavior may be a detrimental factor with regards to fall risk. High levels of sedentary time among older adults may facilitate skeletal muscle declines which was shown to be a risk factor for falls in a 2012 systematic review and meta-analysis of observational studies.[108] However, among 8 total studies measuring sedentary factors impact on falls, 4 were cross-sectional, 2 were case-control studies and 2 were cohort studies. From these included studies, only two were classified as having moderate methodological quality with the remaining having fair to poor quality.[108] A more recent systematic review by de Rezende in 2014 assessed whether sedentary behavior was associated with several health outcomes, one of which was accidental falls. These findings indicated that there was insufficient evidence to draw conclusions on the relationship between greater time spent in sedentary activities and falls.[109] More research is needed to understand how sedentary behavior impacts geriatric-related health outcomes such as falls.

There are several potential biological mechanisms that could link sedentary behavior with detrimental associations with high sitting/sedentary behavior as shown in Figure 14. Several of these biological mechanisms are cardiometabolic-related risk factors including decreased HDL, increased LDL, dyslipidemia, hyperglycemia, insulin resistance, and inflammation.[110] Further understanding how these biological mechanisms moderate the association between sedentary behavior and health outcomes, specifically in mid-to- early old age adults at highest risk, can inform targets for interventions.

Besides these health outcomes, decreasing sedentary behavior may also be related to successful aging outcomes (i.e., social, psychological and physical success)[14]; however, there is limited data on how sedentary behavior impacts physical successful aging (i.e., functional impairments). [111] Typically public health and clinical exercise recommendations focus on increasing moderate-to-vigorous physical activity; however, most adults do not frequently participate in this type of activity and it accounts for the smallest volume of time (Figure 14). In addition, *initially* engaging in moderate physical activity may not be a realistic goal for aging populations with prevalent comorbid conditions such as osteoarthritis and/or type 2 diabetes. [112] Due to the effects of aging on physical function and comorbid conditions, it may be necessary for older adults to start with lower intensity movement, such as decreasing sedentary time and increasing light physical activity, with the ultimate goal of achieving the national recommendations for older adults of 150 minutes per week of moderate intensity physical activity. Therefore, sedentary behavior reduction interventions have the potential to replace a very high-volume activity (sitting time) with light physical activity which is an important determinant of overall energy expenditure and may be initially more feasible for the typical inactive, older adult.

Table 5. Reduction of sedentary time intervention studies that evaluated performance outcomes

Study	Age (years)	Sedentary Behavior	Performance Outcomes								
			SPPB	Chair Stand	Balance	Gait Speed	400-Meter Walk	VO_2max	Pain	Fatigue	Physical Function (HAQ)
Barone Gibbs (n=38)	68 ± 7	—	↑ *	↑ *	—	↓	—				
Overgaard (n=59)	45.8 ± 10.9	↓ *						↑ *			
Rosenberg (n=36)	71.4 ± 6.4	↓ *	↑ *	—		↓ *					
Thomsen (n=75)	59.7 ± 10.7	↓ *							↑ *	↑ *	↑ *

Flat line indicates no change; Arrows indicate improvements (increase or decrease); HAQ=Health Assessment Questionnaire; * indicates statistical significance; Visual Analogue Scale was used to measure pain and fatigue and Multidimensional Fatigue Inventory was used to measure Fatigue

If decreases in sedentary behavior are shown to improve physical function, then this provides a sustainable lifestyle intervention option for individuals who are not able to initially increase their moderate physical activity by offering them an alternate movement goal. Currently, few lifestyle interventions have been aimed at decreasing sedentary time and of these, most lack standard measures of performance outcomes (Table 5).[113–116] A 12-week long intervention (n=38) combined in-person and phone consults with an exercise physiologist with the aim of reducing sedentary time by one-hour each day and found no reductions in sedentary behavior but did demonstrate significant improvements in the Short Physical Performance Battery (SPPB).[113] This specific sedentary intervention may not have been intensive enough to see changes in functional outcomes. There were weekly visits for the first 4 weeks followed by biweekly visits during weeks 5 through 12.[113] Previous research from the Diabetes Prevention Program indicates that weekly contact during the first several weeks and even months of lifestyle interventions may be necessary for participants to both adopt and implement new health behaviors and strategies[87]; therefore, sedentary reduction programs may need weekly contact beyond the first month of intervention to see positive health outcomes such as improved physical function. The sedentary intervention designed in Rosenberg et al. (2015) incorporated 5 phone calls delivered over the course of the 8-week intervention in which a health coach used motivational interviewing to encourage participants to decrease time spent sitting.[115] Another intervention held 3 one-on-one motivational counseling sessions and text message reminders aimed to reduce sedentary behavior over the 16-week intervention.[116] Ultimately, all interventions were feasibility studies with small samples sizes and varying intensities of sedentary interventions (Table 6). In addition, a variety of functional outcomes were assessed, but it is hard to draw conclusions in terms of how sedentary interventions improve function due to a lack of consistency in performance measures across studies, small sample sizes and short follow-up times (3 months or less). Ultimately, *there is a large gap in* *knowledge on the extent to which reduction of sedentary behavior interventions impact physical function in older adults.*

Table 6. Population characteristics, intervention description and sedentary assessment methods of reduction of sedentary time intervention studies that evaluated performance outcomes

Author	Demographics	SED Intervention	SED Assessment	Findings
Barone Gibbs et al 2017[113]	Inactive but higher functioning community dwelling older adults; mean age= 68 +/- 7 years	to reduce sedentary time by 1 hr each day; combo of in-person and phone consults with exercise physiologist; weekly visits for weeks 1-4, biweekly visits in weeks 5-12; **n=38**	SenseWearPro armband (SWA) and self-reported sedentary behavior from CARDIA study questionnaire	Sedentary behavior did not change in either group; only the Sit Less group improved SPPB score
Overgaard et al 2018[114]	Inactive, obese adults; Age:45.8 ± 10.9 years; BMI: 32.9 ± 4.9	SitLess group instructed to reduce sedentary behavior and given list of non-sitting activities to replace sitting time at home, work, leisure, or in transport; ExMore encouraged to increase MVPA to at least 30 min/day; given advice once, re-assessed at 4 weeks (**n=59**)	activPAL and ActiGraph	SitLess group demonstrated greater decrease in sitting time (53 min/day); VO2max improved; cardiometabolic risk factors didn't change after intervention
Rosenberg et al 2015[115]	60+; mean age=71.4; mean BMI=34; patients from electronic health records	5 phone calls delivered over 8 weeks by health coach using MI encouraging decrease in total sitting time by 2 hours per day and an additional 15 breaks form sitting; 8 week intervention; **n=25**	activPAL	Significant decrease in sitting time; 27 min/day
Thomsen et al 2017[116]	Rheumatoid arthritis patients; good function at baseline (HAQ index=0.9)	3 individual motivational counseling sessions and short message service of text messages aimed at reduction of sed	activPAL	Significant difference in reduction in sitting time in intervention group (-1.61h) vs control (0.59h increase)

		behavior over 16 weeks; **n=75**		

Since sitting comprises the majority of an older adult's day, efforts to increase moderate activity may not be as effective as initially focusing on decreasing sitting time and breaking up bouts of continuous sitting.[117] Current studies are suggesting that decreasing sitting time can also be important to health, independent of the effect of bouts of moderate activity and total minutes of moderate-to-vigorous physical activity.[118–120] Research has shown that sedentary behavior assessed both subjectively and objectively is related to risk factors for diabetes, metabolic syndrome, and diabetes development independent of moderate activity.[102,103,121–123] For these reasons, the American Diabetes Association (ADA) is now promoting reducing sedentary behavior in addition to increasing physical activity.[124] Biological plausibility has been established for the relationship between sedentary behavior and diabetes and cardiovascular disease related factors, including insulin sensitivity, glucose levels, adiposity, and impaired lipid metabolism.[119,125–128] It has been shown that time spent sitting is biologically distinct from time spent standing or being physically active.[128] Although, to date, health benefit associated with increasing moderate levels of activity is stronger compared to that of decreasing sitting time, the latter goal provides a valuable intervention option for the older adult who may not be able to initially increase moderate physical activity, such as brisk walking. Therefore, decreasing sedentary time may be an especially important intervention strategy among older adults with chronic conditions that can affect mobility.

The DPP lifestyle intervention showed a significant positive impact on reducing the time spent in sedentary behavior across demographic and BMI subgroups even though reducing sedentary behaviors was not a main goal of the DPP intervention.[102] The mean time spent watching

TV decreased significantly in the lifestyle intervention group by 22 min/day (95% CI: -26 to -17) and the placebo group, but not the metformin group. Therefore, the lifestyle participants reporting significantly greater reductions in TV watching compared to either metformin or placebo participants.[102] Additionally, self-reported TV watching and occupational sitting showed that sedentary time was related to diabetes incidence in the DPP study cohort. Each additional hour per day of TV watching was associated with a 3.4% increased risk of developing diabetes over the follow-up period (mean 3.2 years; $p<0.05$) and this association was attenuated by 2.1% when weight was adjusted for in the model (not significant).[102] Therefore, given that there is preliminary evidence to suggest that breaking up sedentary time may impact physical function[129] , we hypothesize that DPP-based lifestyle interventions with a specific goal of reducing sedentary time may also positively impact geriatric-related outcomes such as physical function. <u>Our Specific Aim 2 will fill this gap in the literature and by being the first study, to our knowledge, to assess 12-month relationships between sedentary behavior and physical function using an effective DPP-based lifestyle intervention.</u>

If the DPP-based sedentary behavior reduction intervention positively impacts physical function, then this would be another community-based intervention program that could be added to the list of preventative options for older adults with the possibility of reimbursement. This DPP-based lifestyle intervention, in which the initial primary movement goal starts with sitting less, would offer an alternative program for public health organizations that service older adults who are limited in their ability to initially increase their moderate physical activity. Our future goal is for this modified DPP-based lifestyle intervention to become part of the cadre of CDC-recognized, CMS-funded programs, which could positively impact geriatric-based health outcomes of older adults across the country.

1.5.4 Modifiable Cardiometabolic-related Risk Factors (i.e., Metabolic Syndrome) as an Intervention Target

The metabolic syndrome has been shown to increase risk for chronic conditions which may subsequently increase risk for functional decline. One pathway by which physical activity and sedentary behavior may impact function is through the metabolic syndrome (MetS). MetS is a cluster of cardiometabolic risk factors including hypertension ($\geq$130 mmHg (systolic) or $\geq$85 mmHg (diastolic) OR history of diagnosed hypertension), abdominal obesity (>40 inches men, >35 inches women), impaired fasting glucose ($\geq$100mg/dL and <126mg/dL), low high-density lipoprotein cholesterol level (<40mg/dL men, <50 mg/dL women) and hypertriglyceridemia ($\geq$150 mg/dL).[130] One is considered to have the MetS if they have at least 3 of these 5 cardiometabolic abnormalities.[130] MetS has been shown to increase the risk of several chronic diseases and conditions such as cardiovascular disease, chronic kidney disease, arthritis, cancer and type 2 diabetes, as well as increase risk for early death.[131–135]

There are many biological mechanisms (e.g., chronic inflammatory processes[136], hyperglycemia-related[137], obesity-related) in which MetS contributes to decreases in muscle mass and strength predisposing individuals to develop functional limitations. One mechanism is related to obesity in which obese adults develop functional limitations due to experiencing pain, having osteoarthritis, and reducing physical activity levels.[138,139] However, recent data suggest that normal-weight, MetS adults compared to normal-weight, no MetS adults are at increased risk for all-cause mortality, cardiovascular disease and cancer mortality after adjustment for age, sex, race/ethnicity, education, poverty-income ratio, smoking history and physical activity (Figure 15). Greater attention must be given to midlife adults who have MetS but may not appear high-risk based on their weight to provide early treatment and prevent future health comorbidities.[140]

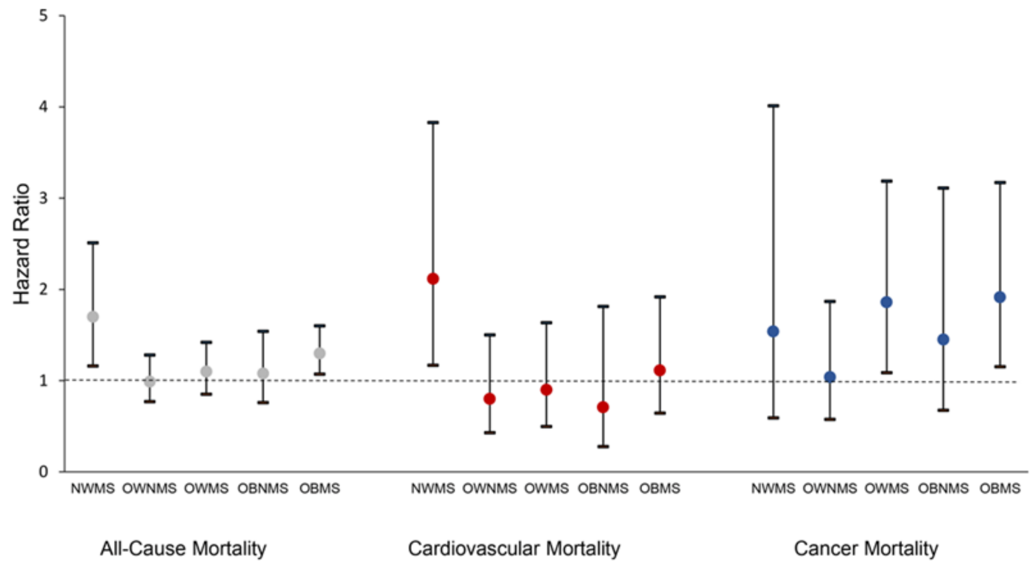

Figure 15. Weight–MetS categories and all-cause and selected cause-specific mortality, National Health and Nutrition Examination Survey, 1999–2010, and National Death Index, 2011.

The normal-weight–no-MetS group was used as the reference group. Models were adjusted for age, sex, race/ethnicity, education, poverty-income ratio, smoking history, and physical activity. Abbreviations: NWMS; normal-weight–MetS; OWNMS, overweight–no MetS; OWMS, overweight–MetS; OBNMS, obese–no MetS; OBMS, obese–MetS

The prevalence of MetS among US adults was 34.2% of all adults between 2007 and 2012 and does not differ greatly by gender (35.3% among males and 33.3% among females).[141] Due to the rising prevalence of hypertension, obesity and type 2 diabetes, adults classified as having MetS has increased, consequently increasing risk for chronic diseases and premature mortality.[142–144] Notably, MetS increases with age with 19.3%, 37.7%, and 54.9% of adults aged 20-39, 40-59 and ≥60 years, respectively classified as having MetS.[144]

How MetS relates to non-cardiovascular outcomes, which also are important for healthy aging (e.g., physical function), is not well understood. Table 7 summarizes existing research studying the relationship between MetS and physical performance outcomes.[137,145–150] Two of the studies are cross-sectional with one having a very small sample size (n=28)[147] and the other showing no association between MetS and gait speed impairment.[145] Two longitudinal studies[148,149] were conducted in Europe (France and Italy) among adults 65 years and older with self-reported disability (limitation in activities of daily living and instrumental activities of daily living). Carriere and colleagues found that MetS was associated with 7-year incidence of instrumental activity of daily living limitations after adjustment for center, baseline age, time, interaction baseline age × time, and sex (OR=1.62, 95% CI: 1.24-2.10).[148] This was an important initial study examining whether components of MetS were associated with the onset of disability-related limitations in a large sample of community-dwelling older adults. However, the disability outcomes were self-reported and therefore the association between MetS and objectively measured physical function is unclear. Two large US-based cohort studies examined how MetS is related to mobility decline in older adults. Findings from the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) cohort (mean age of 77 years) showed that MetS may be a distinct risk factor for self-reported mobility decline over 4 years (i.e., measured using three items from the Rosow-Breslau functional health scale).[146] Results from the Health Aging and Body Composition (Health ABC) study (aged 70-79 years old) showed that baseline MetS was associated with a 1.46-fold increased risk of incident mobility limitations, defined as two consecutive self-reports of inability to climb 10 steps without rest and/or walk ¼ mile.[137] Both US cohort studies only assessed late life and used one measurement of MetS at baseline. The majority of studies measure self-reported disability outcomes rather than measures of functional status. In addition, Liaw et al. (2016) found a strong linear increase in predicted total disability with the increase in total number of MetS components (unadjusted β coefficients for 1, 2, 3, 4, and 5 total MetS components were 0.073, 0.362, 0.446, 0.591 and 0.875, respectively; p for trend = <.0001). After adjustment, the p for trend remained statistically significant with a similar increased gradient pattern with total disability for each additional MetS component among older adults.[150] However, more research is needed to replicate these findings and determine if there is a true multiplicative effect between total number of MetS components and functional outcomes.

Therefore, *there remains a lack of knowledge on how longitudinal changes in MetS over the midlife period, a critical transition period for both MetS and early functional decline, impact late-life objective physical function measures*. Aim 3 fills this gap in knowledge and by increasing our understanding of how modifiable cardiometabolic risk factors impact several objective physical performance outcomes throughout mid-to- early old age.

Table 7. Summary of Metabolic Syndrome (MetS) and Physical Performance Literature

Study	Sample	Study type	Age/sex	Exposure	Outcome	Findings
Okoro, 2006[145]	N=835 NHANES	Cross-sectional	M + W Aged ≥ 50 years	MetS and individual components	Gait speed	No association between MetS and gait speed impairment; Among women, abdominal obesity and low HDL are sig. associated with slower gait speed
Blazer, 2006[146]	N=1229 Urban/rural North Carolina (Duke EPESE)	Longitudinal	M + W Mean age = 77	MetS	Mobility (questions from Rosow-Breslau) scale	MetS may be a distinct risk factor for mobility decline in community-dwelling older people
Pennix, 2009[137]	N= 2920 Health ABC	Longitudinal	M + W Age 70-79 years	MetS	Incident Mobility limitation: difficulty or inability walking ¼ mile or climbing 10 steps over 4.5 years	MetS associated w/ 1.46-fold increased risk of incident mobility limitations; RRs were high for abdominal obesity (RR=1.54) and hyperglycemia (RR=1.44)
Carrier, 2013[148]	N=6141 Three-city cohort (French cities)	Longitudinal	65 and older 60.9% women	MetS/components	7-year incident disability	MetS was associated with incident limited mobility (odds ratio = 1.52, 95% CI: 1.21–1.90), and instrumental activities of daily living limitations

						(odds ratio = 1.62, 95% CI: 1.24–2.10) after adjustment
Laudisio, 2014[149]	N=1155 inCHIANTI	Longitudinal	65+ (median age 74+	Mets	Functional ability: ADL and IADL	MetS is independently associated with ↓ probability of prevalent disability in the ADLs among subjects aged 74+, and of three years incident ADLs disability >65 years
Liaw, 2016[150]	N=1778 NHANES	Retrospective observational study	Aged 60-84 years	MetS/components	Impairments in ADL, IADL, lower extremity mobility	Strong linear increase in predicted total disability with an increase in the number of MetS components in female elderly

2.0 Overall Impact of Proposed Aims

Upon successful completion of the proposed research, we expect our contribution to determine how attending lifestyle intervention maintenance sessions impacts sustained weight loss success and if a DPP-based physical activity versus sedentary behavior intervention maintains or improves physical function. We will also determine how change in critical cardiometabolic risk factors throughout midlife impact objective physical performance among early old age women. *This contribution is expected to be impactful for two reasons*. First, characterizing modifiable risk factors for functional decline in early old age adults will enable us to tailor preventive strategies (e.g., increase physical activity, decrease sedentary behavior and improve cardiometabolic health) in this high-risk population before functional decline advances through the disablement process. Second, determining which interventions are effective at both maintaining weight loss and maintaining/improving physical function in older adults may provide more translatable options to compress the number of years living with disability and ultimately increase independence with aging.

Understanding how both session attendance during the maintenance phase (months 7-12) and weight loss goal success at 6 months impact meeting the 5% weight loss goal at the end of a 12-month DPP-based community lifestyle intervention program has national level impact, *as reimbursement by Medicare in these community lifestyle intervention programs is based on maintenance session attendance and achieving the weight loss goal after 12 months of intervention*. Additionally, this was a DPP-based lifestyle intervention which is CDC-recognized and now being reimbursed by CMS as a preventive behavioral approach to combat type 2 diabetes nationally. More efforts are needed to find ways to help those struggling to reach the 5% goal during the first 6 months and/or to augment the programming in the last 6 months for those who need additional help in DPP-based lifestyle intervention programs. Helping particiapnts reach the 5% weight loss goal at 6 and 12 months, as well as beyond, will not only prevent/delay risk factors for chronic diseases but will also ensure program sustainability through CMS reimbursement.

It has been shown that physical activity maintains or improves physical function and lifestyle interventions in older adults have been shown to improve physical function. However, few of the existing exercise interventions were based on the DPP and the existing literature has limitations with respect to sustainability of the program long-term, feasibility of interventions for most older adults and ability of the intervention to be translated into the community setting. The second proposed manuscript is highly innovative because it will be the first to determine the effect of a DPP-based physical activity lifestyle intervention program on objective measures of physical function.

Additionally, if the DPP-based sedentary behavior reduction intervention positively impacts physical function, then this would be another community-based intervention program that could added to the list of preventative options for older adults with the possibility of future reimbursement by CMS. This DPP-based lifestyle intervention for which the initial primary movement goal would start with sitting less would offer an alternative program for public health organizations that service older adults who are limited in their ability to initially increase their moderate physical activity. Our future goal is for this modified DPP-based lifestyle intervention to become part of the cadre of programs CDC recognizes and CMS funds which could positively impact geriatric-based health outcomes of thousands of older adults across the country.

Physical functioning has most commonly been assessed in geriatric populations in which worse function predicts several future poor health outcomes (e.g., lower quality of life and increased mortality rates) [16,20]. Metabolic syndrome changes throughout midlife likely have important implications on early old age physical performance among women, even prior to clinical classification of MetS. Measuring function among midlife adults (especially high-risk midlife adults, e.g., women, adults with MetS components) in clinical settings using simple, non-invasive tests such as SPPB and 4-m gait speed, could be a strategy to intervene early in the disablement process and help maintain independence with aging [151]. These functional tests that can be performed in a few minutes could be used as a "sixth vital sign" [152,153] for midlife women with cardiometabolic-related risk factors. Evidence suggests that the onset of disability begins in midlife while women still have decades to live [154]; therefore, it is critical to select the most appropriate objective physical performance measures in early old age adults to predict late-life geriatric outcomes. Importantly, it is unknown which test is most appropriate to assess early functional decline in midlife. The third dissertation manuscript contributes to the understanding of preventable and treatable factors in middle age adults that exhibit early declines in physical function and the onset of late-life functional decline.

3.0 Innovation and Public Health Importance of Proposed Aims

As of April 2019, over 324,000 participants across 3,000+ organizations have participated in DPP-based lifestyle intervention programs [92]. However, to our knowledge, the impact of maintenance session attendance during months 7-12 on weight loss success at 12 months has not been examined. Ours is the first study that we are aware of, to investigate the specific impact of maintenance session attendance (per CMS requirements for reimbursement) on meeting the 5% weight loss goal at 12 months. This gap in knowledge exists despite the fact that successful maintenance of weight loss is known to be essential for reaping long-term health benefits [155,156]. Additionally, achievement of the 5% weight loss goal is a benchmark required for continued CMS reimbursement. The ability of providers to receive reimbursement makes sustained delivery of programs possible, which is necessary to increase program reach and ensure long-term health benefits for participants.

Most past sedentary behavior interventions have conducted a pilot or feasibility study in a small number of participants without measuring geriatric outcomes such as objective functional performance measures. This approach has been an appropriate first step to determine the effectiveness of sedentary behavior interventions in decreasing sitting time, but more work needs to be done to understand the long-term implications of this type of lifestyle intervention in larger and more diverse populations with respect to age, race/ethnicity, and functional status. The proposed research is innovative because it represents a substantive departure from the status quo by conducting a yearlong sedentary behavior intervention based on a DPP-based lifestyle intervention. This is the first community-based sedentary behavior reduction intervention to be created within an already existing and effective lifestyle intervention that is currently being delivered nationally to prevent/delay type 2 diabetes. If lifestyle interventions that incorporate sedentary change are shown to maintain or improve physical function, they would provide a novel option for individuals who are initially unable to increase their moderate intensity activity by offering them an initial alternative goal to sit less toward the ultimate goal of increasing movement. This DPP-based modified lifestyle intervention program that focuses initially on sedentary rather than starting with moderate activity change could be adopted for use in current translation efforts for subgroups of the population across a variety of community settings. *Potentially, this modified, novel sedentary behavior intervention program can serve as an alternative DPP-based lifestyle intervention in older adults who are unable to begin with the existing moderate intensity physical activity goal and would become one of the few successful sedentary behavior interventions developed outside of the workplace.*

Preliminary data suggests that the DPP-based lifestyle intervention improves functional outcomes.[157] The DPP-based programs that are nationally delivered by CMS for adults diagnosed with prediabetes are currently reimbursed based on maintenance session attendance and 5% weight loss. If these programs demonstrate to improve physical function, this could be an additional reimbursement criterion in the future. In addition, if DPP-based physical activity lifestyle interventions are effective at improving physical function, this intervention has the potential to positively impact the functional ability of thousands of adults at high-risk for functional decline and late-life disability.

Midlife modifiable cardiometabolic risk factors have mostly been examined with respect to their associations with self-reported disability/mobility outcomes and few studies have used objective performance measures or conducted a longitudinal analysis that accounts for change over time in the cardiometabolic factors and covariates. The proposed research is critical because it longitudinally assesses several cardiometabolic risk factors in midlife and their impact on objective physical performance measures in late life for multiracial and ethnic women. These associations with midlife cardiometabolic risk factors (e.g., components of MetS) are critical to understand in minorities and women as they have higher disability throughout late life vs. non-minority populations and men, respectively. This research has potential to identify cardiometabolic targets for prevention in clinical care and preventive efforts for physical function decline if individuals at high-risk for future functional decline are able to be identified in midlife. Tailoring preventive efforts to compress years of morbidity from functional limitations would have large scale public health implications.

One in 4 Americans lives with at least one disability that greatly impacts major life activities. There is evidence to suggest the disablement process begins in midlife while adults still have decades of life in which remaining functionally independent is a priority. This is a great public health concern, and more research is needed to characterize modifiable risk factors for functional decline in early-late life adults to be able to tailor preventive strategies and compress years of morbidity related to the onset of disability. Our proposal aims to achieve novel and important outcomes to help with these concerns. We will help determine which interventions are effective at both maintaining weight loss and improving/preventing decline in physical performance in mid-to- early old age adults (aim 1 and 2) and provide new insight about the midlife modifiable risk factors associated with functional decline in mid-to- early old age adults (aim 3). By accomplishing these study aims we will be able to tailor preventive strategies in this high-risk population before functional decline has advanced to late-life disability, ultimately helping people maintain independence with aging.

4.0 Overview of Dissertation Manuscripts

We will examine how modifiable risk factors and lifestyle interventions impact physical performance among mid-to-early old age adults. First, we will use data from two NIH-funded DPP-based lifestyle intervention trials (The Group Lifestyle Balance (GLB) Healthy and the GLB MOVES Project) to evaluate the impact of maintenance session attendance and early weight loss goal achievement during a physical activity lifestyle intervention program on longer-term weight loss success in mid-to-early late life adults.

Manuscript 1: To examine how weight loss goal achievement at 6 months and maintenance session attendance in DPP-GLB affects meeting the 5% 12-month weight loss goal in mid-to-early late life adults.

Next, we will use data from the GLB MOVES Project, utilizing data from both intervention arms (increasing moderate physical activity and decreasing sedentary behavior), to assess the impact of a physical activity intervention or a sedentary behavior intervention on physical function outcomes in mid-to-early late life adults.

Manuscript 2: To evaluate objective physical function changes among participants randomized to the DPP-GLB or sedentary behavior intervention (GLB-SED) vs. control at 6 months and pre-post 12 months in mid-to-early late life adults.

Finally, we will utilize data from the Study of Women's Health Across the Nation (SWAN) over 18 years to determine the association between how cardiometabolic risk factors throughout midlife relate to objective physical performance among late life women.

Manuscript 3: To determine how changes in cardiometabolic health in midlife relate to objective physical performance in early late life multi-ethnic women.

5.0 Aim 1 Manuscript: Impact of Maintenance Session Attendance and Early Weight Loss Goal Achievement on Weight Loss Success in a Community Diabetes Prevention Program-Based Intervention

Jenna M. Napoleone MPH[1], Rachel G. Miller PhD[1], Susan M. Devaraj PhD, MS, RD[1], Bonny Rockette-Wagner PhD[1], Vincent C. Arena PhD[2], Elizabeth M. Venditti PhD[3], Kaye Kramer DrPH, MPH, RN[4], Elsa S. Strotmeyer PhD, MPH[1], Andrea M. Kriska PhD[1]

[1]Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; [2]Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; [3]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA; [4]Spark 360, Pittsburgh, PA

Corresponding Author: Bonny Rockette-Wagner; bjr26@pitt.edu; Phone number: (412) 624-0188; ORCiD: 0000-0002-4096-917X; University of Pittsburgh Graduate School of Public Health, 5135 Public Health, 130 De Soto Street, Pittsburgh, PA 15261

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Gerontological Society of America Conference (November 2020). The authors declare that there are no conflicts of interest.

5.1 Abstract

Purpose: The purpose of this study was to examine how maintenance session attendance and 6-month weight loss (WL) goal achievement impacted 12-month 5% WL success in older adults participating in a community-based Diabetes Prevention Program (DPP) lifestyle intervention. This investigation is important as participant attendance and WL inform the program's Medicare reimbursement structure.

Methods: Data were combined from two community trials that delivered the 12-month DPP-based Group Lifestyle Balance (GLB) to overweight/obese adults (mean age=62 years, 76% women) with prediabetes and/or metabolic syndrome. Included participants (n=238) attended ≥4 core sessions (months 0-6), had complete data on maintenance attendance (≥4 of 6 or <4 sessions during months 7-12) and 6- and 12-month WL (5% WL goal, yes/no). Multivariate logistic regression was used to estimate the odds of 12-month 5% WL associated with maintenance attendance and 6-month WL. Associations between age (Medicare-eligible ≥65 vs. <65 years) and WL and attendance were examined.

Results: Both attending ≥4 maintenance sessions and meeting the 6-month 5% WL goal increased the odds of meeting the 12-month 5% WL goal. For those not meeting the 6-month WL goal, maintenance session attendance did not improve odds of 12-month WL success. Medicare-eligible adults ≥65 years were more likely to meet the 12-month WL goal (OR=3.03, 95% CI:1.58-5.81) versus <65 years.

Conclusions: The results of this study provide important information to Medicare-DPP providers across the country. Understanding Medicare reimbursement-defined success will allow providers to focus on and develop strategies to enhance program effectiveness and sustainability.

Keywords: Diabetes Prevention, Weight Loss Success, Lifestyle Changes, Older Adults

5.2 Introduction

The United States Diabetes Prevention Program (DPP) demonstrated that behavioral lifestyle intervention with weight loss and physical activity goals, can prevent/delay the development of type 2 diabetes.[83–85] Despite widespread success of the intervention across all ages, DPP participants aged 60-85 years exhibited greater diabetes risk reduction than participants aged less than 60 years (71% vs. 58% risk reduction, respectively).[158]

Building on the results of the DPP clinical trial, DPP lifestyle intervention translation efforts, such as the Group Lifestyle Balance (DPP-GLB) Program, also then tested and demonstrated success in reducing weight, increasing activity levels and modifying diabetes and cardiovascular disease risk factors in diverse community settings.[159–164] Given the effectiveness of these DPP-based community lifestyle interventions and to aid in disseminating these programs, the Centers for Disease Control and Prevention (CDC) was authorized by Congress to establish the National Diabetes Prevention Program (National DPP).[165] The Diabetes Prevention Recognition Program (DPRP) was created to monitor delivery of the National DPP[90] and collect program data in six month intervals including participant weight change and session attendance in order to *recognize* DPP programs meeting set standards.[89] In 2018, the Centers for Medicare and Medicaid Services (CMS) began reimbursing CDC-recognized programs for delivery to all fee-for-service beneficiaries aged 65 years and older with prediabetes. This CMS reimbursement structure is based upon two parameters: session attendance (at 6 and 12 months) and 5% weight loss goal achievement at 12 months.[91]

The CDC-approved, CMS-reimbursable[91,166] DPP-GLB lifestyle intervention program lasts 12 months and consists of 16 core sessions that comprise the intensive contact phase during the first 6 months, followed by 6 monthly maintenance sessions (months 7 through 12). To our knowledge, the impact of maintenance session attendance during months 7-12 on meeting the 5% weight loss goal at 12 months has not been examined in lifestyle interventions either for the general adult population, or in Medicare-eligible adults. This examination is important given that successful maintenance of the 5% weight loss goal at 12 months is a program requirement for CMS reimbursement and weight loss maintenance is essential for the participant to obtain long-term health benefits.[155,156] The ability of providers to receive full reimbursement makes sustained delivery of programs possible, which is necessary to determine program success, increase program reach and ensure long-term health benefits for participants.

As of April 2019, over 324,000 participants across 3,000+ organizations have participated in DPP-based lifestyle interventions.[92] Yet, many feasibility issues remain unanswered for community implementation of the program[167] including the impact of maintenance sessions on program success and effectiveness, as well as the benefit of these programs in Medicare-eligible older versus middle-aged adults. *Thus*, this investigation examined the association between maintenance session attendance and 1) achievement of the 5% weight loss goal at 12 months in the DPP-GLB in all participants and by Medicare eligibility, and 2) how this association was modified by having met the weight loss goal at 6 months.

5.3 Methods

5.3.1 Resign Design

The current investigation combined data from two NIH-funded intervention trials, the Healthy Lifestyle Project and the Physical Activity and Sedentary Behavior Change Project (PI:

Dr. A. Kriska) that both implemented DPP-based, CDC-recognized lifestyle intervention programs within senior/community centers in Allegheny County, Pennsylvania. The Healthy Lifestyle Project (i.e., GLB Healthy) was conducted between January 2011 and January 2014 and was shown to be both a feasible and effective DPP-based lifestyle intervention across three economically diverse senior/community centers (results have been previously published).[162,168,169] The Physical Activity and Sedentary Behavior Change Project (i.e., GLB Moves) began recruitment in January 2015 in various community settings and finished data collection and clean-up in 2019. GLB Moves was comprised of two intervention arms: one was the same DPP-based CDC-recognized lifestyle intervention program used in GLB Healthy, whereas the experimental intervention arm focused on decreasing sedentary time rather than increasing physical activity. Since the purpose of this current effort is to examine the maintenance phase in the original DPP-GLB, participants in the experimental sedentary reduction intervention arm were not included in these analyses.

In both trials, study staff collaborated with community partners to deliver the DPP-GLB lifestyle intervention program within community center sites. Both trials employed a 6-month delayed control group intervention design in which eligible participants were randomly assigned to start the DPP-GLB lifestyle intervention immediately or were part of a 6-month waitlist control group. After 6 months, waitlisted participants received a yearlong lifestyle intervention identical to the one received by those who began immediately. This waitlist control design is appropriate for community translation research and was well received by both partner organizations and participants alike.[163]

Recruitment procedures were the same in both trials and included presentations at the community centers, flyers and posters, community center newsletters, and targeted direct mailing to zip codes around the community centers. The eligibility criteria were a BMI ≥24 kg/m^2 (≥22 kg/m^2 for Asians; both cut-points consistent with the DPP BMI eligibility criteria[83]) and prediabetes and/or the metabolic syndrome.[170] The only eligibility criterion that differed between studies was age. Participants were eligible for GLB Healthy if they were 18 years or older, while for GLB Moves, they were eligible if 40 years or older. Despite this initial recruitment difference, participant age was similar in both studies (i.e., Median (Interquartile Range): age 65 (54-71) years in GLB Healthy and 63 (57-67) years in GLB Moves).

A priori inclusion criteria for the current analyses were that participants from the two trials had to be recruited from and participate at a community center site (thereby excluding GLB Healthy[163] enrollees from military bases and worksite settings), and take part in the CDC-recognized program with the primary goals of weight loss and moderate intensity physical activity improvement. These inclusion criteria were selected to maximize homogeneity across the two trials and resulted in 284 participants in the combined sample (n=134 from GLB Healthy; n=150 from GLB Moves; Figure 16). Additional eligibility criteria included participants with data on both maintenance session attendance and weight loss at 6 and 12 months. Only participants who received a sufficient "dose" of the core lifestyle intervention (i.e., attending ≥4 sessions during the first 6 months[89]) were included in the current study sample. This is consistent with the minimum attendance requirement that CDC sets for sample inclusion and which CMS requires for potential 12-month reimbursement. Thus, the final analytic sample consisted of 238 adults (Figure 16). Research protocols were approved by the University of Pittsburgh Institutional Review Board and all participants provided written informed consent before study enrollment.

5.3.2 Lifestyle Intervention

The DPP-GLB lifestyle intervention curriculum used in both GLB Healthy and GLB Moves has been detailed elsewhere[87,88] and is available at no cost online (www.diabetesprevention.pitt.edu). Similar to other DPP-based CDC-recognized lifestyle intervention programs, it is a 12-month in-person, group-based program with a total of 16 core sessions and 6 maintenance sessions taught by a trained lifestyle coach. In the first 6 months of *core sessions*, there are 12 weekly sessions followed by 4 bi-weekly sessions. Months 7-12 consist of 6 monthly *maintenance sessions.*[89] The main goals of the DPP-GLB lifestyle intervention were to encourage participants to increase physical activity levels to at least 150 minutes of moderate intensity physical activity per week and achieve and maintain a 7% weight loss in a safe and progressive manner. All lifestyle coaches in both studies completed a standardized 2-day training workshop provided by the Diabetes Prevention Support Center and recognized by the CDC.[88] Group sessions were held at senior/community centers and participants received session handouts, self-monitoring logs, and a pedometer, and were weighed at each session.

5.3.3 Study Measures

All study measures were collected at the community sites using standardized forms and the same measures were used in both clinical trials. At the initial on-site screening visits to determine eligibility, participant age, sex, employment, and other demographic characteristics were completed. Self-reported leisure physical activity levels were assessed using a past month version of the Modifiable Activity Questionnaire (MAQ)[171] which has shown to be both valid and reliable in adult populations.[172,173] Weight and height were measured at clinic assessment visits with shoes removed in light clothing using a standard protocol and a validated medical scale.

For this report, baseline weight was defined as the weight measure taken at the start of group intervention (i.e., after the 6-month delay for participants randomized to that arm). Weight loss success was defined as a loss ≥5% (yes/no). The 5% weight loss goal cut-point was selected as studies have shown this amount of weight loss to be consistently associated with improved health[174,175] and it is the cut-point currently used by both the CDC and CMS as the minimum weight loss goal for lifestyle intervention programs.[176]

Sufficient participant attendance of maintenance sessions (yes/no) was defined in accordance with CMS criteria as completing at least 4 out of 6 maintenance sessions (2 sessions during months 7-9 and 2 sessions during months 10-12).[91] Attending the session in-person or making up the sessions via phone or email were classified as completing a group session, but only if participants received and discussed the information with a trained lifestyle coach. This definition of attendance corresponds to the CMS maintenance session reimbursement criteria.[91]

5.3.4 Statistical Methods

Median and interquartile ranges (IQR) are presented for continuous variables, and frequency (%) for categorical variables. We assessed whether baseline characteristics for participants included in these analyses differed between the two study cohorts using chi-square tests (or Fisher's Exact tests) for categorical variables and t-tests or Wilcoxon rank sum tests (if non-normally distributed) for continuous variables.

The association between maintenance session attendance (attending ≥4 sessions vs. <4 sessions) and weight loss success at 12 months was assessed using multivariate logistic regression.

To initially evaluate effect modification by 6-month weight loss success on this association, we included interaction terms between meeting the 5% weight loss goal at 6 months and maintenance attendance in the logistic regression models. We used a combination of *a priori* and empirically based modeling strategies to address potential confounders of interest for the above logistic regression models. *A priori*, we constructed models including several covariates (e.g., education, sex, smoking, age, leisure activity at 6 months, hours/day spent watching TV, and employment). Backward selection with a significance level cut-point of $p<0.20$ to retain covariates was used to fit the final multivariable models. This resulted in only age being retained in the model; however, we also included sex and self-reported leisure activity at 6 months in the final model, as suggested by prior literature.

Due to the importance of weight loss success at 6 months we also examined differences in maintenance attendance across combined categories of weight loss success at 6 months (yes/no) and 12 months (yes/no), using a 4-level nominal weight loss variable with all possible combinations of success: (1) met weight loss goal at both 6 and 12 months [*maintain*]; (2) did not meet weight loss goal at 6 months but did meet at 12 months [*improve*]; (3) met weight loss goal at 6 but not 12 months [*regress*]; and (4) did not meet weight loss goal at either 6 or 12 months [*fail*]. We assessed differences in baseline characteristics across the combined categories using chi-square tests (or Fisher's Exact tests) for categorical variables and analysis of variance for continuous variables. We also constructed multinomial logistic regression models to assess the association between maintenance attendance and weight loss success at 6 months (yes/no) and 12 months (yes/no) combined, using the 4-level nominal weight loss success variable for combined 6- and 12-month weight loss success defined above as the dependent variable.

The association between age as defined by Medicare eligibility (<65 years: reference, ≥65 years) and both maintenance session attendance and achieving the 5% weight loss goals at 6 and 12 months was assessed using chi-square tests. Multivariable logistic regression models were fit to assess whether meeting weight loss goals at 6 and 12 months or attending ≥4 maintenance sessions was associated with age (<65 years vs. Medicare-eligible older adults: ≥65 years) after controlling for potential confounders, including sex, employment, race/ethnicity, and baseline leisure physical activity.

To ensure the estimated associations were robust, two sensitivity analyses were conducted. In the first, a new attendance variable for "in-person attendance only" vs. any other contact or non-attendance was created and used in univariate and multivariate models. In the second sensitivity analysis, an interaction term between a study indicator variable (GLB Healthy or GLB Moves) and maintenance attendance was included to assess evidence of heterogeneity in the association between attendance and 12-month weight loss success between the two trials. All analyses were performed using SASv9.4 (SAS Institute Inc., Cary, NC) statistical software.

5.4 Results

The demographic characteristics of the two studies were similar with a few exceptions. The GLB Moves relative to the GLB Healthy trial sample included a higher percentage of women (GLB Moves: 82.8%; GLB Healthy: 67.3%), higher median BMI (GLB Moves: 34.5 kg/m^2; GLB Healthy: 32.6 kg/m^2), larger waist circumference (GLB Moves: 43 cm; GLB Healthy: 41 cm), and fewer current smokers.

Participant baseline characteristics for the combined study sample are shown in Table 8. The majority of participants were female (75.6%) and almost half were Medicare-eligible (45.4% ≥65 years). In addition, over half of the participants earned at least a bachelor's degree, and most self-identifed as being non-Hispanic White (89.5%). Mean baseline body mass index (BMI) was 33.8 kg/m^2.

In all, 53.8% and 47.1% of participants met the 5% weight loss goal at 6 and 12 months, respectively. Achieving the 6-month weight loss goal was significantly associated with greater odds of meeting the 12-month weight loss goal (OR: 29.2, 95% CI: 14.0-60.6).

Attendance was high with 84% (n=200) of participants attending at least 4 out of 6 maintenance sessions. As shown in Table 9, the odds of meeting the 12-month 5% weight loss goal were also significantly greater for those who attended ≥4 maintenance sessions compared to those who did not (OR=6.0, 95% CI: 2.4-15.0). For the outcome, *meeting the 12 month weight loss goal,* there was a significant interaction (p=0.05) between maintenance attendance and meeting the 5% weight loss goal at 6 months; suggesting effect modification. When stratified by achieving the 5% weight loss goal at 6 months, attending ≥4 maintenance sessions was associated with meeting the 12-month weight loss goal only in those who had also met the goal at 6 months (OR=11.4, 95% CI: 3.2- 40.7), versus those who failed to meet the weight loss goal at 6 months (OR=1.5, 95% CI: 0.3-7.5) (Table 9). Adjustment for age, sex and leisure activity at 6 months did not have a meaningful effect on the results (Table 9).

Figure 17 shows the combination of 5% weight loss success at both 6 and 12 months by maintenance session attendance (<4 sessions vs. ≥4 sessions) with significant differences found across the combined weight loss categories ($p < 0.001$). The proportion who "improved" between 6 and 12 months (i.e., did not meet weight loss goal at 6 months, but did meet at 12) was similar

(~5%) regardless of attendance. However, those who attended ≥4 maintenance sessions were more likely to "maintain" weight loss between 6 and 12 months (48%) compared to those who attended <4 sessions (10.5%). Additonally, the participants who attended ≥4 maintenance sessions were less likely to "regress" (9.5%) or "fail" (37.5%) than those who attended <4 sessions (23.7% and 60.5%, respectively).

In an additional analysis to determine whether any demographic factors were associated with trends in weight loss success, those who "maintained" (64.7 years ± 9.9) or "improved" (65.8 ± 10.6) were older than those who "regressed" (59.1 ± 10.0) or "failed" (59.9 ± 10.0; p=0.002) (Table 10). Participants that were not working were also more likely to maintain weight loss (63%) compared to those working full- or part-time (37%). Additional demographic differences are shown in Table 10, with some statistically significant differences but no discernable trends in weight success noted.

Attending ≥4 maintenance sessions was associated with significantly higher odds of meeting the 5% weight loss goal at both 6 and 12 months (*maintain*) compared to not meeting the goal at either 6 or 12 months (*fail*) (OR=7.4, 95% CI: 2.4-22.2) (Table 11). Adjustment for age, sex, and leisure activity at 6 months yielded similar results, such that attending ≥4 maintenance group sessions in the last 6 months of the intervention was positively associated with maintaining the weight loss goal at 6 and 12 months. Attending ≥4 maintenance sessions was not signficantly associated with achieving the weight loss goal at 12 months if it was not previously met at 6 months (*improve*) (OR=1.5, 95% CI: 0.3-7.5) (Table 11).

Medicare-eligible participants aged ≥65 years (n=108) were more likely to meet the 6-month weight loss goal (63.0%) versus participants <65 years (n=130; 46.2%; p=0.01). Medicare-eligible adults were also more likely to meet the 12-month weight loss goal (63.9%) versus <65 years (33.1%; $p<0.0001$). Maintenance attendance did not vary by age with about 80% of both Medicare-eligible adults and those <65 years attending ≥4 maintenance sessions (overall $p=0.43$). As shown in Figure 18, after adjusting for sex, employment, race/ethnicity and leisure physical activity, Medicare-eligible adults were more likely to meet the 5% weight loss goal at 6 months, though not reaching statistical significance (OR=1.69; 95% CI: 0.89-3.20; $p=0.11$), and significantly more likely to meet the weight loss goal at 12 months (OR=3.03; 95% CI:1.58-5.81) compared to those <65 years.

In the sensitivity analysis using an alternative definition of attendance (i.e., only in-person session attendance versus any other contact and/or non-attendance) as the independent variable in both univariate and multivariate models, the results were similar compared to the primary analysis presented above. In addition, to determine if results varied by study, an interaction term between study cohort (GLB Moves or GLB Healthy) and maintenance attendance was examined in a univariate model with an outcome of *meeting the 12-month weight loss goal* and was not found to be significant ($p>0.2$).

5.5 Discussion

Our study is the first to identify a significant impact of maintenance session attendance (per CMS reimbursement requirements) on meeting the 5% weight loss goal at 12 months in a DPP-based community lifestyle intervention program. Although both the DPP clinical trial and it’s community translation efforts have demonstrated that earlier weight loss success was associated with maintained weight loss at follow up, maintenance session attendance (i.e., more contact in the second 6 months of the 12-month intervention) has not been examined until now.

Our current significant finding is in line with past research that showed that more frequent contact, in general, facilitates successful behavioral change among participants of a lifestyle intervention program.[173,174] However, a caveat to this finding in our study was that maintenance session attendance only increased the likelihood of meeting the 12-month 5% weight loss goal in those participants who had already met the weight loss goal by 6 months.

Among participants who failed to meet the weight loss goal at 6 months, attending more maintenance sessions did not appear to significantly improve their chances of achieving weight loss success by 12 months. However, this apparent lack of association needs to be examined in a study with greater variation in maintenance session attendance. It is possible that participants who have not achieved clinically meaningful weight loss at 6 months require more tailored resources,[177] or perhaps alternative therapies, in the latter part of the program to reach weight loss success by 12 months or beyond. Maintenance sessions occured monthly and focused on adherence barriers, problem solving, managing self-defeating thoughts and social cues to prevent relapse, building social support, and enhancing motivation.[87] Understanding which components of maintenance sessions are associated with weight loss success may help tailor programs to be effective in diverse populations. This is especially relevant in participants with complex health conditions[178] likley creating greater barriers to achieving their weight loss goals, thereby requiring multiple tailored strategies during the maintenance phase of lifestyle interventions. Successfully improving participants' ability to achieve and maintain goals has important public health implications regarding improving health outcomes among older adults at risk for type 2 diabetes.

Our study also found that Medicare-eligible adults more successfully met the clinically meaningful weight loss goal at 12 months than those <65 years of age. This is in line with previous results from the DPP multicenter clinical trial itself which showed that older adults achieved greater success with weight loss goals and reduction in diabetes incidence versus relatively younger adults.[158,179] This is pertinent because almost half of US adults 65 years and older have prediabetes.[180] These results provide guidance to clinical providers regarding the positive impact that participation in DPP-based lifestyle interventions can have on future health outcomes among Medicare-eligible older adults.

Our study had a few limitations. Due to high levels of session attendance, the impact of varying levels of participant attendance could not be closely examined. Both high study satisfaction (94% reported satified with DPP-GLB program in post-intervention survey) and the convenience of community-based sites (living close to the community center was part of the recruitment strategy and study design) likely led to the high number of participants attending the majority of maintenance sessions. In addition, although our sample reflected the composition of the existing population surrounding Pittsburgh, these findings need to be replicated within more diverse, Medicare-eligible populations to maximize generalizability.

The strengths of our study were many. This was the first study to investigate the impact of maintenance session attendance on achieving the program weight loss goal at 12 months overall and specifically within Medicare-eligible participants alone. Our results have important public health impact as reimbursement by Medicare in these community lifestyle intervention programs is based on two program components at 12 months, maintenance session attendance and 5% weight loss goal acheivement. Additionally, we demonstrated that Medicare-eligible older adults were more successful with weight loss than middle-aged adults in these DPP-based, community intervention programs. We also showed consistent findings across two studies spanning 8 years in various community settings but both using the same DPP-based lifestyle intervention that is CDC-recognized and reimbursable by CMS.

5.5.1 Implications/Relevance for Diabetes Care and Education Specialists

Both attending maintenance sessions and meeting the 6-month weight loss goal in a CDC-recognized, DPP-based community lifestyle intervention were associated with greater odds of meeting the 5% weight loss goal at 12 months. These findings were stronger for Medicare-eligible older adults offering an invaluable prevention opportunity for national Medicare-DPP providers to impact the health of 65 years and older US adults with prediabetes.[180] Understanding Medicare reimbursement-defined success will enable providers to implement strategies that enhance program effectiveness. Thus, evaluating the effectiveness of maintenance session attendance to help participants maintain a clinically meaningful and CMS-reimbursable 5% weight loss goal has broadscale importance for both long-term participant weight loss success and sustaining program funding. In addition, more efforts are needed to find ways to help those struggling to reach the weight loss goal during the first 6 months and/or to augment the programming in the last 6 months for those who need additional help in DPP-based lifestyle intervention programs.

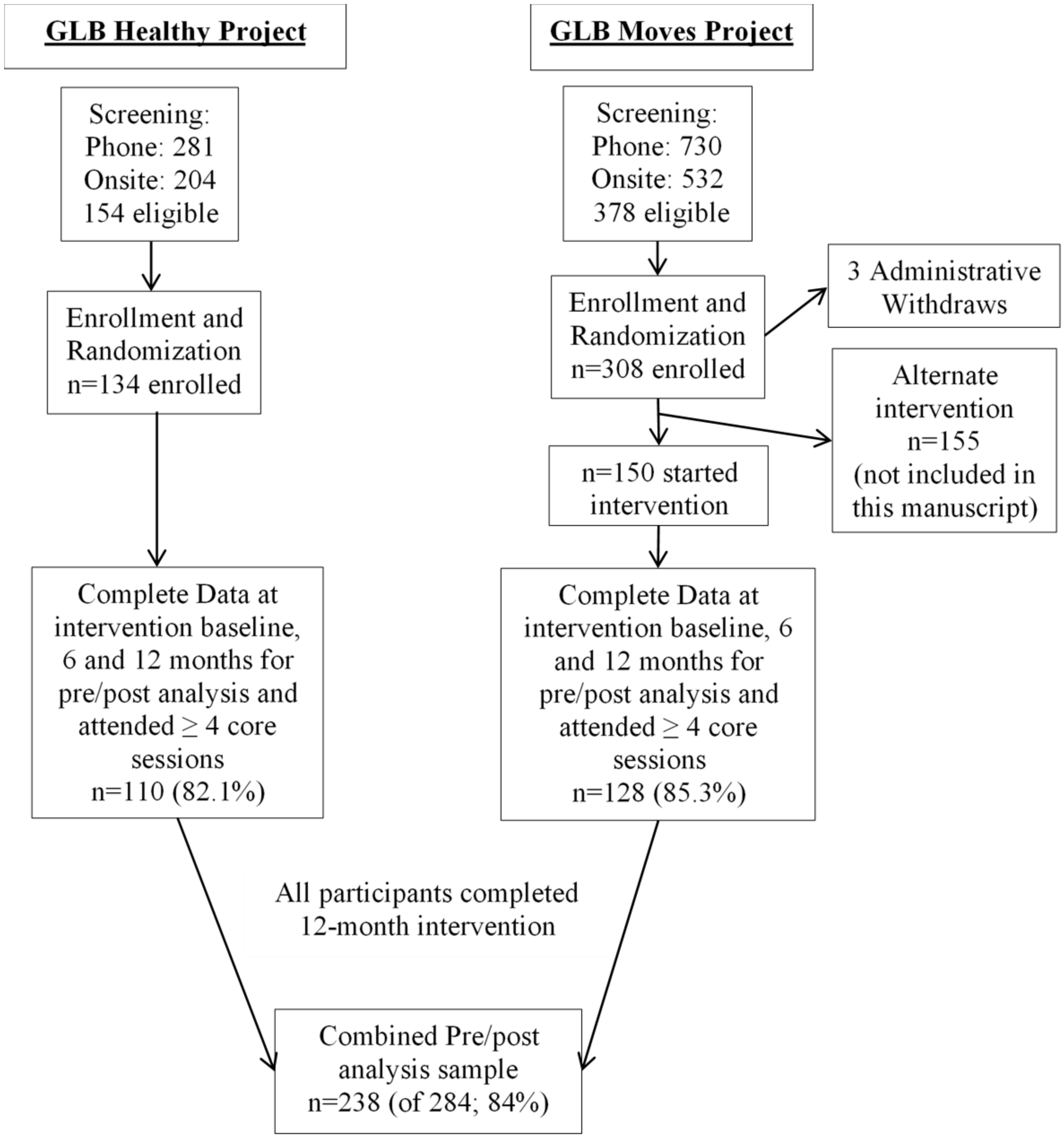

Figure 16. Recruitment, Enrollment and Study Participation Flow Chart in a Community Diabetes Prevention Program-Based Intervention, 2011-2019. The final analytic sample for the combined intervention trials (GLB Healthy and GLB Moves) consisted of 238 adults

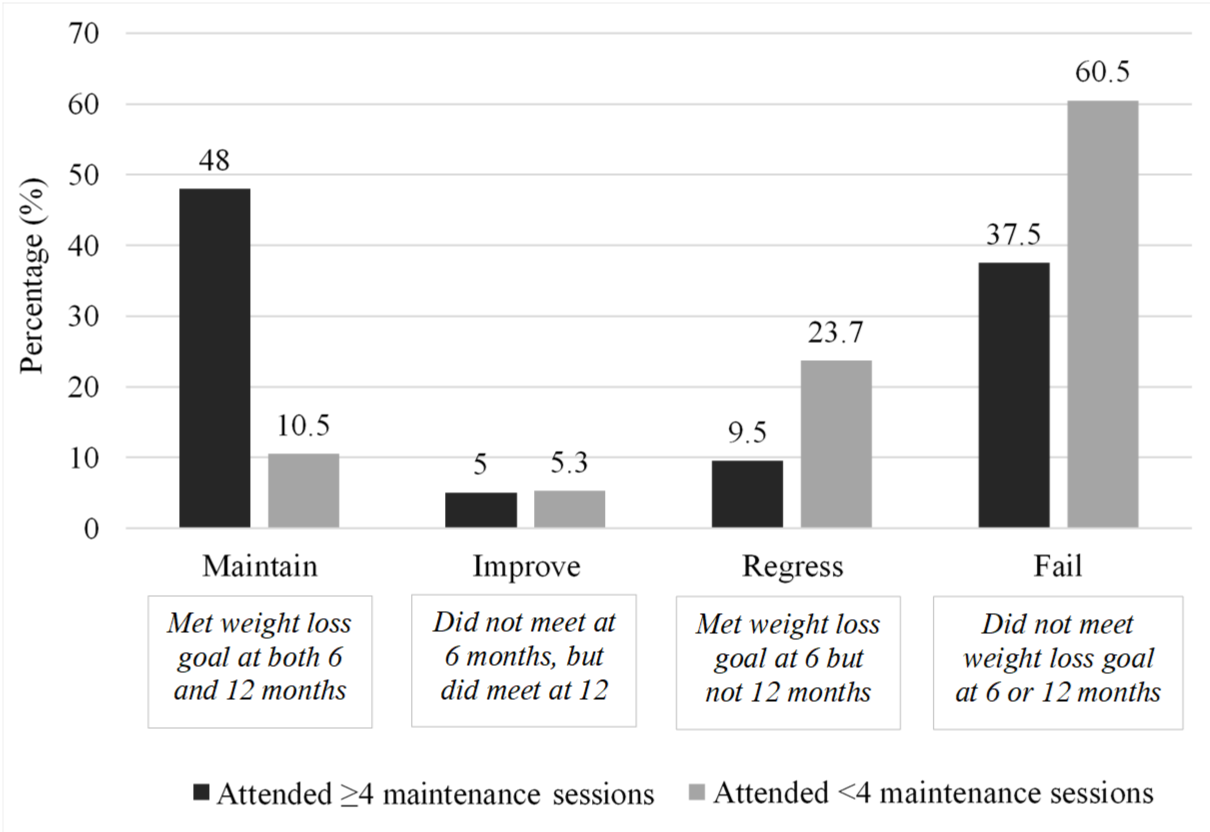

Figure 17. Distribution of Combined Weight Loss Success Status at 6 and 12 Months by Maintenance Session Attendance in a Community Diabetes Prevention Program-Based Intervention, 2011-2019, n=238

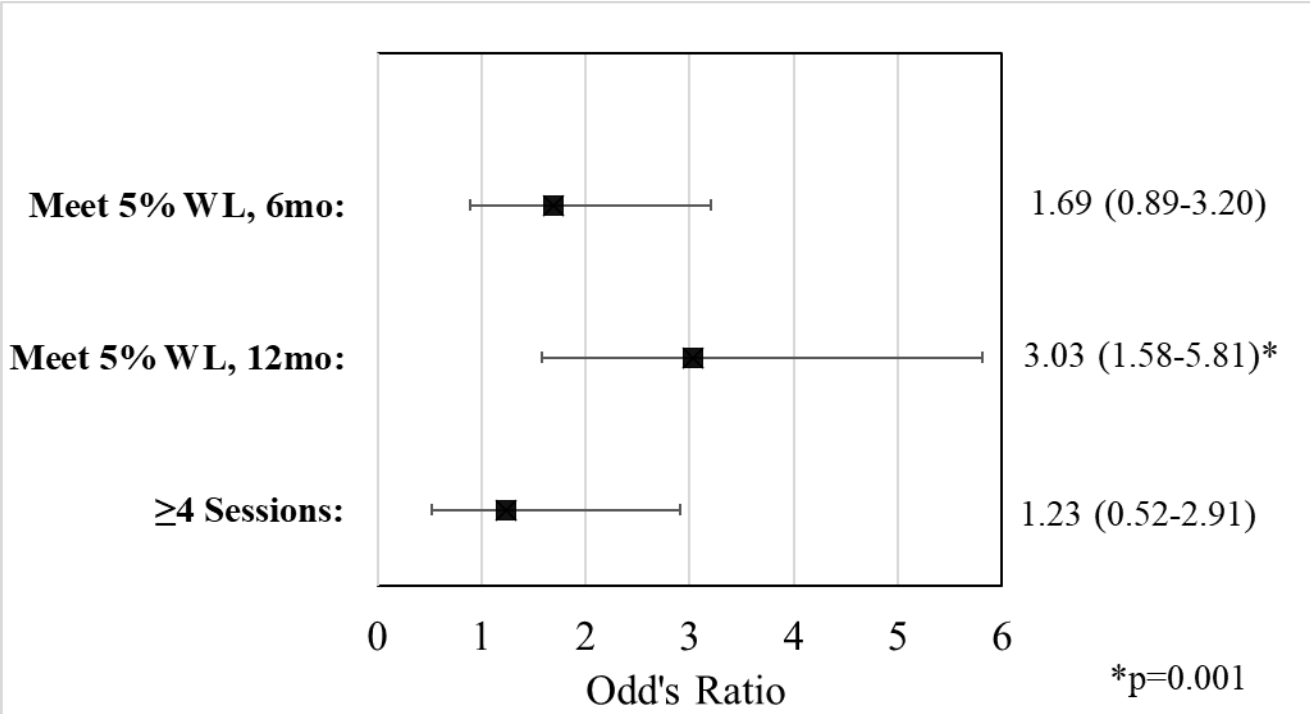

Figure 18. Associations Between Age (Medicare-eligible older adults ≥65 vs. <65 years) and Meeting 6- and 12-Month Weight Loss Goals and Maintenance Session Attendance in a Community Diabetes Prevention Program-Based Intervention, 2011-2019, n=238

Note: All models adjusted for sex, employment, race/ethnicity, and baseline leisure physical activity; WL= Weight Loss; Reference= <65 years

Table 8. Baseline Characteristics for Participants Enrolled in a Diabetes Prevention Program-Based Lifestyle Intervention Program, 2011-2019, n=238

Characteristic	Baseline
Age, years, median (IQR)	64 (55-69)
Medicare-eligible, ≥65 years, n (%)	108 (45.4)
Female sex, n (%)	180 (75.6)
Education, n (%)	
≤Some College	109 (45.8)
≥Bachelor's Degree	129 (54.2)
BMI, kg/m^2, median (IQR)	33.8 (30.0-38.4)
Waist circumference, cm, median (IQR)	42 (39.3-46.0)
MAQ, Hours/Day spent watching TV, median (IQR)	3.0 (2.0-4.0)
MAQ, MET-hours/Week Leisure Activity, median (IQR)	10.5 (3.5-21.4)
Smoking Status, n (%) Current Smoker	9 (3.8)
Employment Status, n (%) Full-time/Part-time	119 (50.0)
Ethnicity, n (%) Non-Hispanic White	213 (89.5)

Abbreviations: MET, Metabolic Equivalent Task; IQR, Interquartile range; BMI, Body Mass Index; MAQ, Modifiable Activity Questionnaire.

Table 9. Odds ratios (95% CI) for Meeting the 5% Weight Loss Goal at 12 Months Associated with Attending ≥4 Maintenance Sessions (reference <4 sessions), Overall and Stratified by Meeting the 5% Weight Loss Goal at 6 Months, 2011-2019, n=238

	Unadjusted OR[a] (95% CI)	Adjusted OR[bc] (95% CI)
Overall	6.0 (2.4, 15.0)[d]	6.4 (2.5, 16.5)[d]
Met 5% weight loss goal at 6 months	11.4 (3.2, 40.7)[d]	10.9 (2.9, 41.0)[d]
Did not meet 5% weight loss goal at 6 months	1.5 (0.3, 7.5)	1.6 (0.3, 8.1)

Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

[a]Attendance*6-month goal status interaction p-value=0.05.

[b]Adjusted for age, sex and leisure activity at 6 months.

[c]Attendance*6-month goal status interaction p-value=0.07.

[d] $p < .001$.

Table 10. Baseline Characteristic Differences Across Combined Weight Loss Success Status at 6 and 12 Months, 2011-2019, n=238

Characteristic n=238	**Maintain** Met weight loss goal at 6 and 12 (n=100)	**Improve** Did not meet at 6 months, but did meet at 12 (n=12)	**Regress** Met weight loss goal at 6 not 12 (n=28)	**Fail** Did not meet weight loss goal at 6 or 12 (n=98)	p-value
Age	64.7 ± 9.9	65.8 ± 10.6	59.1 ± 10.0	59.9 ± 10.0	**0.002**
Medicare-eligible, ≥65 years	61 (61%)	8 (66.7%)	7 (25%)	32 (32.7%)	**<.0001**
Sex					
Female	73 (73%)	11 (91.7%)	18 (64.3%)	78 (79.6%)	**0.0007**^
Male	27 (27%)	1 (8.3)	10 (35.7%)	20 (20.4%)	
Race/Ethnicity					
Non-Hispanic White	93 (93%)	12 (89.3%)	25 (89.3%)	83 (84.7%)	**0.002**^
Other	7 (7%)	0	3 (10.7%)	15 (15.3%)	
Education					
≥Bachelor's degree	46 (46%)	6 (50%)	19 (67.9%)	58 (59.2%)	0.12
≤Some college	54 (54%)	6 (50%)	9 (32.1%)	40 (40.8%)	
Employment					
Full-time/Part-time	37 (37%)	6 (50%)	19 (67.9%)	57 (58.2%)	**0.005**
Other	63 (63%)	6 (50%)	9 (32.1%)	41 (41.8)	
MAQ, Hours/Day spent watching TV at baseline	3.5 ± 2.2	3.1 ± 1.6	3.4 ±3.2	3.1 ± 2.2	0.57
MAQ, MET-hours/Week Baseline Leisure Activity	15.2 ± 17.1	8.2 ± 7.5	21.2 ±19.1	15.0 ± 14.8	0.11
BMI, kg/m^2	35.1 ± 6.4	36.5 ± 7.5	33.5 ± 6.2	34.9 ± 6.7	0.58
Waist circumference, cm	43.4 ± 5.5	43.1 ± 6.3	42.2 ± 5.2	42.1 ±5.2	0.42

Abbreviations: MET, Metabolic Equivalent Task; BMI, Body Mass Index; MAQ, Modifiable Activity Questionnaire; Mean ± standard deviation (analysis of variance) or N (column %) (chi-square) reported; ^ indicates Fisher Exact p-value.

Table 11. Odds ratios (95% CI) for Weight Loss Success Combined Categoriesa at 6 and 12 Months Associated with Attending ≥4 Maintenance Sessions (reference <4 sessions), 2011-2019, n=238

Weight Loss Success Categories	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
Maintain	7.4 (2.4, 22.2)[c]	9.3 (2.9, 30.3)[c]
Improve	1.5 (0.3, 7.5)	1.3 (0.2, 8.3)
Regress	0.6 (0.3, 1.6)	0.5 (0.2, 1.6)
Fail	Ref	Ref

Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

[a]Weight Loss Categories defined as: Maintain=Met weight loss goal at 6 and 12 months; Improve=Did not meet at 6 months but did meet at 12; Regress=Met weight loss goal at 6 not 12 months; Fail=Did not meet weight loss goal at 6 or 12 months.

[b]Adjusted for age, sex and leisure physical activity at 6 months.

[c] $p < .001$

6.0 Aim 2 Manuscript: The Impact of a Yearlong Diabetes Prevention Program-based Lifestyle Intervention on Objective Physical Function in Mid-to-Early Late Life Adults

Jenna M. Napoleone MPH[1] Rachel G. Miller PhD[1], Bonny Rockette-Wagner PhD[1], Vincent C. Arena PhD[2], Robert M. Boudreau PhD[1], Susan M. Devaraj PhD, MS, RD[1], Jennifer S. Brach PhD, PT[3], Elsa S. Strotmeyer PhD, MPH[1], Andrea M. Kriska PhD, MS[1]

1: University of Pittsburgh Graduate School of Public Health, Department of Epidemiology. Pittsburgh, PA, USA.

2: University of Pittsburgh Graduate School of Public Health, Department of Biostatistics. Pittsburgh, PA, USA.

3: University of Pittsburgh School of Health and Rehabilitation Sciences, Department of Physical Therapy. Pittsburgh, PA, USA

6.1 Introduction

Regular physical activity is important for maintaining adequate physical function[75,107,181–183], a top public health priority to aging-related quality of life[20,21], fewer adverse health outcomes[16–19], and mortality[16,19]. Functional limitations significantly increase with age[8] however there is evidence to suggest that the disablement process begins earlier in midlife (~45-60 years of age) while adults still have decades of life for which remaining functionally independent is a priority. Nationally representative data demonstrated that 31%, 37% and 42% of persons aged 45-49, 50-54 and 55-59 years reported functional difficulties, respectively.[9] Trends over time have revealed increased disability for midlife adults and stabilization or little improvement among older and oldest old adults[10] with women experiencing steeper declines in functioning throughout old age.[184] Furthermore, many of the causes of late-life disability stem from accumulated lifestyle behaviors and modifiable risk factors during midlife, thus identifying earlier targets for intervention prior to the onset of disability is essential for compression of morbidity and delaying late life disability.

The Diabetes Prevention Program (DPP) demonstrated that behavioral lifestyle intervention with weight loss and physical activity goals reduced the development of type 2 diabetes by 58% over 3 years,[83] with older DPP participants having a greater reduction of diabetes than those aged <60 years.[158] Physical activity, independent of weight, was found to be inversely related to diabetes development across 12 year of DPP follow-up, with a larger effect among those less active at baseline.[185] Unfortunately, despite the importance of physical activity for diabetes and cardiovascular disease prevention, older adults ≥ 60 years have been reported to spend about 60% of their waking hours in sedentary activities (i.e., sitting, lying)[96,97] and 31 million adults ≥ 50 years are classified as inactive.[76]

Recent findings indicate that both prediabetes and diabetes are associated with decreased physical function and accelerated disability progression.[186] Furthermore, many DPP translation studies, such as the Group Lifestyle Balance, DPP-GLB, have been shown to be effective in reducing weight, increasing physical activity levels and modifying cardio-metabolic risk factors in diverse community settings.[159–163,168] Yet, it remains unknown if these DPP-based community lifestyle interventions with the behavioral goals of increasing physical activity and decreasing weight have additional benefits such as improving and/or maintaining physical function among older adults. Additionally, how a community DPP-based lifestyle intervention that incorporates sedentary behavior as the primary movement goal impacts functional outcomes as a result of intervention participation has not been examined[129,187–191]

The purpose of this investigation is to evaluate objective physical function changes (4-m gait speed, 5-repeated chair stands, and the Short Physical Performance Battery(SPPB)) among overweight participants with prediabetes and/or metabolic syndrome who were either randomized to the original DPP-based lifestyle intervention that includes the goal of increasing physical activity levels (DPP-GLB) or one which has a movement goal of reducing sedentary behavior (GLB-SED). Each intervention was compared to the delayed control group at 6 months. Physical function pre-post changes were also evaluated after all participants completed the intervention at 6 and 12 months (delayed participants included in their respective randomized intervention arm). Finally, we investigated the specific impact of the intervention in groups varying by baseline gait speed over the yearlong study. We hypothesize that both lifestyle interventions, one aimed at increasing moderate physical activity and the other to decrease sedentary behavior, will improve physical function outcomes in mid-to-early late life adults and that higher magnitude improvements will be shown for those with initially lower function.

6.2 Methods

6.2.1 Research Design and Study Participants

This investigation examined data from an NIH-funded study called the Physical Activity and Sedentary Behavior Change project, GLB MOVES (PI: Dr. A. Kriska; R18 DKDK100933-02). This study aimed to determine the effectiveness of a GLB modified program in which the goal is not to initially increase moderate physical activity levels but to sit less within the context of a community-based lifestyle intervention program. GLB MOVES was conducted from September 2014 through July 2019. As part of this study, the PI, colleagues and two international investigators who lead the field of health and sedentary behavior, Dr. Neville Owen and Dr. David Dunstan, designed a sedentary change intervention replacing the movement focus of moderate activity to that of sitting time (GLB-SED). Recruitment and screening took place in Allegheny County in Pittsburgh, PA and included presentations at the community centers, flyers and posters, community center newsletters, and targeted direct mailing to zip codes around the community centers. The eligibility criteria were a BMI ≥24 kg/m^2 (≥22 kg/m^2 for Asians; both cut-points consistent with the DPP BMI eligibility criteria[83]), prediabetes and/or the metabolic syndrome, and participants 40 years or older.[170] *There were no physical activity or sedentary behavior study entry criteria.*

Based on these inclusion criteria, a total of 305 participants were randomized and included in this study (Figure 19). Research protocols were approved by the University of Pittsburgh Institutional Review Board and all participants provided written informed consent before study enrollment.

The study design was a 6-month delayed control group randomized controlled trial intervention in which eligible participants were randomized to one of three arms: 1) DPP-GLB: the original DPP-based CDC-recognized, CMS-reimbursable Group Lifestyle Intervention with the movement goal of increasing moderate physical activity (n=100); 2) GLB-SED: a modified version of the GLB with the movement goal of sedentary reduction (n=101); or 3) a 6-month delayed control group (n=104). After 6-months, delayed participants were randomized to either DPP-GLB or GLB-SED and received the entire yearlong lifestyle intervention. This delayed control design is appropriate for community translation research and was well received by both partner organizations and participants alike.[163]

6.2.2 Lifestyle Intervention

A detailed description of the DPP-GLB lifestyle intervention curriculum used in this study has been previously described[87,88] and is available online at www.diabetesprevention.pitt.edu. The DPP-GLB lifestyle intervention is a 12-month in-person, group-based program with a total of 16 core sessions and 6 maintenance sessions taught by a trained lifestyle coach. In the first 6 months of core sessions, there are 12 weekly sessions followed by 4 bi-weekly sessions. Months 7-12 consist of 6 monthly maintenance sessions.[89] The main goals of the DPP-GLB lifestyle intervention were to encourage participants to increase physical activity levels to at least 150 minutes of moderate intensity physical activity per week and achieve and maintain a 7% weight loss in a safe and progressive manner. All lifestyle coaches completed a standardized 2-day training workshop provided by the Diabetes Prevention Support Center and recognized by the CDC.[88] Group sessions were held at senior/community centers and participants received session handouts, self-monitoring logs, and a pedometer, and were weighed at each session.

The GLB-SED intervention curriculum was adapted from the highly successful DPP-GLB lifestyle intervention program. The movement goal in GLB-SED focused on sedentary change and the importance of decreasing time spent sedentary, particularly sitting. Participants were asked to gradually decrease their sitting time with the ultimate goal of eliminating 30-minute sitting bouts in a day with non-sitting activity. Specifically, the participants monitored the number of 10-minute bouts of TV/computer/video watching or other sitting behaviors that they replaced with any non-sitting activity of their choice, as well as the number of short breaks they took from sitting by getting into the standing position (a sit-to-stand transition).

Around month 9, DPP-GLB and GLB-SED received an additional movement goal, which was the primary movement goal of the other intervention arm (e.g., GLB-SED received the moderate physical activity goal and DPP-GLB received the decreasing sitting time goal).

6.2.3 Objective Physical Function

At baseline, 6 and 12 months, participants completed physical function tasks following standardized protocols by trained staff. The tests included timed 4-m gait speed, timed 5-repeated chair stands, and the Short Physical Performance Battery (SPPB).

Gait Speed: Participants were instructed to walk at their usual pace on a level floor with two tape markers placed 4-meters apart and timing was stopped when the first foot crossed the end line. The 4-meter walk was completed twice and the average of the two trials were used in the analysis (meters/second).

Repeated chair stands: A standard height chair was placed against a wall on a level floor and participants were asked to place their arms across their chest while seated and stand without using their arms five times. Time (seconds) taken to complete five consecutive repetitions of the chair stand was used in this analysis. A total of n=7/305 (2.3%) of participants were not able to complete the repeated chair stands assessment and were set to missing for this outcome, though were not included in analyses due to the low number of participants that could be categorized as an inability to complete the chair stands.

SPPB: Following standardized protocol, the SPPB consists of three physical performance measures: timed 4-m gait speed at usual pace, 5-repeated chair stands, and a series of balance tests (side-by-side, semi-tandem, tandem, and one-foot stands, each held for 10 seconds). This is a well validated measure of lower extremity performance[192] and has shown to be associated with disability, institutionalization and mortality.[193,194] Each component is given a score ranging from 0 (unable to complete) to 4 (best) and a summary score from 0 (worst performance) to 12 (best performance) is calculated and the continuous score was used for this analysis.

6.2.4 Other Study Measures

Covariates included in analyses were collected at baseline and all study measures were collected at the community sites using standardized forms by trained clinic staff. At the initial on-site screening visits to determine eligibility, participant age (years determined from birth date), sex (female, male), employment (full-time/part-time, retired, other), race/ethnicity (White, Black, other race/ethnic groups), education (graduate degree, bachelor's degree, or some college or less), and other demographic characteristics were completed. Self-reported leisure physical activity levels (MET-hours/week) were assessed using a past month version of the Modifiable Activity Questionnaire (MAQ)[171] which has shown to be both valid and reliable in older adult populations.[172,173] Weight and height were measured at clinic assessment visits with shoes removed in light clothing using a standard protocol and a validated medical scale and body mass index (BMI, kg/m^2) calculated from these measures. The Visual Analog Scale (EQVAS) measured overall health status on a specific day from 0 "worst imaginable health state" to 100 "best imaginable health state", in which higher scores indicate better health.[195] Total cholesterol and fasting plasma glucose were determined from a fasting blood draw. Blood pressure was measured twice and then averaged with an automatic digital sphygmomanometer after participants rested for five minutes.

6.2.5 Statistical Analysis

As this was a well-functioning older adult population (with eligibility criteria that included healthcare provider approval to initiate the prudent moderate intensity activity portion of the GLB), a priori, gait speed after the yearlong intervention was considered the primary function outcome for this effort. In all randomized study arms, the median standing balance score component of the SPPB was at the ceiling of 4 (IQR 4-4) at baseline and remained unchanged at 6 and 12 months, thus standing balance was not investigated further as a separate outcome. All participants were included in mixed model analyses at 6 (n=305) and 12 months (n=276) and participants with complete data for physical function outcomes were included in descriptive randomized clinical trial (n=263) and pre-post analyses (n=237 for gait speed over 12 months; n=252 for SPPB over 12 months) (Figure 19).

Differences in baseline demographic and clinical characteristics and objective physical function measures across all randomized intervention arms were examined using analysis of variance or chi-square tests. Between-arm comparisons to the delayed control (DPP-GLB vs. delayed, GLB-SED vs. delayed) for baseline characteristics and physical function measures were tested using t-tests or chi-square tests. We stratified by slow gait at baseline (≥1.0m/s vs. <1.0m/s) and low SPPB at baseline (≥10 vs. <10) and assessed pre-post overall and stratified mean change in gait speed and SPPB at 6 and 12 months. Paired t-tests were used to determine statistical significance for mean change from baseline to 6 and 12 months.

Comparisons for change in continuously measured gait speed and chair stands for the delayed intervention group and DPP-GLB and GLB-SED treatment groups were conducted using repeated measures linear models using all available data, allowing for different error variances at each timepoint (baseline, 6 months) and correlation within timepoints. Randomized clinical trial models were assessed both unadjusted and after adjusting for baseline leisure physical activity and overall health state, due to differences at baseline between arms, as well as baseline gait speed due to suggestions from previous literature.[60]

Pre-post changes between baseline, 6 and 12 months for gait speed and chair stands were modeled using the same repeated measures linear modeling strategy as described above. We used a forward stepwise approach to add in baseline covariates. The modeling strategy was as follows: Model 1: Unadjusted; Model 2: Adjusted for baseline demographics (age, sex, race/ethnicity, education, employment); Model 3: Adjusted for Model 2 covariates plus baseline lifestyle variables (BMI, MAQ leisure time physical activity, EQVAS health rating, gait speed); and Model 4: Adjusted for Model 3 covariates plus baseline clinical characteristics (LDL cholesterol, SBP, DBP, glucose, total cholesterol, triglycerides). Only significant covariates at $p<0.2$ across all outcomes were retained in the final model (age, race, employment, BMI, physical activity, health rating, gait speed, DBP, and triglycerides). Model fit was assessed using AIC and BIC, collinearity tests were evaluated for the final model and residual plots were examined. All analyses were conducted using 2-sided hypothesis testing and SASv9.4 software (SAS Institute, Inc., Cary, North Carolina).

6.3 Results

A total of 305 participants were included in our analysis (Figure 19) and the mean age was 62±9.1 years (range 40 to 88 years). Demographic and clinical characteristics and physical function measures were similar in all arms at baseline (Table 12). The participants were majority female (79%), mostly non-Hispanic white (81.3%), 41.6% are retired, and fairly highly educated (28.5% are a college graduate and 22.6% have a graduate degree). DPP-GLB had significantly higher health rating and leisure physical activity compared to the delayed control group (10.2 (2.4-17.8) vs. 7.0 (2.3-14.4), respectively) (Table 12).

6.3.1 Comparisons between the intervention arms and 6-month delayed control

Improvement in gait speed, chair stands and SPPB was evaluated by randomization assignment (Table 16). At 6 months, GLB-DPP (+0.05± 0.17), GLB-SED (+0.06 ± 0.16) and the delayed control (+0.04 ± 0.18) had faster gait speed compared to baseline, with both treatment arms experiencing clinically meaningful changes in gait speed.[71] DPP-GLB had lower chair stands time (mean (SD): -0.17 (2.7)) while GLB-SED participants had significantly lower chair stands time (-0.55 (2.2)) compared to delayed. Change in SPPB total score was significantly higher in GLB-DPP versus delayed (+0.19 (1.28)) and GLB-SED also had higher total SPPB but did not reach statistical significance (+0.11 (1.0)).

Repeated measure linear models demonstrated similar results to the descriptive changes over time (Table 13), with only GLB-SED demonstrating significantly reduced chair stands time at 6 months versus delayed and no other changes reaching statistical significance. Participants in both treatment arms demonstrated clinically meaningful faster gait speed at 6 months with the delayed control also getting faster at gait speed, though at a smaller amount. GLB-SED and DPP-GLB participants improved repeated chair stands times at 6 months compared to baseline with the delayed control showing slower time (worse) at 6 months. Adjusting for baseline overall health rating, leisure physical activity and baseline gait speed (<1.0 vs. ≥1.0 m/s) did not change the magnitude or significance of the associations (Table 13).

6.3.2 Pre-post change in physical function by intervention group

Figure 20 shows pre-post mean gait speed and SPPB total score at baseline, 6 and 12 months for DPP-GLB and GLB-SED, overall and stratified by slow gait or low SPPB at baseline. Compared to baseline, DPP-GLB had significantly faster mean gait speed at both 6 and 12 months (Figure 20a), whereas GLB-SED did not significantly improve gait at either time point (Figure 20b). Neither treatment group had significant changes in SPPB total score at 6 or 12 months (Figure 20c,d). When stratified by slow gait at baseline, DPP-GLB and GLB-SED experienced significantly substantial faster gait speed at 6 and 12 months (DPP-GLB: +0.10 and +0.09, respectively; GLB-SED: +0.07 and +0.07, respectively) (Figure 20a,b). Those that started with normal gait speed at baseline (>1m/s) in GLB-SED had significantly slower gait speed at 12 months compared to baseline, yet still maintained a fast mean gait speed of 1.16m/s at 12 months. When stratified by low SPPB at baseline, GLB-SED had significantly higher SPPB total score at 6 (+1.33) and 12 months (+1.53) compared to baseline (Figure 20d) and DPP-GLB had higher mean SPPB scores at both time points (+1.3 at 6 months, +1.1 at 12 months), though not statistically significant (Figure 20c).

Unadjusted pre-post repeated measures linear models demonstrated significantly faster mean gait speed change at 6 months in both DPP-GLB (+0.04 (0.01, 0.07)) and GLB-SED (+0.03 (0.01, 0.06)), and DPP-GLB maintained significantly faster gait at 12 months (+0.04 (0.01, 0.07); Table 14). At 6 months, GLB-SED improved mean change chair stands time compared to baseline (-0.49 (-0.92, -0.07)) and DPP-GLB showed significantly improved chair stands time at 12 months versus baseline (-0.69 (-1.21, -0.16)). The magnitude and significance of these estimates were similar after adjusting for potential confounders (Table 14).

6.4 Discussion

Both the standard DPP-based lifestyle intervention with its typical goal of increasing physical activity levels as well as the modified intervention in which the movement goal focused on decreasing sedentary time were effective at improving physical function with clinically meaningful changes in gait speed at 6 months. However, these changes were not significantly greater than the change in the delayed control group in final clinical trial models for the entire group. Notably, the largest magnitudes of change in both intervention groups were seen among those that started with the lowest physical function measures at baseline (slow gait speed and low SPPB).

DPP-GLB and GLB-SED demonstrated statistically significant, meaningful mean gait speed changes (>0.05m/s)[71] at 6 and 12 months among those that had slower gait speed at baseline (<1.0 m/s). Additionally, we found statistically significant and substantial differences in mean SPPB total score[71] at 6 and 12 months compared to baseline in GLB-SED (≥ +1.0 point) and similar substantial magnitudes in change in DPP-GLB though not significant, likely due to small number of participants who had low SPPB measures at baseline. Finally, our results showed that GLB-SED participants had significantly faster chair stand time 6 months compared to baseline, which makes sense since they were initially given goals to take breaks from sitting. Previous research has shown that lower rates of mobility disability in older adults after engaging in a physical activity intervention were largely attributable to improved chair-stand performance, which is a surrogate measure of lower extremity muscle strength/power.[60] Therefore, muscle strength may also be a mechanism by which physical activity prevents future disability.

Our results suggest that DPP-based lifestyle interventions, DPP-GLB and GLB-SED, combining both goals of achievement and maintenance of weight loss with increased physical activity/reduction of sedentary time improved future functional outcomes. Thus, our findings suggest another possible benefit of these DPP-based community interventions, especially among lower functioning older adults. The fact that the DPP-GLB represents a real-world lifestyle intervention that is reimbursable by CMS and currently available nationally to prevent functional decline adds to the importance of these initial findings. In addition, the DPP-based sedentary behavior reduction intervention would be another community-based intervention program that could be added to the list of prevention options for improving function in older adults, with the possibility of potential future CMS-reimbursement.

Previous literature has demonstrated that physical activity interventions in older adults lead to improved physical function.[55,57,62,80–82] The LIFE study included sedentary, older adults (mean age=78.9±5.2 years) and involved a moderate physical activity intervention (i.e., center-based 2x per week, home-based 3-4x per week) versus a health education arm. The intervention showed significantly improved objective physical function and physical performance, reductions in major mobility disability over the course of 2.6 years vs. the health education group.[60,79] Yet, magnitudes of change were small to modest and the results were only generalizable to older adults at high risk for mobility disability. Additional limitations with existing activity interventions include concerns with long-term sustainability, feasibility of the intervention for inactive, older adult populations with comorbidities and the ability for the intervention to be effectively translated into the community setting.[55,57,62,80–82] Our results add to the current literature as being an effective, community-based, and sustainable real-world intervention shown to improve physical function among mid-to-early late life adults. An important future direction of this work is to include more individuals with higher comorbidities and lower functional ability, similar to those older adults now eligible for Medicare-DPP reimbursed by CMS,[196] as these individuals are likely to show a larger magnitude of improvements with our lifestyle intervention versus our current study sample.

Most of the benefit of the intervention in improving function was found in those whose function, no matter how measured, was lower to begin with. This methodological issue is in line with previous DPP analyses showing that change in activity is significant when limited to those less active at baseline, since activity level was not an eligibility criterion in the original DPP.[185] This is also pertinent to our current community translation study since physical activity, sedentary level and physical function cut points were *not* required for entry into the study. As this study was open to all functioning community dwelling adults, many of these adults had fairly high function when enrolled. In contrast with previous studies, we found *larger* magnitudes of change in both gait speed and SPPB compared to the MOVE UP study[197] and LIFE study.[60] Importantly, MOVE UP was not a randomized design, and neither of these studies used a DPP-based intervention.[197] Furthermore, LIFE only enrolled older adults with some functional limitation which makes the results less generalizable to midlife adults prior to the onset of more substantial functional decline. Compared to prior research, our results would suggest that these DPP-based community lifestyle interventions may be an effective prevention program for functional decline in middle aged and early late life adults, particularly once these adults enter later old age.

It remains unclear based on existing literature how interventions that incorporate goals of decreasing sedentary behavior impact physical function. The few studies that have been conducted are feasibility studies with small sample sizes, varying functional outcomes and intensities of movement goals, and short follow-up times (≤3 months).[113–116] Our novel GLB-SED lifestyle intervention with the primary movement goal of reducing time spent in sedentary behaviors has shown to improve objective physical function at both 6 and 12 months. Having several effective lifestyle interventions with varying movement goals that improve physical function would expand potential reach of these programs. Thus, our future goal is for this modified DPP-based lifestyle intervention to become an additional CDC-recognized, CMS-reimbursable program that could positively impact aging-related health outcomes of thousands of older adults across the country.

This study had several limitations. First, in the second half of the program after the RCT part of the study had ended, DPP-GLB received the sit-less goal and GLB-SED received the moderate physical activity goal at 9 months so the design was not to compare these two arms. This should be taken into consideration when interpreting the 12-month data. Secondly and most importantly, our participants represent a highly functioning cohort of mid-to-early late life adults vs. those typically evaluated for lifestyle interventions. As the greatest impact of the intervention on function was shown in those in need of the most change, further studies should investigate this issue in cohorts of low functioning adults. Additionally, since only a few participants could not complete the chair stands, chair stand speed (total # of chair stand completed/seconds) was not assessed. Fourth, diverse populations with higher comorbidity need to be studied as older adults eligible for DPP-based lifestyle interventions offered by CMS have heterogenous health profiles. Finally, gait speed improved in the delayed control group at 6 months which may be due in part to difficulty measuring gait speed since it was collected in community centers rather than in a controlled laboratory setting. A more standardized protocol for measuring gait speed both in the community and clinical settings will be critical for future studies.[198,199]

The current study had several important strengths. In addition to being the first study to assess whether a DPP-based lifestyle intervention improves/maintains physical function, we were also the first to develop and implement GLB-SED, a DPP-based community lifestyle intervention that incorporates reducing sedentary behavior as the primary movement goal. This novel GLB-SED program offers an additional movement goal for someone unable to initially engage in moderate intensity physical activity. The fact that the DPP-GLB represents a real-world lifestyle intervention that is reimbursable by CMS and currently available nationally to prevent/delay functional decline adds to the public health importance and long-term sustainability of this work. In addition, the DPP-based lifestyle intervention with sedentary behavior reduction goals could be an additional program added to the list of CDC-recognized prevention options for improving function in older adults, with the possibility of becoming a CMS-reimbursable program in the future. Additionally, participants enrolled in this study are at the cusp of substantial functional decline which contrasts with most studies that enroll only older adults with existing functional limitations. Therefore, to truly prevent initial functional decline and delay the onset of disability in late life, it is essential to include both midlife and early late life adults in prevention efforts to have the largest public health impact possible.

Future research should examine the long-term impact of these two DPP based lifestyle interventions that vary by the movement goal on physical function through the transition from midlife to early late life. Of great interest would be to have two interventions, one aimed at reducing sedentary time and the other focusing on increasing physical activity levels (or some combination of both), that are both effective at improving/maintaining physical function long-term. Also, it is critical to select the most appropriate objective performance measures in midlife adults to predict late life disability. Importantly, it is currently unknown which test is most appropriate to assess early functional decline in midlife adults.[151] Lack of statistically significance may be due to ceiling effects in higher functioning individuals. More challenging performance measures (i.e., 400-meter walk and expanded SPPB)[200,201] should be considered if the population is high functioning at baseline.

In conclusion, we demonstrated that DPP-based community lifestyle interventions with weight loss and physical activity/sedentary behavior reduction goals successfully improved or maintained objective physical function at 6 and 12 months (faster gait speed and chair stand time, higher total SPPB among those that started lower at baseline). These programs should be implemented earlier in the midlife period to prevent or delay the onset of disability in late life. Future work should focus on effectively *adapting* DPP-based lifestyle interventions based on a person's comorbid conditions (e.g., MetS, prediabetes, obesity) and current functional status (gait speed <1.0 m/s) to have the largest public health impact on functional outcomes. Examples of tailoring sessions to an older adult populations at high-risk for future functional decline could include sessions regarding how to stay mobile in the community and the importance of function with aging. There is immense potential to modify the already existing CMS-reimbursable, DPP-based lifestyle interventions offered nationally as both feasible and sustainable options that extend healthy years of life lived without disability. Thus, intervening earlier in midlife is essential to halt, slow or even reverse functional limitations among adults at high-risk for late life disability and ultimately increase independence with aging.

Table 12. Baseline Demographic and Clinical Characteristics and Physical Function Measures by Randomized Intervention Arm in GLB MOVES, n=305

Baseline Variable	DPP-GLB N=100 mean ± SD median (IQR)	GLB-SED n=101 mean ± SD median (IQR)	Delayed Control N=104 mean ± SD median (IQR)	p-value
Demographic Characteristics				
Sex, n (% female)	81 (81.0%)	80 (79.2%)	81 (77.9%)	0.86
Age (years) range: 40-88 years	63.3 ± 8.4	61.8 ± 9.6	61.9 ± 9.4	0.43
Race/ethnicity, n (%)				0.14
White	85 (85.0%)	76 (75.3%)	85 (81.7%)	
Black	13 (13.0%)	21 (20.8%)	14 (13.5%)	
Other combination	2 (2%)	4 (3.9%)	5 (4.8%)	
Education, n (%)				0.65
Graduate degree	22 (22%)	25 (24.8%)	22 (21.2%)	
Bachelor’s degree	26 (26%)	33 (32.7%)	28 (26.9%)	
Some college or less	52 (52%)	43 (42.6%)	54 (51.9%)	
Employment, n (%)				0.58
Full-time/part-time	51 (51%)	50 (49.5%)	51 (49.1%)	
Retired	44 (44%)	42 (41.6%)	41 (39.4%)	
Others	5 (5%)	9 (8.91%)	12 (11.5%)	
Clinical Characteristics				
Weight (kg)	97.9 ± 21.5	95.6 ± 18.6	94.8 ± 19.3	0.50
Waist (cm)	111.8 ± 13.5	110.0 ± 12.9	108.8 ± 13.5	0.29
BMI (kg/m^2)	36.0 ± 7.0	35.5 ± 6.1	35.2 ± 6.3	0.65
Total Cholesterol (mg/dl)	195.5 (175-220.5)	193 (173-228)	199 (174-219)	0.98
LDL Cholesterol (mg/dl)	117 (94.5-140)	111 (93-137)	118 (93-138)	0.94
Triglycerides (mg/dl)	117.5 (91-168.5)	119 (85-166)	119.5 (91-193)	0.97
Glucose (mg/dl)	92 (87-98)	93 (86-102)	90 (84-99)	0.17
SBP (mmHg)	122.5 (112.5-134.3)	125 (115-139)	121.8 (113-132.8)	0.60
DBP (mmHg)	74.8 (69-81.8)	78.5 (72.5-83.5)	77.3 (71-84.8)	0.42
Health Rating (EQ 5D-VAS; 0-100)	80 (70-90)*	75 (70-86)	72.5 (60-85)	0.15
MET-Weighted Leisure Activity (MET-hours/week)	10.2 (2.4-17.8)*	7.2 (1.4-16.4)	7.0 (2.3-14.4)	0.11
Physical Function Measures				
4-Meter Gait Speed (meters/second)	1.04 ± 0.2	1.09 ± 0.2	1.07 ± 0.2	0.34
5-Repeated Chair Stands (seconds)	11.6 ± 3.2 11.3 (9.4-12.9)	11.3 ± 3.1 10.6 (9.4-12.5)	10.1 ± 11.2 10.8 (8.7-12.8)	0.27
SPPB, total score (0-12)	10.63 ± 1.6 11 (10-12)	10.96 ± 1.6 12 (11-12)	10.88 ± 1.7 11 (10-12)	0.34

EQ-5D, EuroQol 5 Dimension; MAQ, Modifiable Activity Questionnaire; MET, metabolic equivalent; SD, standard deviation; SPPB, Short Physical Performance Battery; VAS, Visual Analog Scale; ^ indicates Fisher exact test

*indicates significant p-value <0.05 compared to delayed

Table 13. Fixed Effects for Randomized Clinical Trial 6-Month Repeated Measures Linear Models Estimating Means Changes (95% Confidence Interval) in Gait Speed and Chair Stands in GLB MOVES, n=305

Randomization assignment	Gait Speed (m/s) 6-month change from baseline (95% CI)	p-value vs. delayed	Chair Stands (secs) 6-month change from baseline (95% CI)	p-value vs. delayed
Model 1: Unadjusted				
GLB-DPP	+0.05 (0.01, 0.09)	0.70	-0.19 (-0.74, 0.35)	0.11
GLB-SED	+0.05 (0.02, 0.09)	0.70	**-0.47 (-0.97, 0.03)**	**0.01**
Delayed Control	+0.04 (0.01, 0.08)	**-**	+0.43 (-0.07, 0.92)	**-**
Model 2: Adjusted for baseline leisure physical activity				
GLB-DPP	+0.05 (0.01, 0.09)	0.71	-0.19 (-0.73, 0.35)	0.12
GLB-SED	+0.05 (0.02, 0.08)	0.72	**-0.47 (-0.97, 0.03)**	**0.01**
Delayed Control	+0.04 (0.01, 0.08)	-	+0.42 (-0.12, 0.96)	-
Model 3: Adjusted for baseline leisure physical activity, health rating and gait speed				
GLB-DPP	+0.05 (0.01, 0.09)	0.70	-0.19 (-0.73, 0.36)	0.12
GLB-SED	+0.05 (0.02, 0.09)	0.72	**-0.48 (-0.98, 0.02)**	**0.01**
Delayed Control	+0.04 (0.01, 0.08)	-	+0.42 (-0.12, 0.96)	-

Mean difference (95% Confidence Interval) calculated as 6 months minus baseline; Positive changes for gait indicate better performance and negative changes for chair stands indicate better performance.

Table 14. Fixed Effects for Pre-Post (6 Months or 12 Months minus baseline) Repeated Measures Linear Regression Models Estimating Changes in Gait Speed and Chair Stands in GLB MOVES, n=276

	Gait Speed (m/s)				**Chair Stands (secs)**			
Pre-Post Assignment	6 months change from baseline (95% CI)	within group p-value	12 months change from baseline (95% CI)	within group p-value	6 months change from baseline (95% CI)	within group p-value	12 months change from baseline (95% CI)	within group p-value
Unadjusted								
DPP-GLB	+0.04 (0.01, 0.06)	**0.008**	+0.04 (0.01, 0.07)	**0.003**	-0.20 (-0.64, 0.23)	0.36	-0.69 (-1.21, -0.16)	**0.01**
GLB-SED	+0.03 (0.01, 0.06)	**0.01**	0.00 (-0.02, 0.03)	0.78	-0.49 (-0.92, -0.07)	**0.02**	-0.38 (-0.91, 0.15)	0.16
Fully adjusted								
DPP-GLB	+0.04 (0.01, 0.06)	**0.006**	+0.4 (0.02, 0.07)	**0.002**	-0.25 (-0.68, 0.18)	0.26	-0.75 (-1.27, -0.22)	**0.006**
GLB-SED	+0.04 (0.01, 0.06)	**0.01**	0.00 (-0.03, 0.03)	0.87	-0.50 (-0.92, -0.07)	**0.02**	-0.39 (-0.93, 0.14)	0.15

Fully adjusted baseline covariates: age, race, employment and baseline BMI, physical activity, health rating, gait speed, DBP, and triglycerides

Table 15. Baseline Demographic and Clinical Characteristics by Randomized Intervention Arm stratified by Slow Gait at Baseline (<1.0 m/s) in GLB MOVES, n=305

	GLB MOD N=100 mean ± SD median (IQR)		GLB-SED n=101 mean ± SD median (IQR)		Delayed Control N=104 mean ± SD median (IQR)	
	Slow vs. Normal Gait		**Slow vs. Normal Gait**		**Slow vs. Normal Gait**	
	<1.0 m/s n=42	≥1.0 m/s n=58	<1.0 m/s n=37	≥1.0 m/s n=63	<1.0 m/s n=43	≥1.0 m/s n=60
Demographic Characteristics						
Sex, n (% female)	33 (78.6%)	48 (82.8%)	31 (838%)	48 (76.2%)	36 (83.7%)	44 (73.3%)
Age (years) range: 40-88 years	67.3 ± 7.2*	60.4 ± 8.1*	65.3 ± 10.5*	59.9 ± 8.5*	65.0 ± 9.2*	59.9 ± 9.0*
Race/ethnicity, n (%)						
White	35 (83.3%)	50 (77.8%)	26 (70.3%)	49 (77.8%)	32 (74.4%)	52 (86.7%)
Black	6 (14.3%)	7 (12.1%)	10 (27.0%)	11 (17.5%)	9 (20.9%)	5 (8.3%)
Other combination	1 (2.4%)	1 (1.7%)	1 (2.7%)	3 (4.8%)	2 (4.7%)	3 (5%)
Education, n (%)						
Graduate degree	8 (19.1%)	36 (62.1%)	10 (27.0%)	35 (55.6%)	5 (11.6%)*	34 (56.7%)*
Bachelor’s degree	9 (21.4%)	20 (34.5%)	10 (27.0%)	22 (34.9%)	8 (18.6%)	21 (35%)
Some college or less	25 (59.5%)	2 (3.5%)	17 (46.0%)	6 (9.5%)	30 (69.8%)	5 (8.3%)
Employment, n (%)						
Full-time/part-time	15 (35.7%)*	14 (24.1%)*	14 (37.8%)	15 (23.8%)	17 (39.5%)	17 (28.3%)
Retired	24 (57.2%)	17 (29.3%)	20 (54.1%)	23 (36.5%)	19 (44.2%)	19 (31.7%)
Others	3 (7.1%)	27 (46.6%)	3 (8.1%)	25 (39.7%)	7 (16.3%)	24 (40%)
Clinical Characteristics						
Weight (kg)	98.7 ± 22.5	97.4 ± 20.9	97.3 ± 18.2	94.6 ± 19.0	93.7 ± 20.2	95.3 ± 18.8
Waist (cm)	112.8 ± 14.7	110.9 ± 12.6	111.3 ± 12.9	109.3 ± 13.1	108.3 ± 14.0	109.0 ± 13.2
BMI (kg/m^2)	36.8 ± 8.3	35.4 ± 5.9	36.9 ± 5.7	34.7 ± 6.3	35.3 ± 6.6	35.0 ± 6.2
Total Cholesterol (mg/dl)	196.5 (176-222)	195 (172-217)	194 (174-227)	193 (171-230)	199 (174-217)	199 (176-220)
LDL Cholesterol (mg/dl)	115 (98-134)	118.5 (94-145)	109 (91-139)	116 (95-137)	124 (96-137)	117 (93-141)
Triglycerides (mg/dl)	129 (97-167)	111 (89-179)	111 (95-167)	121 (83-166)	115 (85-156)	122.5 (96-167)
Glucose (mg/dl)	94 (88-100)	91.5 (87-98)	95 (86-101)	92 (86-102)	90 (84-99)	90 (84-98)
SBP (mmHg)	123 (112-135)	122 (112.5-132)	128 (119.5-139.5)	123.5 (111.5-135.5)	122.5 (113.5-140)	120.3 (111.3-131)
DBP (mmHg)	71.8 (67-77)*	78 (71.5-84.5)*	78.5 (72.5-83.5)	78 (72-83.5)	76 (68.5-84)	77.5 (71.3-85.4)
Health Rating (EQ5D-VAS; 0-100)	80 (70-90)	75 (68-85)	80 (70-87)	75 (67-85)	71 (55-88)	75 (65-85)
MET-Weighted Leisure Activity (MET-hours/week)	8.0 (1.5-17.5)	11.8 (4-18.3)	5.3 (0.9-12.5)	8.8 (1.8-16.9)	5.8 (2.3-12.4)	7.9 (2.0-15.3)

Note: Slow gait at baseline could not be calculated for two participants: n=1 missing in GLB-SED and n=1 missing in delayed control.

*indicates within group p-value of <0.05 by gait speed at baseline.

Table 16. Physical Function Mean (SD) baseline and 6 months by Randomization assignment (n=263)

	Gait Speed (m/s)		Change	**Chair Stands (secs)**		Change	**SPPB (0-12)**		Change
	Baseline	6-M		Baseline	6-M		Baseline	6-M	
GLB-DPP n=89	1.06 (0.2)	1.11 (0.2)	+0.05 (0.17)	11.48 (3.3)	11.31 (3.3)	-0.17 (2.7)	10.79 (1.4)	10.98 (1.4)	**+0.19 (1.28)**
GLB-SED n=85	1.08 (0.2)	1.14 (0.2)	+0.06 (0.16)	11.32 (3.1)	10.77 (2.9)	**-0.55 (2.2)**	11.11 (1.4)	11.21 (1.3)	+0.11 (1.0)
Delayed Control n=89	1.08 (0.2)	1.12 (0.2)	+0.04 (0.18)	11.08 (3.1)	11.51 (3.2)	+0.44 (2.5)	11.10 (1.1)	10.91 (1.4)	-0.19 (1.2)

Note: Bolded values indicate significant mean change at 6 months between intervention group vs. delayed control at $p < 0.05$; Sample size has complete data for gait speed, chair stands and SPPB at baseline and 6 months. Positive changes for gait indicate better performance, negative changes for chair stands indicate better performance, and positive changes for SPPB indicate better performance.

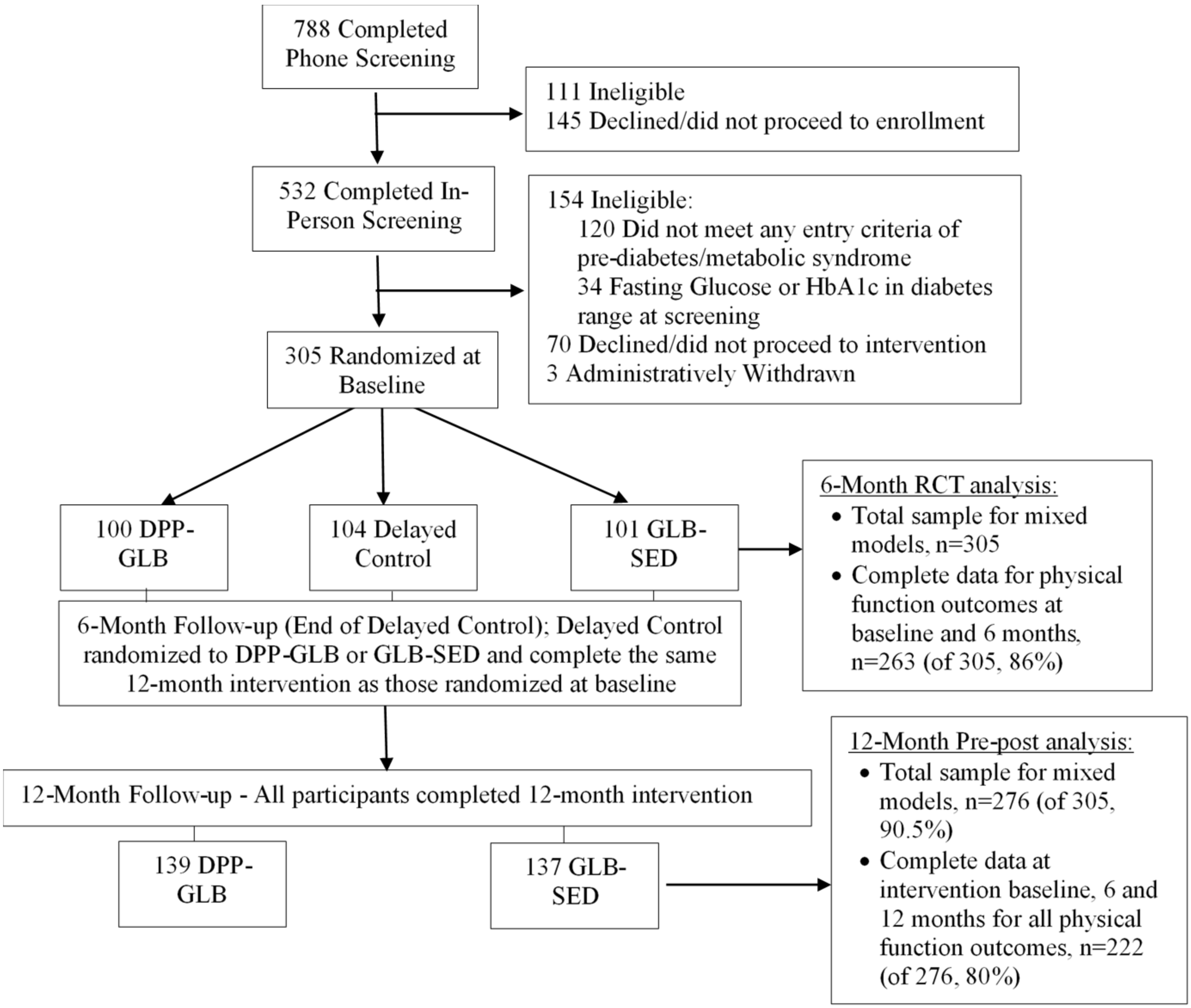

Figure 19. Flow Chart for GLB MOVES Participant Recruitment, Screening, Randomized Clinical Trial and Pre-Post Completion

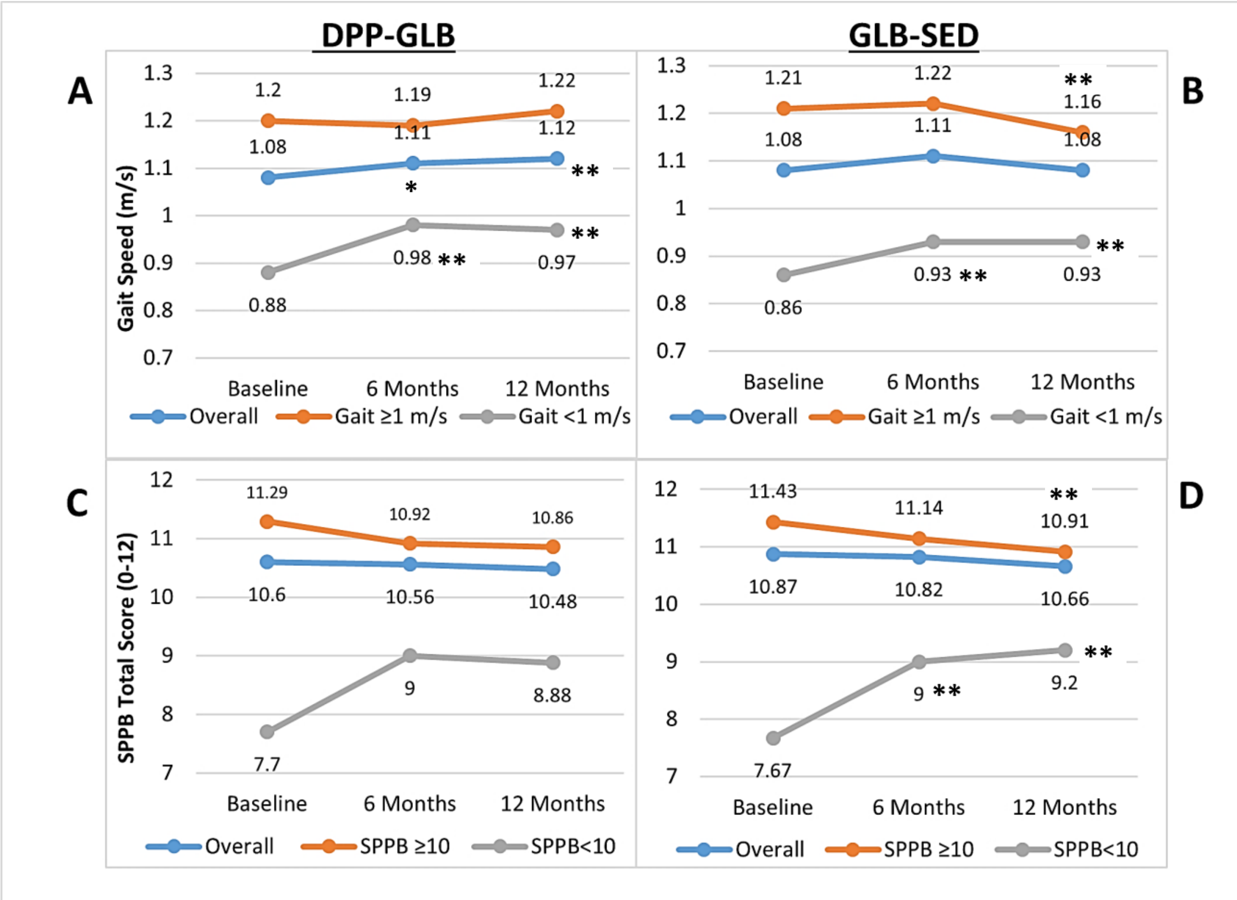

Figure 20. Pre-Post Analysis of Mean Gait Speed (m/s) and Short Physical Performance Battery Total Score (SPPB; 0-12) at Baseline, 6 Months, and 12 Months Overall and by Slow Gait at Baseline (≥1 vs. <1) or Low SPPB at Baseline (≥10 vs. <10) in GLB MOVES

***Figure 20a*: DPP-GLB Mean Pre-Post Gait Speed (m/s) Overall and by Slow Gait at Baseline (≥1 vs. <1 m/s); *Figure 20b*: GLB-SED Mean Pre-Post Gait Speed (m/s) Overall and by Slow Gait at Baseline (≥1 vs. <1 m/s); *Figure 20c*: DPP-GLB Mean Pre-Post SPPB Overall and by SPPB at Baseline (≥10 vs. <10); and *Figure 20d*: GLB-SED Mean Pre-Post SPPB Overall and by SPPB at Baseline (≥10 vs. <10). Paired t-tests for 6 months compared to baseline and 12 months compared to baseline used to determine statistical significance. *p<0.05, **p<0.01. Note: For Figures 20a and 20b, n=237 with complete data at all 3 time points (n=121 in DPP-GLB, n=116 in GLB-SED); n=89 (37.6%) participants with Gait speed <1m/s at baseline (n=47 in DPP-GLB, n=42 in GLB-SED). For Figures 20c and 20d, n=252 complete data at all 3 time points (n=131 in DPP-GLB, n=121 in GLB-SED); n=43 (17%) participants with SPPB <10 at baseline (n=25 in DPP-GLB, n=18 in GLB-SED).**

7.0 Aim 3 Manuscript: Metabolic Syndrome Trajectories and Objective Physical Performance in Mid-To-Early Late Life: The Study of Women's Health Across the Nation (SWAN)

Jenna M. Napoleone[1] MPH, Robert M. Boudreau[1] PhD, Brittney S. Lange-Maia[2] PhD, Samar R. El Khoudary[1] PhD, Kelly R. Ylitalo[3] PhD, Andrea M. Kriska[1] PhD, Carrie A. Karvonen-Gutierrez[4] PhD, Elsa S. Strotmeyer[1] PhD

[1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

[2]Department of Preventive Medicine, Rush University Medical Center, 1700 W. Van Buren St., Suite 470, Chicago, IL, 60612, USA.

[3]Department of Public Health, Robbins College of Health and Human Sciences, Baylor University, Waco, Texas, USA.

[4]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, USA.

7.1 Abstract

Background: Little is known about how adverse, midlife metabolic profiles impact future physical functioning. We hypothesized that a higher number of midlife metabolic syndrome (MetS) components are associated with poorer physical performance in early old age for multi-ethnic women. Methods: MetS status from 1996-2011 (8 visits) and objective physical performance in 2015/2016 (short physical performance battery (SPPB; 0-12), 40-foot walk (m/s), 4-meter gait speed (m/s), chair stands (sec), stair climb (sec)) were assessed in the Study of Women's Health Across the Nation (SWAN; n=1722; age 65.4±2.7 years; 26.9% African American, 10.1% Chinese, 9.8% Japanese, 5.5% Hispanic). Poisson latent class growth modeling identified MetS component trajectory groups: none (23.9%), 1=low-MetS (28.7%), 2=mid-MetS (30.9%), and ≥3=high-MetS (16.5%). Adjusted linear regression related MetS groups to physical performance outcomes. Results: High-MetS versus none had higher BMI, pain, financial strain, and lower physical activity and self-reported health ($p<0.0001$). Compared to White, African American and Hispanic women were more likely to be in the high-MetS groups and had worse physical functioning along with Chinese women (SPPB, chair stand, stair climb, and gait speed - not Hispanic). After adjustments, high-MetS versus none demonstrated significantly worse 40-ft walk (β:-0.08; 95% CI:-0.13, -0.03), gait speed (β:-0.09; 95% CI:-0.15, -0.02), SPPB (β:-0.79; 95% CI: -1.15, -0.44), and chair stands (β:0.69; 95% CI: 0.09, 1.28), but no difference in stair climb. Conclusions: Midlife MetS groups were related to poor physical performance in early old age multi-ethnic women. Midlife management of metabolic function may improve physical performance later in life.

Keywords: Longitudinal, Physical Functional Performance, Metabolic, Successful aging, Racial disparities

7.2 Introduction

Chronic diseases are the leading cause of disability in late life [202], though whether changes in metabolic function among midlife adults are predictive of physical performance declines in early old age is unknown. Metabolic syndrome (MetS) is clinically defined as having at least 3 of the following cardiometabolic risk factors including hypertension, abdominal obesity, impaired fasting glucose, low high-density lipoprotein cholesterol level and hypertriglyceridemia [130]. The relationship between MetS and chronic diseases including cardiovascular disease and diabetes, as well as premature mortality, has been well documented [203,204]. In the U.S., over one-third of adults have MetS [205] and the prevalence increases dramatically with age [144]. Non-Hispanic Black and Mexican American women are more likely to have MetS versus non-Hispanic White women [205], and over half of women and Hispanic adults 60 years and older are classified as having MetS [206]. Although MetS has been associated with loss of mobility among adults aged ≥70 years [207,208], and despite evidence that the midlife is a critical window for changes in MetS [209], the impact of midlife MetS changes on physical function in early old age among diverse populations is unclear.

Women have longer life expectancies than men, yet often live with more disability [184] and experience steeper declines in functioning throughout old age [210]. Additionally, midlife and older African American and Hispanic women experience greater functional limitations versus White women [211,212]. Importantly, whether similar functional disparities exist between Asian subgroups relative to White women is currently not known. The multi-ethnic Study of Women's Health Across the Nation (SWAN) examined self-reported function during and after the menopausal transition among White, African American, Chinese, Japanese and Hispanic women [13,213]. From 40-55 years, 10% of women reported some functional limitations and 9% reported substantial limitations [13] and by 56-66 years, 50% reported having some limitations [214]. Midlife women experience both onset and increases in physical function limitations, yet the highly dynamic patterns may make it an ideal time for risk factor prevention [214]. There are many biological mechanisms (e.g., chronic inflammatory processes [136]; hyperglycemia-related [207]; obesity-related due to pain, osteoarthritis, and reduced physical activity levels [138,139]) in which MetS contributes to decreases in muscle mass and strength. Additionally, midlife functional decline has been associated with greater risk for early old age disability [215,216]. Therefore, identifying targets for early intervention in midlife women is a priority to help tailor intervention strategies to delay the onset of disability.

Previous studies examining the contribution of MetS and its components on function have only included old age adults that identified as White of Black, used one assessment of MetS, and/or self-reported measures of mobility as a proxy of objective function with lack of objective physical performance outcomes [207,208]. We used a prospective design to assess how changes in the number of components of MetS across midlife are associated with objective physical performance among early old age women from five racial/ethnic groups (White, African American, Chinese, Hispanic, and Japanese). We hypothesize that 1) higher total components of MetS will be associated with worse physical performance in midlife to early old age women, and 2) women from some racial/ethnic groups will experience worse physical performance compared to White counterparts.

7.3 Methods

7.3.1 Study Design and Participants

The Study of Women's Health Across the Nation (SWAN) is an ongoing, multi-ethnic, multicenter, prospective community-based cohort study of the menopausal transition. A full description of the SWAN recruitment and methodology has been published previously [217]. Women were eligible for SWAN if they were aged 42-52 years at baseline (1996/97), had an intact uterus and at least one ovary, were premenopausal or early peri-menopausal (i.e., had at least one menstrual period in the past 3 months), and were not pregnant, lactating or breastfeeding. A total of 3,302 women were recruited from 7 sites across the U.S.: Boston, MA; Chicago, IL; Detroit, MI; Oakland, CA; Los Angeles, CA; Hudson County, NJ; and Pittsburgh, PA. All sites recruited White participants; additionally, each site recruited a non-White sample including African American (Boston, Chicago, Detroit, Pittsburgh), Japanese (Los Angeles), Hispanic (Newark), and Chinese (Oakland) women. Prior to visit 15, 149/3302=4.5% deaths occurred. Overall retention for those alive at the visit 15 follow-up exam in 2015/16 was 75% (2366/(3302-149)). Participants provided written informed consent before enrolling and at each follow-up visit and all protocols were approved from each site's Institutional Review Board.

Of those that completed a clinic visit at visit 15 (2091/2366=88%), 97% (2029/2091) were available to participate in the Physical Functioning Assessment. Of these participants, 307 did not complete any physical functioning repetitions (reasons for missing function data included 267 were unwilling/unable to come to the office, 5 refused and 35 had other reasons such as being out of state). Prior to visit 15, women were excluded for having less than 2 time points for MetS (n=232; collection occurred at baseline, visit 1, 3, 4, 5, 6, 7, and 12). A total of 1,722 women were included in this analytic sample from baseline (1996/97) to follow-up visit 15 (2015/16). Excluded women were more likely to be African American or Hispanic, have ≤high school diploma, fair/poor self-rated health, higher mean BMI, bodily pain, and physical difficulties (at visit 4 on the SF-36) (all $p < 0.05$).

7.3.2 Study Variables

7.3.2.1 Metabolic Syndrome

Using clinically accepted and current diagnostic criteria of MetS [218], the five MetS components were defined as: hypertriglyceridemia (fasting triglycerides ≥150 mg/dl), abdominal obesity (if Japanese/Chinese, obese if waist circumference ≥80 cm; otherwise, obese if waist circumference >88 cm), impaired fasting glucose (glucose ≥100 mg/dL fasting value), hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or taking any blood pressure medication), low high-density lipoprotein (<50 mg/dL). Fasting blood draws were taken in the morning and assayed for triglycerides, total cholesterol and high-density lipoprotein [219]. Standardized protocols were used to measure waist circumference and blood pressure. Blood pressure was measured with readings taken on the right arm, with the respondent seated and feet flat on the floor for at least 5 minutes prior to measurement. Two sequential blood pressure values were completed, with a minimum two-minute rest period between measures. Respondents had not smoked or consumed any caffeinated beverage within 30 minutes of blood pressure measurement. Waist circumference at the umbilicus was measured by a trained technician with participants wearing nonrestrictive undergarments. The present analysis summed total MetS components (range 0-5) with 5 being the most severe.

7.3.2.2 Physical Performance

During the visit 15 exam (2015/16), SWAN participants completed physical performance tasks following standardized protocols conducted by trained clinic staff. The tests included the timed 40-ft walk, timed stair climb test and the Short Physical Performance Battery (SPPB; includes standing balance, timed 4-m gait speed, and timed 5-repeated chair stand).

40-foot walk: The walking course was set up on a level floor with two tape markers indicating the start and end points (located 40-ft apart). Participants were instructed to complete the walk in a "comfortable but steady, brisk pace as in the manner of showing purpose, but not being late." Timing was stopped when both feet crossed the end line. If necessary, use of a walking assistive device was permitted. The 40-ft walk protocol was conducted twice and the faster time (meters per second) was used in analysis.

Stair Climb Test: The timed stair climb was comprised of four standard stairs of steps that are 10 inches deep and 6 inches high. This measure captured several components of physical function including balance, strength, and endurance. Participants ascended and descended the stairs for three consecutive cycles, using hand rail for assistance if necessary [220]. Total time (seconds) taken to complete the three consecutive cycles was used for analysis. A slower time in seconds indicates worse time to complete the stair climb [221].

4-meter gait speed: The course was set-up on a level floor with markers at the start and stop point, located 4-meters apart [222]. Participants were instructed to walk at their usual pace and timing was stopped when the first foot completely crossed the end line, with use of assistive devices allowed if needed. The 4-meter walk was completed twice, and the faster time (meters/second) was used in analysis.

Repeated chair stands: A standard height chair or bench with a back was placed on a level floor [222]. While seated, women were asked to sit and place their arms across their chest and stand without using their arms. The stopwatch was started when the participant visually responded and ended when the participant was standing in a fully upright position. Time (seconds) taken to complete five consecutive repetitions was used in analysis.

Short Physical Performance Battery (SPPB): The standard SPPB protocol consisted of three physical performance measures: 4-m gait speed at usual pace, 5-repeated chair stands, and a series of balance tests (side-by-side, semi-tandem, tandem, and one-foot stands, each held for 10 seconds). This measure has well-known validity and reliability and was originally implemented in the Established Populations for the Epidemiologic Study of the Elderly (EPESE) study population [222]. For data analysis, the traditional scoring cutoffs for the balance component were used, but with SWAN-specific time quartiles to score gait speed and chair stand components [223]. The total SPPB score ranges from 0 (worst performance) to 12 (best performance) and the continuous score was used.

7.3.2.3 Covariates

All covariates of interest were measured at the same time point as the physical performance measures (visit 15; 2015/16) unless otherwise indicated. They included demographic characteristics and health conditions associated with cardiovascular disease and/or physical performance. Self-reported sociodemographic variables included age (years); education assessed at baseline (≤high school, some college, ≥college degree); self-reported difficulty paying for basics (very hard/somewhat hard versus not very hard representing financial difficulty); and marital status (single/never married, married/living as married, separate/widowed/divorced). Health indices included: self-rated health status (excellent/very good, good, or fair/poor), objectively measured

BMI (kg/m^2), menopausal status (collected at each annual exam based on bleeding patterns), current hormone use and hysterectomy and oophorectomy history (natural post-menopausal, post-menopausal by bilaterial salpingo-oophorectomy, or pre- or early/late perimenopausal), hormone user (ever use of hormone therapy), presence of depressive symptoms (≥16 on Center for Epidemiological Studies Depression (CES-D) scale) [224], physician-diagnosed self-reported comorbidities (osteoarthritis, heart attack, and/or stroke). Although different designations of race/ethnicity may be used currently, our recruitment for this longitudinal study was done in 1996/97. Therefore, race/ethnicity was defined during a screening interview prior to the baseline examination from participants' response to the question, "How would you describe your primary racial or ethnic group?" The response categories included: black/African American; Puerto Rican/Dominican/Central American/Cuban or Cuban American/South American/Spanish or other Hispanic (all categorized as Hispanic), Chinese/Chinese American; Japanese/Japanese American, and Caucasian/white Non-Hispanic (referent group). Participants who identified as Mexican/Mexican American, Mixed, or Other were not included in the cohort [211]. Bodily pain severity in the past four weeks and self-reported physical function (assessed at visit 4 and 15) were estimated from the Short Form Health Survey (SF-36; score 0-100) [225,226]. Self-reported physical activity was assessed using the Kaiser Permanente Activity Survey, a self-administered valid and reliable questionnaire [227]. This questionnaire contains 38 items about physical activity patterns within the past year and was modified from the Baecke physical activity questionnaire [228]. Three domains of physical activity were evaluated for frequency, duration and relative intensity: sports/exercise, active living and household/caregiving. Total physical activity scores summing the three activity indexes can range from 3-15, with higher values indicating greater physical activity participation. Smoking status at visit 15 was defined as current smoking (yes/no). Clinical site was also included in analyses based on potential site differences confounding the main relationships of interest.

7.3.3 Statistical Methods

Baseline characteristics for those included vs. excluded in the analysis were compared using two sample t-tests or ANOVA and chi-square tests for continuous and categorical variables, respectively. Variable distributions were assessed for normality. Analysis of variance was used to describe racial/ethnic differences across each objective physical performance measure (40-ft walk, 4-m gait speed, 5-repeated chair stand, SPPB, and stair climb).

Latent class group modeling was used to identify subgroups of women following similar patterns of trajectories in counts of MetS components in midlife. Models were compared based on Bayesian Information Criteria (BIC) and varying degrees of polynomial trends for each group [229]. After the trajectory groups were determined, women were assigned to the group that reflected their highest probability [230]. Trajectory groups were created from total number of MetS components across the midlife period. Information for MetS trajectories was available from baseline (1996-97) and visits 1 (1997-99), 3 (1999-2001), 4 (2000-2002), 5 (2001-2003), 6 (2002-2004), 7 (2003-2005), and 12 (2009-2011). Once MetS component trajectory groups based on patterns of MetS during midlife were determined, groups were entered into separate models as predictors for physical function outcomes. Means and standard deviations and frequencies and percentages were used to describe the analytic sample by MetS groups. Differences by MetS groups in demographic and health characteristics, MetS individual components (visit 12) and physical performance outcomes were examined using analysis of variance for continuous variables and chi-square for categorical variables.

Linear regression analyses were used to model each continuous objective physical performance measure in early old age as a function of the MetS groups throughout midlife. The referent group was designated as the healthiest trajectory: MetS=none. Unadjusted linear regression models were fit followed by minimally adjusted models that included age, race, site, difficulty paying for basics, self-rated health and BMI. Then, fully adjusted models added additional health risk factors and comorbidities including bodily pain, self-reported physical activity, current smoking status, hormone use, menopause status, osteoarthritis, and depressive symptoms to the above list of covariates. Covariates were determined based on prior literature and associations with the physical performance outcomes at $p<0.10$ with collinearity of covariates assessed. In each model, only covariates that reached significance of $p<0.10$ were retained. Because some racial/ethnic groups were enrolled at only one site so race and site may be collinear, models with age and site were compared to models with age and race. Model assumptions and goodness of fit tests were assessed to determine the best predictive model. All analyses were conducted using 2-sided hypothesis testing and SASv9.4 software (SAS Institute, Inc., Cary, North Carolina).

We conducted sensitivity analyses to ensure the robustness of the findings by adjusting for baseline self-reported physical function at the first possible time point (visit 4), excluding women who reported moderate or substantial functional limitation (n=589 excluded; substantial limitation: < 50 (n=140, 8.8%); moderate limitation: 51-85 (n=449, 28.2%); no limitations in physical function: 86-100 (n=1001, 63%)) based on the SF-36 [13], and adjusting for comorbidities (e.g., cumulative self-reported stroke or heart attack from baseline until visit 15).

7.4 Results

Four MetS groups were determined from the latent class growth model with patterns reflecting the number of MetS components: none (16.5%), low-MetS (1 component; 30.9%), mid-MetS (2 components; 28.7%), and high-MetS (≥3 components; 23.9%) (Figure 21). The percent probability of women being assigned to none, low-MetS, mid-MetS and high-MetS was >80%. On examination of the trajectories, we defined MetS groups based on the number of components rather than change in the number of components over time since the number of MetS components in each group remained relatively stable with only slight average increases over time.

Characteristics of participants by MetS groups are shown in Table 17. Compared to White women, Hispanic and African American women were more likely to be in higher MetS groups. White, Chinese and Japanese women were more likely to be in the none-MetS group. Demographic and health characteristics significantly differed by MetS group, with the high-MetS group exhibiting the poorest health. The high-MetS group had more class 2 obesity (34.9 kg/m^2), fair/poor self-reported health, current smoking, bodily pain, osteoarthritis, and lower self-reported physical activity, lower education and had somewhat/very hard time paying for basics. Previously self-reported physical function was lower in the high-MetS vs. none (63.0±28.2 vs. 86.9±16.9; $p<0.0001$). Additionally, the mid-MetS group had higher BMI, worse self-reported overall health, more osteoarthritis, more bodily pain, and lower physical activity vs. none and low-MetS groups. Low-MetS tended to have more prevalent hypertension and abdominal obesity. With each progressive MetS group, higher prevalence was found in each of the individual MetS components (Table 17).

Physical performance outcomes were significantly different by racial/ethnic groups (all $p<0.0001$; Table 18). Japanese women had the highest function on gait speed, SPPB, chair stand

and stair climb versus all other racial/ethnic groups. African American, Hispanic and Chinese women had worse physical functioning vs. White women on the SPPB (African American: 14.5%, Hispanic: 21.3%, Chinese: 8.2% worse, respectively), chair stand (13.1%, 19.8%, 2.1% worse, respectively) and stair climb (13.5%, 31.7%, 4.6% worse, respectively). African American and Chinese women had a 14% and 16%, respectively, slower gait speed vs. White women.

The percent unadjusted mean difference in all physical performance outcomes was worse with each higher MetS group vs. none (Figure 22) indicating a possible dose-response relationship (all outcomes: p-value for trend <0.0001). Women in the high-MetS group vs. none had: 20.1% slower (*worse*) 40-ft walk time, 22.6% slower 4-m gait speed, 28.9% slower repeated chair, 35% higher (*worse*) stair climb. In addition, women in the high-MetS and mid-MetS groups had a 26.6% lower and 16.1% lower (*worse*) total SPPB score respectively vs. none. Finally, the mid-MetS group vs. none women had 13.2% slower (*worse*) gait speed.

In unadjusted models, the magnitude of worsening for each physical performance outcome relative to the none-MetS group approximately doubled with each MetS group (all p-value for trend <0.0001; Table 19). In fully-adjusted multivariable models (Table 19), the high-MetS group had significantly consistently worse physical performance on the 40-ft walk, 4-m gait speed, SPPB, and chair stand vs. none (β=-0.08, β=-0.09, β=-0.79, β=0.69, respectively). The high-MetS group had slower total stair climb vs. none although this was not statistically significant (β=1.10, 95% CI: -0.04, 2.23). The mid-MetS group also had poorer SPPB performance and chair stand time vs. none, yet these comparisons did not reach statistical significance. For all outcomes, the strength of association increased with each additional MetS component in a gradient pattern.

When excluding women with previous moderate/substantial physical limitations, results remained consistent in final models. In the sensitivity analysis adjusting for previous self-reported physical function, β coefficients were largely consistent and all groups remained statistically significant with high-MetS becoming significant for stair climb (β=1.30; 95% CI: 0.15, 2.45; $p<0.05$). In addition, results were consistent after adjusting for comorbid conditions (i.e., stroke and heart attack) throughout the study period (baseline through visit 15). Finally, to ensure relationships with race/ethnicity were not site specific (e.g., sites recruiting Hispanic and Japanese women did not perform the 40-ft walk speed), we created models with race only versus site only with estimates also consistent to the fully adjusted model with no changes in significance except the mid-MetS group reaching significance at $p<0.05$ for SPPB in site only and race only models.

7.5 Discussion

Midlife women in the high-MetS group, those classified as having clinical MetS (≥ 3 components), were more likely to have worse objective physical performance in early old age across all outcomes (i.e., 40-ft walk, 4-m gait speed, SPPB, 5-repeated chair stand, and stair climb performance) versus women with no MetS components. Women in the mid-MetS group (approximately 2 components), typically not considered a clinical syndrome [218], also demonstrated worse early old age function with respect to the SPPB total score and the repeated chair stand, though these results were not statistically significant after adjustments. In addition, after excluding women with moderate or substantial self-reported physical limitations, the main results were consistent. Importantly, African American and Hispanic women were more likely to be in the higher MetS groups. Our findings contribute to the understanding of preventable and treatable factors in midlife adults, particularly in Black and Hispanic racial/ethnic populations, known to have higher late-life mobility disability [205,211].

Even prior to clinical classification of MetS, metabolic changes throughout midlife likely have important implications on early old age physical performance among women. Our results indicate that early old age physical performance is worse in African American, Hispanic and Chinese women versus White women and suggest that this performance for African American and Hispanic women may be associated with their generally higher earlier midlife numbers of MetS components. Although African American and Hispanic women have more late life disability vs. White [205], less is known regarding prevalence of disability among U.S. Asian subgroups (i.e., Chinese and Japanese). Previous work in SWAN found that midlife Chinese women experienced an apparent disparity in a composite physical performance decile score derived from grip strength, gait speed and chair stand than White women, but Japanese women did not [211]. Our current SWAN effort was consistent with these previous findings, that Chinese women had worse SPPB, gait speed, chair stand and stair climb performance than White women. Future research should include more focus on differences among race/ethnic groups to further understand early risk factors for physical function and disability across these populations.

Evidence suggests that the onset of disability begins in midlife while women have decades of life expectancy [154]. Worse physical function in old age predicts several future poor health outcomes (e.g., lower quality of life and increased mortality rates) [16,20], which are more prevalent in African American and Hispanic women. Life course factors likely contribute to old age physical function and should be considered particularly among African American and Hispanic older adults [231]. Midlife high-MetS group had significantly worse objective physical performance in early old age except stair climb. Additionally, we observed that midlife women with only 2 components of MetS had worse early old age physical performance, though the relationships were not as consistent. Therefore, by the time adults are clinically diagnosed with MetS, functional changes have already occurred in midlife and prevention efforts for disability should be initiated at an earlier timepoint, particularly in racial/ethnic minority women with MetS.

Measuring function among midlife adults (especially high-risk midlife adults, e.g., women, racial/ethnic minorities, adults with MetS components) in clinical settings using simple, non-invasive tests such as the SPPB could be a strategy to identify early signs of physical limitations and help maintain independence with aging [151]. Certain functional tests such as SPPB or gait speed (37) that are able to be performed quickly could be used as a “sixth vital sign” [152,153] for midlife women with cardiometabolic-related risk factors. Importantly, it is currently unknown which test is most appropriate to assess early functional decline in midlife [151]. We found stronger associations with MetS for the SPPB, an inexpensive and feasible test that could be implemented in clinical settings for midlife women [151,232]. Several studies of older adults have found that diabetes is related to worse SPPB score [233], gait speed, and chair stand [234] and we showed consistent relationships among women with MetS for these outcomes. Therefore, determining the appropriate physical performance test for midlife women with MetS is important to assess functional decline and initiate early prevention efforts.

Common midlife cardiometabolic health conditions, especially diabetes [235], obesity [236] and MetS [207], may impact age-related outcomes such as physical function and disability [237]. The highest prevalence of severe obesity is among adults 40-59 years, women (9.2% higher rates vs. men) and specifically non-Hispanic Black women (56.9% vs. 39.8% among non-Hispanic White women) [34]. Almost 40% of midlife adults are classified as having MetS and this high prevalence increases with age [144]. Previous research showed that SWAN women with worse self-reported physical function were more likely to have MetS and almost 50% aged 55-66 years self-reported having functional limitations [214,238]. Therefore, slower gait speed may be a marker for early cardiovascular disease risk [239]. Although the relationship between function and cardiometabolic-related outcomes are likely bidirectional, our work suggests that MetS evaluated longitudinally over midlife contributes to function decline and the timing of the onset of limitations in early old age [213].

Our findings are consistent with previous studies that were either cross-sectional in nature [208] or used self-reported measures of physical function [148,149], and showed MetS was related to functional impairment (i.e., Rosow and Breslau scale, and limitations in instrumental/basic activities of daily living). However, these could not determine onset or changes in objective physical function. One study of older diverse adults (age=73.6±2.9 years; 52.5% women; 41.3% Black) found MetS increased risk of incident mobility limitations, defined as two consecutive self-reports of inability to climb 10 steps without rest and/or walk ¼ mile [207]. We observed consistent findings, though with objective performance measures instead of self-report questions. While previous cohort studies used one measurement of MetS at baseline in late-life [240,241], our study demonstrated that MetS (2 or ≥3 components) measured longitudinally during midlife was an independent predictor of worse physical performance after adjusting for lifestyle and other comorbid conditions.

Midlife MetS counts of 2 (pre-clinical MetS counts) or ≥3 (MetS clinical syndrome) should be viewed as a potential risk factor for future functional decline in old age. Abdominal obesity was the most frequent component of MetS with 86% of SWAN women having abdominal obesity. Notably, among SWAN women with only obesity at study enrollment, 30% progressed to pre-clinical MetS counts (2 components) and 15% developed the clinical syndrome (≥3 components) [209]. Our results indicate that in mid-MetS and high-MetS groups, there were not one or two components that appeared to be most common, but rather all individual components were prevalent in midlife. Additionally, prevalence for each MetS component increased with each progressive

MetS group. Thus, midlife women experience changes in preventable/treatable risk factors, such as blood pressure, lipid, and glucose control that are related to developing MetS. Therefore, midlife is a critical point for implementing preventive strategies aimed at adopting healthy behaviors for risk reduction of future MetS.

The current study had several limitations. Only women during midlife to early old age were assessed so results may not be generalizable to men or other ages. In addition, we did not examine how each individual component of MetS during midlife impacts future functional changes. Understanding which MetS components are associated with functional changes could guide intervention efforts and is an important future direction of this research. Also, not all sites measured 40-ft walk and stair climb which may have attenuated the findings slightly due to lower numbers of women. However, many notable strengths of our study exist. To our knowledge this is the first assessment of MetS in midlife and early old age objective physical performance in a multi-ethnic population of women. Since our recruitment for this longitudinal study occurred in 1996/97, language used for racial/ethnic groups may differ from preferred language currently. Our study had 26.9% African American and 5.5% Hispanic women. Women are at higher risk for old age disability than men, with African American and Hispanic women at the highest risk among women [211]. The multi-ethnic composition of the sample allowed us to identify important racial/ethnic disparities among midlife MetS component patterns and physical performance. Women excluded due to incomplete in-person measures were more likely to be African American and Hispanic with poorer health status; therefore, the true difference may be larger if these women were included. It also may be important to investigate the impact of MetS component groups within specific racial/ethnic groups at greater risk for early functional decline. A longitudinal design enabled us to establish temporality between MetS and functional outcomes. The importance of onset of function limitation is overlooked in many studies of older adults, in which temporality cannot be determined and in which life course factors in disability are understudied. Further, we examined several measures of objective physical performance, which may capture early subclinical changes versus self-report, allowing us to better understand which measures are most sensitive to change in early old age.

Given the potential clinical utility of our findings, future studies should examine the relationship of individual MetS components over time in midlife adults with functional decline and by racial/ethnic subgroups. Both initial prevention of comorbidity and slowing comorbidity severity might reduce the number of years living with disability in late life. Focusing efforts on the preliminary stages of the disablement process will allow clinical care and preventive efforts to be tailored for midlife women at high-risk for future functional decline with the goal of compressing years of morbidity, delaying the onset of old age disability and extending independence with aging.

Conflicts of interest: None.

Author Contributions:

J.M.N, E.S.S and R.M.B conceived/designed the manuscript; J.M.N performed statistical analyses; J.M.N, E.S.S, R.M.B, and S.R.E interpreted the data; and all coauthors contributed to and revised the manuscript for important intellectual content and provided final approval.

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Chris Gallagher, Former Chair

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Table Captions

Table 17. Characteristics of Study of Women's Health Across the Nation (SWAN) participants at visit 15 (when the physical performance measures were assessed, 2015/16) by metabolic syndrome groups. Values are N (%) unless otherwise noted.

Table 18. Mean and standard deviation of physical performance measures by self-identified racial/ethnic group.

Table 19. Beta coefficients and 95% confidence intervals from multivariable linear regression models of metabolic syndrome component groups (1996-2011) and objective physical performance outcomes (2015/16). Unadjusted and fully adjusted models (all significant predictors across outcomes: age, BMI, site, overall health, bodily pain, difficulty paying for basics, physical activity, current smoking status, hormone use, and arthritis) are presented in 1772 Study of Women's Health Across the Nation (SWAN) participants.

Table 17. Characteristics of Study of Women's Health Across the Nation (SWAN) participants at visit 15 (when physical performance measures were assessed, 2015/16) by metabolic syndrome component group

	Metabolic Syndrome Component Groups				
Participant characteristics (N=1,722)	None N=412 (23.9%)	Low-MetS N=494 (28.7%)	Mid-MetS N=532 (30.9%)	High-MetS N=284 (16.5%)	*p* Value
Demographic Characteristics					
Age, mean ± SD	65.2 ± 2.6	65.4 ± 2.6	65.8 ± 2.7	65.7 ± 2.8	.003
Race/ethnicity					<.0001
White	247 (60.0%)	246 (49.8%)	214 (40.2%)	114 (40.1%)	
African American	35 (8.5%)	121 (24.5%)	198 (37.2%)	109 (38.4%)	
Hispanic	10 (2.4%)	24 (4.9%)	36 (6.8%)	25 (8.8%)	
Chinese	61 (14.8%)	50 (10.1%)	43 (8.1%)	20 (7.0%)	
Japanese	59 (14.3%)	53 (10.7%)	41 (7.7%)	16 (5.6%)	
Education					<.0001
≤ High school	64 (15.7%)	92 (18.7%)	116 (22.0%)	70 (24.8%)	
Some college	94 (23.0%)	158 (32.2%)	180 (34.2%)	100 (35.5%)	
≥ College degree	250 (61.3%)	241 (49.1%)	231 (43.8%)	112 (39.7%)	
Marital status					<.0001
Single/never married	48 (11.7%)	49 (10.0%)	65 (12.2%)	52 (18.3%)	
Married/living as married	277 (67.2%)	305 (62.0%)	280 (52.6%)	126 (44.4%)	
Separate/widowed/divorced	87 (21.1%)	138 (28.1%)	187 (35.2%)	106 (37.3%)	
Difficulty paying for basics, somewhat/very hard	52 (12.9%)	92 (19.1%)	130 (25.0%)	104 (38.2%)	<.0001
Health Characteristics					
BMI, mean ± SD	23.6 ± 3.9	27.2 ± 5.1	32.4 ± 6.8	34.9 ± 6.7	<.0001
Menopause status					.007
Natural post	386 (93.7%)	455 (92.1%)	482 (90.8%)	244 (85.9%)	
Post by BSO	26 (6.3%)	39 (7.9%)	48 (9.0%)	40 (14.1%)	
Pre/early/late peri	0	0	1 (0.2%)	0	
Hormone user, ever	198 (48.1%)	248 (50.2%)	251 (47.2%)	143 (50.4%)	.73
Current Smoking	13 (3.2%)	37 (7.6%)	36 (6.8%)	23 (8.2%)	0.02
Overall Health					<.0001
Excellent/very good	282 (69.3%)	268 (54.9%)	204 (38.6%)	69 (24.7%)	
Good	92 (22.6%)	159 (32.6%)	28 (43.2%)	118 (42.3%)	
Fair/poor	33 (8.1%)	61 (12.5%)	96 (18.2%)	92 (33.0%)	
Depression, CESD score ≥ 16	40 (9.71%)	59 (11.9%)	67 (12.6%)	50 (17.6%)	0.02
SF-36 Bodily Pain (0-100), mean ± SD	75.9 ± 19.8	69.7 ± 21.6	64.5 ± 23.3	59.5 ± 24.9	<.0001
KPAS Physical Activity Score, mean ± SD	8.31 ± 1.72	7.70 ± 1.78	7.17 ± 1.72	6.66 ± 1.80	<.0001
Osteoarthritis	103 (25.3%)	170 (34.6%)	224 (42.4%)	145 (51.2%)	<.0001
Metabolic Syndrome Components					
Hypertension	52 (13.0%)	214 (45.7%)	347 (69.1%)	241 (86.7%)	<.0001
Abdominal Obesity	32 (8.0%)	194 (42.1%)	406 (82.0%)	261 (96.3%)	<.0001
Impaired fasting glucose	19 (4.9%)	69 (15.3%)	191 (39.2%)	211 (75.9%)	<.0001
Low high-density lipoprotein	6 (1.6%)	51 (11.3%)	148 (30.64)	160 (58.2%)	<.0001
Hypertriglyceridemia	21 (5.4%)	60 (13.36%)	102 (21.2%)	140 (51.7%)	<.0001
Physical Function Measures					
SF-36 Physical Function score (0-100), mean ± SD	86.9 ± 16.9	80.7 ± 20.9	71.7 ± 25.0	63.0 ± 28.2	<.0001
40 ft gait speed (m/s), mean ± SD	1.49 ± 0.25	1.41 ± 0.25	1.31 ± 0.27	1.19 ± 0.24	<.0001

4 m gait speed (m/s), mean ± SD	1.06 ± 0.37	1.00 ± 0.33	0.92 ± 0.42	0.82 ± 0.27	<.0001
SPPB (0-12), mean ± SD	9.71 ± 1.84	9.10 ± 1.98	8.15 ± 2.20	7.13 ± 2.45	<.0001
5-Repeated chair stand (sec), mean ± SD	9.87 ± 2.80	10.73 ± 3.29	11.55 ± 3.56	12.72 ± 3.60	<.0001
Total stair climb time (sec), mean ± SD	18.89 ± 3.77	20.17 ± 4.56	22.83 ± 7.31	25.51 ± 8.20	<.0001

Note. Continuous variables are represented as mean ± standard deviation (SD) and categorical variables are represented as frequency (percentage). Metabolic syndrome components are from visit 12. MetS= Metabolic syndrome; BSO= Bilateral salpingo-oophorectomy; CESD=Center for Epidemiologic Studies Depression Scale; BMI=Body Mass Index (kg/m^2); KPAS= Kaiser Physical Activity Questionnaire.

Table 18. Mean and standard deviation of physical performance measures by self-identified racial/ethnic group

	Racial/Ethnic Groups					
mean ± SD sample size	White	African American	Hispanic	Chinese	Japanese	p-value
40-ft walk speed, m/s	1.39 ± 0.26 n=657	1.27 ± 0.27 n=439	-	1.46 ± 0.28 n=173	-	<.0001
4-m gait speed, m/s	1.00 ± 0.34 n=798	0.86 ± 0.19 n=445	1.05 ±1.11 n=80	0.84 ±0.16 n=173	1.13 ± 0.18 n=164	<.0001
SPPB, 0-12	9.02 ± 2.07 n=805	7.71 ± 2.36 n=455	7.10 ± 2.06 n=84	8.28 ± 1.93 n=174	10.38 ± 1.75 n=168	<.0001
5-Repeated chair stand, sec	10.70 ± 2.99 n=787	12.10 ± 3.63 n=423	12.82 ± 6.36 n=83	10.92 ±2.88 n=172	9.61 ± 2.33 n=167	<.0001
Total stair climb time, sec	20.61 ± 5.48 n=626	23.40 ± 8.10 n=332	27.15 ± 7.00 n=76	21.56 ±6.00 n=171	18.80 ± 3.40 n=165	<.0001

Note. Sites recruiting Hispanic and Japanese women did not perform the 40-ft walk speed. SPPB=Short Physical Performance Battery; SD=standard deviation

Table 19. β coefficients and 95% confidence intervals from univariate and multivariable linear regression models of metabolic syndrome component groups (1996-2011) and objective physical performance outcomes (2015/16)

	40-ft walk speed, m/s	4-m gait speed, m/s	SPPB, 0-12	5-Repeated chair stand, sec	Total stair climb time, sec
Model 1:					
High-MetS	-0.30 (-0.34, -0.25)***	-0.24 (-0.29, -0.18)***	-2.58 (-2.90, -2.26)***	2.85 (2.33, 3.37)***	6.61 (5.58, 7.65)***
Mid-MetS	-0.18 (-0.21, -0.14)***	-0.13 (-0.18, -0.08)***	-1.56 (-1.84, -1.29)***	1.68 (1.24, 2.11)***	3.94 (3.06, 4.82)***
Low-MetS	-0.07 (-0.11, -0.03)**	-0.05 (-0.10, -0.00)*	-0.61 (-0.88, -0.33)***	0.86 (0.41, 1.30)***	1.27 (0.39, 2.16)**
None	REF	REF	REF	REF	REF
Model 2:					
High-MetS	-0.08 (-0.13, -0.03)**	-0.09 (-0.15, -0.02)**	-0.79 (-1.15, -0.44)***	0.69 (0.09, 1.28)*	1.10 (-0.04, 2.23)
Mid-MetS	-0.01 (-0.06, 0.03)	-0.01 (-0.06, 0.04)	-0.26 (-0.55, 0.02)	0.17 (-0.31, 0.65)	-0.17 (-1.10, 0.75)
Low-MetS	0.02 (-0.02, 0.06)	0.007 (-0.04, 0.05)	0.01 (-0.24, 0.27)	0.00 (-0.42, 0.43)	-0.54 (-1.36, 0.28)
None	REF	REF	REF	REF	REF

Note. β estimates (per unit, e.g. m/s) and 95% confidence intervals are presented above.

MetS=Metabolic Syndrome; SPPB=Short Physical Performance Battery; KPAS= Kaiser Physical Activity Questionnaire.

Model 1= Unadjusted model.

Model 2= Fully adjusted model: age, BMI (kg/m^2), race/ethnicity, site, overall health, bodily pain, difficulty paying for basics, KPAS physical activity, current smoking status, hormone use, and osteoarthritis.

*p < 0.05; **p < 0.01; ***p < 0.0001

Figure Captions

Figure 1. Metabolic syndrome (MetS) component groups by study visits from 1996-2011 based on a Poisson latent class growth model. Four MetS groups were determined with patterns reflecting the number of MetS components: none (16.5%), low-MetS (1 component; 30.9%), mid-MetS (2 components; 28.7%), and high-MetS (3 or more components; 23.9%)

Figure 2. Percent difference in mean objective physical performance outcomes by metabolic syndrome component group. % difference calculated as [(mean MetS group (High-MetS, Mid-MetS, Low-MetS) – mean None-MetS (referent))/ mean None-MetS group]*100; negative values indicate lower means for low-/mid-/high-MetS group vs. none (e.g., Participants in high-MetS group took 20% longer to complete the 40-ft walk (m/s) vs. those with no MetS components); MetS=Metabolic syndrome; * indicates p-value for trend <0.0001 for all physical performance outcomes.

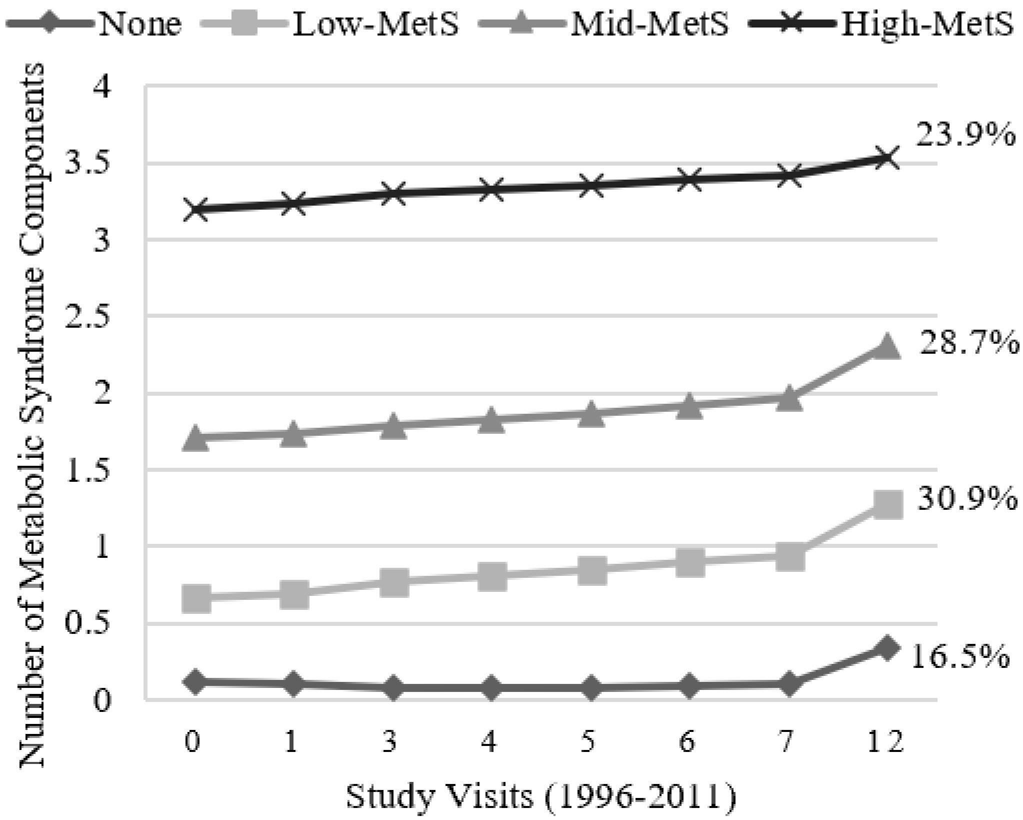

Figure 21.Metabolic syndrome (MetS) component groups by study visits from 1996-2011 based on a Poisson latent class growth model

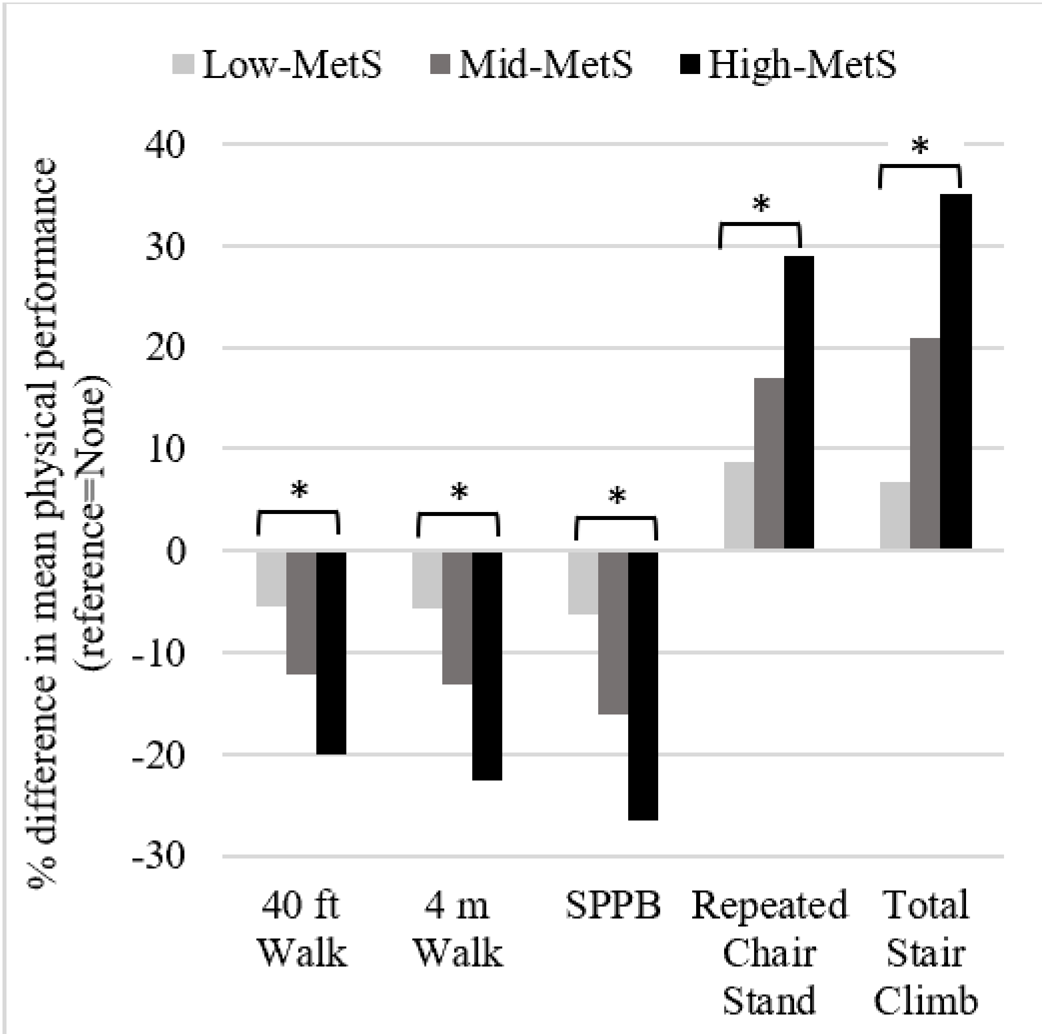

Figure 22. Percent difference in mean objective physical performance outcomes by metabolic syndrome component group

8.0 Discussion

8.1 Summary and Implications of Findings

The overall objective of this dissertation sought to examine how a combination of modifiable cardiometabolic-related risk factors and lifestyle interventions impact physical performance among mid-to-early late life adults, as these associations may be critical to preventing the onset of developing disability in older adults. Our results established that modifiable risk factors such as weight loss/weight maintenance, physical activity, sedentary behavior, and metabolic syndrome are related to physical function outcomes in midlife and early late life. Early modifiable risk factors for physical functioning in older adults are critical for early prevention of disability.[26–28] In contrast to our results, few previous studies have examined early modifiable risk factors in mid-life and early late life and have not related these factors to multiple measures of physical function. Importantly, our current research utilized both longitudinal cohort data spanning almost 20 years and two real-world randomized clinical trial lifestyle intervention studies, both including mid-to-early late life adults with overweight/obesity, prediabetes and/or the metabolic syndrome. Ultimately, this dissertation utilized diverse and novel study populations and innovative methodological research designs to inform disability prevention efforts and provide evidence-based suggestions for how to individualize prevention-oriented community-based interventions to have large-scale public health impact.

Our results extend the success of the GLB lifestyle intervention, based on the highly effective DPP which was the first lifestyle intervention with weight loss and physical activity goals shown to prevent type 2 diabetes and metabolic syndrome in a diverse cohort of adults,[65] to indicate for the *first time that maintenance session attendance during months 7-12 improves meeting the 5% weight loss goal at 12 months for the general adult population and in Medicare-eligible adults, among mid-to-early late life adults at high-risk of developing type 2 diabetes*. One version of the community translation of this work, the CDC-approved, CMS-reimbursable[91,166] DPP-GLB lifestyle intervention program is nationally utilized and lasts 12 months. It consists of 16 core sessions that comprise the intensive contact phase during the first 6 months, followed by 6 monthly maintenance sessions (months 7 through 12). Given the effectiveness of DPP-based community lifestyle interventions (including our DPP-GLB),[159–164] CDC began delivering the National Diabetes Prevention Program (National DPP)[165] and monitoring program delivery based on weight change and session attendance. In 2018, the Centers for Medicare and Medicaid Services (CMS) began reimbursing CDC-recognized programs for delivery to all fee-for-service beneficiaries aged 65 years and older with prediabetes, which makes the DPP-based lifestyle intervention the first government-reimbursed program of its kind. We showed that both attending ≥4 maintenance sessions and meeting the 6-month weight loss goal increased the odds of meeting the 12-month 5% weight loss goal, which is the CMS reimbursement requirement. Our findings are in line with past research that showed that more frequent contact facilitates successful behavioral change among participants of a lifestyle intervention program.[173,174] However, a caveat to this finding in our study was that maintenance session attendance only increased the likelihood of meeting the 12-month weight loss goal in those participants who had already met the weight loss goal by 6 months. Therefore, focusing on the 5% weight loss goal at 6 months may be critical for 12-month success.

Notably, we were also the first to find that Medicare-eligible adults (65 years and older) were more likely to meet the 12-month weight loss goal which corresponds with previous DPP results, demonstrating that older adults achieved greater success with weight loss goals and reduction in diabetes incidence versus younger adults.[158,179] Although these results need to be duplicated in more diverse, Medicare-eligible populations with varying levels of attendance, our sample did reflect the existing population surrounding Pittsburgh. Since, obesity and chronic conditions impact physical function and future disability proportionate to their severity[47], it is critical to focus our efforts on preventing these health co-morbidities and their worsening. Obesity has been specifically linked to difficulty walking and increased risk of disability, due to associations with osteoarthritis,[44] diabetes, MetS and cardiovascular disease.[45,46] Thus, evaluating the effectiveness of maintenance session attendance to help participants maintain a clinically meaningful and CMS-reimbursable weight loss goal has broadscale importance for both long-term participant weight loss success and future aging-related health concerns.

Future research should focus on developing effective, tailored ways to help those struggling to reach the weight loss goal during the first 6 months and/or augment the programming in the last 6 months for those who need additional help in DPP-based lifestyle intervention programs. Maintenance sessions occured monthly and focused on adherence barriers, problem solving, managing self-defeating thoughts and social cues to prevent relapse, building social support, and enhancing motivation.[87] Investigating which components of both core and maintenance sessions are associated with weight loss success may help adapt programs to be effective in diverse populations. This is especially relevant in participants with complex health conditions[178] likley crseating greater barriers to achieving their weight loss goals, thereby requiring multiple tailored strategies throughout lifestyle interventions. Understanding Medicare reimbursement-defined success, as we have done, will enable providers to implement strategies that enhance program effectiveness and reduce morbidity associated with being overweight/obese. Overall, these community-based lifestyle interventions have the potential to not only help with initial weight loss but also maintaining weight loss especially among Medicare-eligible older adults at risk for developing type 2 diabetes and future functional decline related to obesity.

Our GLB Moves results demonstrate that *both the DPP-based lifestyle intervention with its standard goal of increasing physical activity levels (DPP-GLB) as well as a goal focused on decreasing sedentary time (GLB-SED) were effective at improving physical function with clinically meaningful changes in gait speed at 6 months*. Although these changes were not shown to be significant when compared to the delayed control group in final clinical trial models for the entire group. Notably, the largest magnitudes of change in both intervention groups were seen among those that started with lower function measures at baseline (slow gait speed and low SPPB). DPP-GLB and GLB-SED demonstrated statistically significant, meaningful mean gait speed changes (>0.05m/s)[71] at 6 and 12 months among those that had slower gait at baseline (<1.0 m/s). We also showed that GLB-SED participants had significantly reduced (better) chair stand time at 6 months compared to baseline, which makes sense since they were initially given goals to take breaks from sitting. In addition to being the first study to assess whether a DPP-based lifestyle intervention improves/maintains physical function, we were also the first to develop and implement GLB-SED, a DPP-based community lifestyle intervention that incorporates reducing sedentary behavior as the primary movement goal.[129,187–191] This novel GLB-SED program is likely a more feasible prevention program for inactive, older adults unable to *initially* engage in moderate intensity physical activity and improve physical function.

Additionally, we found statistically significant and substantial differences in mean SPPB total score[71] at 6 and 12 months compared to baseline in GLB-SED (≥+1.0 point), and similar substantial magnitudes in change in DPP-GLB though not significant. This is likely the results of the small number of participants who had low SPPB measures at baseline. In contrast with previous studies, we found *larger* magnitudes of change in both gait speed and SPPB compared to the MOVE UP study[197] and LIFE study.[60] Importantly, MOVE UP was not a randomized design, and neither of these studies used a DPP-based intervention (instead used a center-based 2x per week, home-based 3-4x per week in LIFE and community health worker behavioral weight management intervention in MOVE UP).[197] Also, LIFE only enrolled older adults with some functional limitation which makes the results less generalizable to midlife adults prior to the onset of more substantial functional decline. Overall, our results clearly found that lifestyle interventions combining achievement and maintenance of weight loss and increased physical activity/reduction of sedentary time delivered in mid-to-early late life adults improve future functional outcomes. This underscores the national impact our CMS-reimbursable, DPP-based lifestyle intervention could have on maintaining/improving function with the long-term goal extending the number of healthy years lived free of disability. As this program is mostly geared towards weight loss and improving physical activity, future research should focus on ways to tailor intervention sessions around the importance of remaining functional with age and ways to stay mobile in the community to promote independence with aging.

Our results from SWAN established that *midlife women in the high-MetS group (≥ 3 components) were more likely to have worse objective physical performance in early late life across every functional outcome assessed versus women with no MetS components*. This study was the first assessment of MetS in midlife and early late life objective physical performance in a multi-ethnic population of women. Importantly, African American and Hispanic women were more likely to be in the higher MetS groups which is a concern since they are known to have higher late-life mobility disability.[205,211] Women excluded due to incomplete in-person measures were more likely to be African American and Hispanic with poorer health status; therefore, the magnitude of difference in all function outcomes may be larger if these women were included. Interventions aimed at reducing the number of MetS components and prevention of disability should focus efforts on diverse women from these groups. Interestingly, the mid-MetS group (~2 components) also demonstrated worse early late life function with respect to the SPPB total score and the repeated chair stand, though these results were not statistically significant after adjustments. In addition, after excluding women with moderate or substantial self-reported physical limitations, the main results were consistent suggesting even "incident" functional decline was occurring in early old age women. Our findings contribute to identifying targets for preventable and treatable factors in midlife adults, particularly in African American and Hispanic racial/ethnic populations, which may reduce functional decline. The longitudinal study design enabled us to establish temporality between midlife MetS and functional outcomes. Our results include several physical performance measures which allows us to better understand which measures are most sensitive to change in early late life and we showed that these were gait speed, SPPB and chair stand assessments of physical function.

The MetS trajectories that we examined are associated with common cardiometabolic health conditions in midlife and older age, especially diabetes,[235] obesity[236] and clinical MetS,[207] and are one pathway by which physical activity and sedentary behavior may impact function. There are many biological mechanisms (e.g., chronic inflammatory processes[136], hyperglycemia-related[137], obesity-related) in which MetS contributes to decreases in muscle mass and strength predisposing individuals to develop functional limitations. Another pathway for decline is related to obesity in which obese adults develop functional limitations due to pain, osteoarthritis, and reduced physical activity levels.[138,139] These cardiometabolic conditions clearly impact age-related outcomes such as physical function and disability.[237] Though the trajectories of MetS components may be more clinically relevant, we did not examine if specific individual components of MetS during midlife impacted future physical function. Understanding which MetS components are associated with functional decline could guide intervention efforts and is an important future direction of this research. However, midlife MetS trajectories had not been previously examined in relationship to physical function before our study, even though the highest prevalence of severe obesity is in diverse women, thus justifying the importance of our research in SWAN.[34] Previous SWAN research showed that worse self-reported physical function was associated with MetS and half of midlife women self-reported functional limitations.[214,238] Although the relationship between function and cardiometabolic-related outcomes are likely bidirectional, our work suggests that MetS evaluated longitudinally over midlife contributes to function decline and the timing of the onset of limitations in early late life.[213]

Ultimately, being able to characterize subgroups of the population that need earlier intervention during midlife will help streamline prevention efforts and maximize program effectiveness. *Maintaining* physical function from midlife to late life should be viewed as a successful intervention outcome rather than solely focusing on improving over time, as maintenance also is preventing decline. Another methodological consideration is selecting the most appropriate objective performance measures in midlife adults to predict late life disability. Importantly, it is currently unknown which test is most appropriate to assess early functional decline in midlife.[151] Measuring function among midlife adults (especially high-risk midlife adults, e.g., women, racial/ethnic minorities, adults with MetS components) in clinical settings using simple, non-invasive tests such as the SPPB, gait speed or standing up from a chair could be a strategy to identify early signs of physical limitations and help maintain independence with aging.[151] Certain functional tests such as SPPB or gait speed[137] that are able to be performed quickly could be used as a "sixth vital sign"[152,153] for high-risk midlife adults, though these measures may not be as sensitive to very early decline they could facilitate the referral system for physical therapy or occupational therapy programs based on quickly identifying concerns with function in a clinical setting. Importantly, we found stronger associations with MetS for the SPPB[151,232] and small but clinically meaningful faster gait speed changes in both DPP-based lifestyle intervention arms. Several studies of older adults have found that diabetes is related to worse SPPB score,[233] gait speed, and chair stand[234] and we showed consistent relationships among women with MetS for these outcomes. More challenging performance measures (e.g., 400-meter walk and expanded SPPB)[200,201] should be considered if the population for the intervention has high physical function at baseline. Additionally, previous research in the LIFE study showed that the lower rate of mobility disability in the physical activity intervention vs. health education group was largely attributable to improved chair-stand performance, which is a surrogate measure of lower extremity muscle strength/power.[60] Our results showed that chair stand time was significantly faster at 6 months among those in the GLB-SED arm, likely because the intervention goal instructed them to take breaks from sitting throughout the day which would require performing the type of sit-to-stand required in the chair stand test. Therefore, muscle strength may also be a mechanism by which physical activity prevents future disability. Yet, future studies that directly measure lower extremity strength/power, cardiorespiratory fitness and body composition in younger midlife populations are needed to understand mechanistic pathways. More research is needed to identify which types of interventions (strength vs. aerobic vs. a combination, and activity intervention alone or combined with weight loss goals) are most effective at improving muscle strength/power and lower extremity function during midlife to refine approaches for the prevention of late life disability.

8.2 Public Health Significance

Mobility disability affects 14% of US adults and is the most prevalent type of disability, particularly for women, and also increases with age.[6] The increasing prevalence of disability is a public health problem because it has been shown to be associated with greater health care costs,[15] increased risk of falls,[242] increased mortality rates[16–19] and reduced quality of life.[20,21] Physical function represents a stage of the disablement process that is amenable to intervention and preventive efforts, particularly in early stages of decline that may occur in mid-life and early late life,[6,8,29,30] and the goal should be to modify this decline at an early stage to compress morbidity and extend independence with aging. Our findings indicate that midlife women with MetS were more likely to have worse physical function in early late life based upon a large observational study of multiethnic women. Examining this issue is a one-year community clinical trial, we also showed that a DPP-based lifestyle intervention with weight loss and movement goals of either increased physical activity or decrease time spent sedentary was effective at improving physical function among mid-to-early late life adults with MetS and/or prediabetes. These results may also have important implications for falls prevention, which would have widescale public health implications as well.[243] Furthermore, we demonstrated both the effectiveness and importance of intervening prior to the onset of functional decline in late life, as midlife adults are able to successfully achieve clinically meaningful weight loss, physical activity and sedentary behavior reduction goals and improve/maintain physical function.

The fact that the DPP-GLB represents a real-world lifestyle intervention that is reimbursable by CMS and currently available nationally to prevent/delay functional decline adds to the public health importance and long-term sustainability of this work. In addition, the DPP-based lifestyle intervention with sedentary behavior reduction goals could be an additional program added to the list of preventative options for improving function in older adults, with the possibility of becoming a CMS-reimbursable program in the future. Based on our findings, we argue that government reimbursed programs should reconsider eligibility for program entry into DPP-based lifestyle interventions; these programs should be available for midlife adults at greater risk for future health complications (those with MetS and slow gait speed aged <65 years). Our results provide important information to national Medicare-DPP providers across the country and offers an invaluable prevention opportunity for these providers to impact the current health of older US adults with prediabetes.[180] Future efforts should prioritize the dissemination, implementation, and sustainability of these nationally available, effective DPP-based lifestyle intervention programs for several aging-related health outcomes.

8.3 Conclusions

To reduce the prevalence of disability in older adults, an understanding of which modifiable risk factors in midlife are associated with early late life functional decline is critical. Incorporating performance measures as a "sixth vital" sign in the clinical setting for mid-to-early late life adults with cardiometabolic risk factors, such as prediabetes and components of the metabolic syndrome, may help target individuals at high-risk for functional decline and implement effective interventions in both community and clinical settings. In the future, clinicians may be able to use chair rise time and slowness of gait as a referral for physical therapy or occupational therapy programs to prevent future functional decline and promote the maintenance of functional status into old age. Lifestyle interventions with weight loss and physical activity or sedentary behavior reduction goals aimed at improving physical function should be implemented earlier in the midlife period and adapted based on the person's comorbid conditions and current functional status. For instance, older adults with metabolic syndrome, prediabetes and/or functional impairments may need tailored intervention sessions specific to these health issues to be as successful as possible both early on and long-term in these programs. Therefore, the immense potential exists to develop and implement effective approaches to slow functional decline and prevent late life disability through both lifestyle intervention and clinically targeted interventions, which is currently not being utilized for mid-life and early old age adults. Use of simple physical function assessments in the clinical setting as well as widescale implementation and adherence to CMS-reimbursed, DPP-based lifestyle interventions could help delay the onset of disability by improving/maintaining functional ability in mid-to-early late life adults.

Overall, we have found strong evidence to suggest that the disablement process begins in midlife while adults still have decades of life in which remaining functionally independent is a priority. This research helped to determine which interventions were effective at both weight loss/maintenance and improving physical function and provided new insights about midlife cardiometabolic risk factors associated with early late life physical function that could be targeted for prevention efforts. The public relevance of these current findings is that intervening earlier in midlife will not only decrease the burden on the health care system (reduce health care utilization and cost) but will also have a substantial impact on reducing disability and mortality and improving quality of life in older adults.

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