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Living Fit (LIVFIT) with HIV: Reducing inflammation and improving vascular function with exercise among older persons with HIV

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Abstract

Background: Persons with HIV experience endothelial dysfunction due in part to chronic inflammation that increases their risk for poor vascular function and cardiovascular disease (CVD). Routine moderate to vigorous aerobic exercise intensity has been shown to improve inflammation and vascular function, but the level of exercise adherence required for improvement among older persons with HIV (OPWH) has not been established. In addition, validation studies for the activity monitors to determine exercise intensity was also not established in OPWH. The purpose of this study was to: conduct a systematic review on the validity and accuracy of the FitBit Charge 2 for measuring aerobic exercise intensity level; utilize data from a secondary analysis to test the level of exercise adherence on measures of inflammation, and endothelial vascular function among OPWH.

Methods: Participants (n=115, mean age 55, 65% male, 82% Black) were enrolled in the 2-arm randomized controlled trial (RTC) Healing Hearts and Mending Minds parent study. The intervention group consisted of a progressive walking program (*Let's Move*) compared to attention control participants (*Let's Flex*) which were evaluated at baseline (BL) for cardiorespiratory fitness using the modified Balke $VO2_{max}$ test. Inflammatory biomarkers Interleukin-6 (IL6), Tumor necrosis factor (TNF), and soluble C-differential-14 (sCD14) were drawn at BL, 3, 6-, and 12-months. Endothelial vascular function was measured by flow-mediated dilation (FMD) at BL and 6-months. Participants were provided with activity trackers and an exercise prescription based on their individual target heart rate at 60-70 % intensity and progressed to a minimum of 300 minutes per week. T-test were also used to compare the changes in inflammatory values between adherent and non-adherent participants in the exercise intervention group between BL and 3-, 6-, and 12-month timepoints. Change in FMD was examined between both groups from baseline to 6-months. Multilevel linear modeling was performed within the exercise intervention group to examine the incremental change in the biomarker values over time in association with a cumulative adherence level. Cumulative exercise was calculated by adding up whether exercise adherence was met (yes=1, no=0) at each 3-, 6-, and 12- month timepoint (i.e. cumulative adherence values ranged from 0 to 3).

Results: A systematic review of validation studies suggests that the Fitbit Charge2 activity tracker adequately measured HR at moderate intensity exercise levels. Over 60% of the participants in the intervention group maintained adherence to ≥300 minutes of moderately to vigorous (60-70% HR maximum) exercise throughout the 12-month study duration. Attrition rate was <10% in both groups over the study duration. The change in FMD was not significant between the intervention and attention control groups but was significantly improved among the participants who were adherent to their exercise prescription at least 70% of the time compared to those who were not adherent (adherent = 0.58, not adherent = -1.61, p=0.025) at 6-months. Among the participants in the exercise intervention who were adherent to their exercise prescription at least 70% of the time, sCD14 and TNF values decreased without statistical significance with small to moderate effect sizes (0.42 and 0.35 respectively).

Conclusions: Findings from this study indicated that OPWH were willing to remain engaged in a study over a 12-month period with very low attrition rates observed. Although reductions in the inflammatory markers were minimal, this was likely due to participants being well-controlled on their antiretroviral therapy (ART) with little room for improvement or change. Higher exercise adherence was associated with improved endothelial vascular function among OPWH and may lower CVD risk. Future studies are needed to examine exercise dose and modes on CVD risk reduction among OPWH.

Key words: Aerobic exercise, cardiovascular disease, HIV, inflammatory cytokines, flow-mediated vasodilation, vascular endothelial function

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Chapter I

Statement of the problem

Due to advances in antiretroviral therapy (ART), HIV is now considered a chronic illness, with longevity approaching that of the general population (Nasi, 2017, Ballocca, 2017). Chronic inflammation and cardiovascular disease (CVD), more commonly seen in the aging population, are occurring with greater frequency in PWH who are on average at least a decade younger than in persons without HIV. (Nasi et al., 2017, Ballocca et al., 2017, Duprez et al., 2012, Shah et al., 2018, Tatanji et al., 2020). Despite optimal medication adherence and viral load suppression, older persons with HIV (OPWH) who are $\geq$40 years of age have higher levels of sustained inflammation due in part to the disease itself as well as heightened stress associated with lifestyle and the social determinants of health than those without HIV (Neuhaus et al., 2010, Hanna et al., 2017, Nordell et al., 2014, Samji et al., 2013, Denning and DiNenno, 2008). In addition, there is a well-established health disparity in longevity outcomes among OPWH that is associated with race; Black persons with HIV die on average 8 years earlier than white PWH and comprise 42% of the US population with HIV (CDC, 2021). Effective interventions that are accessible, low-cost, and scalable in many community settings are greatly needed to reduce the risk of CVD among OPWH.

Inflammation and HIV

The higher levels of chronic inflammation often experienced by PWH are measured by inflammatory biomarker levels such as tumor necrosis factor (TNF), Interleukin-6 (IL-6), and the monocyte binding protein soluble C-differential-14 (sCD14) (Brenchley et al. 2006, Neuhaus et al., 2010). Over time, prolonged inflammation contributes to endothelial dysfunction causing fibrosis and arterial thickening leading to much earlier vascular aging and CVD (Nasi et al., 2017, Hanna et al., 2017, Nordell et al., 2014). Elevated serum levels of IL-6 have been reported in fatal cardiac events in OPWH who have a higher inflammatory burden due to vascular aging than younger PWH (Nasi et al., 2017, Shah et al., 2018). Additionally, higher CVD risk including elevated sCD14 levels were associated with coronary artery calcifications and a 6-fold increase in mortality for PWH (Sandler et al., 2011, McKibben et al., 2015). TNF is another important inflammatory cytokine released by macrophages that are responding to an acute infection such as HIV. The HIV-1 protein controls the TNF signaling pathways thereby permitting HIV proliferation and elevated inflammation (Kumar, Coquard and Herbein, 2016). The monocyte sensor binding protein, sCD14, is detected in the blood in response to elevated inflammation typically following acute infection (Kumar, Coquard and Herbein, 2016). Levels of sCD14 can remain elevated. Moderate intensity exercise tested in mostly site-based studies has been shown to reduce these inflammatory biomarkers (Pedro et al., 2017). However, site-based supervised exercise studies have experienced high attrition among participants and may not be feasible in real-world settings as an adjunctive therapy for PWH due to lack of access, travel time and economic challenges (Nwaka et al., 2019, Pedro et al., 2017). OPWH are more likely to engage in a home-based, low to moderate intensity aerobic training program such as walking (Ashworth et al., 2005, Li et al., 2019, Webel et al., 2015).

Endothelial Function and HIV

Endothelial function is measured with brachial artery flow-mediated vasodilation (FMD) and is used to identify individuals at high risk for vascular dysfunction and CVD (Black et al., 2009). Factors associated with vascular endothelial dysfunction including lower muscle oxygenation and diminished arterial contraction have been reported as more common among PWH compared to persons without HIV (Volino-Souza et al., 2020). Aerobic and resistance exercise is reported to mitigate CVD risk by improving endothelial function, but few studies have evaluated whether aerobic exercise enhances endothelial function among PWH.

Exercise, inflammation, and endothelial function in HIV

Exercise and physical activity, often used synonymously, differ in that exercise is defined as structured, planned, and repetitive physical activity and is a commonly used intervention to improve cardiovascular fitness (Caspersen, Powel, Christenson, 1985). In contrast, physical activity can include low intensity activities of daily living such as walking and housework. During moderate intensity aerobic exercise, an individual's HR should reach 60-70% of their maximum HR for 150 minutes per week for optimal healthful benefits (Office of Disease Prevention and Health Promotion, 2019. This intensity level has been demonstrated to lower cardiovascular risk for individuals with and without HIV (Office of Disease Prevention and Health Promotion, 2019, Hotting and Roder, 2013, Jaggers and Hand, 2016, Nwaka et al., 2019, Owusu et al., 2020, Pedro et al., 2017, Roos et al., 2014, Sallam and Laher, 2016, Vingren et al., 2017, Zheng et al., 2014). However, less than half of adults in the United States (U.S.) general population meet these current guidelines and the exercise adherence rates among OPWH are unknown (Office of Disease Prevention and Health Promotion, 2019).

Exercise adherence

Exercise adherence that meets the minimum CDC recommendations produces beneficial, healthful effects on the cardiovascular system through several mechanisms including reducing inflammation and maintaining and improving vascular endothelial functioning. This level of exercise reduces inflammation by blocking some pro-inflammatory cytokines and increasing other myokine repairing cytokines (Green et al., 2017). During moderate intensity exercise, the increased blood flow exerts pulsatile pressure on the endothelial cells within the vascular walls which stretch and resurface the endothelial lining (Green et al., 2017). Habitual activity that achieves these cellular changes that is accompanied by periods of rest between sessions, repairs damaged vessels (Green et al., 2017). This function of exercise has been shown to mitigate CVD and reduce mortality for persons with chronic health conditions such as

HIV and hypertension (Green et al., 2017). Exercise dose >160 minutes per week and at least 70% of maximum HR has been shown to induce a positive change in vascular function measured by FMD among healthy young males but has not been studied among PWH (Birk et al., 2012). Further, exercise intervention studies have not assessed adherence to exercise interventions.

Additionally, many exercise intervention studies including PWH were conducted in a laboratory or gym under supervision by an exercise physiologist and experienced high attrition rates (>50%) (Nwaka et al., 2019, Pedro et al., 2017). Interventions performed in site-based settings are often less accessible to older, vulnerable populations due to travel, time, and economic challenges making OPWH are more likely to engage in a home-based (HB), low to moderate intensity aerobic training program such as walking (Ashworth et al., 2005, Webel et al., 2015).

Exercise and physical activity measurement in HIV

Incorporating exercise prescriptions into healthcare protocols show major benefits among a variety of health conditions including cardiovascular disease, depression, and HIV, as well as for preventative medicine (Luan et al., 2019). Providers need cost-effective, reliable wearable devices that accurately measure physical activity to assess and provide feedback to patients regarding their physical activity and to fully utilize the benefits of an exercise prescription.

Current research grade devices have been validated to measure either HR by electrocardiogram (ECG) (Willemsen et al., 1996), step count by the ACTi graph accelerometer (Sasaki, John, Freedson, 2011), or sensing HR pulse with the Polar chest strap (Gillinov et al., 2017), but to date no wearable device is validated to measure both HR and steps concurrently. Exercise equipment manufacturers continuously develop multifunction activity trackers worn as watches that purport to accurately capture step and heart rate. However, these wearable activity trackers have been tested against research grade accelerometers and heart rate monitors with variable results. The Fitbit Charge 2 (FBC2) (Fitbit; Fitbit Inc., San Francisco, CA, USA) is a wearable device that tracks heart rate which has been studied among a variety of populations in home-based and healthcare settings. However, consensus of the tracker's accuracy has not been established.

Motivation to exercise

While there are ample sources of data that support the effectiveness of habitual exercise on improving health outcomes, being motivated to exercise is complicated and personal. Often persons with multiple chronic conditions have compounding barriers to exercise. Motivational interviewing (MI), a behavior change strategy, has been found to improve exercise adherence among persons with chronic conditions, but has not been tested among PWH (Halloran et al., 2017). MI techniques have, however, been effective in increasing adherence to ART regimens among PWH (Hogan et al., 2020) and may be a promising approach to engage this high-risk for CVD group in consistent and frequent aerobic exercise. Community-based exercise programs for PWH found that social interactions and peer support groups with supportive techniques similar to MI have helped individuals problem solve exercise barriers, set goals, and find motivations to exercise.

Purpose

Exercise intervention studies typically lack report of adherence rates. No studies have examined aerobic exercise adherence within an exercise intervention and the effects on inflammation and CVD risk among PWH. Additionally, few exercise studies have investigated the impact of an exercise intervention on inflammatory biomarkers or endothelial function and CVD risk in a home-based (HB) exercise program for persons with HIV over a longer duration of

6-months. The primary purpose of this study was to examine adherence to a 12-month moderate intensity aerobic exercise program on the inflammatory biomarkers TNF, IL-6, and CD14 among OPWH. A secondary purpose was to compare the effects of higher exercise adherence on FMD among the exercise intervention participants and the attention control participants over 6-months. Behavioral change techniques to support exercise adherence and the validity of the exercise tracker were also examined. Developing effective biobehavioral interventions that target the underlying inflammation known to accelerate CVD in OPWH is of paramount importance.

Specific Aims

Aim 1: Review validation studies using the Fitbit Charge 2 tracker for consensus on its accuracy. **H:** The Fitbit Charge 2 will accurately measure heart rate within a 90% error rate while walking at moderate intensity.

Aim 2a and 3a. Assess exercise adherence among the intervention group (n=76), measured by the number of minutes per day and days per week the participants met their target HR of 60-70% HR max during the scheduled assessment periods. **H**: Intervention participants will have high adherence to their exercise prescriptions due to the use of motivational interviewing and other supportive methods of the parent study.

Aim 2b: Examine the effects of adherence to the aerobic exercise intervention, measured by heart rate intensity, on improved vascular function measured by flow-mediated dilation among the intervention group (n=76) who were adherent and those who were not adherent at 6-months and the attention control group (n=39). **H:** Participants who are adherent to their exercise prescription will have greater improvements in endothelial function.

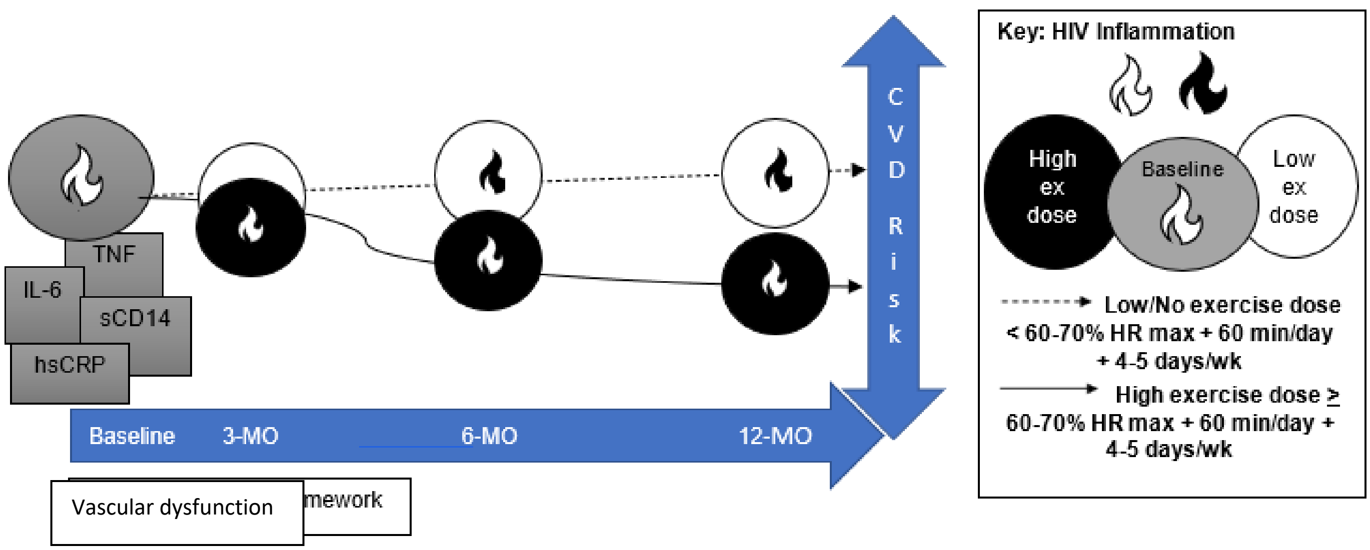
Aim 3b: Examine whether higher aerobic exercise adherence, measured by heart rate intensity, improves inflammatory biomarkers (TNF, sCD14, IL-6) among the intervention group (n=76) over time from baseline and at 3-, 6-, and 12-months. **H:** Participants will have an incrementally greater inflammatory biomarker reduction as a function of the exercise adherence levels (adherent versus non-adherent) over the 12-month duration.

Manuscript descriptions

Chapter II includes a systematic review of validation studies including the Fitbit Charge 2 tracking device used in the parent Fitbrain study. This manuscript was published in the Translational Journal of the American College of Sports Medicine in November 2022. Chapter III includes the manuscript entitled, “Higher exercise adherence among older persons with HIV is associated with improved flow mediated dilation,” which is under review with the Journal of AIDS care. The manuscript addressed the association between exercise adherence and improved cardiovascular endothelial function. The third dissertation manuscript contained in Chapter VI is entitled, “Higher exercise adherence lowers inflammation among older persons with HIV.” The manuscript reports the results of testing whether inflammatory biomarker levels were lowered among persons who were adherent to the exercise prescription in the parent study.

Conceptual Framework

The framework in Figure 1 is hypothesized to improve the underlying physiological mechanisms that contribute to heightened CVD risk at an earlier age in persons with HIV. Aerobic exercise



has been shown to lower inflammatory markers (TNF-alpha, sCD14, IL-6, hsCRP) and arterial stiffness in primarily non-infected HIV populations and in animal models (Office of Disease Prevention and Health Promotion, 2021, Sallam and Laher, 2016, Hotting and Roder, 2013, Nwaka et al., 2019, Pedro et al., 2017, Roos et al., 2014, Zheng et al., 2019, Owusu et al., 2020, Vingren et al., 2017). In the proposed study, we hypothesize that increased adherence will increase dose (HR intensity, duration) of exercise; higher dose is proposed to have a greater influence on reducing inflammatory biomarkers than moderate or low dose exercise and when compared to control participants over 12-month the study duration.

Background and Significance

Chronic inflammation and cardiovascular disease (CVD), more commonly seen in the aging population, are occurring with greater frequency in PWH who are on average at least a decade younger than in persons without HIV (Nasi et al., 2017, Ballocca et al., 2017, Duprez et al., 2012, Shah et al., 2018, Titanji et al., 2020). Regardless of medication adherence and viral load suppression, OPWH have higher levels of inflammation due in part to the disease and heightened stress related to the social determinants of health associated with HIV (Samji et al., 2021, Denning and DiNenno, 2018). In addition, there is a well-established health disparity in longevity outcomes among OPWH that is associated with race (Center for Disease Control and Prevention, 2021). A recent scientific statement by the American Heart Association, for example, reported that lower socioeconomic status and stress-related racism places Black persons at 2 to 3 times higher risk for mortality from CVD than whites and may in part account for the HIV disparity in this population (Havranek et al., 2015). Because Black persons are at a higher risk for mortality from developing CVD and HIV, effective interventions that are accessible, low cost and scalable in most community settings are greatly needed and are of high research priority.

Effect of exercise on CVD

Exercise defined as structured, planned, and repetitive physical activity is a commonly used approach to intervention designs that are targeted to improve cardiovascular fitness (Caspersen, Powell, and Christenson, 1985). Moderate intensity aerobic exercise that meets 60-70% of an individual's maximum HR for 150 minutes per week is established to have cardiovascular benefits including CVD risk reduction and improvements to overall health for people with and without HIV (Hotting and Roder, 2013, Nwaka et al., 2019, Jaggers and Hand, 2016, Office of Disease Prevention and Health Promotion, 2021, Owusu et al., 2020, Pedro et al., 2017, Roos et al., 2014, Sallam and Laher, 2016, Vingren et al., 2017, Zheng et al., 2019). Exercise studies including predominantly white and younger PWH have shown decreased levels of inflammatory biomarkers with moderate to high intensity aerobic exercise (Hotting and Roder, 2013, Nwaka et al., 2019, Pedro et al., 2017, Owusu et al., 2020). However, less is known about the effects of adherence to an exercise program on inflammatory biomarkers and endothelial function among OPWH.

Even fewer exercise studies have investigated the impact of exercise adherence on inflammatory biomarkers and CVD risk in a home-based (HB) exercise program for persons living with HIV. A recent scientific statement presented by the American Heart Association/ American College of Cardiology (AHA/ACC) established that HB exercise programs produce comparable clinical outcomes to results observed in studies testing site-based programs among persons without HIV infection (Thomas et al., 2019). Advantages to HB exercise programs include greater accessibility and flexibility to vulnerable populations (i.e., older, minority, low SES, chronically ill) similar to our HIV population who often had transportation and financial limitations (Thomas et al., Quigley et al., 2018, Tang et al., 2017). HB exercise programs, such as the parent "Fitbrain" study, that offered a combination of face to face and telephonic support and used an individualized exercise prescription based on a maximal treadmill test may also bolster exercise adherence among PWH. Comparing exercise options, approximately 50% of persons chose a home-based approach due to greater flexibility and less travel and time burden (Tang et al., 2017).

To date, exercise studies investigating inflammatory biomarker changes among PWH under short time durations (3-6 months) have primarily included participants 50 years of age or younger. In a meta-analysis of 11 studies of PWH (n=490), interventions using a combined aerobic and resistance training approach reported significant reductions in IL-6 (Z=2.77, p=0.006) (Nwaka et al., 2019). Five of the studies included male only participants (n=227) and all were site-based (Nwaka et al., 2019). One of the RCTs (n=28) included in the meta-analysis examined changes in cytokines in response to aerobic plus resistance exercise (Pedro et al., 2017). Intervention participants (n=17, 47% male, mean age 43.4) exercised under HR guided aerobic exercise at 50-70% of their maximum HR for 20 minutes and performed resistance exercises, 3 times per week for 16 weeks (Pedro et al., 2017). Findings reported significant differences and Cohen's effect sizes (CI 90%) in IL-5 (-0.68), IL-8 (-0.87) and IL-10 (-0.74), but not IL-6 or CRP in the training group as compared to controls engaging in low-intensity recreational activities. Cohen's effect size is considered small at <0.5, moderate between 0.5-<0.8, and large at >0.8 (Hopkins et al., 2009). There was also a 55% attrition rate among the intervention participants which is high and suggests different exercise designs may be more appealing and beneficial (Pedro et al., 2017). Additionally, a study in Denmark showed reductions in IL-6 (p=0.01), TNF (p=0.009), and hsCRP (p<0.001) among a small sample (n=8) of PWH in a supervised aerobic (50-75% HR max, 35 minutes, 3 days per week interval training) 16-week intervention, compared to resistance training (n=10), but lacked a control group (Lindegard et al., 2008). A 12-week pilot study among PWH (n=35, mean age 48, all white, 74% male) reported significant reductions in IL-6 among female participants (p=0.031) and hsCRP in male participants (p=0.012) engaged in a moderate intensity walking (60 min/day, 3 days/wk at 60-70% max HR) versus a walking and resistance training group (30 min each type/day, 3 days/wk at 60-70% max HR) (Bonato et al., 2017). Cytokine level reductions were similar between exercise groups, but also lacked a control group (Bonato et al., 2017). These studies were performed under close supervision using site-based programs which are less accessible and more challenging for participation among older, vulnerable populations. Only one previously conducted RCT has examined the long-term effects of exercise over a one-year period among of 84 PWH (mean age 39, 21% male). This study consisted of a low intensity (30 minutes or 3,000 steps/day), HB walking + education program conducted 3-5 times per week on CVD risk factors measured as hsCRP changes (Roos et al., 2014). Participants were provided pedometers and encouraged to walk briskly at 60-70% of their age predicted maximum heart rate (Roos et al., 2014). The program did not show significant reductions in hsCRP, likely because the exercise dose may have been too low, participant adherence levels were not reported, and the baseline hsCRP levels were significantly higher among intervention participants (8.5 vs 5.45) which may suggest potential selection bias (Roos et al., 2014). From these previous studies, the biomarker IL-6 has consistently responded to exercise training over 6 weeks to 12 months, and in a variety of age ranges in PWH, and therefore may be an important measure for understanding the inflammatory response in this population.

The role of inflammatory biomarkers in CVD etiology and disease progression in PWH

Chronic inflammation is common among HIV despite optimal ART adherence or normal viral loads (Brenchley et al., 2006). Inflammatory biomarker levels including tumor necrosis factor (TNF), Interleukin 6 (IL-6), and the monocyte binding protein (sCD14), are higher in PLWH (Neuhaus et al., 2010), but have not been examined in response to aerobic exercise dose among OPWH participating in a HB program. The pleiotropic proinflammatory cytokine and muscle repairing myokine, **IL-6**, is an important mediator of the inflammatory response during infection and repairs tissue after physical activity. Normal levels of IL-6 are considered to be between 5-15 pg/ml. In a study of PWH with no prior cardiac history (n=288) fatal CVD events occurred more often (OR=1.39, CI 1.07-1.79) among those with higher IL-6 levels (Sarwar et al., 2012). In a meta-analysis examining IL-6 levels in noninfected persons, persistently elevated IL-6 was significantly associated with CVD risk (Sarwar et al., 2012). In the SMART study of 4544 HIV+ participants (mean age 44, 73% male, 54% Black), elevated IL-6 were associated with higher CVD risk in PWH after controlling for other CVD risk factors including prior CVD and smoking (Duprez et al., 2012). Muscle contraction from physical exercise induces IL-6 as a myokine to generate new muscle myofibrils and to initiate toll-like receptors to downregulate chronic inflammation (Handschin and Spiegelman, 2008) which could be key in reducing chronic inflammation in OPWH. **Soluble CD14**, is a monocyte sensor that detects bacterial lipopolysaccharide (LPS) and activates macrophages responding to elevated inflammation (Kitchens and Thompson, 2005). Serum LPS binds with CD14 to produce sCD14 creating a cascade of systemic inflammation (Kitchens and Thompson, 2005). sCD14 levels were higher in n=906 HIV+ persons (mean age 44, 50% Black, 37% male), versus those without HIV infection (normal levels 0.49- 0.97 mu g/ml) (Hanna et al., 2017). Elevated sCD14 levels were also associated with a 6-fold increase in mortality for PWH and higher risk of CVD associated with coronary artery calcifications (Sandler et al., 2011, McKibben et al., 2015). Therefore, sCD14 may be an important biomarker for CVD related risk in OPWH (McKibben et al., 2015). sCD14 binds with the proinflammatory cytokine **TNF** which is released by macrophages during an acute inflammatory response to signal cellular apoptosis. HIV-1 proteins mimic and control the TNF signaling pathways inhibiting apoptosis and instead allows viral proliferation and elevated inflammation (Kumar, Coquard and Herbein, 2016). Moderate exercise significantly reduced TNF (normal levels between 0-16 pg/ml) and CVD risk in non-infected persons with chronic heart failure (Smart et al., 2011). Therefore, reducing TNF with activity may be effective in reducing risk or slowing progression of CVD among OPWH.

Endothelial vascular function and CVD/HIV

Endothelial vascular function is measured with brachial artery flow-mediated vasodilation (FMD) and is used to identify individuals at high risk for vascular dysfunction and

CVD (Black et al., 2009). Factors associated with vascular endothelial dysfunction including lower muscle oxygenation and diminished arterial contraction have been reported as more common among PWH compared to persons without HIV (Volino-Souza et al., 2020). Comorbidities including hypertension, Type II diabetes, dyslipidemia, and smoking influence the degree of vascular endothelial dysfunction due to the deleterious effects of these comorbidities on arterial stiffness. (Wing, 2016, Ballocca et al., 2017). Hypertension constrains the flexibility of blood vessels and diabetes reduces the biochemical nitric oxide (NO) which leads to endothelial dysfunction (Antony, Lerebours, and Nitenberg, 1995, Cosentino et al., 1997).

Flow mediated dilation (FMD)

The rate at which the vascular endothelium responds to an increase in blood flow during exercise is a reliable indicator of cardiovascular function. (Black et al., 2009). Flexibility within the vascular endothelia promotes normally functioning vasodilation and deters platelet aggregation (Black et al., 2009, Corretti et al., 2002). Flow-mediated dilation (FMD) measures the aptitude of the endothelium to respond to a sudden change in blood flow using a brachial artery cuff constricted for 5 minutes (Black et al., 2009, Corretti et al., 2002, Alley et al., 2014). As flexibility or vascular elasticity improves, FMD increases. A study examining the sensitivity of FMD to predict cardiac artery disease (CAD) found that an FMD measurement of <4.5% was reliably associated with CAD (Schroder et at., 1999).

Exercise and endothelial function

There are significant associations between endothelial dysfunction and CVD risk (Quyyumi and Patel, 2010). Further, more than a decade of research has used FMD as a non-invasive approach for measuring endothelial function and as a method to evaluate vascular changes following an intervention such as exercise (Birk et al., 2012, McCully, 2012, Quyyumi and Patel, 2010). Exercise adherence that meets the minimum CDC recommendations produces healthful effects on the cardiovascular system through several mechanisms including maintaining and improving vascular endothelial functioning. Aerobic and resistance exercise is reported to mitigate CVD risk by improving endothelial function, but few studies have evaluated whether aerobic exercise enhances endothelial function among PWH.

Research Methods and Design

Parent Fitbrain Study design

The Fitbrain Study was a two-arm RCT which tested the efficacy of a HB moderate intensity aerobic exercise intervention on neurocognition, vascular function, and inflammatory biomarkers compared to attention controls who participated in a stretching and flexibility program. Blood samples were obtained from all participants at baseline, 3, 6, and 12-month study visits. Participants in the intervention group were given a Fitbit Charge 2 activity watch that tracked continuous step and heart rate data.

Table 1: Exercise Rx	**Weeks 1-2**	**Weeks 3-4**	**Weeks 5-7**	**Weeks 8-9**	**Weeks 10-12**	**Weeks 13-52 (maintenance)**
Intensity	60%	60%	70%	70%	70%	70%
Duration	30 minutes	45 minutes	45 minutes	60 minutes	60 minutes	60 minutes
Frequency	5 days/wk	5 days/wk	5 days/wk	5 days/wk	5 days/wk	5 days/wk

Intervention group. At BL, an individualized exercise prescription was provided to each participant that was calculated as 60-70% of maximum heart rate based on the Balke treadmill test. Participants in the intervention group were asked to walk at graduated levels, 5 days per week at moderate intensity using an exercise prescription shown in Table 1. Activity data was collected via download to a commercially available API for the first 3 months and then directly from the Fitbit site for the remainder of the study. Weekly follow up calls using motivational interviewing techniques were made from BL- 3 months, then bi-monthly from 3- 6months to encourage exercise adherence and to identify and resolve barriers to exercise (Table 2).

Control Group. Participants in the control group received the same amount of attention by research staff as the intervention group. They were provided with face-to-face instructions on how to perform the stretching and flexibility movements and asked to perform them 4-5 times weekly for 30-60 minutes. Control participants were followed using the same procedures as the intervention group for study visits (Table 2).

Table 2: Fitbit assessment schedule			
Week	1-12	14 - 24	28 - 52
Frequency	Weekly	Bi-monthly	Monthly

Parent Fitbrain study recruitment and sample.

Participants for the parent study were recruited as a convenience sample from infectious disease clinics and from community HIV centers, in the metro-Atlanta area. Participants were randomly assigned at BL into the intervention (n=76) or attention control groups (n=39) using 2:1 intervention/control block randomization procedures before measures were taken. Data collectors were blinded to group assignments. Inclusion criteria: men and women aged 40 and over with HIV and willing to participate, English speaking, live independently and within a 50-mile radius of Atlanta, had a minimum of 2 CVD risk factors (e.g., diabetes, dyslipidemia, hypertension, overweight/obesity), clinically stable and on ART 6 months before enrollment. Exclusion criteria: (a) hospitalized within 60-days before enrollment, (b) involved in any structured exercise program or exercising 3 or more times per week for a minimum of 30 minutes, (c) involved in any weight loss program, (d) had a medical or physical condition that would preclude participation in the exercise component of the study (e.g., severe arthritis or mobility problems, uncontrolled hypertension or diabetes, renal failure, or a history of angina with activity, ischemic changes or inappropriate BP changes on BL exercise (modified Balke) treadmill test, (f) were prescribed corticosteroids, (g) experienced acute inflammation at time of baseline or follow-up testing, (h) presented with a current opportunistic infection, (i) diagnosed with a terminal illness, (j) used anti-inflammatory medications regularly such as non-steroidal anti-inflammatory agents excluding low dose aspirin, (k) pregnant women, (l) severe learning disabilities, intellectual disabilities, psychotic disorders to minimize confounding effects on neurocognitive data, or were diagnosed with other confounding neuro-medical conditions (e.g., active CNS opportunistic infections, seizure disorders, head injury with loss of consciousness greater than 30 minutes, intracranial neoplasms, stroke with neurological or neuropsychiatric sequelae, and non-HIV-associated dementias.

Human subjects and Informed consent

The study was approved by Emory University IRB#00080302. All participants were consented according to Emory University IRB protocols.

Sample size and power calculation

***AIM2*.**

The sample sizes used in the FMD examinations of the secondary analysis were in 2 phases. The 1st phase in the FMD study, the sample sizes of participants with complete FMD data for the 2 timepoints were n=64 in the intervention group and n=33 attention control group. In the 2nd phase, the adherent and non-adherent groups were stratified, and the sample sizes changed at each timepoint (Table 3). Therefore, the parent study sample size provided adequate power to detect small to moderate differences in inflammatory biomarker changes among exercise variations.

***AIM 3*.**

For analyses of biomarker measures, the parent study sample size (exercise adherence n=39 (3MO), n=33 (6MO) and n=30 (12-MO) vs low + moderate + controls: n=70, total n=115) did not provide adequate power (95%) to detect effect sizes of Cohen's f^2=0.6 or larger at alpha=0.05 at any timepoints (Faul et al., 2007, Hopkins et al., 2009). Therefore, the parent study sample size only provide adequate power to detect small to moderate differences in inflammatory biomarker changes among exercise variations.

F tests – ANOVA: Repeated measures, between factors

Analysis:	A priori: Compute required sample size		
Input:	Effect size f	=	0.6
	α err prob	=	0.05
	Power (1−β err prob)	=	0.95
	Number of groups	=	4
	Number of measurements	=	4
	Corr among rep measures	=	0.5
Output:	Noncentrality parameter λ	=	20.7360000
	Critical F	=	2.9011196
	Numerator df	=	3.0000000
	Denominator df	=	32.0000000
	Total sample size	=	36
	Actual power	=	0.9620616

Table 3: Adherent vs non-adherent sample sizes	3MO	6MO	12MO
Adherent group	N=39	N=33	N=30
Non-adherent group	N=20	N=26	N=29

Variables and Measures

Sociodemographic variables

The majority of the participants (n=115) were male (n=66, 57%) and African American (n=99, 86%). Mean age was 55 years (SD ±5.3) and 38% (n=44) attended some college or vocational school. While 84% (n=97) of the participants reported living on their own or with family, 16% (n=18) were experiencing housing insecurity including living in hotels, government subsidized housing or being without shelter (Table 4).

Table 4: Demographics

Socioeconomics	'Fitbrain' study N=115	Let's Move (LM) Intervention group n=76	Let's Flex (SF) Attention Control group N=39
Age M(SD)	55.2 (± 5.3)	55.75 (± 5.1)	54.26 (± 5.5)
Gender			
Men	66 (57.4%)	48 (63.2%)	18 (46.2%)
Women	44 (38.3%)	25 (32.9%)	19 (48.7%)
Transgender	5 (4.4%)	3 (3.9%)	2 (5.1%)
Race			
Black	99 (86.1%)	64 (84.2%)	35 (89.8%)
White	12 (10.4%)	10 (13.2%)	2 (5.1%)
Others reported	4 (3.5%)	2 (2.6%)	2 (5.1%)
Education			
HS or less	66 (57.4%)	33 (53.9%)	25 (64.0%)
Some College/voc ed	44 (38.3%)	31 (40.8%)	13 (33.4%)
Graduate	5 (4.3%)	4 (5.2%)	1 (2.6%)

Housing			
Own home or apt	**83 (72.2%)**	**56 (73.6%)**	**27 (69.2%)**
With family	**14 (12.2%)**	**10 (13.2%)**	**4 (10.3%)**
Housing insecurity	**18 (15.6%)**	**10 (13.2%)**	**8 (20.5%)**
***No BL differences**			

Clinical variables

The most frequently occurring baseline CVD risk factors among study participants included hypertension (56%, n=64), smoking (31%, n=36), dyslipidemia (19%, n=22), Type 2 diabetes (13%, n=15), and high BMI. Approximately two-thirds, (n=76, 66%) of participants were overweight (BMI≥25), and 35% (n=40) were obese (BMI≥30) (Table 5).

Table 5: Baseline clinical variables	**Fitbrain M (SD)**	**LM M (SD)**	**SF M (SD)**
Six-minute walk test (m)	**446.7 (± 63.6)**	**446.2 (± 66.7)**	**447.6 (± 57.8)**
VO2 max (mL/kg-min)	**20.6 (± 5.3)**	**20.6 (± 5.6)**	**20.5 (± 4.9)**
BMI	**28.25 (± 6.1)**	**28.2 (± 6.2)**	**28.4 (± 5.9)**
Cholesterol	**179.7 mg/mL (± 33.9)**	**178.54 mg/mL (± 35.2)**	**181.9 mg/mL (± 31.8)**
CVD Risk Factors (yes)			
HTN	**65 (57.0%)**	**36 (47.3%)**	**28 (20.5%)**
BMI ≥30	**40 (35.0%)**	**27 (35.5%)**	**13 (33.3%)**
Smoking status	**36 (31.3%)**	**26 (34.2%)**	**10 (25.6%)**
Hyperlipidemia	**22 (19.1%)**	**18 (23.7%)**	**4 (10.3%)**
T2 Diabetes	**15 (13.0%)**	**10 (13.2%)**	**5 (12.8%)**
***No significant BL differences**			

Parent study data collection

Cardiorespiratory fitness testing

Cardiorespiratory fitness was measured prior to randomizing participants using the modified Balke treadmill test which was conducted at baseline by an exercise physiologist and supervising clinician to determine maximum heart rate using a symptom limited, gas inspired protocol (Balke and Ware, 1959, Gibbons et al., 2002). Target HR was calculated at 60% – 70% of the maximum HR achieved. During the test, VO2max was calculated (1 MET = resting metabolic rate, defined as oxygen uptake of 3.5 mL x kg^{-1} x min^{-1}). The study cardiologist reviewed the continuous electrocardiogram (EKG) during the treadmill test to determine if there were any ischemic or other changes that required further diagnostic testing using the American Heart Association/ American College of Cardiology (AHA/ACC) exercise testing guidelines (Fletcher et al., 2013).

AIM 1. Fitbit tracker validation. Consensus of the validation studies including the Fitbit Charge 2 activity trackers in a systematic review suggested that the trackers adequately measured HR during low to moderate intensity exercise such as walking (Nelson and Allen, 2019, Reddy et al., 2018, Tedesco et al., 2019). Fitbit uses microelectronic triaxial accelerometer technology and the Fitbit corporation's proprietary algorithms to measure distance and energy expenditure; all participants were provided with the same Fitbit model for data consistency (Fitbit; Fitbit Inc., San Francisco, CA, USA). Study designs for the Fitbit validations have included all genders, athletes, older adults, and adults with various physical barriers and comorbidities. Therefore, the validation of the Fitbit in a wide range of population samples supports the device's generalizability for OPWH.

AIM 2. Flow mediated dilation data collection. Prior to FMD measurement, participants were required to be fasting for >6 hours, without exercise for > 24 hours, avoid caffeine and smoking for > 6 hours. Assessment of endothelial function was conducted using FMD in the morning for all participants. Endothelium-dependent brachial artery FMD was obtained at baseline and at 6-months using a standardized protocol by an experienced research sonographer. Images were obtained before cuff inflation and at 60- and 90-seconds after the onset of reactive hyperemia induced by 5-minute cuff occlusion of the forearm. FMD and endothelium dependent vasodilation were reported as an increase in percent change in diameter from baseline. Figure 1 represents how FMD measures are obtained using the brachial artery. Values of FMD below 4.5% are indicative of endothelial dysfunction (Schroder et at., 1999).

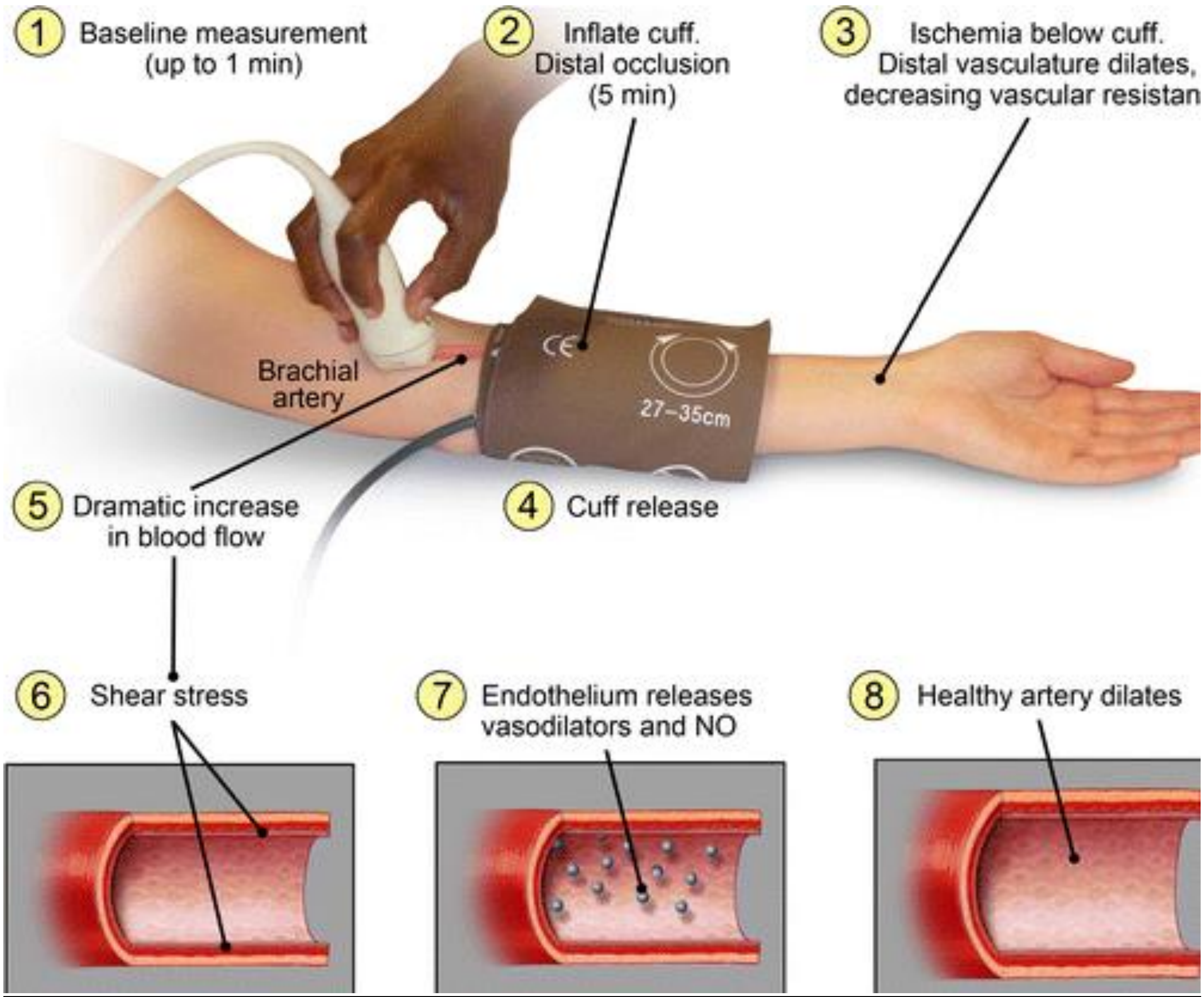


Figure 2. Flow-mediated dilation

AIM 3. Inflammatory biomarker data collection. Inflammatory biomarker collection by blood draw was performed per protocol for the Fitbrain study at baseline, 3-, 6-, and 12-months for all participants. Inflammatory indicators (TNF, sCD14, IL-6, hsCRP) were included in the assays. After overnight fasting, all blood samples were collected with an intravenous (IV) catheter placed into a forearm vein. Blood samples were collected after 30 minutes of rest between 8-10 am (to control for circadian variation) in EDTA or Heparin tubes and immediately placed on ice. Where indicated, blood was spun at 3,000 rpm for 15 minutes at 4C within 4 hours of collection. Plasma was aliquoted into pre-cooled siliconized polypropylene tubes and stored at -80C until assayed for relevant biomarkers. Processing and analyses of specimens was performed according to manufacturer ELISA recommendations.

Table 6: Variables, Measures and Timepoints

Variable	Measure	Baseline	3-months	6-months	12-months
VO2Max	Mod Balke treadmill	X			
Target HR	Mod Balke treadmill	X			
Exercise adherence	Fitbit Charge 2		X	X	X
Exercise adherence support	Motivational Interviewing	X	X	X	X
Endothelial function	FMD	X		X	
Inflammatory biomarkers: TNF, IL6, sCD14	Blood Draw	X	X	X	X

Data analysis

AIM 1. Systematic review of Fitbit Charge 2 validation studies for exercise tracking

Eight articles were examined in accordance with the eligibility criteria alignment and agreement among the authors and the research librarian. Concordance correlation coefficients (CCC) is a measurement of agreement between tracker and criterion devices considered to the “gold standard” to measure accurate HR in research studies such as the EKG or the Polar chest strap. The mean absolute percent error (MAPE) is the average of the individual absolute percent errors, which compared criterion devices and the Fitbit Charge 2.

AIM 2a and 3a: Exercise Adherence Assessment. Collection of step count intensity and cumulative number of minutes per day and heart rate was collected weekly from the intervention participants’ Fitbit account from baseline to 3 months, bimonthly from 3-6 months and monthly from 6-12 months. During the week after each data collection, participants were called to discuss target attainment, exercise barriers, and continuing exercise goals to encourage exercise prescription adherence. These procedures from the parent study were leveraged to calculate weekly exercise adherence (# days/week participants exercised at 60-70% HR maximum for at least 60 minutes/day)**. Adherence was considered met if the participants met their exercise prescription >70% of the days during the assessment week.** Target heart rate attainment and exercise prescription adherence was completed for the 12-month study duration.

AIM 2b: Flow mediated dilation and exercise adherence. Continuous variables are described as means ± SD and percentages were determined within the adherent and non-adherent exercise groups among the intervention group participants. Linear regression was performed to test associations of differences in FMD measurements between baseline and 6-months between the intervention and control groups with pertinent covariates and CVD risk factors. The change of FMD values between baseline and 6-mo was compared between the exercise intervention participants and the attention control group using T-tests. Additionally, T-tests were used to examine the change in FMD values between adherent, non-adherent, and attention control groups from baseline to 6-months.

AIM 3b. Inflammatory biomarker changes with exercise adherence

Due to right-tailed skewness of IL-6 values, natural log transformations were performed prior to analysis. The change of biomarker values between BL and 3-, 6- and 12-mo was calculated for each participant by subtracting the 2 values. Mean changes were calculated at each follow up timepoint stratifying the adherent and non-adherent groups. T-tests were then used to compare the mean difference between the stratified adherent and non-adherent exercise intervention participants. Multilevel linear modeling was performed within the exercise intervention group to examine the incremental change in the biomarker values over time in association with a cumulative exercise adherence level. Cumulative exercise adherence was calculated by adding up the number of timepoints at which exercise adherence was met (yes=1, no=0) (i.e., cumulative adherence values could range from 0, not adherent at any timepoint to 3, adherent at 3-, 6- and 12-month timepoints).

Summary

The Fitbit Charge 2 was hypothesized to adequately measure HR and exercise adherence while walking at moderate intensity (Chapter 2). Higher adherence of aerobic exercise was hypothesized to have greater changes in vascular endothelial function following 6-months and reduce inflammation following 12-months of aerobic exercise (Papers 2 and 3). The addition of exercise prescriptions and supportive mechanisms to encourage greater adherence to exercise was anticipated to foster improvements in cardiovascular health among OPWH.

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Chapter II

Systematic Review of Fitbit Charge 2 Validation Studies for Exercise Tracking

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Abstract

Context Current research grade devices have been validated to measure either heart rate (HR) by electrocardiogram (ECG) and the Polar chest strap, or step count by the ACTiGraph accelerometer. However, wearable activity trackers measuring HR and steps concurrently have been tested against research grade accelerometers and HR monitors with conflicting results. This review examines validation studies of the Fitbit Charge 2 (FBC2) for accurately measuring heart rate and step count and evaluates the device's reliability for recommended use by researchers and clinicians.

Eligibility Criterion and Study Selection Eight articles published between 2018 and 2019 identified by PubMed, CINHAL, Embase, Cochran, World of Science databases and hand-searches were examined based on inclusion criteria: heart rate and/or steps validation studies for the FBC2 in adult ambulatory populations.

Main Outcome Measures Measurement agreement between tracker and criterion devices - concordance correlation coefficients (CCC); average of the individual absolute percent errors-Mean absolute percent error (MAPE).

Results Studies that measured concordance correlation coefficients (CCC) (95%) found agreement between the FBC2 and criterion devices ranged between 26%-92% for HR monitoring decreasing in accuracy as exercise intensity increased. Inversely, CCC (95%) increased from 38%-99% for step counting when exercise intensity increased. Heart rate error between MAPE 9.21% - 68% and showed more error as exercise intensity increased. Step measurement error MAPE was 12% for healthy persons aged 24-72 years but was reported at 46% in an older population with heart failure.

Conclusions Relative agreement with criterion and low to moderate MAPE were consistent in most studies reviewed and supports validation of the FBC2 for accurately measuring HR at low or moderate exercise intensities. However, more investigation controlling testing and measurement congruency is needed to validate step capabilities. The literature is inconclusive regarding validation for step count and may not be suitable for recommended use by all populations.

Key words: Fitbit Charge 2, exercise tracker, heart rate, step count

Introduction

Background

Current universal guidelines recommend at least 150 minutes of weekly moderate intensity exercise of between 3-6 metabolic equivalent of task (MET) for persons across the health strata (1). Moderate intensity exercise can be achieved by brisk walking at a pace of 100 steps per minute or measured by 60-70% of heart rate (HR) maximum (2). Persons with chronic conditions who routinely participate in physical activity at moderate intensity for a minimum of 150 minutes per week exhibit significant improvements in cardiovascular function and reduction in inflammation (3-13). Incorporating exercise prescriptions into healthcare protocols show major benefits among a variety of health conditions including cardiovascular disease, depression, and HIV, as well as for preventative medicine (14). Providers need cost-effective, reliable wearable devices that accurately measure physical activity to assess and provide feedback to patients regarding their physical activity and to fully utilize the benefits of an exercise prescription.

Current research grade devices have been validated to measure either HR by electrocardiogram (ECG) (15), step count by the ACTi graph accelerometer (16), or sensing HR pulse with the Polar chest strap (17), but to date no wearable device is validated to measure both HR and steps concurrently. Exercise equipment manufacturers continuously develop multifunction activity trackers worn as watches that purport to accurately capture step and heart rate. However, these wearable activity trackers have been tested against research grade accelerometers and heart rate monitors with variable results. The Fitbit Charge 2 (FBC2) (Fitbit; Fitbit Inc., San Francisco, CA, USA) is a low-cost, wearable device that tracks steps and heart rate which has been studied among a variety of populations in home-based and healthcare settings. The purpose of this review is to examine validation studies of the FBC2 for accurately measuring HR and step count and evaluate the device's reliability to determine whether the device can be recommended by healthcare providers for use by patients.

Fitbit Charge 2: Features

Fitbit trackers use microelectronic triaxial accelerometer and proprietary algorithms to measure step gait and distance and continuous LED lighting to measure pulse continually. They are multifunction, wrist-worn devices that not only measure steps and heart rate but include a multitude of user-friendly features. The device must be wirelessly connected via Bluetooth to a network connected mobile phone. By this connectivity, the device may receive text and call notifications. Through special permissions the device may be connected to the owner's contact list to develop community support networks for exercise motivation. The device software often sends supportive messages to encourage movement throughout the day or once the owner achieves personal activity goals set by him/herself. The package also includes workout videos that can be accessed on the mobile phone application. The device also functions as a watch and has timer, mileage, relaxation, and stopwatch features.

Limitations of the Fitbit Charge 2

Because the device requires smart phone and internet access and has an average price-point of $150, the FBC2 may be a difficult option for low-income populations. Many basic and low functioning mobile phones lack the capability to support the Fitbit application. The watch is rechargeable and includes the charging cord which is easily misplaced and/or broken and needs 6-7 hours charging time that lasts approximately 3-4 days. Consumers report frequent watchband and equipment failure after 12-18 months of use. Additionally, the manufacturer does not report whether the updated models released about every 18 months have been altered significantly and, therefore, require updated testing and validation.

Methods

Design

This review was registered on PROSPERO and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in conducting the review and reporting the appropriate articles. Figure 1 illustrates the PRISMA flow diagram of included articles. Eight (8) validation articles published between 2018 and 2019 were examined for this review. The relatively short article timeline range is due in part to the exponential speed at which the commercially available wearable exercise tracker technology changes.

Strategy

The methods for this review included a search of PubMed, CINAHL, Cochran, Embase, World of Science, hand searches, and assistance by Emory University's Health Sciences Librarian, SL. Key words and combinations of the words used in the search were: Fitbit Charge 2, exercise tracker, activity tracker, activity monitor, heart rate, steps, and validation. Article inclusion criteria were heart rate and/or steps validation studies for the Fitbit Charge 2 in adult ambulatory populations.

Data Extraction

Each validation article included in this review was required to assess heart rate and step count accuracy. Articles were also included if they evaluated intra reliability testing of the Fitbit Charge 2 activity trackers between the FBC2 trackers used in the testing as well as inter reliability among other trackers assessed. Criterion measures for heart rate were based on the research validated electrocardiogram (ECG) (15) and the Polar chest strap (16) for ambulatory activities. Step count data was compared to the validated ACTi Graph wGT3X-BT (17).

To assess the tracker's accuracy, seven of the eight studies in this review explained the differences in the data collected by the FBC2 using the following measures (Table1): mean error, the difference between the criterion measure and the consumer device; mean absolute error, the average absolute distance between data from the consumer and the criterion devices; mean percent error or relative error rate, the difference between the criterion measure and the consumer device represented by a percentage; and mean absolute percent error (MAPE), the average of the individual absolute percent errors. Mean absolute percent error (MAPE) analyzes individual overestimation and underestimation values taken by the device, and therefore may offer more appropriate representation of the activity monitors when comparing studies.

Concordance correlation coefficients (CCC) 95% CI were used to describe strength of agreement between the devices in four studies (18-20). Inter-class correlation (ICC) is used when comparing multiple devices to each other and with the criterion. Additionally, because precise data congruency collected between consumer devices is unlikely, Bland-Altman (BA) analysis was used by 4 studies to evaluate proximity to data measured by criterion devices (18,20,23,24).

Another article was included in this validation review because the authors tested the FBC2 tracker's accuracy for measuring cardiorespiratory fitness compared to VO_{2max} (25). Cardiorespiratory fitness (CRF), defined as the circulatory and respiratory systems' transport and utilization of oxygen to the skeletal muscles, is typically measured by maximal graded exercise testing on a treadmill and measured in units of $mL*kg^{-1}min^{-1}$. Under strict laboratory protocols by a trained exercise physiologist using precise equipment, the "gold standard" for evaluating cardiorespiratory fitness levels is by maximal oxygen uptake or VO_{2max} (26). Researchers have found that low levels of CRF measured by VO_{2max} treadmill testing have been associated with cardiovascular disease risk (25,27,28). The Fitbit Charge 2 purports to evaluate CRF using proprietary algorithms which include an individual user's age, weight, height, resting HR and peak HR.

Articles were evaluated by 2 independent researchers and inclusion agreement was discussed in detail. Validation articles included in this review are listed in Table 1.

Risk of bias assessment

Each study was evaluated for risk of bias (Table 2). Criteria used for the assessment included randomization bias, recruitment bias, protocol deviation bias including criterion tool bias, missing outcome bias, and reporting bias. The selected studies were consistently evaluated as high quality based on these criteria with few concerns for risk of bias. Most of the concerns were regarding racially homogenous or small samples. One study included a single participant and most of the studies included majority white persons and healthy populations. The robvis tool was used to create the risk of bias Table 2 (31).

Results

Accuracy testing

Of the 8 studies found, n=5 reported MAPE values of the FBC2 against criterion for each study which are considered acceptable at <10%. The MAPE values for the studies evaluating HR accuracy include 9.21% (18), 10.79% (19), and 69% (24). Mean absolute percent error values investigating step count acuity were 12.36% (22), 46% for participants with HF, and 12% among healthy controls (21). Another study measured the HR difference between the FBC2 and criterion using relative error rate (RER) (light activity 5.36% - moderate activity 9.3%) (20).

Intra reliability testing

The 24-hour evaluation study found 91% CCC (CI 95%) (CI 0.896, 0.914) agreement of the criterion with the FBC2 in a single participant (male, 29 years) (18). Another study cited 92% CCC (CI 95%) (0.92, 0.93) agreement of the criterion with the FBC2 among their RCT including n=20 participants (mean age 27.5, SD 6, 55% female) while walking on a treadmill (19). Additionally, researchers collected data from n=30 (mean age 23.5, SD 3, 50% female) and found as exercise intensity increased, agreement decreased (20). At very light heart rate (HR) intensity ranging between 55-90 beats per minute (bpm), CCC (CI 95%) agreement between the criterion and the FBC2 was 89% (CI 0.79, 0.95) (20). When HR ranged between 90-120 bpm, CCC agreement was moderate at 55%, (CI 0.28, 0.74) and CCC was poor at 26% (CI 0.01, 0.46) when HR ranged between 110-150 (20). In contrast, step counting criterion reliability increased with treadmill speeds in a 3-day field study of n=15 (mean age 65.5, SD 12.6, 40% female) with heart failure compared to n=14 (mean age 43, SD 18.9, 64% female) healthy controls. (21). CCC (CI 95%) agreement of the step criterion with the FBC2 ranged from 38% (CI 0.00, 0.67) at 2.4 km/h (slow walk), 82% (CI 0.68, 0.97) at 3.0 km/h (moderate walk) to 99% (CI 0.98-1.0) at 3.6 km/h (brisk walk) (21).

Inter reliability testing

In a 24-hour, n=20 (mean age 70.2, SD 2.9, 55% female) study of older healthy adults in Ireland, results showed >0.89 ICC strength of agreement between the devices for step count evaluation (22). In addition, a study from Korea including n=51 participants (mean age 44.4, SD 16.6, 53% male, 100% Asian) who were undergoing electrophysiological study and ablation to treat paroxysmal tachycardia or supraventricular tachycardia found >0.98 ICC strength of agreement between the FBC2 and the ECG for heart rate monitoring (23). Recorded baseline heart rate monitoring with the FBC2 was within $\pm$ 5 beats per minute of the criterion ECG at 95% accuracy (23). However, device agreement of the FBC2 and criterion results by Pearson correlations assessed in other studies in the review were incongruent measuring 0.23 (poor) and 0.94 (equivalent) respectively (19,24).

Cardiorespiratory fitness assessment

Researchers compared the VO_{2max} values obtained from the standard treadmill tests with the CRF values estimated by the FBC2 (25). In a sample of n=65 healthy adults aged 18-45 (55% female), Bland-Altman analyses showed that the FBC2 CRF had a positive bias of 1.59 $mL*kg^{-1}min^{-1}$ when compared to the treadmill testing at 15s and a positive bias of 0.30 $mL*kg^{-1}min^{-1}$ at 60s with MAPE values <10% for each comparison (26).

Discussion

Heart rate validation

Four studies in this review assessed the FBC2 for HR accuracy validation. All except one study included healthy participants, aged 21-73 and generally reported more accuracy at lower intensity activity levels (18-23). Heart rate MAPE values while walking at low to moderate intensity levels, reflecting 9.21%, 10.79%, and 69%, reveal a wide interval of error results, with two of the three that are similar (18,19,24). Relative error rate (RER) reported by one group of researchers supports validation with their statistically moderate error rate at low to moderate walking intensity (light activity 5.36% - moderate activity 9.3%) (20). Another study used the pacing cycle lengths (PCL) data obtained during scheduled electrophysiological studies to evaluate the heart rate accuracy of the FBC2 (23). At 100 bpm, the FBC2 measured within ± 5 bpm when compared to the ECG criterion at a rate of 93% accuracy with Atrial pacing and 80% accuracy with Ventricular pacing (23). However, the FBC2 device became significantly less accurate at higher beats per minute (23). Heart rate and steps inherently fluctuate with intensity. These results are similar to the other studies reviewed.

Step count validation

In the Irish study of older adults, the FBC2 overestimated step count (MAPE 12.36%), which approaches the acceptable range of <10%, but had vastly different results than the study comparing the older HF subjects (MAPE 46%) to younger healthy controls (MAPE 12%) 21,22). The explanation for why the MAPE values of the 2 healthy populations in the 2 studies were similar while the MAPE values among the HF participants showed much higher error rates is unclear. However, alterations in gait and slower walking speed among the HF patients is likely a challenge for the FBC2 to track steps reliably and may be a concern when using this device to track steps in populations with ambulation limitations or considerable exercise intolerance due to symptom severity.

FBC2 as HR monitor

Reliability results as determined by criterion agreement with the FBC2 reported in this review gave markedly varied outcomes. Scores < .50 indicate poor reliability, .50 to .75 moderate reliability, and >.75 good reliability (29). Nelson et.al., 2019 and Reddy et.al., 2018 reported high CCC (CI 95%) scores of >90% (18,19). However, Thomson et.al., 2019, showed decreasing reliability from 56% (moderate) to 26% (poor) as HR intensity increased (20). Pearson coefficient results from two studies revealed the widest reliability agreement strength discrepancy from 0.23 (weak) and 0.94 (equivalent) (19,24). Finally, Bland Altman analysis plots revealed HR underestimation measured by the FBC2 compared to criterion at all intensity levels (18,20,24). The differences of the results may be caused by erratic arm movements or misplacement of the tracker bands as the participants move and perspiration. These varied results make it difficult to reach a definitive conclusion regarding reliability across intensity levels, but support reliability at low to moderate exercise dose levels.

FBC2 as step counter

Reliability of the FBC2 is in agreement with the step criterion which is the opposite of the HR results. CCC (CI 95%) agreement increased from 38% at lower speeds to 99% at a brisk walk (21). ICC results of >0.89 supports evidence for high agreement strength, between the FBC2 step counter compared to actigraphy (22).

Cardiovascular fitness validation

Researchers reported that the FBC2 could be validated to evaluate CRF in relatively young, healthy persons, especially those with a high level of fitness (26). Nearly 92% of the total participants in this study were classified as having high CRF (26). Although the study found CRF agreement between the FBC2 and the Balke treadmill test among users with lower fitness levels, the low numbers in the “good” or “poor” fitness leveled groups sampled in the study do not provide sufficient evidence of variation to determine validity nor is the sample representative of the general population who are typically less engaged in cardiorespiratory fitness activities. Validation studies are needed in populations with chronic conditions or who have ambulation challenges to further evaluate the CRF feature in the FBC2.

Study limitations

Validation consensus of the FBC2 is limited due to the studies' small sample sizes (n=1 – n=60) and non-standardized activity settings with some conducted in laboratories on treadmills and others in free-living conditions. Most of the HR examinations were only conducted using young and healthy subjects and may not be generalizable to populations who have chronic conditions or among older adults with other physical limitations. The study that compared HF subjects to healthy controls included far different age demographics (21). In addition, the review is limited by the small number of relevant studies available within a short time span which is due in part to the development speed of new technology. The Fitbit company released the FBC2 in 2016 and the FBC3 became available in 2018. The cost and research effort needed to perpetually study and validate new technology limits the viability of commercial wearable devices such as the FBC2 for research and use in primary care. Developers of commercial devices would benefit monetarily from strategic collaborations with healthcare researchers in producing devices that are technologically consistent and reliable. There is great potential for wide use of more accessible and affordable devices by healthcare providers worldwide.

Conclusion

Although the FBC2 has been validated for moderate heart rate and step count accuracy in some studies, more investigation controlling testing and measurement congruency is needed to validate both heart rate and step capabilities. The literature supports validity of the FBC2 to accurately monitor HR at low to moderate exercise intensities, but validation for step count is inconclusive and may not be suitable for recommended use by populations with gait speed or ambulation challenges.

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Conflicts of Interest and Sources of Funding

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Fig. 1 PRISMA 2009 Flow Diagram

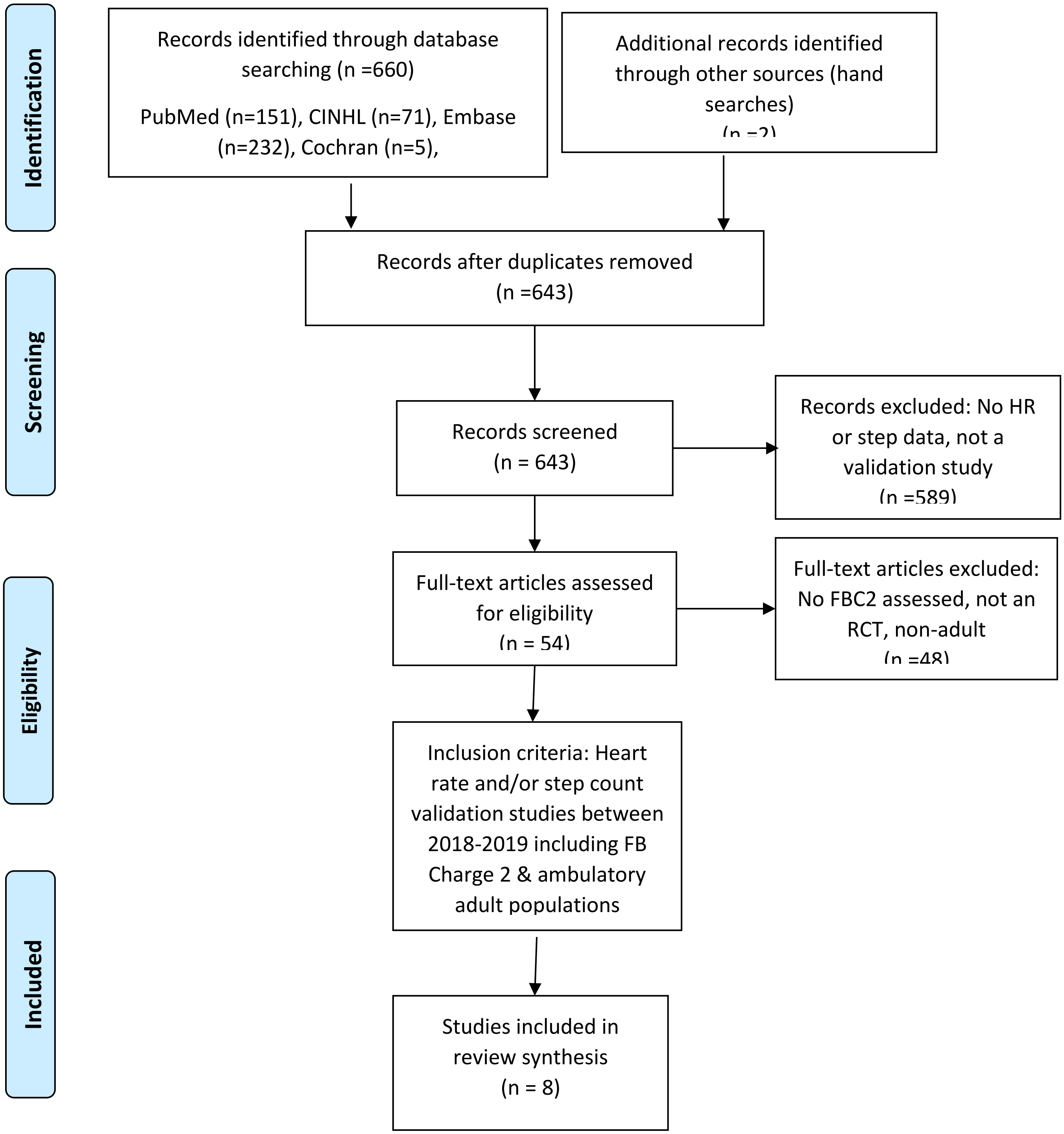

Table 1: Summary of measurements

Study/Year	Criterion measure	HR	Steps	CCC	ICC	PC	BA	ME	MAE	MPE/ RER	MAPE
Hwang J, et at. (2019)	ECG	X			X		X				
Klepin K, et at. (2019)	$VO2_{max}$	X			X						X
Nelson BW, et al (2019)	ECG	X		X			X		X		X
O'Driscoll R, et al. (2019)	Polar chest strap	X				X	X		X		X
Reddy RK, et al. (2018)	Polar chest strap	X		X		X		X		X	X
Tedesco S, et al (2019)	ActiGraph wGT3X-BT and New-Lifestyles NL2000i		X		X			X		X	X
Thomson EA, et al (2019)	ECG	X		X			X			X	
Vetrovsky T, et al. (2019)	ActiGraph wGT3X-BT		X	X							X

Key: **CCC**- Concordance correlation coefficients; **ICC** – Interclass correlation; **PC** - Pearson Correlation; **BA** - Bland-Altman analysis; MPE/RER – Mean percent error OR relative error rate; **MAPE** -Mean absolute percent error; ROB – Risk of Bias, overview of study qua assessment categories.

Table 2. Summary of study findings			
Study/Year	**Sample population**	**Design/Methods**	**Summary of findings**
Hwang J, et at. (2019)	N=51, mean age 44.4 (SD 16.6), n=24 female, Korean.	Compared FBC2 to ECG; participants with history of paroxysmal supraventricular tachyarrhythmia were undergoing electrophysiological study; baseline, HR during induced SVT and post ablation of SVT were measured	FBC2 accurately measures HR (94%) compared to EKG
Klepin K, et at. (2019)	N=60, mean age 31 (SD7.3), n=33 female, race not reported.	Compared FBC2 to VO^2_{max}; all healthy adults, study duration 1-week taking 3 GPS tracked, 15-minute outdoor runs and wearing continuously	FBC2 60 second cardiorespiratory fitness (CRF): highly associated with VO2max; MAPE 9.14%
Nelson BW, et al (2019)	N=1, age 29, white male.	Compared FBC2 to ECG; single subject healthy adult male used to minimize variable differences; 24-hour data collected across sedentary, walking, running, activities of daily living (ADLs) and sleeping.	FBC2: Mean difference -3.47 bpm compared to criterion and comparable tracker, MAE 5.96%, CCC 91%, compared to ECG over 24 hours; MAPE 9.21% walking
O'Driscoll R, et al. (2019)	N=59, mean age 44.2 (SD 14.1), n=41 females, European.	Compared FBC2 to Polar chest strap, activities evaluated in a 1-day laboratory setting included running, walking, cycling, mimicked ADLs, and sedentary conditions with rest periods between	FBC2: HR = CM, but not consistent across activity levels; MAPE 31% walking incline; MAPE 69% walking
Reddy RK, et al. (2018)	N=20, mean age 27.5 (SD 6.0), n=11 females, n=17 (85% white)	Compared FBC2 to Polar chest strap; 2-day data collection, all healthy adults, max oxygen uptake testing, included resistance exercise, interval training, and ADLs conditions	FBC2: > error high intensity exercise; MAPE 10.79 %
Tedesco S, et al (2019)	N= 20, mean age 70.2 (SD 2.9), n=11 females, all white (English/Irish).	Compared FBC2 to ActiGraph; 24-hour free-living data collection; all older, healthy adults; activities assessed included a range of moderate	All devices highly correlated (ICCs>0.89), FBC2 overcounted steps, MAPE 12.36%

		to vigorous walking and sleeping conditions	
Thomson EA, et al (2019)	N=30, mean age 23.5 (SD 3), n=15 females, race not reported.	Compared FBC2 to ECG; measurements taken at intervals: rest (3min), standing (2min), treadmill (every 3min with gradual speed and uphill increase (until volitional fatigue), recovery.	FBC2 error rate (3.9-13.5%). RER per activity level: light (5.36%), moderate (9.20%), vigorous (11%).
Vetrovsky T, et al. (2019)	Healthy control participants: n=15, mean age 65.5 (SD 12.6), n=6 females. HF field-based study: n=14, mean age 43.3 (SD 18.9), n=9 females. (Czech Republic)	Compared FBC2 to accelerometer, main purpose was to evaluate step accuracy of activity trackers in persons with heart failure (HF); laboratory and field study	FBC2: Healthy participants: MAPE 12%; HF study: MAPE 46%; > correlation low speeds on treadmill.

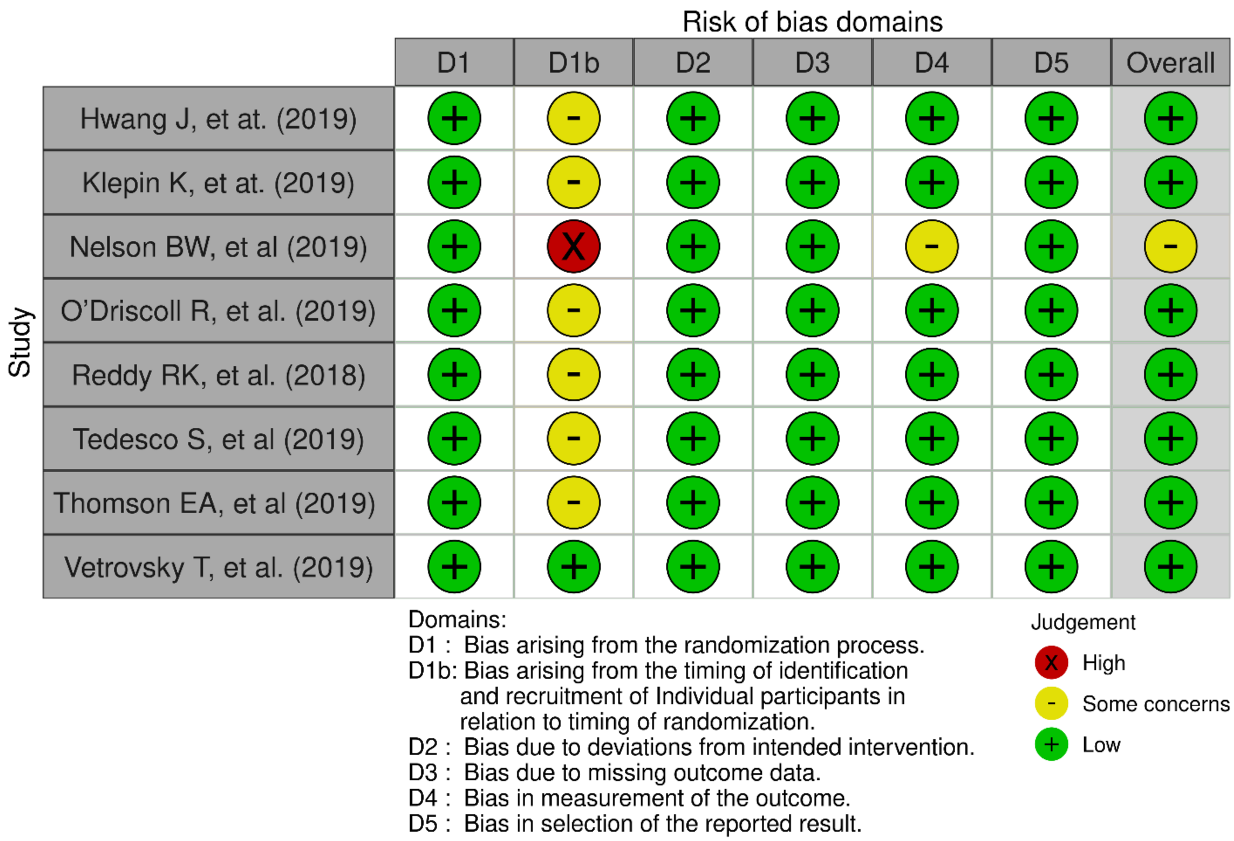

Figure 2. Risk of bias assessment

Chapter III

Higher exercise adherence among older persons with HIV is associated with improved flow mediated dilation

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FMD changes with exercise among older PWH

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Persons with HIV experience endothelial dysfunction due in part to chronic inflammation that increases their risk for poor vascular function and cardiovascular disease (CVD). Routine aerobic exercise of moderate to vigorous physical activity has been shown to improve vascular function, but the dose of exercise required for improvement among older persons with HIV (OPWH) has not been established.

The purpose of this study was to examine the relationship between exercise adherence and endothelial vascular function among OPWH.

Participants (n=115, mean age 55, 65% male, 82% Black) were evaluated at baseline (BL) for cardiorespiratory fitness using the modified Balke $VO2_{max}$ test. Endothelial vascular function was measured by flow-mediated dilation (FMD) at BL and 6-months. Participants were provided with activity trackers and an exercise prescription based on their individual target heart rate at 60-70 % intensity and asked to walk a minimum of 240 minutes per week. T-tests were used to examine the change in FMD between groups from baseline to 6-months.

The change in FMD was not significant between the intervention and attention control groups but was significantly improved among the participants who were adherent to their exercise prescription at least 70% of the time compared to those who were not adherent (adh=0.58, not adh= -1.61, p=0.025) at 6-months.

Findings from this study suggest that higher exercise dose may improve endothelial vascular function among OPWH and in turn reduce CVD risk.

Key words: Aerobic exercise, cardiovascular disease, HIV, flow-mediated vasodilation, vascular endothelial function

Introduction

Due to advances in antiretroviral therapy (ART), HIV is now considered a chronic illness, with longevity approaching that of the general population (Nasi, 2017, Ballocca, 2017). Chronic inflammation and cardiovascular disease (CVD), more commonly seen in the aging population, are occurring with greater frequency in PWH who are on average at least a decade younger than in persons without HIV. (Nasi et al., 2017, Ballocca et al., 2017, Duprez et al., 2012, Shah et al., 2018, Tatanji et al., 2020). Despite optimal medication adherence and viral load suppression, older persons with HIV (OPWH) who are 40 years of age or older have higher levels of sustained inflammation due in part to the disease itself as well as heightened stress associated with social determinants of health than those without HIV (Neuhaus et al., 2010, Hanna et al., 2017, Nordell et al., 2014, Samji et al., 2013, Denning and DiNenno, 2008). In addition, there is a well-established health disparity in longevity outcomes among OPWH that is associated with race (CDC, 2017). Effective interventions that are accessible, low-cost, and scalable in many community settings are greatly needed to reduce the risk of CVD among OPWH.

Exercise defined as structured, planned, and repetitive physical activity, is a commonly used approach to improve cardiovascular fitness (Caspersen, Powel, Christenson, 1985). Moderate intensity aerobic exercise that meets 60-70% of an individual's maximum HR for 150 minutes per week is established to have cardiovascular benefits that include enhancing endothelial function, CVD risk reduction, and improvements in overall health for people with and without HIV across the health strata (ODPHP, 2019, Hotting and Roder, 2013, Jaggers and Hand, 2016, Nwaka et al., 2019, Owusu et al., 2020, Pedro et al., 2017, Roos et al., 2014, Sallam and Laher, 2016, Vingren et al., 2017, Zheng et al., 2014). However, less than half of adults meet this recommendation (ODPHP, 2019). Motivational interviewing (MI), a behavior change strategy, has been found to moderately improve exercise adherence among persons with chronic conditions, but not including HIV (Halloran et al., 2017). MI techniques have, however, been effective in increasing adherence to ART regimens among PWH (Hogan et al., 2020) and may be a promising approach to engage this high-risk group in consistent and frequent aerobic exercise.

Exercise adherence that meets the minimum CDC recommendations produces healthful effects on the cardiovascular system through several mechanisms including maintaining and improving vascular endothelial functioning. Endothelial function is measured with brachial artery flow-mediated vasodilation (FMD) and is used to identify individuals at high risk for vascular dysfunction and CVD (Black et al., 2009). Factors associated with vascular endothelial dysfunction including lower muscle oxygenation and diminished arterial contraction have been reported as more common among PWH compared to persons without HIV (Volino-Souza et al., 2020). Aerobic and resistance exercise is reported to mitigate CVD risk by improving endothelial function, but few studies have evaluated whether aerobic exercise enhances endothelial function among PWH.

This need was addressed in a randomized controlled trial that tested the effects of a moderate intensity, at-home, aerobic exercise program among a sample of mostly Black, older PWH (OPWH). The study herein reports the effects of the intervention on FMD after six months of intervention compared to an attention control. Analysis of the dose of exercise on FMD was additionally investigated. It was hypothesized that the intervention and higher doses of the intervention would improve endothelial function.

Methods

Ethical considerations

The study was approved by Emory University IRB#00080302. All participants were consented according to Emory University IRB protocols.

Study design

The study was a two-arm randomized controlled trial that tested the effects of an aerobic exercise intervention on cognitive function, inflammatory biomarkers, and endothelial function among OPWH with a minimum of 2 cardiovascular risk factors participating in either a walking group (Let's Move intervention) or a flexibility and stretching group (Let's Flex, attention control). Participants were followed for 52 weeks. Let's Move intervention participants (n=76) were provided an exercise prescription based on their individual target HR at 60 - 70 % of their maximum heart rate and provided with activity trackers to monitor exercise adherence. Participants were asked to walk 5 times per week for 30 minutes initially and gradually progressed to 60 minutes by week 12 (Table 1). The study protocol increased the exercise prescription from the standard 150 minutes per week to 300 minutes of moderate to vigorous physical activity (MVPA) for the participants in the exercise intervention to maximize their cardiovascular benefits based on a review of the literature citing greater physiological improvements with higher exercise dose (Jaggers and Hand, 2014). Let's Flex participants (n=39) were taught a series of head, neck, shoulder, back, and lower body flexibility movements and stretches, provided a written guide and prescription, and asked to perform the flexibility/stretching movements 5-times weekly for 30-minutes daily. This attention control protocol has been used in prior studies by the Fitbrain study authors to influence the outcomes of interest (Gary et al., 2019). The primary aim of this study focused on the endothelial function measured at baseline (BL) and at 6-months using standardized ultrasound protocols (Corretti, et al., 2002, Alley et al., 2014).

Exercise prescription adherence assessment

The study team accessed the participant exercise tracker accounts via data downloaded from the Fitbit Charge 2 exercise tracker (Fitbit Inc., San Francisco, CA) and recorded the number of minutes participants reached their target HR as prescribed in the baseline assessment. For each week in the first 12 weeks of participation, target HR was monitored daily. On weeks-1 through 4, adherence was determined by evaluating whether the participant walked at 60% of their maximum heart rate for at least 30 minutes per day and 5 days per week (Table 2). During weeks-5 through 8, participants were asked to increase walking time to 45 minutes and continue walking at 60% HR maximum. At week 9 through week 12, the participants were asked to increase to 70% of their HR maximum for 45 minutes for at least 5 days per week (Table 2). Beginning at week 13, participants were asked to increase their walking time to at least 60 minutes per day and walk at 70% of their HR maximum for at least 5 days per week and continue at this exercise dose for the remaining duration of the study through 36 weeks (Table 2).

The number of minutes per day and days per week the participant reached their target HR were recorded on the subsequent week following the activity and at scheduled timepoints throughout the study duration. Assessment intervals for the first 12 weeks were weekly and then change in subsequent weeks (Table 2). For each assessment interval, adherence was considered met if the participant met the exercise prescription at least 70% of the days in the previous assessment interval. This minimum of >150 minutes of moderate to vigorous aerobic activity was established by the American Heart Association to support health and cardiovascular benefits. Additionally, exercise dose >160 minutes per week and at least 70% of maximum HR has been shown to induce a positive change in FMD among health young males but has not been studied among PWH (Birk et al., 2012).

Motivational Interviewing guided interaction

Following each exercise assessment week, participants were contacted via telephone by the research staff who were trained to use Motivational Interviewing (MI) techniques (Miller and Rollnick, 2002). Developed by clinical psychologists Miller and Rollnick, MI is a behavioral change model that has been used successfully for smoking cessation, excess weight loss, and exercise participation (Miller and Rollnick, 2002). Staff members who were trained in MI techniques evaluated successes and barriers of the participants' exercise prescription adherence during the MI sessions and assessments, which were dependent on the dose of exercise achieved the previous week. For example, future exercise goals and plans for consistency and/or modification were reviewed with participants. In addition, participants were encouraged to enlist friends, family, and similar cultural groups to support their exercise goals and adherence.

Fitbrain study recruitment and sample

Participants for the study were recruited as a convenience sample from infectious disease clinics in the metro-Atlanta area. Participants were randomly assigned after BL assessments were completed by intervention (n=76) or attention control groups (n=39) using 2:1 intervention/control block randomization procedures. Data collectors were blinded to group assignments. Inclusion criteria included: men and women aged 40 and over with HIV and willing to participate, English speaking, living independently and within a 50-mile radius of Atlanta, had a minimum of 2 CVD risk factors (e.g., diabetes, dyslipidemia, hypertension, overweight/obesity), clinically stable and on ART 6 months before enrollment. Exclusion criteria: (a) hospitalized within 60-days before enrollment, (b) involved in any structured exercise program or exercising 3 or more times per week for a minimum of 30 minutes, (c) involved in any weight loss program, (d) had a medical or physical condition that would preclude participation in the exercise component of the study (e) pregnant, (f) intellectual disabilities, major depression, psychotic disorders or were diagnosed with other confounding neuro-medical conditions that would interfere with neurocognitive measurement.

Measurement of endothelial function

There are significant associations between endothelial dysfunction and CVD risk (Quyyumi and Patel, 2010). Further, more than a decade of research has used FMD as a non-invasive approach for measuring endothelial function and as a method to evaluate vascular changes following an intervention such as exercise (Birk et al., 2012, McCully, 2012, Quyyumi and Patel, 2010). Prior to FMD measurement, participants were required to be fasting for >6 hours, without exercise for > 24 hours, avoid caffeine and smoking for > 6 hours. Assessment of endothelial function was conducted using FMD in the morning for all participants. Endothelium-dependent brachial artery FMD was obtained at baseline and at 6-months using a standardized protocol by an experienced research sonographer. Images were obtained before cuff inflation and at 60- and 90-seconds after the onset of reactive hyperemia induced by 5-minute cuff occlusion of the forearm. FMD and endothelium dependent vasodilation were reported as an increase in percent change in diameter from baseline. Figure 1 represents how FMD measures are obtained using the brachial artery. Values of FMD below 4.5% are indicative of endothelial dysfunction (Schroder et at., 1999).

Data analysis

Continuous variables are described as means ± SD and percentages were determined within the adherent and non-adherent exercise groups among the intervention group participants. Linear regression was performed to test associations of differences in FMD measurements between baseline and 6-months with exercise dose among the intervention group participants with pertinent covariates and CVD risk factors. The change of FMD values between baseline and 6-mo was compared between the exercise intervention participants and the attention control group using T-tests. Additionally, T-tests were used to examine the change in FMD values between adherent, non-adherent, and attention control groups from baseline to 6-months.

Results

Baseline characteristics

The majority of the participants (n=115) were male (n=66, 57%) and African American (n=99, 86%) (Table 3). Mean age was 55 years (SD ±5.3) (Table 3) and 38% (n=44) attended some college or vocational school (Table 3). While 84% (n=97) of the participants reported living on their own or with family, 16% (n=18) were experiencing housing insecurity including living in hotels, government subsidized housing or being without shelter (Table 3). The most frequently occurring baseline CVD risk factors among study participants included hypertension (56%, n=64), smoking (31%, n=36), dyslipidemia (19%, n=22), Type 2 diabetes (13%, n=15), and high BMI. Approximately two-thirds, (n=76, 66%) of participants were overweight (BMI≥25), and 35% (n=40) were obese (BMI≥30) (Table 3). Social determinants and CVD risk variables were tested covariates with FMD in linear regression models and none were significantly associated with the outcome.

Change in FMD

Mean %FMD among participants in the intervention group after 6-months of activity was 4.3% (SD ±2.1). The mean FMD among the attention control group at 6-months was 5.5% (SD ±2.5). The percent change in FMD at 60 seconds decreased from baseline to 6-months among the participants in both groups. For the intervention group, the mean change was -0.45 (SD ± 3.9) percentage points. Among the attention controls the mean change was –0.06 (SD ± 4.1), which was not significantly different from the intervention group (p=0.652) (Table 4). Similarly, there was not a significant difference between groups in their mean change of % FMD at 90 seconds (p=0.291) (Table 4). However, adherence to the exercise prescription at 70% or higher showed a significant improvement in FMD% at 60 seconds (p=0.025). Specifically, participants who did not meet exercise adherence goals (–1.61%, SD ± 4.5) and exhibited worse endothelial function at 6-months compared to those who did meet the exercise adherence prescription (0.58%, SD ± 3.1) (Table 4). There was also a significant difference between these groups in % FMD at 90 seconds (p=0.016) for those who adhered versus not meeting adherence (Table 4). Figure 2 shows the comparison of the difference between BL and 6-months of FMD at 60s between adherence groups and the attention control results.

Exercise adherence

The average exercise adherence among the general population is less than 150 minutes per week of moderate to vigorous physical activity (ODPHP, 2019). The protocol for participants in the exercise intervention arm of the study was to walk at least 300 minutes per week at 60-70% of their maximum HR. Of participants in the exercise intervention arm, 60 % met that threshold at 6-months. Adherence among participants in the attention control group declined over time. Among the attention control participants who self-reported performing their stretching and flexibility exercises, an average of 53% were adherent to their stretching and flexibility exercises at 6-months.

Discussion

Results from this analysis examining FMD changes with aerobic exercise showed that moderate intensity walking may improve endothelial function in OPWH. Previous assessment of physical activity among PWH found less than 25% reported exercising at the recommended 150 minutes per week minimum (Fillipas, et al, 2008). In this analysis, where 60% of the participants met their exercise prescription of walking at 60-70% of their maximum HR, 300 minutes per week for at least 70% of the time, higher exercise dose was associated with a greater improvement in FMD over 6-months and supports study hypotheses.

The CDC reports that HIV infection, which is associated with higher rates of poverty, housing insecurity, and food insufficiency, affects Black persons at higher rates as compared to other demographics (CDC, 2017). Additionally, a recent scientific statement by the American Heart Association reported that lower socioeconomic status and stress-related racism places Black persons at 2 to 3 times higher risk for mortality from CVD than whites (Havranek et al., 2015). In our study, 86% of the participants identified as Black. Although not directly tested, our findings suggest that this type of intervention may be beneficial to address disparities in CVD-related illness among Black persons living with HIV.

Many participants in the study were overweight or obese with multiple comorbidities including hypertension, Type II diabetes, dyslipidemia, and smoking which may have influenced the degree of change in vascular endothelial function due to the deleterious effects of these comorbidities on arterial stiffness. (Wing, 2016, Ballocca et al., 2017). There were some reports of pain attributed to high BMI, prior injuries, neuropathy and arthritis among participants during the follow calls which were identified as deterrents to exercise. Hypertension constrains the flexibility of blood vessels and diabetes reduces the biochemical nitric oxide (NO) which leads to endothelial dysfunction (Antony, Lerebours, and Nitenberg, 1995, Cosentino et al., 1997) The rate at which the vascular endothelium responds to an increase in blood flow during exercise is a reliable indicator of cardiovascular function. (Black et al., 2009). Flexibility within the vascular endothelia promotes normally functioning vasodilation and deters platelet aggregation (Black et al., 2009, Corretti et al., 2002). Flow-mediated dilation (FMD) measures the aptitude of the endothelium to respond to a sudden change in blood flow using a brachial artery cuff constricted for 5 minutes (Black et al., 2009, Corretti et al., 2002, Alley et al., 2014). As flexibility or vascular elasticity improves, FMD increases. A study examining the sensitivity of FMD to predict cardiac artery disease (CAD) found that an FMD measurement of <4.5% was reliably associated with CAD (Schroder et at., 1999). In this study participants in the intervention group on average had %FMD values < 4.5% after 6-months of activity which is indicative of CVD. The %FMD values among the attention control group on average were above 4.5%. Although there was not a significant difference between the change in FMD comparing the intervention group and the attention control group, higher exercise dose among the participants in the intervention group did produce %FMD improvement (Table 4, Fig 3). This analysis showed that as exercise dose increased among the participants in the exercise intervention group, there was a greater change in FMD from baseline to 6-months suggesting they had an improvement in the elasticity or less stiffness in the vasculature.

Additionally, there was low attrition in the study (<10%). Current research also suggests that at home, self-motivated exercise increases adherence to exercise prescriptions and may be more feasible and scalable in real-world conditions as an adjunct therapy to HIV treatment (Ashworth et al., 2005, Webel et al., 2015). Consistent contact with the participants may have further increased engagement in this study. The exercise intervention group maintained above the 150 minutes per week U.S. average adherence to their exercise protocols which highlighted the effectiveness of the walking intervention on vascular function improvement (ODPHP, 2019). However, participants in the attention control arm showed a marked decrease in their self-reported adherence to the stretching and flexibility exercises and had a negative FMD change after 6-months of performing stretching and flexibility exercises. One group of qualitative researchers pilot tested a 4-month short message (SMS) and multimedia message service (MMS) to improve exercise adherence among PWH (Montoya et al., 2015). Focus groups determined that self-monitoring and family support were facilitators to exercise adherence which is similar to the results in our study (Montoya et al., 2015).

Another research group qualitatively examined a community-based exercise program for PWH (Li et al., 2017). The study found that PWH preferred the social interaction and peer support of group activities (Li et al., 2017). These researchers used similar techniques to the motivational interviewing techniques used in this study (Li et al., 2017). Targeted question and response paraphrasing directed at an individual's perceived barriers and experienced successes to exercise adherence, provided individuals space and opportunity to problem solve and plan next steps to achieve subsequent exercise goals (Bandura, 1997, Li et al., 2017, Miller and Rollnick, 2002). Among the responses that emerged during the follow up calls in this study were that many participants found support for their walking within their families and communities and made new connections with one another in the study. Using MI techniques to support positive exercise behavior change among the exercise intervention participants combined with the physical improvement experienced by the participants who were exercising at higher doses seemed to be an effective strategy to improve vascular function.

Strengths

The strengths of the study included low attrition and significant CVD risk reduction as evidenced by improved endothelial function among those who adhered to the exercise goals 70% of the time. Participant satisfaction with the exercise program was high with many commenting that the exercise program was a positive way to change their health outcomes versus focusing on primarily on medication adherence. Findings from this study suggest that a low cost, flexible, home-based exercise program may potentially inform a future community-based model.

Limitations

Despite the strengths of the study, there were also some limitations. Although there is evidence in the literature that racial discrimination and stressors contribute to negative cardiovascular outcomes among Black persons with HIV, this study was not designed to directly test this important issue. Notably, exercise adherence may have been negatively influenced by pain with exercise related to the presence of arthritis, prior musculoskeletal injury, high BMI, or peripheral neuropathy which were common physical complaints among the participants in the study. Participants experiencing pain were advised to rest and to consult their physician if pain inhibited their activities of daily living. Additionally, the exercise trackers required internet access for data transfer from the wearable device to a cell phone. When connectivity was interrupted, data transfer was delayed until the tracker could be reconnected by the study staff, thus delaying exercise data acquisition. The exercise data of participants without cell phones or sufficient cellular capability was downloaded to a designated study cell phone through scheduling and meeting with the study staff. Watchband breakage also inhibited data transfer because the watch required wrist wearing and skin contact for HR detection. However, the frequent remote tracking and fast action (usually within 4 hours) to reconnect the devices and replace watchbands by the research staff reduced the time of data interruption.

Future directions

Based on the findings from this study, additional research is needed to test the implementation of an adjunctive exercise prescription with drug therapy to lower the rapidly increasing CVD risk among this population. More studies are also needed modeling the consistent and frequent feedback protocols likely responsible for the successful exercise adherence uptake shown in this study. This consistent contact model provides a unique opportunity to foster exercise adherence. Providing participants with goal directed exercise therapy and progression using exercise tracking and remote monitoring may be useful tools in future research. Further biological testing may also determine additional health outcome benefits of the exercise intervention among the participants who remained adherent throughout the 12-month study duration. Social determinants of health are important considerations when discussing the viability of interventions within affected communities as well as when assessing the compounding factors of CVD and warrant targeted approaches to understand more about these relationships. Additional research is needed in larger, more diverse samples of OPWH to examine the influence of other modes of exercise and access to exercise on endothelial vascular function.

Conclusions

Higher adherence and dose of aerobic exercise was associated with greater changes in vascular endothelial function following 6-months of aerobic exercise. The addition of exercise prescriptions and supportive mechanisms to encourage greater adherence to exercise may foster improvements in cardiovascular health among OPWH.

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Table 1: Exercise Rx	**Weeks 1-2**	**Weeks 3-4**	**Weeks 5-7**	**Weeks 8-9**	**Weeks 10-12**	**Weeks 13-36 (maintenance)**
Intensity	60%	60%	70%	70%	70%	70%
Duration	30 minutes	45 minutes	45 minutes	60 minutes	60 minutes	60 minutes
Frequency	5 days/wk	5 days/wk	5 days/wk	5 days/wk	5 days/wk	5 days/wk

Table 2: Fitbit assessment schedule			
Week	**1-12**	**14,16,18,20,22,24**	**28, 32, 36**
Frequency	Weekly	Bi-monthly	Monthly

Table 3: Demographics			
Socioeconomics	**'Fitbrain' study N=115**	**Let's Move Intervention group n=76**	**Let's Flex Attention Control group N=39**
Gender			
Men	**66 (57.4%)**	**48 (63.2%)**	**18 (46.2%)**
Women	**44 (38.3%)**	**25 (32.9%)**	**19 (48.7%)**
Transgender	**5 (4.4%)**	**3 (3.9%)**	**2 (5.1%)**
Race			
Black	**99 (86.1%)**	**64 (84.2%)**	**35 (89.8%)**
White	**12 (10.4%)**	**10 (13.2%)**	**2 (5.1%)**
Others reported	**4 (3.5%)**	**2 (2.6%)**	**2 (5.1%)**
Education			
HS or less	**66 (57.4%)**	**33 (53.9%)**	**25 (64.0%)**
Some College/voc ed	**44 (38.3%)**	**31 (40.8%)**	**13 (33.4%)**
Graduate	**5 (4.3%)**	**4 (5.2%)**	**1 (2.6%)**
Housing			
Own home or apt	**83 (72.2%)**	**56 (73.6%)**	**27 (69.2%)**
With family	**14 (12.2%)**	**10 (13.2%)**	**4 (10.3%)**
Housing insecurity	**18 (15.6%)**	**10 (13.2%)**	**8 (20.5%)**
***No BL differences**			

Baseline clinical variables	M (SD)	M (SD)	M (SD)
Age	55.2 (± 5.3)	55.75 (± 5.1)	54.26 (± 5.5)
Six-minute walk test (m)	446.7 (± 63.6)	446.2 (± 66.7)	447.6 (± 57.8)
VO2 max (mL/kg-min)	20.6 (± 5.3)	20.6 (± 5.6)	20.5 (± 4.9)
BMI	28.25 (± 6.1)	28.2 (± 6.2)	28.4 (± 5.9)
Cholesterol	179.7 mg/mL (± 33.9)	178.54 mg/mL (± 35.2)	181.9 mg/mL (± 31.8)
CVD Risk Factors (yes) • T2 Diabetes • Smoking status • HTN • Hyperlipidemia • BMI ≥30 *No significant BL differences	 15 (13.0%) 36 (31.3%) 65 (57.0%) 22 (19.1%) 40 (35.0%)	 10 (13.2%) 26 (34.2%) 36 (47.3%) 18 (23.7%) 27 (35.5%)	 5 (12.8%) 10 (25.6%) 28 (20.5%) 4 (10.3%) 13 (33.3%)

Table 4: T-Test of FMD change between baseline and 6-months	Baseline	6-months M (±SD)	% Difference btw BL – 6Mo	P-value (df)
FMD % at 60 seconds LM (n=76) SF (n=39)	4.62 (±3.2) 5.64 (±3.8)	4.31 (±2.1) 5.48 (±2.5)	-0.45 -0.06	0.652 (95)
FMD % at 90 seconds LM (n=64) SF (n=33)	3.17 (±2.7)	2.87 (±1.8)	-0.35	0.291

	3.96 (±2.9)	3.88 (±2.1)	-0.06	(95)
FMD % @ 60 seconds				
Met exercise Rx	**4.13 (±2.7)**	**4.67 (±2.3)**	**0.58**	
Not met exercise Rx	**5.13 (±3.7)**	**3.90 (±1.8)**	**-1.61**	**0.025 (62)**
FMD % @ 90 seconds				
Met exercise Rx	**2.73 (±2.5)**	**3.32 (±1.9)**	**0.54**	
Not met exercise Rx	**3.63 (±3.2)**	**2.39 (±1.5)**	**-1.35**	**0.016 (62)**

Fig. 1. Flow-mediated dilation Permission by Springer Nature

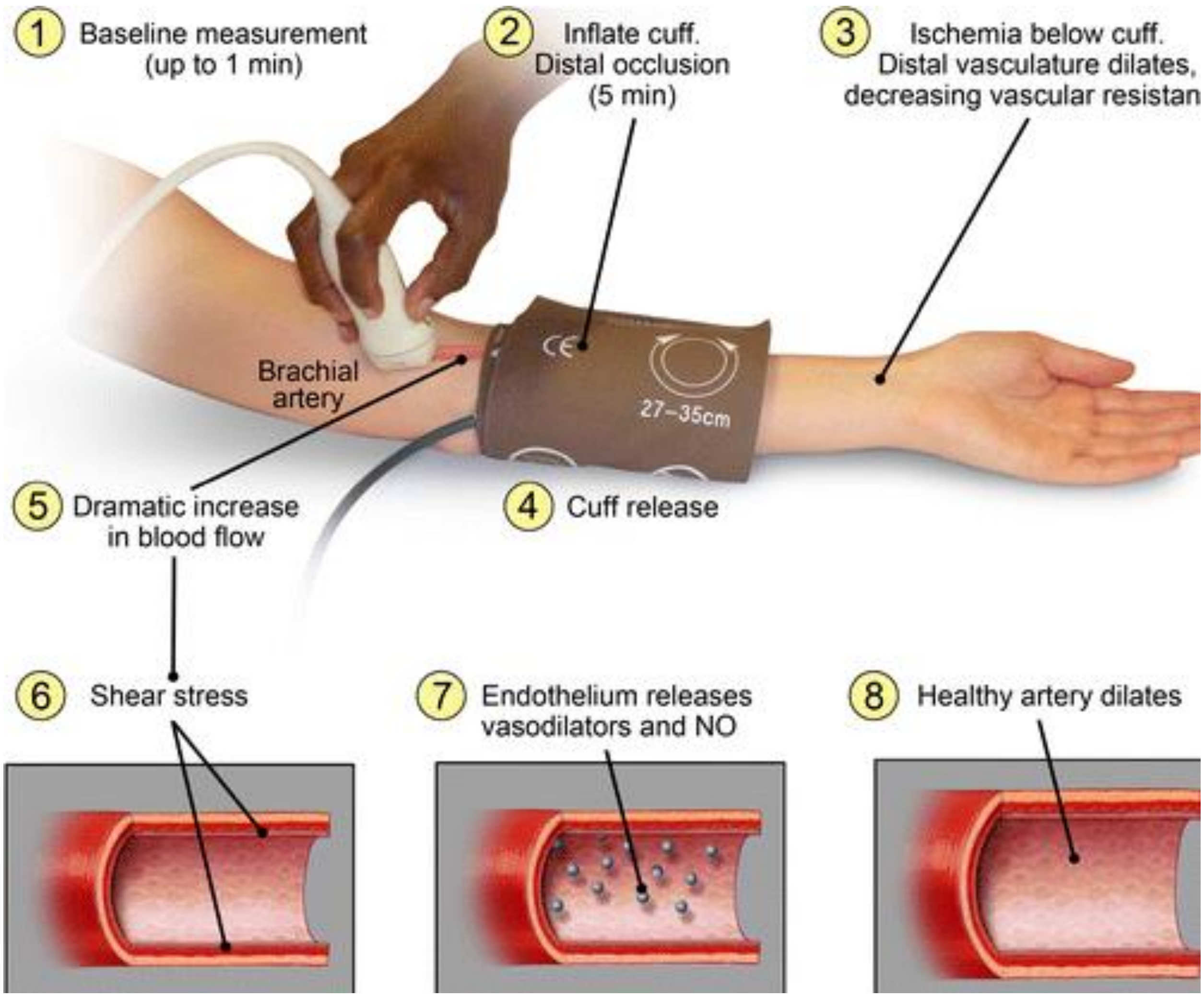
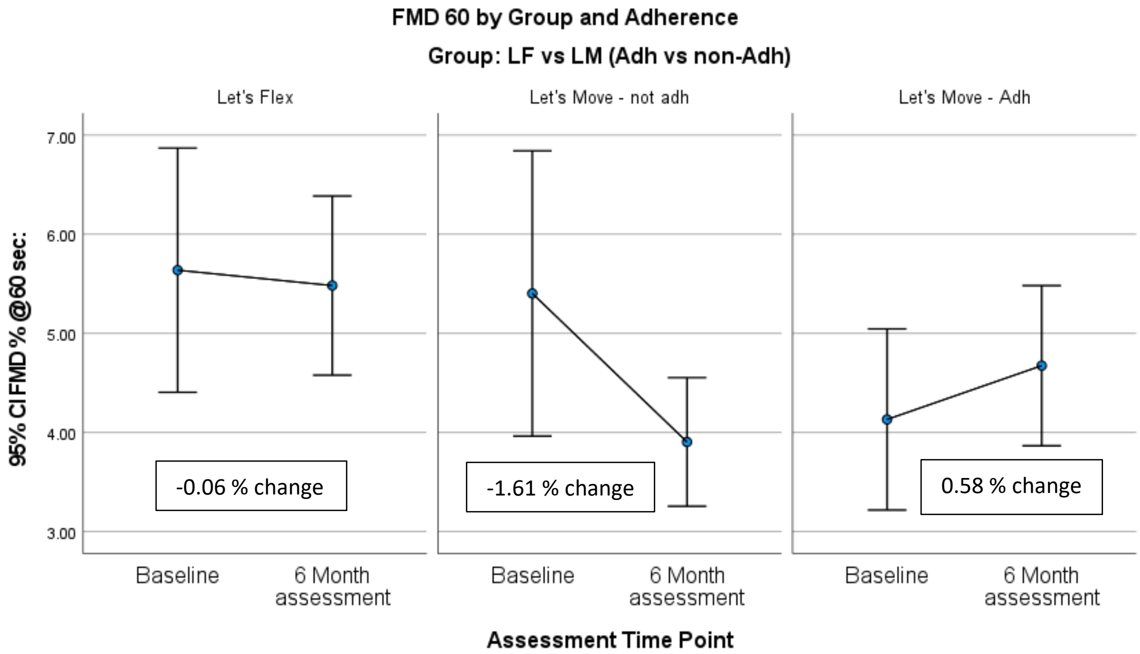


Figure 2: T-test Comparison by group of FMD at 60s



Chapter IV

Higher exercise adherence lowers inflammation among older persons with HIV

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Inflammation reduction with exercise among older PWH

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Persons with HIV (PWH) experience sustained inflammation that increases their risk for cardiovascular disease (CVD) and mortality. Routine aerobic exercise of moderate to vigorous intensity has been shown to lower inflammatory cytokine biomarker levels, but the dose of exercise adherence required for improvement among older PWH (OPWH) has not been established.

The purpose of this study was to examine the relationship between exercise adherence and inflammatory biomarkers among OPWH.

Participants were evaluated at baseline for cardiorespiratory fitness and target heart rate (HR) using the modified Balke $VO2_{max}$ test. Inflammatory biomarkers tumor necrosis factor (TNF), interleukin-6 (IL6), and the monocyte binding protein soluble CD14 were measured at BL, 3-, 6- and 12-months. Activity trackers and exercise prescriptions were provided based on participants' individual target HR at 60-70 % intensity and progressed to 300 minutes per week over 12-weeks. T-tests were used to test for group differences in the changes in inflammation from baseline at each time point over the 12-month study period accounting for whether they were adherent or not at each timepoint.

Among the participants (n=115, mean age 55, 65% male, 82% Black) in the exercise intervention who were adherent to their exercise prescription at least 70% of the time, sCD14 and TNF values demonstrated non-significant decreases with small to moderate effect sizes (d=0.42 and d=0.35 respectively).

Findings from this study suggest that higher levels of exercise adherence may lower inflammation and CVD risk among OPWH. Future research is needed to develop strategies to increase exercise adherence for OPWH who are at high risk for CVD.

Key words: Aerobic exercise, cardiovascular disease, HIV, inflammation

Introduction

People with HIV (PWH) are twice as likely to develop cardiovascular disease (CVD) at a much younger age than people without HIV independent of known risk factors (Ballocca et al., 2017). As a result, CVD is a major cause of morbidity and mortality in older PWH (OPWH) who are ≥40 years of age (Nasi et al., 2017, Ballocca et al., 2017, Duprez et al., 2012, Shah et al., 2018, Titanji et al., 2020). The life expectancy of OPWH is at least 6 years shorter than persons without HIV (Samji et al., 2021). Chronically high levels of inflammation are a known contributor to the higher rates of CVD in OPWH (Neuhaus et al., 2010).

Despite optimal medication adherence and viral load suppression, evidence supports sustained immune activation for some OPWH. Inflammatory cytokine biomarkers, tumor necrosis factor (TNF), Interleukin 6 (IL-6), the monocyte binding protein soluble CD14 (sCD14), are often consistently elevated in PWH even when HIV treatment is optimal and viral load is undetectable (Neuhaus et al., 2010). Over time, prolonged inflammation contributes to endothelial dysfunction causing fibrosis and arterial thickening leading to much earlier vascular aging and CVD (Nasi et al., 2017, Hanna et al., 2017, Nordell et al., 2014). Studies to further examine modes of exercise on reduction of cardiovascular disease risk for OPWH will give providers cost effective tools that may be readily utilized to support routine exercise to lower CVD risk.

Exercise and physical activity are often used synonymously, but they are different. Exercise is defined as structured, planned, and repetitive physical activity and is a commonly used intervention to improve cardiovascular fitness (Caspersen, Powel, Christenson, 1985). In contrast, physical activity can include low intensity activities of daily living such as walking and housework. During moderate intensity aerobic exercise, an individual's HR should reach 60-70% of their maximum HR for 150 minutes per week (Office of Disease Prevention and Health Promotion, 2019. This intensity level has been demonstrated to lower cardiovascular risk for individuals with and without HIV (Office of Disease Prevention and Health Promotion, 2019, Hotting and Roder, 2013, Jaggers and Hand, 2016, Nwaka et al., 2019, Owusu et al., 2020, Pedro et al., 2017, Roos et al., 2014, Sallam and Laher, 2016, Vingren et al., 2017, Zheng et al., 2014). However, less than half of adults in the United States (U.S.) general population meet these current guidelines and the rates are unknown in OPWH (Office of Disease Prevention and Health Promotion, 2019).

Exercising muscles release proteins that block inflammatory pathways and regular exercise has been shown to protect the body from chronic inflammation (Pedersen, 2017). Prior study has supported the protective benefits of exercise on chronic inflammation among persons without HIV and in site-based (e.g., gyms and laboratories) exercise studies. However, little to no research to date on the benefits of adherence to home-based (HB) aerobic exercise on inflammatory contributors to CVD among OPWH has been conducted. Developing effective biobehavioral interventions that target the underlying inflammation known to accelerate CVD in OPWH is of paramount importance.

The current study reports effects of exercise adherence on inflammation over 12-months among a sample of OPWH participating in a home-based, moderate-intensity aerobic exercise program. Higher levels of exercise adherence $\geq$ 70% was hypothesized to reduce inflammation compared to lower adherence $\leq$ 70%.

Methods

Ethics statement

The study was approved by the Emory University institutional review board committee (IRB#00080302). All participants were consented according to Emory University IRB protocols.

Study design

This study examined participants enrolled in a two-arm randomized controlled trial that tested the effects of an aerobic exercise intervention on cognitive function, inflammatory biomarkers, and endothelial function among OPWH with a minimum of two cardiovascular risk factors participating in a walking group (Let's Move intervention). Participants were followed for 52 weeks. Let's Move intervention participants (n=76) were provided with a tailored exercise prescription to ensure each individual would maintain their target HR goal of 60 - 70 % of their maximum heart rate and an activity tracker to monitor exercise adherence. Intervention participants were asked to walk 5 times per week for 30 minutes initially and were gradually progressed to 60 minutes, 5 days per week by week 12 (Table 1). For the participants in the exercise intervention, the study protocol increased the exercise prescription from the recommended 150 minutes per week to 300 minutes of moderate to vigorous physical activity (MVPA) for the participants in the exercise intervention to maximize their cardiovascular benefits (Jaggers and Hand, 2014). Strategies for achieving target heart rate while walking were given at baseline such as including arm movements and hill or stair climbing. The primary aim of the current study focused on the inflammatory biomarker measures assessed at baseline BL, 3-, 6-, and 12-months using standardized laboratory assay protocols (ELISA guide, 2023).

Parent study recruitment and sample

Participants for the study were recruited as a convenience sample from infectious disease clinics in the metro-Atlanta area where HIV prevalence is highly concentrated in the U.S (AIDSVu.org, 2023) Participants were randomly assigned after BL assessments were completed. Data collectors were blinded to group assignments. Inclusion criteria included: men and women aged $\geq$40 years having HIV infection and were willing to participate, English speakers, living independently and within a 50-mile radius of Atlanta, had a minimum of two CVD risk factors (e.g., smoking, diabetes, dyslipidemia, hypertension, overweight/obesity), clinically stable and on ART$\geq$ 6 months prior to enrollment. Exclusion criteria included those who were hospitalized within 60-days before enrollment, involved in any structured exercise program or exercising ≥3 times per week ≥30 minutes per day, involved in any weight loss program, had a medical or physical condition that would preclude participation in the exercise component of the study, were pregnant, major depression, a psychotic disorder or were diagnosed with another comorbid neurological condition that would interfere with the assessments.

Motivational Interviewing guided interaction

Participants were contacted weekly via telephone by Motivational Interviewing (MI) trained research staff following each exercise assessment week (Miller and Rollnick, 2002). Developed by clinical psychologists Miller and Rollnick, MI is a behavioral change model that has been used successfully for smoking cessation, excess weight loss, and exercise participation (Miller and Rollnick, 2002). Participants' barriers and challenges to the exercise prescription were discussed with MI trained staff members, which were dependent on their adherence achieved the previous week. For example, future exercise goals and plans for consistency and/or modification were reviewed with participants. In addition, participants were encouraged to enlist friends, family, and similar cultural groups to support their exercise goals and adherence.

Measures

Cardiorespiratory fitness testing

Two tests were used to measure cardiorespiratory fitness among randomized participants. The modified Balke treadmill test was conducted at baseline by an exercise physiologist and supervising clinician to determine maximum heart rate using a symptom limited, gas inspired protocol (Balke and Ware, 1959, Gibbons et al., 2002). Target HR was calculated at 60% – 70% of the maximum HR achieved. During the test, VO2max was calculated (1 MET = resting metabolic rate, defined as oxygen uptake of 3.5 mL x kg^{-1} x min^{-1}). The study cardiologist reviewed the continuous electrocardiogram (EKG) during the treadmill test to determine if there were any ischemic or other changes that required further diagnostic testing using the American Heart Association/ American College of Cardiology (AHA/ACC) exercise testing guidelines (Fletcher et al., 2013).

Functional capacity testing

In addition, a six-minute walk test (6MWT) was administered at baseline and at 3-, 6-, and 12-month timepoints according to American Thoracic Society guidelines (ATS, 2002). After 5 minutes of rest, participants were asked to walk in a hallway between 2 cones set up 50 meters apart for 6 minutes. The total distance walked was measured and recorded. Participants were instructed to cease activity if symptoms such as dyspnea, syncope, or fatigue were experienced. The 6MWT has been shown to be an accurate assessment of functional capacity and accurately estimates cardiorespiratory fitness (Ross et al., 2010).

Exercise prescription adherence assessment

The study team accessed the participant exercise tracker accounts via data downloaded from the Fitbit Charge 2® exercise tracker (Fitbit Inc., San Francisco, CA) and recorded the number of minutes participants reached their target HR as prescribed in the baseline assessment. For each week in the first 12 weeks of participation, target HR was monitored daily. During weeks-1 through 4, adherence was determined by evaluating whether the participant walked at ≥60% of their maximum HR achieved during the treadmill tests for ≥ 30 minutes per day and ≥5 days per week (Table 2). During weeks -5 through 7, participants were asked to increase walking time to ≥45 minutes and continue walking at ≥60% HR maximum. At week 8, the participants were asked to increase to ≥70% of their HR maximum for ≥60 minutes for ≥5 days per week and continue at this exercise dose for the remaining duration of the study through 52 weeks (Table 2).

The number of minutes per day and days per week the participant reached their target HR were recorded on the subsequent week following the activity and at scheduled timepoints throughout the study duration. Assessment intervals for the first 12 weeks were weekly and then change in subsequent weeks to less frequent (Table 2). For each assessment interval, adherence was considered fulfilled if the participant met the exercise prescription ≥70% of the days (i.e. 4 out of 5 days) in the previous week of assessment. Additionally, site-based, supervised exercise studies have shown decreases in inflammatory cytokine levels among PWH with ≥150 minutes per week and at 60-70% of maximum HR, but few studies have tested home-based exercise models (Nwaka et al., 2019).

Measurement of inflammation

Prior to the blood draw, participants were required to be fasting for >6 hours, to avoid exercise for > 24 hours, and to avoid caffeine and smoking for > 6 hours. All blood samples were collected with an intravenous (IV) catheter placed into a forearm vein. Blood samples were collected after 30 minutes of rest between 8-10 am (to control for circadian variation) in EDTA tubes and immediately placed on ice. Blood was spun at 3,000 rpm for 15 minutes at 4C within 4 hours of collection. Plasma was aliquoted into pre-cooled siliconized polypropylene tubes and stored at -80C until assays were analyzed. Processing and analyses of specimens were performed according to manufacturer ELISA recommendations (ELISA guide, 2023). Blood collections were run in batch sets from all timepoints.

Data analysis

Continuous variables were described as means ± standard deviations (SD) and percentages were determined within the adherent and non-adherent exercise groups among the intervention group participants. Due to right-tailed skewness of IL-6 values, natural log transformations were performed prior to analysis. The change of biomarker values between BL and 3-, 6- and 12-mo was calculated for each participant by subtracting the 2 values. Mean changes were calculated at each follow up timepoint stratifying the adherent and non-adherent groups. T-tests were then used to compare the mean difference between the stratified adherent and non-adherent exercise intervention participants. Multilevel linear modeling was performed within the exercise intervention group to examine the incremental change in the biomarker values over time in association with a cumulative exercise adherence level. Cumulative exercise adherence was calculated by adding up the number of timepoints at which exercise adherence was met (yes=1, no=0) (i.e., cumulative adherence values could range from 0, not adherent at any timepoint to 3, adherent at 3-, 6- and 12-month timepoints).

Results

Baseline characteristics

Most of the participants (n=76) were male (n=48, 63%) and African American (n=64, 84%) as shown in the baseline characteristics (Table 3). Mean age was 56 years (SD $\pm$5.1) and 41% (n=31) attended some college or vocational school (Table 3). The most frequently occurring baseline CVD risk factors among study participants included hypertension (47%, n=36), smoking (34%, n=26), dyslipidemia (24%, n=18), Type 2 diabetes (13%, n=10), and high BMI. Approximately two-thirds, (n=46, 60%) of participants were overweight (BMI$\geq$25), and 30% (n=23) were obese (BMI$\geq$30). Mean cardiorespiratory fitness measured by VO^2_{max} was 20.6$\pm$5.6 mL/kg-min. Mean functional capacity measured by the 6MWT was 446.2$\pm$66.7 meters. None of the BL CVD risk or demographic variables were statistically significantly associated with inflammatory biomarker changes.

Inflammatory response to exercise

The majority of participant IL6 values were low or within normal ranges (5-15 pg/ml). The untransformed IL6 median was 1.01 and interquartile range was (0.81, 1.32) at BL (Table 4). The transformed IL6 mean at BL among the intervention group in this study was 1.08 pg/ml (SD ±0.53) (Table 4). Normal range for TNF values is between 0-16 pg/ml and the mean for this study was 1.67 pg/ml (SD 1.04) (Table 4). The normal sCD14 level is ≤1600 ng/mL.(Reiner et al., 2013). The mean value for sCD14 in this study was higher at 2327.09 ng/ml (SD 656.71) (Table 4).

There were no significant differences in biomarker values between participants in the exercise intervention (adherent versus non-adherent subjects) at any timepoint. However, sCD14 and TNF levels decreased over time among participants who were adherent to their exercise prescription ≥70% of the time compared to those who were not adherent, but this difference was non-significant. Effect sizes were small to moderate effect sizes (Cohen's d between 0.2 and 0.5) (Cohen, 1988) (Table 5). The difference of sCD14 levels between adherent and non-adherent groups at 12-months was 282.89 (SD±177.1) with a Cohen's *d* effect size of 0.42 (p=0.116) (Table 5). The difference in TNF values between adherent and non-adherent groups at 12-months was 0.268 (SD±0.21) with a Cohen's *d* effect size of 0.345 (p=0.211) (Table 5). Additionally, multilevel modeling associations of changes in TNF levels and cumulative adherence over the 12-month study duration was significant (p=0.006) (Table 6).

Discussion

Results from this analysis examining inflammatory cytokine changes with aerobic exercise showed that moderate intensity walking may have contributed to modest reductions in inflammation among OPWH. The pleiotropic proinflammatory cytokine and muscle repairing myokine, IL-6, is an important mediator of the inflammatory response during infection and repairs tissue after physical activity (Fontes, Rose, Clhahova, 2015). Periods of higher IL-6 levels are important for reducing acute infection and repairing muscles after exercise, but chronic high levels of IL-6 are associated with vascular deterioration (Fontes, Rose, Clhahova, 2015). Elevated serum levels of IL-6 have been reported in fatal cardiac events in OPWH who have a higher inflammatory burden due to vascular aging than younger PWH (Nasi et al., 2017, Shah et al., 2018). In a study of PWH having no prior cardiac history fatal CVD events occurred more often (OR=1.39, CI 1.07-1.79) among those with higher IL-6 levels (Nordell et al, 2014). In a meta-analysis examining IL-6 levels in noninfected persons, persistently elevated IL-6 was significantly associated with CVD risk (Sarwar et al., 2012). In the SMART study, elevated IL-6 was associated with higher CVD risk in PWH after controlling for other CVD risk factors including prior CVD and smoking (Duprez et al, 2012). Muscle contraction from physical exercise induces IL-6 as a myokine to generate new muscle myofibrils and to initiate toll-like receptors to downregulate chronic inflammation (Handschin et al., 2008) which could be key in reducing chronic inflammation in OPWH. In this study, the changes in IL6 values at each timepoint were slight among the exercise intervention participants and were not moderated by exercise dose which may be partly explained by the cytokine's pleiotropic qualities. Additionally, mean IL-6 values of participants in this study were low or within the normal ranges which is likely contributed to the lack of change in the findings.

Changes in sCD14 which is a monocyte sensor that detects bacterial lipopolysaccharide (LPS) and activates macrophages responding to elevated inflammation (Kitchens and Thompson, 2005) was also measured. Serum LPS binds with CD14 to produce sCD14 creating a cascade of systemic inflammation (Kitchens and Thompson, 2005). In another study, sCD14 levels were higher in PWH than those without HIV infection (Hanna et al., 2017). Elevated sCD14 levels were also associated with a 6-fold increase in mortality for PWH and higher risk of CVD associated with coronary artery calcifications (Sandler et al., 2011, McKibben et al., 2015). In the current study, mean sCD14 levels were elevated and decreased with higher exercise adherence over time. Additionally, a significant change in sCD14 levels with cumulative exercise adherence over the 12-month study duration suggests that there may be an additive effect of exercise on this biomarker.

The proinflammatory cytokine TNF binds with sCD14 which is released by macrophages during an acute inflammatory response to signal cellular apoptosis (Kumar, Coquard and Herbein, 2016, Wu et al., 2019). HIV-1 proteins mimic and control the TNF signaling pathways inhibiting apoptosis and instead allows viral proliferation and elevated inflammation (Kumar, Coquard and Herbein, 2016). Moderate exercise was observed to significantly reduce TNF and CVD risk in non-infected persons with chronic heart failure (Smart et al., 2011). Reducing TNF with activity may be effective for reducing risk or slowing progression of CVD among OPWH. TNF levels were reduced with higher exercise adherence dose compared to the non-adherent group but was not significant; there were small to moderate effect sizes.

Considering effect sizes of biological outcomes following an intervention may be important clinically (Wassertein, Schim, Lazer, 2019). In studies with small sample sizes, although there may not be statistically significant changes overall, there may be significant differences with an intervention for some individuals who may have higher chronic inflammation, for example. Further, the exercise intervention may be effective and beneficial for other health outcomes, such as vascular endothelial function improvement or functional capacity and may warrant additional examination.

Current recommendations for exercise adherence from both the CDC and the American Heart Association is at for all persons to exercise between 150-300 minutes per week at moderate to vigorous intensity (HIV.gov, 2022, Office of Disease Prevention and Health Promotion, 2022). This level of exercise reduces inflammation by blocking some pro-inflammatory cytokines (TNF/sCD14), increasing other myokine repairing cytokines (IL6) temporarily, and promoting increased blood flow through the vascular system (Green et al., 2017). During moderate intensity exercise, the increased blood flow exerts pulsatile pressure on the endothelial cells within the vascular walls which stretch and resurface the endothelial lining

(Green et al., 2017). Habitual activity that achieves these cellular changes that is accompanied by periods of rest between exercise sessions, repairs damaged vessels (Green et al., 2017). This function of exercise has been shown to mitigate CVD and reduce mortality for persons with chronic health conditions such as HIV and hypertension (Green et al., 2017).

Comorbidities such as obesity, type II diabetes, dyslipidemia, hypertension, and smoking that are known to elevate inflammation regardless of HIV infection were also present in our participants (Tatanji et al., 2020, Wing, 2016). These conditions may have influenced the degree to which inflammatory biomarker levels changed and the ability of the patients to meet their exercise adherence goals. When considering the value and effectiveness of interventions for populations with multi-morbidity, multilevel and layered approaches including community engagement and provider feedback may be effective strategies to support higher exercise adherence (Li et al., 2019). PWH interviewed about exercise considerations requested that interventions be tailored to their goals and functional abilities and that exercise programs need to be integrated with mental and nutrition education within social events (Li et al.,2019).

The participants in our study were moderately adherent to the exercise prescription in the study protocol (>60%) as compared to the general public (<50%) (Office of Disease Prevention Health Promotion, 2019). Additionally, there was low attrition over the 12-month study duration (<10%). Other exercise intervention studies that are site-based, and not home-based, often experience attrition at much higher rates of 50% or more (Pedro et al., 2017). Interventions performed in site-based settings are also often less accessible to older, vulnerable populations due to travel, time, and economic challenges (Ashworth et al., 2005, Webel et al., 2015). Our study protocol included regular contact with the study participants that likely contributed to the low attrition. The study team used behavioral change counseling techniques that supported participants in overcoming barriers to exercise which may have also contributed to low attrition (Miller and Rollnick, 2002).

Cardiorespiratory fitness measured by VO^2_{max} was similar at baseline (Mean =20.6$\pm$5.6 mL/kg-min) to PWH in another study (Mean age 52.2$\pm$8.3 years, mean VO^2_{max} = 15.4$\pm$4.4 mL/kg-min) (Oliveira et al., 2018) (Table 3). Mean functional capacity measured by the 6MWT was (446.2$\pm$66.7 meters) which is comparable to the average among other PWH (400.7$\pm$72.3 meters) (Oliveira et al., 2018) (Table 3). Cardiorespiratory fitness and functional capacity did not change significantly over the study duration.

Strengths

The strengths of the study included low attrition and slight reductions in inflammation with home-based exercise which may be easily translatable to community settings and is supported by HIV care guidelines provided by the CDC (HIV.gov). Frequent face to face contact which may have supported greater adherence initially, along with weekly telephone contact with study participants by the study team over the 12-month study duration, were key components to fostering participant exercise adherence.

Limitations

There were also imitations of the study. The low cytokine levels across the study duration made it difficult to detect associations between the slight changes from baseline and exercise adherence. The small sample sizes of the adherence groups within the exercise intervention (Adherent N=33, Non-adherent N=34) also contributed to the low probability of statistical significance. However, current data support that effect size interpretation is an important consideration when evaluating the clinical significance of an intervention, especially with smaller sample sizes, because effective treatments can be overlooked when they do not meet the more traditional statistical p-value threshold (Wassertein, Schim, Lazer, 2019). Many of the participants had multiple comorbidities and continued to smoke during the study which may have contributed to the lack of change in the inflammatory biomarkers across the study timepoints. The time of day when blood samples were drawn varied for some participants and may have inadvertently influenced inflammatory outcomes (Fontes, Rose, Clhahova, 2015). Exercise adherence may have been negatively influenced by pain with exercise related to arthritis, use of over-the-counter pain medications such as Ibuprofen, prior injury, high BMI, or peripheral neuropathy which were common physical complaints among the participants in the study and may have contributed to the lack of significant changes in the inflammatory response. Participants experiencing pain were advised to rest and to consult their physician if pain inhibited their activities of daily living.

Additionally, the exercise trackers required internet access for data transfer from the wearable device to a cell phone. When connectivity was interrupted, data transfer was delayed until the tracker could be reconnected by the study staff, thus delaying exercise data acquisition. The exercise data of participants without cell phones or sufficient cellular capability was downloaded to a designated study cell phone through scheduling and meeting with the study staff. Watchband breakage also inhibited data transfer because the watch required wrist wearing and skin contact for HR detection. However, the frequent remote tracking and fast action (usually within 4 hours) to reconnect the devices and replace watchbands by the research staff reduced the time of data interruption.

Future directions

Based on the findings from this study, future studies may test exercise prescriptions within community and primary care settings for OPWH. Implementation studies are needed to investigate exercise prescription feasibility and barriers to exercise adherence in primary care settings. Future studies may also include consistent and frequent follow up which was used in this study. Concomitant therapy that incorporates goals, tracking, and incremental progression of exercise intensity also applied in this study may be useful tools when designing future research interventions. Larger samples of OPWH are needed to test other biological outcomes with additional modes of training such as resistance exercise and other types of aerobic exercise such as high intensity swimming or dancing.

Conclusions

In a 12-month home-based walking program, higher adherence and levels of aerobic exercise resulted in lower inflammation for some participants. The addition of exercise prescriptions and supportive mechanisms to encourage more adherence to exercise may foster improvements in cardiovascular health among OPWH.

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Conflicts of Interest

VCM has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Eli Lily, Bayer, Gilead Sciences and ViiV. The other authors have no conflicts of interest to report.

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Table 1: Exercise Rx	**Weeks 1-2**	**Weeks 3-4**	**Weeks 5-7**	**Weeks 8-9**	**Weeks 10-12**	**Weeks 13-78 (maintenance)**
Intensity	60%	60%	70%	70%	70%	70%
Duration	30 min	45 min	45 min	60 min	60 min	60 min
Frequency	5 days/wk	5 days/wk	5 days/wk	5 days/wk	5 days/wk	5 days/wk

Table 2: Fitbit assessment schedule			
Week	**1-12**	**14,16,18,20,22,24**	**28, 32, 36, 40,44,48,52**
Frequency	Weekly	Bi-monthly	Monthly

Table 3: Baseline demographics	
Socioeconomics	Let’s Move Intervention group n=76
Gender Men Women Transgender	 48 (63.2%) 25 (32.9%) 3 (3.9%)
Race Black White Others reported	 64 (84.2%) 10 (13.2%) 2 (2.6%)
Education HS or less Some College/voc ed Graduate	 33 (53.9%) 31 (40.8%) 4 (5.2%)
Housing Own home or apt With family Housing insecurity *No BL differences	 56 (73.6%) 10 (13.2%) 10 (13.2%)
Baseline clinical variables	M (SD)
Age	55.75 (± 5.1)
Six-minute walk test (m)	446.2 (± 66.7)
VO2 max (mL/kg-min)	20.6 (± 5.6)
BMI	28.2 (± 6.2)
Cholesterol	178.54 mg/mL (± 35.2)
CVD Risk Factors (yes) • T2 Diabetes • Smoking status • HTN • Hyperlipidemia • Obesity (BMI≥30) *No significant BL differences	 10 (13.2%) 26 (34.2%) 36 (47.3%) 18 (23.7%) 23 (30.0%)

Table 4: Mean biomarker values of LM at each timepoint			
Biomarker	CD14 Mean (SD)	LN IL-6 Mean (SD) Median IQR (25, 75)	TNF n=80 Mean (SD)
Baseline LM	N=59 2306.00 (±711.95)	N=53 Mean=1.08 (SD ±0.53) Median=0.93 IQR 0.75, 1.23	N=55 1.68 (±1.18)
3-months LM	N=59 2315.58 (±748.55)	N=53 Mean=1.05 (±0.57) Median=0.86 IQR 0.71, 1.24	N=55 1.71 (±1.09)
6-months LM	N=59 2404.48 (±743.86)	N=53 Mean=1.08 (±0.46) Median=1.01 IQR 0.75, 1.30	N=55 1.70 (±1.03)
12-months LM	N=59 2462.01 (±742.12)	N=55 Mean=1.12 (±0.49) Median=1.06 IQR 0.73, 1.36	N=54 1.67 (±0.83)

Table 5: Mean biomarker CHANGE values btw BL and each follow up timepoint - **ADHERENT vs NON-ADHERENT**									
Biomarker mean	CD14 M change (SD)	M diff (SE)diff	Effect Sz Cohen's d p-value	N, IL-6 M(SD)	M diff (SE)diff	Effect Sz Cohen's d p-value	N, TNF M(SD)	M diff (SE)diff	Effect Sz Cohen's d p-value
BL-3-months Adherent Non-adherent	N=39, -31.59 (+719.22) N=20 33.36 (+830.96)	64.96 (208.55)	0.09 P=0.757	N=36 0.06 (+0.47) N=17 0.06 (+0.58)	0.00 (0.15)	0.00 P=0.995	N=36 -0.03 (0.38) N=19 -0.04 (0.53)	0.01 (0.12)	-0.02 P=0.934
BL-6-months Adherent Non-adherent	N=33 -10.61 (+549.54) N=26 -209.99 (+704.24)	-199.38 (+168.01)	-0.32 P=0.227	N=31 -0.02 (+0.46) N=22 -0.02 (+0.50)	0.00 (0.13)	0.00 P=1.00	N=31 -0.06 (+0.38) n=24 0.17 (+0.79)	0.07 (0.16)	0.12 P=0.656
BL-12-months Adherent Non-adherent	N=30 -295.05 (+635.50) N=29 -12.16 (+723.29)	282.89 (177.11)	0.42 P=0.116	N=27 -0.05 (+0.54) N=26 -0.11 (+0.56)	-0.05 (0.15)	-0.10 P=0.72	N=28 -0.12 (+0.67) N=26 0.15 (+0.88)	0.27 (0.21)	0.35 P=0.211

Table 6: Type III test of fixed effects Dose adherent and non-adherent within LM			
LN IL6	**Df (Num,den)**	**F test**	**Sig (p-value)**
Adh vs non	1, 77	0.096	0.757
Time	3, 230	2.511	0.059
Group/time	3,230	0.394	0.758
Adherence met SUM	1,77	2.460	0.121
TNF	**Df (Num,den)**	**F test**	**Sig (p-value)**
Adh vs non	1,77	2.6	0.111
Time	3,232	0.214	0.887
Group/time	3,232	0.210	0.889
Adherence met SUM	1,77	7.968	0.006
CD14	**Df (Num,den)**	**F test**	**Sig (p-value)**
Adh vs non	1, 89	0.239	0.626
Time	3,264	0.764	0.515
Group/time	3,264	0.253	0.859
Adherence met SUM	1,89	0.615	0.435

Chapter V

Integrative Summary

The purpose of this secondary analysis was to examine the effects of adherence to an aerobic exercise intervention on endothelial function and inflammatory biomarker levels among OPWH.

Aim 1 of this secondary analysis began with an examination of validation studies that included the fitness tracker tool used in the parent study to measure exercise adherence. The fitness tracker, the Fitbit Charge2, was found to adequately measure HR and steps during moderate intensity aerobic exercise such as walking. Although the Fitbit Charge2 was found to be moderately accurate in measuring HR in the study, exercise trackers are constantly being updated by the manufacturers and are sold at a price point that may not be affordable by all populations. Additional research is needed to develop tools that are tested across populations, particularly low-income populations to provide more affordable devices to improve physical activity levels and lower risk for CVD.

Having an exercise tracking tool that measured HR achieved by the participants during their home-based exercise sessions, was key in determining adherence to their exercise prescriptions. Based on current research that has tested the dose of exercise required to achieve cardiovascular benefits among persons with and without HIV, weekly adherence was considered “met” when the participant walked at 60-70% of their HR maximum intensity, $\geq$300 minutes $\geq$70% of the time. The participants in the exercise intervention arm of the parent study were moderately adherent to the exercise prescription protocol in that more than 60% of the participants met their adherence goal at each 3-, 6-, and 12-month follow up timepoints. This level is above the average exercise adherence reported among the general U.S. population in which fewer than 50% exercise 150 minutes per week at moderate intensity (Office of Disease Prevention and Health Promotion, 2019). The recommended dose of exercise is between 150-300 minutes per week to reduce cardiovascular disease risk and promote optimal health benefits intensity (Office of Disease Prevention and Health Promotion, 2019). Exercise adherence of the participants in the parent study was supported by using Motivational Interviewing (MI) which is a behavioral change model that has been used successfully for smoking cessation, excess weight loss, and exercise participation (Miller and Rollnick, 2002). These behavioral change techniques were utilized during weekly phone calls to address barriers and provide encouragement to exercise. Future exercise goals and plans for consistency and/or modification were also reviewed with participants. In addition, participants were encouraged to enlist friends, family, and similar cultural groups to support their exercise goals and adherence. The second aim examined the effect of adherence to the exercise intervention on endothelial dysfunction as measured by FMD. Based on the results of this secondary analysis of the Fitbrain study, adherence to an exercise prescription of walking ≥300 minutes per week at 60-70% of HR maximum significantly improved endothelial vascular function among OPWH compared to those who were not adherent to the exercise program (%FMD change 0.58%, and -1.61 respectively, p=0.025). These findings are significant because this strongly suggests that it is possible to reverse atherogenic stiffness, a contributor to endothelial dysfunction and CVD, with adherence to a home-based walking program in OPWH who are at high risk for CVD.

The third aim of the study examined the effects of the exercise adherence on inflammatory biomarkers TNF, IL6 and sCD14. Adherence to 150-300 minutes per week of aerobic exercise has been shown to reduce chronic inflammation that causes endothelial dysfunction and arterial stiffness over time. HIV infection induces an inflammatory cascade that, if sustained, can lead to endothelial dysfunction. Current antiretroviral medications control viral load, and thus inflammation, which was observed in this cohort of OPWH in the parent study.

Inclusion criteria for enrollment into the study included participants who were well-controlled on their ART for ≥6-months which likely explains their low inflammatory biomarker levels over the duration of the study period and the nonsignificant reductions in biomarker levels with exercise. It is notable, however, that even though their biomarker levels were low, inflammation levels were reduced over the study duration among those who were adherent to their exercise prescription with small to moderate effect sizes.

Strengths and limitations

The study had many strengths. There was very low attrition; less than 10% throughout the 12-month study duration, likely due in part to the consistent follow–up protocols. Using the tested MI techniques was also an important component to keeping participants on task with their adherence. Assessing FMD among PWH in an exercise study is novel as was stratifying exercise adherence within the intervention group.

Limitations of the study included the participants having low cytokine levels likely a result of the HIV control on ART, which is clinically positive. Other biomarkers may be more useful for detecting exercise related changes that are associated with CVD risk should be identified and used for future investigations. Small sample sizes within the adherent and non-adherent groups may have made it difficult to detect any significant changes and participants had multiple comorbidities that contribute to inflammation and endothelial dysfunction. The timing between blood draw and last exercise event may also have affected accuracy of biomarker collection. Adherence to the exercise prescription may have been negatively influenced by pain and social determinants such as safe walking spaces, having proper footwear, nutrition, and family support. Additionally, there were many issues with the activity trackers (e.g., connectivity loss and watchband breakage).

Implications and Future directions

As a follow up to this study, implementation studies to examine the feasibility and effectiveness of exercise prescriptions as adjunctive therapies within primary care settings for PWH are this researcher's top priority. Using Motivational Interviewing behavior change techniques and consistent follow up to support exercise adherence are important considerations. Exercise programs that are goal-directed with intensity progression, remote or virtual monitoring may be useful tools in further research. Community-based interventions that include input from providers, exercise professionals, and families alongside PWH may provide the support for exercise adherence needed to achieve optimal health benefits from exercise for this population to reduce CVD risk. Social determinants of health are important considerations when discussing the viability of interventions within affected communities as well as when assessing the compounding factors of CVD and warrant targeted approaches to understand more about these relationships. Additional research is needed in larger, more diverse samples of OPWH to examine the influence of access to exercise, as well as other modes of exercise such as resistance exercise and other types of aerobic exercise such as high intensity swimming or dancing on endothelial vascular function and inflammation.

Conclusions

In a 12-month home-based walking program, adherence to the exercise prescription of 240-300 minutes per week of moderate intensity exercise resulted in a nonsignificant trend towards lower inflammation. Additionally, higher exercise adherence was associated with significant improvements in vascular endothelial function at the 6-month follow-up. The addition of exercise prescriptions and supportive mechanisms to encourage higher may foster improvements in cardiovascular health among OPWH.