Fall 2020

Examination of Daily Steps in People With Parkinson's Disease & Stroke: Two Steps Forward

Reed Handlery

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by

Reed Handlery

Bachelor of Science
McKendree University, 2012

Doctor of Physical Therapy
University of South Carolina, 2016

Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Philosophy in

Exercise Science

Arnold School of Public Health

University of South Carolina

2020

Accepted by:

Stacy Fritz, Major Professor

Jill C. Stewart, Committee Member

Christine Pellegrini, Committee Member

Courtney Monroe, Committee Member

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

DEDICATION

This document is dedicated to my mom, Barbara, and step-father, Darrel. Together, they provided me with all the resources needed to pursue an advanced degree, and for that I am forever grateful. To my mom, thank you for putting your children first, teaching me manners, and essentially completing that elementary science fair for me. To Darrel, thank you for teaching me basic life skills such as throwing a ball, driving and grilling. Though I ended up a vegetarian, I can still grill some mean veggie kabobs.

ACKNOWLEDGEMENTS

I have been in school in some form for the last 22 years. The irony is, all that time was spent working towards the same goal of staying in school as a teacher. Throughout my schooling journey, I have had many people who greatly influenced my learning and helped me achieve this PhD. While I do not recall all of my teacher's names, I would like to acknowledge the following:

Stacy Fritz, who developed my interest in research and taught me to never settle. She is a mentor unlike any other and her positivity and kindness are traits I hope to develop with time. Jill Stewart, who always impressed me with her unique takes on research and her ability to make me think. Christine Pellegrini, who taught me to write at a scholarly level but also have fun while doing it.

Courtney Monroe, who encouraged me to think outside of the box about physical activity interventions.

To Elizabeth Regan, who served as my role model for a successful PhD student and shares my goal of improving the health of those with disability.

In addition, I acknowledge Garrett Hainline for his friendship and hope he will surpass Elizabeth as Stacy's favorite mentee, a title I simply could not compete for.

Finally, I must acknowledge my best friend and partner in life, Kaci, who brought me to South Carolina in the first place and encouraged me to get off my ass and do something I care about.

ABSTRACT

Despite the well-known health benefits associated with physical activity (PA), the majority of people with Parkinson's disease (pwPD) and people with stroke do not meet national PA guidelines. As a result, these two groups of people are at increased risk for development of cardiovascular disease, additional disability and death.

Walking as a mode of PA has been shown to improve the health of both pwPD and people with stroke. In fact, a step count of $\geq$6000 steps per day is related to a decreased risk of subsequent cardiovascular events in people with stroke. Daily walking is also strongly recommended by the U.S. surgeon general and national PA guidelines. Currently, however, guidelines do not recommend a specific daily step count for pwPD or stroke and the relationship between daily steps and health in these individuals is unclear.

The overall purpose of the following two studies was to identify daily step counts associated with health outcomes in pwPD and people with stroke. Specifically for pwPD (Chapter 2), the purpose was to 1) determine a step threshold that corresponds to meeting aerobic PA guidelines, 2) determine effects of treadmill exercise performed at varying intensities on PA and 3) quantify the relationship between changes in daily steps and fitness. For people with stroke (Chapter 3) the purpose was to 1) determine which factors at two months post-stroke can predict daily step counts at one year, and 2) determine

what step count at two months corresponds to obtaining ≥6000 daily steps at one year post-stroke.

Data for both studies were obtained from publicly available datasets. The first study included 110 individuals with de novo Parkinson's disease who were allocated to one of three groups (high-intensity treadmill exercise, moderate-intensity treadmill exercise or control) for six months. Baseline step data and Receiver Operating Characteristic (ROC) curves were used to determine which step count corresponded to meeting PA guidelines. The effect of treadmill exercise on PA was examined in those below the step threshold (i.e. the least active participants). Pearson's r correlations determined the relationship between daily steps and fitness. The second study included 206 participants with stroke who were allocated to one of three groups (36 sessions of body weight–supported treadmill training at two months post-stroke, 36 sessions of body weight–supported treadmill training at six months post-stroke, or 36 sessions of progressive supervised home exercise program). Daily steps were assessed at two months and one year post-stroke. Linear regression was used to predict daily step counts at one year based on factors including age, gender, race and/or ethnicity, stroke severity, walking speed and endurance, fitness, motor function, balance and balance confidence. A Receiver Operating Characteristic (ROC) curve determined which step count corresponded to reaching ≥6000 steps at one year.

Results indicate that for pwPD, a daily step count of ≥4200 corresponds to meeting PA guidelines. For participants with <4200 daily steps at baseline, high-intensity treadmill exercise led to improvements in daily steps but these changes were not associated with changes in fitness. Overall, pwPD should be encouraged to take $\geq$4200 daily steps in order to meet PA guidelines through walking. For people with stroke, daily steps and balance at two months post-stroke were the strongest predictors of future daily steps. Thus, improving daily PA and balance early after stroke may be necessary to increase PA levels at one year post-stroke. A step count of $\geq$1632 steps per day at two months post-stroke corresponded to obtaining $\geq$6000 daily steps at one year.

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CHAPTER 1: INTRODUCTION

Lack of physical activity (PA) is a global public health problem.[1] While nearly half of U.S. adults are not meeting PA guidelines,[2] for adults living with movement disability the prevalence of inactivity is even higher.[3] Of the nearly 930,000 U.S. adults with Parkinson's disease (PD),[4] only 27% are meeting PA guidelines[5] and of the 6.8 million people in the U.S. with stroke,[6] only 18% are meeting PA guidelines.[7] High levels of inactivity for people with PD (pwPD) and stroke is a substantial problem as both groups are at a heightened risk for cardiovascular disease, further disability and premature death,[8–12] all of which can be mitigated through performing adequate amounts of PA.

Various modes of PA have proven health benefits for pwPD and stroke. Walking, in particular, has been shown to improve walking speed,[13] cardiorespiratory fitness,[13–15] fatigue, depression, quality of life and slow disease progression[15] in pwPD. Similarly, for individuals with stroke, walking interventions have led to improvements in walking speed,[16] walking endurance[17] and cardiorespiratory fitnesss.[18] Walking as a mode of PA is also strongly recommended by the U.S. surgeon general[19] and the 2018 PA Guidelines for Americans, which state that individuals with chronic health conditions should perform at least 150 weekly minutes of moderate-intensity aerobic PA.[20] Unfortunately, these guidelines are not being met by the majority of pwPD or stroke and alternative methods to increase PA (e.g. by promoting increased daily steps) are warranted. One limitation with current guidelines is that measuring and tracking PA intensity requires individuals to assess intensity through heart rate, respiratory rate, perceived effort, or speed (among others), which may be difficult for individuals with cognitive impairment from PD or stroke. Daily step counts, on the other hand, provide users with a single metric that is easy to understand and can be used to set goals and track individual progress. In addition, daily steps can be measured relatively inexpensively and accurately using commercially available wearables.[5,21–23]

While current PA guidelines recommend walking, they do not endorse a specific daily step count and research involving clinical populations is sparce. Previous research has suggested 7000 to 10000[24] steps per day is appropriate for healthy older adults to achieve health benefits through walking. PwPD and stroke, however, often have walking impairments,[25,26] making these recommendations unrealistic and unobtainable.[27,28] For example, pwPD take 2300 less steps than their age-matched peers[27] and daily steps decrease as the disease progresses.[29,30] People with stroke may walk even less, averaging 4000 fewer steps per day compared to healthy adults.[28] While higher levels of PA (or steps) provide additional health benefits, lower levels may still be beneficial. Lee et al[31] examined nearly 17,000 older women (mean age=72 years) across four years and found that just 4400 steps per day was related to a 41% decrease in mortality rates compared to 2700 steps per day. Additionally, mortality rates continued to decrease until reaching a plateau at 7500 steps per day. Interestingly, the authors found that after adjusting for daily step count, the importance of step intensity was reduced, which led the authors to conclude that daily step counts may be of greater value than metrics of intensity.

Overall, there is little evidence to guide daily step recommendations for those with PD or stroke. Additionally, few interventions to date have successfully increased daily steps in these populations.[14,16,32,33] Therefore, using two large and publicly available datasets, the purpose of the following two studies was to identify daily step counts associated with health outcomes and provide data that can be used to inform future interventions aimed at improving PA in those with PD or stroke. Specifically, for people with PD (Chapter 2), there were three questions targeted:

1) What daily step threshold corresponded to meeting PA guidelines?

2) For those below the determined daily step threshold, what were the effects of treadmill exercise performed at varying intensities on daily steps and moderate-to-vigorous intensity PA (MVPA)?

3) For those below the determined daily step threshold, what was the relationship between changes in daily steps and cardiorespiratory fitness?

For people with stroke (Chapter 3), there were two aims:

1*) Determine which factors (both nonmodifiable and modifiable) present at two months post-stroke can predict daily step counts at one year post-stroke.*

2) Determine a daily step threshold at two months post stroke that corresponds to obtaining $\geq$6000 daily steps at one year post-stroke.

CHAPTER 2: PHYSICAL ACTIVITY IN DE NOVO PARKINSON'S DISEASE: DAILY STEP RECOMMENDATION AND EFFECTS OF TREADMILL EXERCISE ON PHYSICAL ACTIVITY

INTRODUCTION

Parkinson's disease (PD) is a progressive degenerative neurological disease that reduces function, independence, and quality of life for millions of people around the world.[34] Physical activity (PA) and more specifically walking, has been shown to improve walking speed,[13] cardiorespiratory fitness,[13–15] fatigue, depression, quality of life and slow disease progression.[15] Walking is also strongly recommended by the U.S. surgeon general[19] and the 2018 PA Guidelines for Americans.[20] Unfortunately, people living with PD are 29% less physically active than those without,[35] and, as the disease progresses, daily step counts and PA levels also decrease.[29,30] Therefore, there is an urgent need for interventions aimed at increasing PA levels in pwPD.

Steps are an appealing method of objectively measuring PA in pwPD given they can easily be captured and displayed using inexpensive commercially available wearables. Additionally, because nearly one third of people newly diagnosed with PD exhibit mild cognitive impairment,[36] steps may be an especially preferential PA target as they provide a single and simple metric to comprehend and track. While 7,000 to 10,000[24] daily steps has been suggested as the number needed to meet PA guidelines in healthy older adults, there is no current step recommendation for those with PD and the relationship between steps and other established health outcomes such as cardiorespiratory fitness[37] is unclear.

Most research regarding step counts in pwPD has been from cross sectional assessments.[5,27,38–40] To date, few interventions have examined changes in daily steps in pwPD. Two recent randomized controlled trials which used walking for exercise as the intervention found no significant changes in daily steps.[14,33] These null findings are of interest, especially considering that both interventions recruited individuals who reported not being regular exercisers prior to study onset. In the Study in Parkinson's Disease of Exercise (SPARX) trial,[14,41] which had two exercise groups and one control group, authors suggested that those in the exercise groups may have reduced the number of steps taken outside the intervention so that average daily steps remained unchanged. While this may have been true when considering the entire sample, what about the individuals who were the least active? Would they see meaningful improvements in steps, PA, and/or other health outcomes as a result of the exercise intervention?

Using data from the SPARX trial, the present study examined the effects of treadmill exercise on PA levels in people with de novo PD. We analyzed the least active participants, as these individuals arguably have the most to gain (in terms of health benefits) from increasing PA. Specifically, there were three aims: 1) What daily step threshold corresponded to meeting PA guidelines? 2) For those below the determined daily step threshold, what were the effects of treadmill exercise performed at varying intensities on daily steps and moderate-to-vigorous intensity PA (MVPA)? 3) For those below the determined daily step threshold, what was the relationship between changes in daily steps and cardiorespiratory fitness?

METHODS

Study Design and Participants

This research is based on a deidentified dataset obtained from the National Institute of Neurologic Disease and Stroke's (NINDS) Archived Clinical Research data (*Study in Parkinson's Disease of Exercise [SPARX], Margaret Schenkman, PT, PhD, NCT01506479*) received from the Archived Clinical Research Dataset website. The SPARX trial was a multicenter, randomized, controlled, single-assessor-blinded, Phase II study.[41] Participants with de novo PD were randomized to one of three groups: high-intensity treadmill exercise (80-85% maximum heart rate [HRmax]), moderate-intensity treadmill exercise (60-65% HRmax) or a waitlist control who received usual care. All participants from the SPARX trial provided informed consent and the study was approved by associated institutional review boards.[14] The present secondary analysis received exemption from the University of South Carolina's institutional review board.

Recruitment procedures, inclusion and exclusion criteria for the SPARX trial have previously been described.[14,41] In summary, included participants were between the ages of 40 and 80 years, with idiopathic PD, Hoehn and Yahr stage less than III and who were in the early stages of PD and naïve to therapy (also known as de novo).[42–44] Individuals were excluded if they were currently being treated pharmacologically for PD, unable to perform high-intensity exercise or if they reported regularly (>2 days/week for $\geq$ 4 months) participating in moderate to vigorous aerobic exercise. To be included in the present study, participants were required to have step data at baseline (i.e. before intervention) for aim one, step or VO2peak data at baseline and at five and/or six months for aim two and both step data and VO2peak data at baseline and at five and/or six months for aim three. A flow diagram demonstrating how participant data were utilized is displayed in Figure 1.

Treadmill Exercise Intervention & Waitlist Control Group

Both high-intensity and moderate-intensity exercise groups were prescribed the same mode, frequency and duration of exercise, which was treadmill exercise (i.e. walking) performed 4 days/week for 26 weeks with 45 minute sessions.[14] Frequency and intensity of exercise were gradually increased for the first 8 weeks of the intervention until target HR levels were reached. Treadmill speed and/or incline was adjusted to maintain target HR. Both high and moderate-intensity exercise groups met the prescribed exercise intensities and frequencies over the six month intervention, demonstrating intervention fidelity.[14]

Those in the waitlist control group were instructed to continue their regular behavior.

Participant Descriptors

Participant age, sex, time since Parkinson's disease diagnosis, Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) motor score (part III),[45] item 9 on the Parkinson's Disease Questionnaire - 39 (PDQ-39)[46] and the presence or absence of a cardiovascular health condition (e.g. hypertension) were used to describe the sample. Previous literature found these factors to be significant explanatory variables for daily steps, with higher daily step counts associated with less time since diagnosis, lower MDS-UPDRS motor scores, no reported fear or worry of falling (Item 9 of the PDQ-39) and the presence of a cardiovascular condition.[37]

Activity Monitoring

To capture PA (steps and activity counts), participants were instructed to don a waist-worn Actigraph GT3X [+ and BT]; Actigraph, Pensacola, Florida) during waking hours over a 10-day period, once a month for the duration of the six month (26 week) intervention.[37,41] The activity monitors have demonstrated moderate to high validity and reliability in assessment of free-living activity[47–49] and steps in pwPD.[5,21] Steps and activity counts were summed over each 60 second epoch and then averaged over total monitor wear time. With the 3-axis activity monitor, steps are based on vertical axis acceleration whereas activity counts are based on acceleration in all 3-axes and reflect the frequency and intensity of movement.[37] Activity counts per minute of wear time were used to classify activity as sedentary (<100 counts/min), light (100-1951 counts/min), moderate (1952-5724 counts/min) and vigorous (>5725 counts/min) intensity PA.[50,51]

Valid activity monitoring days were considered those with at least 10 hours of valid wear time and a maximum of 90 minutes of non-wear time.[37,52] For each assessment point (i.e. baseline and five and/or six months) participants needed at least four valid days to be included in the analysis. To examine the effect of treadmill exercise on average daily step counts (aim two), participants in the two exercise groups (i.e. high and moderate intensity treadmill exercise) were required to have at least two treadmill exercise session in which steps (and activity counts) were recorded. If activity data were available at both five and six months, these data were averaged, whereas if data were only available for one of these timepoints, these data were used. We chose to examine activity data at five and/or six months when present as it was postulated that this would represent the peak activity levels during the progressive six month intervention.

Cardiorespiratory Fitness

Assessment of cardiorespiratory fitness was performed at baseline and at six months via a maximal graded exercise test (treadmill walking) with assessment of VO2peak (mL/min/kg) by indirect calorimetry and HRmax.[37,41] Treadmill walking speed was adjusted so that participants were exercising at 70% of their age-predicted maximum heart rate. Participants using chronotropic medications walked at a speed that corresponded to a 4 out of 10 on the modified Borg Rating of Perceived Exertion scale.[53,54]

Data Analysis

Descriptive statistics were calculated for all participants with valid baseline step data. The Shapiro-Wilk test was used to assess all data for normality.[55] Using baseline (prior to intervention) activity data, participants were first categorized as "meeting" or "not meeting" aerobic PA guidelines, which states individuals should perform $\geq$150 weekly minutes of moderate intensity aerobic PA.[20] Average daily activity minutes (measured via activity monitor) performed at a moderate intensity or greater was multiplied by seven for an estimate of weekly PA for each participant. Accumulation of vigorous activity was low (less than one second per hour for those not meeting guidelines) and therefore was combined to form MVPA.[5] To determine the diagnostic accuracy of average daily step count and VO2peak (independent variables) to correctly classify those who meet PA guidelines (dependent variable), receiver operating characteristic (ROC) curves, including the area under the curve (AUC), were generated.[56] Sensitivity, specificity, likelihood ratios and Youden's index (*J*)[57] were also calculated. The single highest *J* value was chosen as the optimal threshold[58] to accurately classify participants as "meeting" or "not meeting" PA guidelines (i.e. $\geq$150 or <150 minutes of at least moderate-intensity PA). Based on the determined step threshold, participants were dichotomized into two step groups (i.e. participants above and below the step threshold), with participant descriptors and PA variables (e.g. steps, moderate intensity PA) compared with independent t-tests or Mann-Whitney U tests, and chi-squared tests.

A comparison within and between subjects was made for participants below the determined step threshold in each of the three SPARX groups (i.e. high-intensity exercise, moderate-intensity exercise and waitlist control). Three separate Mixed-Design Two-Way Repeated Measures Analysis of Variance identified differences in the dependent variables of daily steps, MVPA and VO2peak between assessment points (baseline and five and/or six months), groups, and/or the interaction between time and group. A Bonferroni adjustment was applied to control for multiple comparisons. Post-hoc tests (i.e. t-tests or one way analysis of variance) were performed and effect sizes (Cohen's d) were then calculated to determine the effects of treadmill exercise performed at varying intensities on PA. Effect sizes of 0.8 were considered large, 0.5 were considered medium and 0.2 were considered small.[59] The relationship between changes in daily steps and VO2peak were examined using Pearson's r correlations.

Alpha level was set at $\leq .05$ for all statistical tests, and all analyses were performed using IBM SPSS Statistics for Macintosh, Version 26.0 (IBM SPSS, Chicago, IL, USA).

RESULTS

Step threshold that corresponds to meeting aerobic PA guidelines

Of the 110 participants with valid PA data at baseline (Figure 1), 84 (76.4%) had $\geq$ 150 weekly minutes of MVPA and thus met aerobic PA guidelines (Table 1). ROC curves are displayed in Figure 2. Resulting thresholds that corresponded to meeting aerobic PA guidelines were 4197 daily steps and a VO2peak of 23.9mL/min/kg. Corresponding AUC are displayed in Table 2. The threshold of 4197 daily steps correctly classified 87% (sensitivity) of participants who met/exceeded PA guidelines and 96% (specificity) of people who did not meet PA guidelines. A comparison of participants with ≥4200 and <4200 daily steps is displayed in Table 1. Those averaging <4200 daily steps were older, more likely to report a fear of falling and had lower baseline fitness levels.

Effects of treadmill exercise performed at varying intensities on PA

Of the 36 participants with an average of <4200 daily steps, 33 had the appropriate data and were analyzed (Figure 1). Descriptive baseline data for the 33 participants, including group allocation are displayed (Table 3). At five and/or six months, 85.7% (12/14), 33.3% (2/6) and 23.1% (3/13) of participants met PA guidelines in the high-intensity, moderate-intensity and waitlist control groups, respectively (data not in table).

At five and/or six months, participants in the high intensity group (n=14) had a median of 5.5 (2, 11) treadmill exercise sessions with activity monitoring and averaged 2604 (1283) steps per session, whereas those in the moderate intensity group (n=6) had a median of 7.5 (2, 9) treadmill exercise sessions with activity monitoring and averaged 1809 (1418) steps; neither number of exercise sessions with activity monitoring nor average steps were statistically different (p=0.54 and p=0.23, respectively). Average daily activity monitor wear time at five and/or six months was not significantly different between the three groups (p=0.60; high-intensity group 817 (138), moderate-intensity group 765 (99) and waitlist control 795 (114) minutes per day). Analysis of daily steps revealed a main effect for time (p=0.03), with no main effect for group (p=0.14) nor time*group interaction (p=0.10, Figure 3). Subsequent paired t-tests revealed that the high-intensity group significantly increased daily steps by 1220 (1614) steps (p=.01, 95% CI 288 to 2152) whereas within group differences in steps for the moderate-intensity group and the waitlist control group did not reach statistical significance: 435 (845) steps (p=.26, 95% CI -452 to 1322) and 85 (1207) steps (p=.80, 95% CI -644 to 815, respectively). Within group effect sizes (Cohen's d) for changes in average daily steps were 0.98, 0.52 and 0.08 for high intensity, moderate intensity and waitlist control groups, respectively.

For MVPA, there was a main effect for time (p=0.01) and group (p=0.02) but no statistically significant time*group interaction (p=.16, Figure 3). Post-hoc paired t tests revealed an average daily MVPA increase of 13 (14.6) minutes for the high intensity group (p=0.01, 95% CI 4.8 to 21.2) but no change for moderate intensity 5.1 (10.2) minutes (p=0.27, 95% CI -5.6 to 15.80) or waitlist control 3.7 (12.5) (p = 0.31, 95% CI -3.8 to 11.2). Within group effect sizes for changes in average daily MVPA were 0.91, 0.48 and 0.30 for high intensity, moderate intensity and waitlist control groups, respectively. Between group comparisons using independent t-tests showed that MVPA at five and/or six months was higher in the high intensity group compared to both the moderate intensity group (mean difference = 14.5 minutes, p= 0.04, 95% CI .41 to 28.7) and waitlist control (mean difference = 17.4 minutes, p=0.01, 95% CI 5.7 to 29.1). The moderate intensity group obtained higher levels of MVPA compared to waitlist control but the difference was not statistically significant (mean difference = 2.9 minutes, p=0.70, 95% CI -12.5 to 18.2).

Relationship between changes in daily steps and fitness

For changes in VO2peak, there were no significant main effects for time (p=0.81) or group (p=.94); however, a group*time interaction was present (p=0.03, Figure 3). A post-hoc one way analysis of variance revealed no significant between-group differences in VO2peak at six months (p=0.91). Within group effect sizes (Cohen's d) for changes in VO2peak were 0.23, 0.10 and -0.44 for high intensity, moderate intensity and waitlist control groups, respectively. Changes in daily steps were not significantly associated with changes in VO2peak (r=.183, p=0.16)

DISCUSSION

What daily step threshold corresponds to meeting PA guidelines?

Using the 4200 steps per day threshold correctly classified 87% of participants who met PA guidelines and 96% of participants who did not. In other words, those obtaining ≥4200 steps were 23 times more likely to meet PA guidelines compared to those with <4200 steps. At face value, 4200 daily steps may appear low, especially compared to the popular 10,000 steps per day[60] or the frequently cited 7,000 steps per day thresholds.[61,62] The aforementioned thresholds, however, are geared towards healthy adults. For people with disability, there is limited evidence supporting a daily step recommendation[24] but our value of 4200 daily steps may provide a starting point. Lee et al.[31] found that just 4400 steps per day was related to a decrease in mortality rate in older women. In addition, Lee et al.[31] found that after adjusting for daily step count, the importance of step intensity was reduced, leading authors to conclude that daily step counts may be of greater value than metrics of intensity. Because Parkinson's adversely impacts both cognition and mobility, setting a goal of 4200 daily steps may be a more obtainable target for pwPD as compared to assessment of time spent in moderate-intensity PA. To provide further support for the recommendation of 4200 daily steps, future longitudinal studies should examine the relationship between 4200 daily steps, mortality and other PD-specific outcomes.

Out of 110 participants at baseline (i.e. before intervention), over 75% met PA guidelines. Our highly active sample is in contrast to the 27% of participants who met PA guidelines in a recent study (n=95).[5] Differences found between the two studies may be due to differences in participant age (mean age of 73 versus our median of 65 years) and disease severity (H&Y II and III versus <III in the present study). Furthermore, though the same activity monitor (ActiGraph GT3X+) was used, the present study utilized a slightly lower cutoff (i.e. 1,952 vs. 2,019 counts per minute[5]) to classify moderate intensity PA and thus the number of participants meeting PA guidelines in the present study may have been inflated. Because the SPARX trial consisted of a rigorous six month exercise intervention, our participants may represent a more active group of pwPD. Interestingly, participants who reported performance of moderate-to-vigorous aerobic exercise more than twice per week for the last four months were excluded from the SPARX trial. The fact that our sample was highly active at baseline as measured by activity monitor, reiterates the known discrepancies between PA assessed by self-report and activity monitors.[38,63] Alternatively,

participants may not have been regular exercisers prior to their diagnosis. With a median time since diagnosis of less than one year, participants may have become physically active only after receiving their PD diagnosis, which could have been within the four months prior to beginning the SPARX trial. Though MVPA was higher in the current study, daily step counts (4817) were similar to previous studies (3615 to 5452)[5,27,38] but also lower than others (8686 to 10,261).[30,33,39] Participants in the present study may have accumulated MVPA in relatively few bouts, with minimal stepping activity for the remainder of the day.

For those with <4200 daily steps, what are the effects of treadmill exercise performed at varying intensities on PA?

Participants with less than 4200 steps at baseline who engaged in high-intensity treadmill exercise observed a large and significant increase in daily minutes spent performing MVPA. For pwPD, the benefits of MVPA are well established and include improvements in cardiorespiratory fitness,[14,15] fatigue, depression, quality of life and slowing of disease progression.[14,15] For older adults, replacing 10 minutes of sedentary time with 10 minutes of MVPA led to a 21% risk reduction in mortality.[64] While the smallest amount of MVPA required to see PD-specific benefits has yet to be determined, current PA guidelines clearly state that any amount of MVPA is beneficial to health.[20] Thus, when interpreting changes in MVPA, especially in those with the lowest activity levels, researchers should be encouraged to look at the magnitude of change, rather than just statistical significance, to ensure meaningful gains in MVPA are captured. Though our findings suggest that high-intensity exercise may be superior to moderate-intensity exercise in terms of accumulating MVPA, other factors such as participant preference and capability must also be considered when prescribing exercise regimens.

Participants with less than 4200 steps at baseline who were in the high-intensity exercise group also observed a large and significant increase in daily steps (1220, 95% CI 288 to 2152). While there is no available minimally clinically important difference (MCID) for daily step counts in pwPD, in individuals with Multiple sclerosis, a change of 800 steps per day reflected changes in participant reported walking ability.[65] For adults at risk for type 2 diabetes, an increase of 2000 daily steps was associated with reduced cardiovascular events.[66] This last finding is pertinent, as pwPD are at greater risk for development of cardiovascular disease,[10,11] which is responsible for nearly one in five deaths in those with PD.[12] While only participants in the high-intensity exercise group had significant increases in daily steps, there was a medium within group effect size for the moderate-intensity exercise group and a miniscule effect size for the control group. Though no significant between group differences in daily steps were found, this may have been a result of the small number of participants in each group. Overall, our results imply that treadmill exercise of any intensity may be enough to make positive changes in daily step counts.

For those with <4200 daily steps, what is the relationship between changes in daily steps and cardiorespiratory fitness?

In a cross-sectional analysis of the same sample as the present study, Christiansen et al.[37] found that cardiorespiratory fitness (VO2peak) explained the largest amount of variability (10%) in daily step counts. Using the longitudinal data from the SPARX trial, the present study found that changes in daily step counts were not significantly associated with changes in VO2peak. This finding is not surprising given the lack of significant changes found in VO2peak amongst those with <4200 daily steps. While linking step counts to a powerful health outcome such as cardiorespiratory fitness would be welcome, the two metrics may provide meaningful but unique information. Cardiorespiratory fitness, which is considered a clinical vital sign,[67] is largely determined by genetics.[68] Genetics also determines up to 50% of an individual's response to exercise training.[69] On the other hand, daily steps are more fluid and vary based on age, gender, walking ability, and disease severity,[70] as well as other factors such as weather,[71] motivation[72] and the physical environment.[73] Another possible explanation for the lack of a significant association could be due to the fact that steps counts do not provide information on intensity. For the least active participants in our sample, obtaining MVPA outside of exercise sessions may have been difficult and thus daily steps may have been performed predominantly as light-intensity PA. If the majority of steps were of light-intensity, changes in cardiorespiratory fitness would likely be minimal. For these individuals, increasing light, rather than MVPA, may be more feasible.[74] The role light-intensity PA plays in health outcomes is becomingly increasingly apparent and future research examining light-intensity PA may help inform guidelines that include more than just MVPA recommendations.[75]

Limitations

Strengths of the present study include calculation of a sample-specific step threshold to classify those who meet PA guidelines and analysis of pwPD with the lowest PA levels (i.e. steps). Nevertheless, the study has several limitations. Calculation of the 4200 steps per day threshold relied on two metrics (steps and minutes spent in MVPA) which were both derived from the same activity monitor. Use of different cutpoints to define MVPA would likely yield a different step threshold. As a retrospective study, no power analysis was conducted and could explain lack of significant findings between the two exercise groups and the waitlist control group. In addition, only 33 participants had <4200 daily steps at baseline and sample sizes became even smaller when comparing groups (i.e. high-intensity, moderate-intensity, waitlist control). Finally, the activity monitor cutpoints used to classify sedentary behavior, light-intensity PA and MVPA were derived from studies in healthy adults and may not be ideal for people with physical impariments.[76] Cutpoints to accurately determine PA intensity vary by age,[77] activity being performed[78] and walking speed.[79] Researchers must consider these factors when choosing appropriate cutpoints for their sample.

CONCLUSION

The present study determined that for people with de novo PD, 4200 daily steps corresponded to meeting PA guidelines. In addition, for those with <4200 daily steps, high-intensity treadmill exercise led to increases in daily steps and MVPA, though these gains were not associated with changes in cardiorespiratory fitness. Collectively, our results have important research and clinical implications. The least active participants at baseline in both exercise groups outperformed (in terms of effect size) the waitlist control group in terms of steps and MVPA. For clinicians working with patients recently diagnosed with PD, the 4200 steps per day threshold may be used, albeit cautiously, to infer whether or not PA guidelines are being met. While the true value of daily step counts is still being determined, the present study provides new information on the relationship between steps and health, and provides evidence supporting exercise as a tool to increase PA in people with de novo PD. Additional work is needed to determine the best means of maintaining and continuing to improve both PA and health in pwPD.

Table 2.1 Pre-Randomized Baseline Descriptors of Participants[a]

Descriptor	Participants (n=110)	≥ 4200 Steps/day (n=74)	< 4200 Steps/day (n=36)	*P*
Age, years	65 (40, 80)	**61.5 (39, 79)**	**70.5 (48, 80)**	**<0.001[b]**
Female, n (%)	48 (43.6)	29 (39.2)	19 (52.8)	0.18[c]
Time since PD diagnosis, years	0 (0, 5)	0 (0, 5)	1 (0, 4)	0.10[b]
MDS-UPDRS motor score (III)[d]	19 (5, 60)	18.5 (7, 39)	22 (5, 60)	0.06[b]
Fear/worry of falling (PDQ-39, Item 9)[e]	77 (70)	**61 (82.4)**	**16 (44.4)**	**<0.001[c]**
Never, n (%)	33 (30)	**13 (17.6)**	**20 (55.6)**	
Any, n (%)				
Cardiovascular condition present, n (%)	52 (47.3)	39 (52.7)	13 (36.1)	0.10[c]
VO2peak, mL/min/kg	22.8 (9.2, 43.7)[f]	**24.1 (13.1, 43.7)**	**20.9 (9.2, 33.3)[f]**	**<0.001[b]**
Sedentary activity, min/hr wear time, mean (SD)	33.5 (6.1)	32.3 (6.3)	36 (4.8)	0.75[g]
Light activity, min/hr wear time, mean (SD)	23.3 (5.5)	23.5 (5.8)	22.9 (5.0)	0.21[g]
MVPA, min/hr wear time	2.8 (0.1, 9.5)	**3.5 (1.3, 9.5)**	**0.8 (0.1, 3.4)**	**<0.001[b]**
Total daily MVPA, min	36.8 (0.8, 131.1)	**49 (19.7, 131.1)**	**11.1 (0.8, 45.3)**	**<0.001[b]**

Meets aerobic PA guidelines, n (%)[h]	84 (76.4)	**73 (98.6)**	**11 (30.6)**	**<0.001[c]**
Steps per day	4817 (763, 15802)	**6066 (4202, 15802)**	**2852 (763, 4192)**	**<0.001[b]**
Monitor wear time, min, mean (SD)	809 (87)	809 (83)	810 (94)	0.94[g]

Abbreviations: PD, Parkinson's disease; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionaire-39, VO2peak, maximal rate of oxygen consumption during maximal graded exercise test, measured in milliliters (mL) per minute (min) per kilogram (kg) of body mass; min/hr, minutes per hour; MVPA, moderate-to-vigorous intensity physical activity; PA, physical activity

[a] Data presented as median (minimum, maximum) unless otherwise stated. Physical activity intensity classified as sedentary (<100 counts/min), light (100-1951 counts/min), moderate (1952-5724 counts/min) and vigorous (>5725 counts/min).[50,51] Boldface indicates significant at p $\leq$0.05.

[b] Independent samples, Mann-Whitney U test.

[c] Pearson Chi-Square, 2-sided

[d] The MDS-UPDRS motor score (part III) consists of 33 items including but not limited to assessment of speech, upper and lower extremity coordination, sit to stand ability and gait. Examiners rate participants on a five pinot scale ranging from 0 (normal) to 4 (severe) with higher scores indicating greater disease severity.[45]

[e] Item 9 of the PDQ-39 asks participants, "Due to having Parkinson's disease, how often during the last month have you felt frightened or worried about falling over in public?" Participants respond via five-point Likert scale ranging from "never" to "always."[46] The present study followed previously reported methods[37] and dichotomized responses to item 9 by considering any response other than "never" as having fear or worry about falling present.

[f] VO2peak data was missing from one participant (n=109) in the <4200 steps/day group (n=35)

[g] Independent samples t-test, 2-sided

[h] Physical activity guidelines are from the U.S. Department of Health and Human Services which recommend adults participate in at least 150 minutes of moderate-intensity physical activity each week.[20]

Table 2.2 Accuracy of Daily Step Count and VO2peak to Classify People with Parkinson's Disease as Meeting or Not Meeting Aerobic Physical Activity Guidelines[a]

Thresholds	AUC[b] (95% CI)	Sensitivity	Specificity	+LR (95% CI)	-LR (95% CI)
Daily Steps 4,197	**0.95 (.90 to 1.00)**	87%	96%	23 (7.72 to 68)	0.14 (.05 to 0.37)
VO2peak (mL/min/kg) 23.9	**.76 (.66 to .85)**	52%	92%	6.55 (1.74 to 25)	0.52 (.40 to 0.67)

Abbreviations: AUC, area under the receiver operating characteristics curve; 95% CI, 95% confidence interval; VO2peak, maximal rate of oxygen consumption during maximal graded exercise test, measured in milliliters (mL) per minute (min) per kilogram (kg) of body mass; +LR, positive likelihood ratio; -LR, negative likelihood ratio

[a] Physical activity guidelines are from the U.S. Department of Health and Human Services which recommend adults participate in at least 150 minutes of moderate-intensity physical activity each week.[20] Using the daily step count threshold of 4197 steps correctly classified 87% (sensitivity) of participants who met/exceeded 150 minutes of MVPA and 96% (specificity) of participants who did not meet guidelines. Participants meeting/exceeding aerobic physical activity guidelines were between 7.72 and 68 times more likely to have at least 4200 steps compared to those not meeting guidelines. Boldface indicates significant at $p < 0.001$.

[b] An AUC value of 1.0 indicates a perfect diagnostic test, whereas an AUC of 0.5 is equal to chance (i.e. the test has no value).

Table 2.3 Baseline Descriptors For Participants with <4200 Daily Steps[a]

Descriptor	Participants (n=33)	High Intensity (n=14)	Moderate Intensity (n=6)	Waitlist Control (N=13)	*P*
Age, years	71 (48, 80)	73 (48, 77)	69 (54, 80)	71 (57, 76)	0.94[b]
Female, n (%)	17 (51.5)	10 (71.4)	2 (33.3)	5 (38.5)	0.14[c]
Time since PD diagnosis, years	1 (0, 4)	1 (0, 3)	1 (0, 2)	1 (0, 4)	0.73[b]
MDS-UPDRS motor score (III)	22 (5, 60)	23.5 (5, 34)	17.5 (16, 36)	22 (12, 60)	0.99[b]
Fear/worry of falling (PDQ-39, Item 9)[c]	15(45.5)	5(35.7)	2(33.3)	8(61.5)	0.33[c]
Never (%)	18 (54.5)	9(64.3)	4(66.7)	5(38.5)	
Any (%)					
Cardiovascular condition present, n (%)	11 (33.3)	5 (35.7)	4 (66.7)	2 (15.4)	0.09[c]
VO2peak, mL/min/kg	21.4 (15.7, 33.3)	18.8 (15.7, 33.3)[d]	22.1 (16.5, 25)	22 (16.2, 28)[d]	0.54[b]
Sedentary activity, min/hr wear time, mean (SD)	35.7(4.8)	35 (6.1)	35.9 (3.2)	36.4 (4.0)	0.77[e]
Light activity, min/hr wear	23.2 (5.1)	23.5 (6.5)	23.2 (3.6)	22.8 (4.1)	0.93[e]

MVPA, min/hr wear time, mean (SD)	1.1 (0.8)	1.5 (1.0)	1(0.6)	0.9 (0.6)	0.17[e]
Total daily MVPA, min, mean (SD)	15.5 (11.7)	19.9 (14.6)	13.2 (7.4)	11.8 (8.5)	0.18[e]
Meets aerobic PA guidelines, n (%)[f]	10 (30.3)	7 (50)	1 (16.7)	2 (15.4)	0.11[c]
Steps per day, mean (SD)	2918 (799)	2904 (943)	3218 (547)	2795 (745)	0.58[e]
Monitor wear time, min, mean (SD)	813 (95)	813 (127)	798 (29)	821 (80)	0.89[e]

Abbreviations: PD, Parkinson's disease; PDQ-39, MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; Parkinson's Disease Questionaire-39, VO2peak, maximal rate of oxygen consumption during maximal graded exercise test, measured in milliliters (mL) per minute (min) per kilogram (kg) of body mass; min/hr, minutes per hour; MVPA, moderate-to-vigorous intensity physical activity; PA, physical activity

[a] Data presented as median (minimum, maximum) unless otherwise stated. Physical activity intensity classified as sedentary (<100 counts/min), light (100-1951 counts/min), moderate (1952-5724 counts/min) and vigorous (>5725 counts/min)

[b] Kruskal–Wallis one-way analysis of variance

[c] Pearson Chi-Square, 2-sided**;**

[d] VO2peak data was missing from two participants (n=31) with one from high-intensity group (n=13) and one from waitlist control group (n=12)

[e] One-way analysis of variance

[f] Physical activity guidelines are from the U.S. Department of Health and Human Services which recommend adults participate in at least 150 minutes of moderate-intensity physical activity each week.[20]

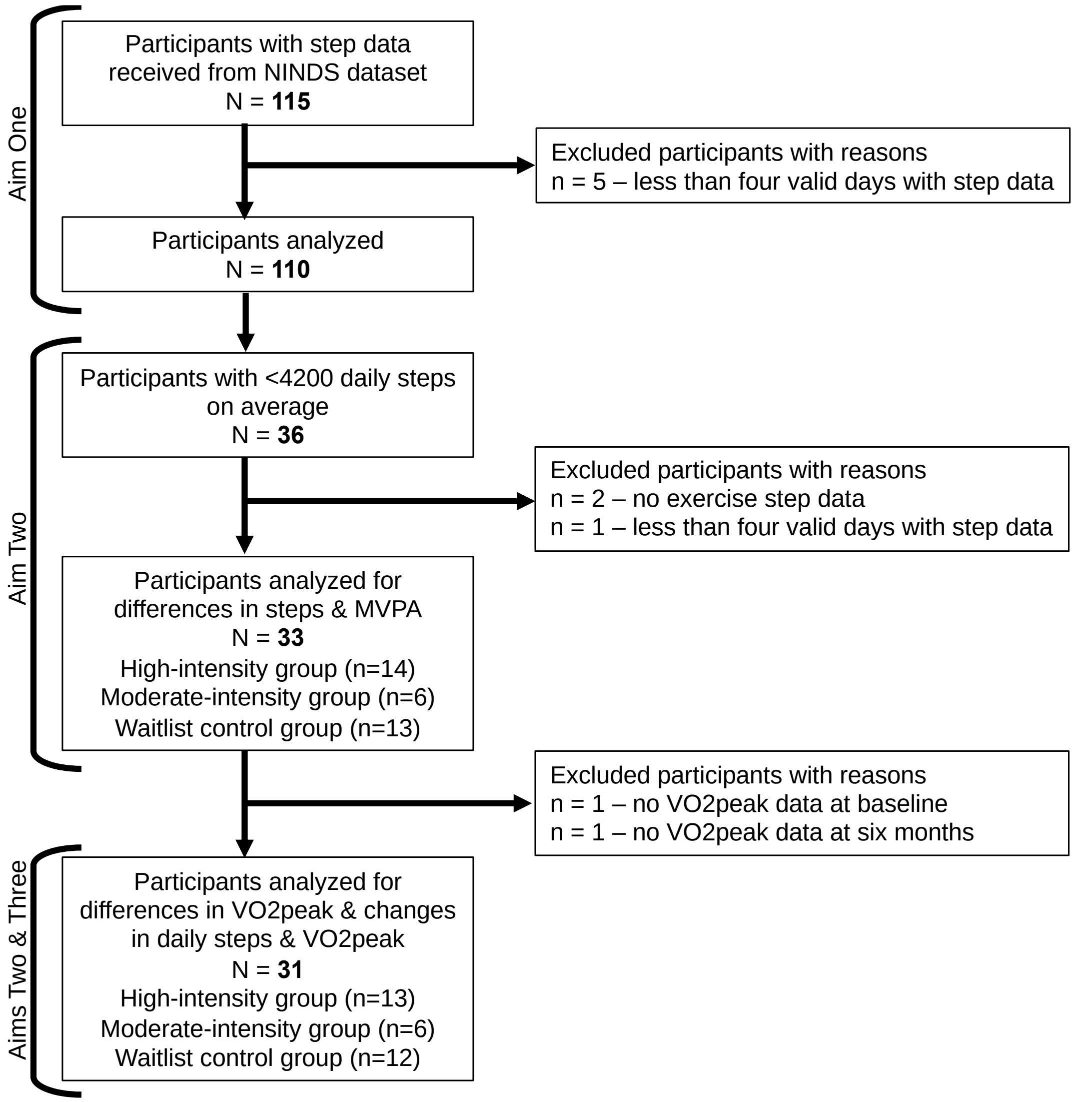

Figure 2.1 Flow Diagram of Participant Data

Abbreviations: NINDS, National Institute of Neurologic Disorders and Stroke; MVPA, moderate-to-vigorous intensity physical activity; VO2peak, maximal rate of oxygen consumption during maximal graded exercise test, measured in milliliters per minute per kilogram of body mass

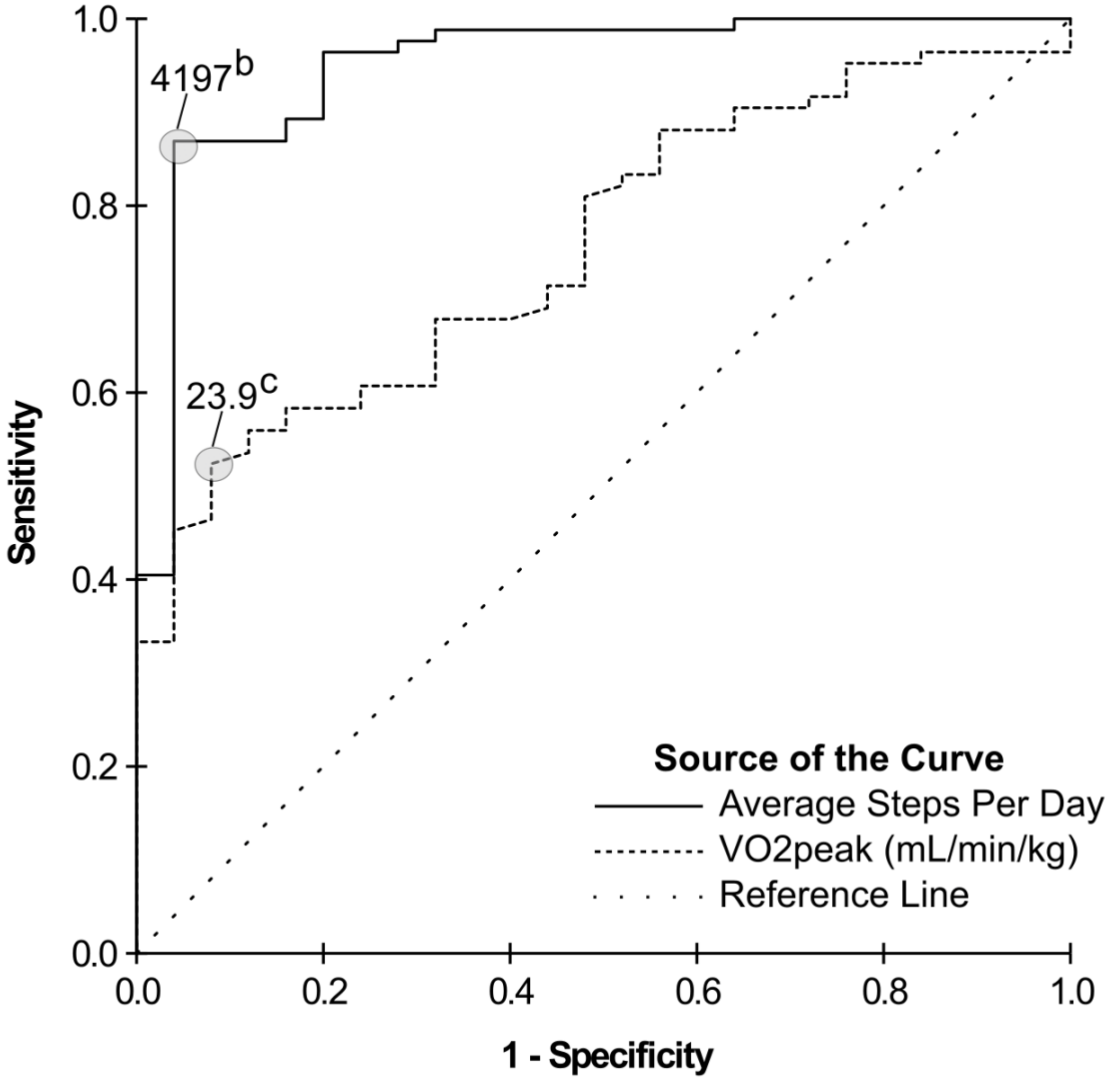

Figure 2.2 Receiver Operating Characteristics Curves for Average Daily Steps and VO2peak to Classify People with Parkinson's Disease as Meeting or Not Meeting Aerobic Physical Activity Guidelines[a]

Abbreviations: VO2peak, maximal rate of oxygen consumption during maximal graded exercise test, measured in milliliters (mL) per minute (min) per kilogram (kg) of body mass;
[a] Physical activity guidelines are from the U.S. Department of Health and Human Services which recommend adults participate in at least 150 minutes of moderate-intensity physical activity each week.[20] Dashed reference line indicates a test that randomly classifies a condition (i.e. a test with 50% accuracy).
[b] Optimal daily step threshold found in the present study
[c] Optimal VO2peak threshold found in the present study

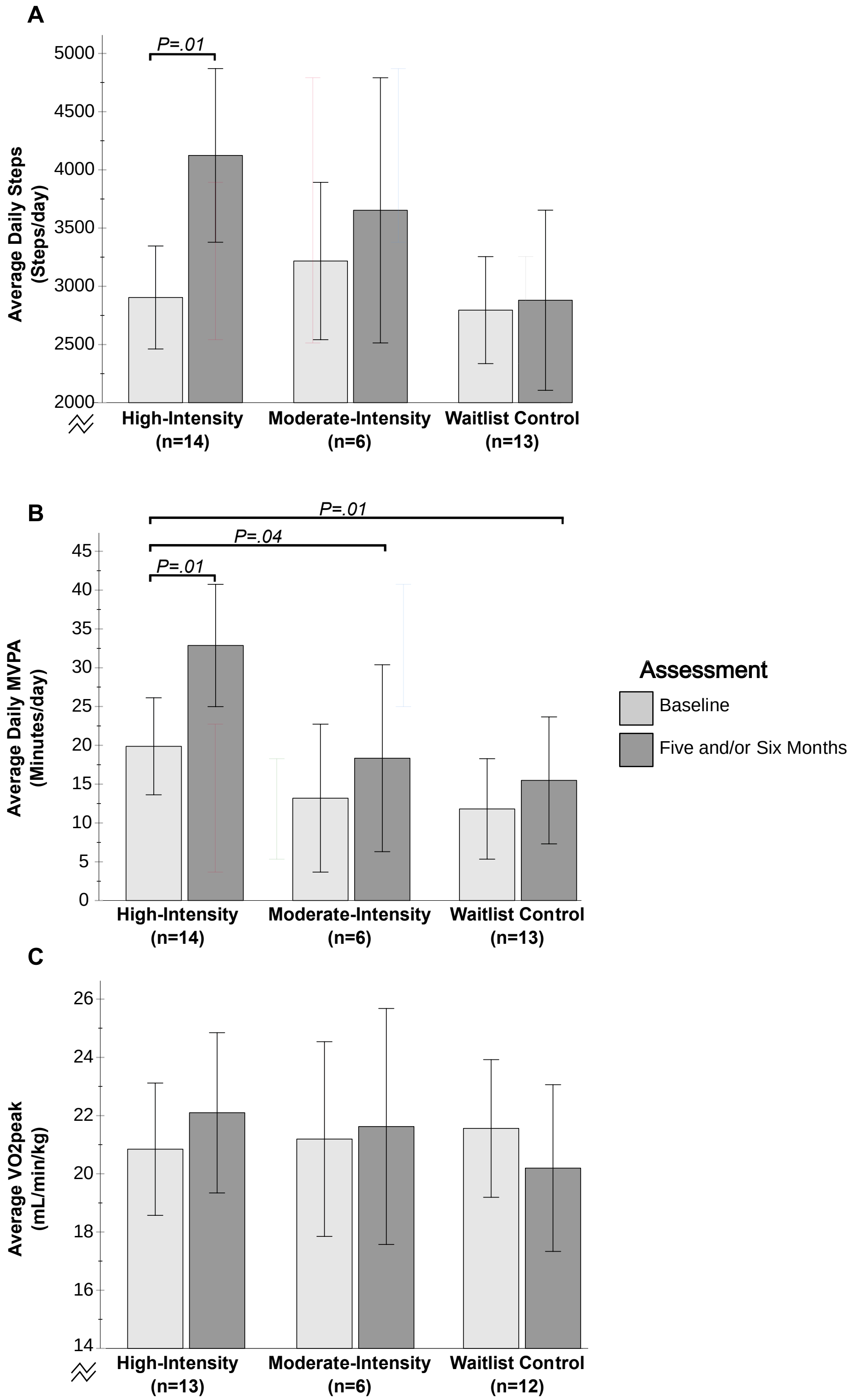

Figure 2.3 Within and Between Group Comparison of A) Average Daily Steps, B) Average Daily MVPA, C) Average VO2peak[a]

Abbreviations: MVPA, moderate-to-vigorous intensity physical activity; VO2peak, maximal rate of oxygen consumption during maximal graded exercise test, measured in milliliters (mL) per minute (min) per kilogram (kg) of body mass.
[a] Data presented as means with vertical black bars indicating 95% Confidence Intervals. For all dependent variables (steps, MVPA, VO2peak), groups were not statistically different at baseline.

CHAPTER 3: DAILY STEP COUNT AND BALANCE AT TWO MONTHS POST-STROKE ARE THE STRONGEST PREDICTORS OF DAILY STEPS AT ONE YEAR POST-STROKE

INTRODUCTION

Improving walking ability is a predominant goal for people after stroke.[80] Not surprisingly, rehabilitation primarily focuses on regaining and improving walking ability.[81] While components of walking, including speed and endurance, have been heavily researched and shown to improve in response to interventions,[16,18,82] there has recently been an increased interest in free-living walking behavior, as measured by daily step counts.[23,32,40,83] Unlike walking speed or endurance, daily steps are thought to represent participation outside the clinical environment and thus offer a unique insight into physical activity (PA) and walking behavior.[82,84] Daily steps may even predict future health outcomes, with attainment of $\geq$6000 steps related to a decreased risk for subsequent cardiovascular disease in adults with stroke.[85] Decreasing risk in adults with stroke is paramount considering nearly one in four survivors will experience a second stroke,[86] which is often more debilitating and deadly than their initial stroke.[8,87]

Examination of what contributes to daily steps after stroke is needed in order to inform interventions aimed at increasing PA through walking. A 2018 meta-analysis[88] examined correlates of PA (including daily steps) in people with stroke and found that the modifiable factors of physical function, cardiorespiratory fitness, fatigue, falls and balance self-efficacy, depression and health-related quality of life were significantly associated with PA, in addition to the nonmodifiable factors of age and sex. A limitation to this analysis was that the majority of the included studies were cross sectional, used subjective measures (i.e. participant-reports) of PA, or included only those in the chronic (i.e. $\geq$ 6 months) phase of stroke. Ideally, identification of people with stroke at risk for leading insufficiently active lifestyles would be done as close to stroke onset as possible. In this manner, individualized education and behavioral interventions could be implemented early for those most at risk for poor health outcomes associated with physical inactivity.

The purpose of the present study was twofold: 1) determine which factors (both nonmodifiable and modifiable) present at two months post-stroke can predict daily step counts at one year post-stroke and 2) determine a daily step threshold at two months post stroke that corresponds to obtaining $\geq$6000 daily steps at one year post-stroke.

METHODS

Study Design and Participants

The present study is a secondary analysis of deidentified data from the National Institute of Neurologic Disease and Stroke's (NINDS) Archived Clinical Research data (*Locomotor Experience Applied Post-Stroke [LEAPS], Pamela W. Duncan, PhD, PT, NCT00243919*) received from the Archived Clinical Research

Dataset website. The LEAPS trial was a three arm, single blinded, phase III randomized controlled trial, which examined the effects of three interventions (early body weight–supported treadmill training at two months post-stroke, late body weight–supported treadmill training at six months post-stroke, and a progressive supervised home exercise program) on self-selected walking speed.[16] Adults were screened between 5 and 30 days after experiencing an initial stroke and, after a baseline assessment at two months post-stroke, randomized to one of the three groups. Each intervention consisted of 36 sessions lasting 90 minutes each and performed for a total of 12 to 16 weeks. Results demonstrated no superiority of any treatment group, with 52% of all participants transitioning from a walking speed of [<0.40 m/s to >0.40 m/s] or [between 0.40 m/s to <0.80 m/s] to >0.80 m/s. In addition, 52% of participants attained clinically meaningful improvements in daily steps at one year post-stroke. During the trial, 82% of participants received physical therapy (outside of study) with 74% of therapy provided in an outpatient setting between two and six months post-stroke.[16] Ethical approval for the LEAPS trial was obtained from several associated institutional review boards and all participants provided informed consent prior to participation.[16] The secondary analysis used in the present study was not considered human subjects research and received exemption from the University of South Carolina's institutional review board.

Criteria for inclusion and exclusion in the LEAPS trial have been reported.[16,89] To be included in the trial, participants had to have a first time diagnosis of ischemic hemorrhagic stroke, be able to walk at least 3m with or without help from another person and have a self-selected walking speed of <0.80m/s. Eligible participants were then randomized to one of three treatment groups. Participant data was collected at multiple time points during the trial but the present study analyzed only data at baseline (two months post-stroke) and one year post-stroke (the final assessment).

Daily Step Counts

Daily steps were measured on two consecutive days at baseline (two months post-stroke) and at one year post-stroke using the highly reliable[90,91] and valid[23,92] StepWatch Activity Monitor (Orthocare Innovations, Oklahoma City, OK, USA). Participants were instructed to wear the monitor on the non-paretic ankle during all waking hours with the exception of water-based activities (e.g., bathing or swimming).[93] For step data to be considered valid for the present study, participants needed two days of monitoring[94] with an overall average monitor wear time of at least 10 hours[95] at two months and at one year post-stroke. The average daily step count for the two days of monitoring was used for analysis. Participants without valid step data were excluded.

Candidate Predictors of Daily Steps – Nonmodifiable

Nonmodifiable factors previously found to be associated with PA in people with stroke were examined as potential predictors of daily steps. These factors included age and gender (males accumulating more PA than females),[88] race and/or ethnicity (Hispanics and non-Hispanic black adults obtaining less PA than non-Hispanic whites),[96] and initial stroke severity[97] (measured at the initial screen using the National Institutes of Health Stroke Scale [NIHSS]).[98,99]

Candidate Predictors of Daily Steps – Modifiable

Modifiable factors previously found to be associated with PA in people with stroke[88] were also examined as potential predictors of daily steps and included:

Self-selected[100] *and fast paced*[24] *walking speed,* which were measured as the time taken to walk 10 m (at either a self-selected or a fast pace) with an untimed 3 m section both preceding and following the timed 10 m section.[89]

The Six Minute Walk test[101] which assessed walking endurance by having participants walk as far as they could in 6 minutes using a standardized protocol.[26] A path of ~30 m (100 ft) was used for the test and results were recorded as meters walked.

The Lower extremity Fugl-Meyer Assessment[102] which assessed motor impairment with scores ranging from 0 to 34, with higher scores indicating less impairment.

The Berg Balance Scale[103] which assessed balance and consists of 14-items scored 0 to 4 with a maximum score of 56 (indicative of higher balance and mobility).

Cardiorespiratory fitness which was assessed via an exercise tolerance test (stationary bicycle) performed just prior to randomization.[89,104] Participants began pedaling at 40-60 revolutions per minute with increasing workload increments of 10 watts per minute. The test was stopped when maximum effort was reached (defined as reaching 90% of age predicted maximum heart rate or a rating of perceived exertion[54] of 18/20 in those taking beta blockers) or if symptoms limited completion of the test (e.g. a blood pressure reading that warranted cessation of exercise). Exercise duration during the test was recorded and used for analysis.

The Activities Specific Balance Confidence Scale,[105] which is a participant-reported measure that asks participants to rank their level of confidence for performing 16 different tasks (e.g. walk around the house and walk up and down a ramp). Scores range from 0 to 100% with higher scores indicating greater balance confidence.

The Patient Health Questionnaire (PHQ-9),[106] which is a 9 item participant reported measure examining the presence and severity of depressive symptoms with a score >10 suggestive of major depression.

The Stroke Impact Scale (mobility and participation dimensions),[107] which is a participant-reported measure examining disability and health related quality of life with higher scores indicating less disability and greater quality of life.

Daily Steps at two-months post-stroke was also examined as a candidate predictor of future PA and was measured via activity monitor.

Additionally, in older adults, being married,[108] employed, and having a higher level of education has also been associated with increased PA[109] and were considered candidate predictors of daily steps.

Data Analysis

A priori power analysis using G*Power was performed to determine the sample size needed to achieve an R^2 value of 0.25 (effect size f^2 of 0.33), with 18 tested predictors and power set at 0.80. An R^2 value of 0.25 was chosen based on a meta-analysis which showed that most factors explained <30% of the variance in PA in people with stroke.[88] The minimum sample size needed to conduct the analysis was determined to be 77 participants.

Univariate analysis using Pearson's *r* (or Spearman's rho [r_s] for ordinal data) was performed to determine the association between candidate predictors (independent variables assessed at two months post-stroke) and average daily step counts at one year (dependent variable). Candidate predictors found to be statistically significantly associated ($P<0.05$) with daily step counts were entered into multivariate analysis with dummy coding applied for categorical predictors. Forward selection stepwise regression determined the strongest predictors (i.e. largest R^2 values) of daily steps at one year post-stroke, using a probability of <0.05 for a predictor to enter the model and >0.10 for a predictor to be removed. Forward selection was used to minimize the number of predictors in the model and arguably make assessment of such predictors more clinically feasible (i.e. clinicians will need to assess fewer factors to gain insight into future PA levels). Predictors found to exhibit multicollinearity (determined as a variance inflation factor or VIF >5)[110] were removed from the model.

Step data at one year post-stroke was used to classify participants into two groups (participants with <6000 and participants with $\geq$6000 daily steps) and descriptive statistics were calculated. A step count of 6000 was chosen as it has been found to be related to a decreased risk for subsequent cardiovascular disease (i.e. stroke and myocardial infarction) in people with stroke.[85]

Demographic variables between the two groups were compared through independent t-tests or Mann-Whitney U tests, and chi-squared tests.

To determine a daily step threshold at two months post-stroke (independent variable) which corresponds to obtaining ≥6000 steps at one year post-stroke (dependent variable), receiver operating characteristic (ROC) curves, including the area under the curve (AUC) were generated.[56] Sensitivity, specificity, likelihood ratios and Youden's index (*J*)[57] were calculated. *J* can be used to identify optimal thresholds for diagnostic tests.[58] The highest *J* value was chosen as the optimal threshold to accurately classify participants as obtaining <6000 or ≥6000 daily steps. All data were analyzed using IBM SPSS Statistics for Macintosh, Version 26.0 (IBM SPSS, Chicago, IL, USA).

RESULTS

A flow diagram of how participant data were used is displayed in Figure 1. After removal of participants with invalid data and a single outlier (in terms of daily steps), data from 206 participants were analyzed (in Table 1). Participants averaged 63 years of age with a median self-selected walking speed of 0.42m/s and an average of 2922 daily steps.

Eight modifiable factors at two months post-stroke were found to be significantly associated with daily steps at one year post-stroke: self-selected (r=.371, p=<0.001) and fast paced (r=.401, p=<0.001) walking speed, walking endurance (r=.476, p=<0.001), lower extremity impairment (r_s=.308, p=<0.001), balance (r_s=.473, p=<0.001), average daily steps at two-months (r=.598, p=<0.001), participant reported mobility (r_s=.257, p=<0.001), and balance confidence (r=.231, p=<0.001). The only nonmodifiable factor significantly associated with daily steps at one year post-stroke was initial stroke severity (r_s=-.333, p=<0.001). Forward selection regression was performed using these 9 factors. The first to enter in the model was average daily steps at two months post-stroke which yielded an adjusted R^2 of 0.36. The final model added balance (Berg Balance Scale score) and increased the adjusted R^2 to 0.39 (increase of 0.03); both models were significant at p=<0.001. No other factors significantly increased R^2 and no multicollinearity was observed. The final regression equation is below and a graphical representation of the equation is shown in Figure 2.

Predicted daily steps at one year-post stroke=

1031 +0.56(daily steps at two months post-stroke)+47(Berg Balance Scale score)

Descriptive data and a comparison of participants with <6000 and $\geq$6000 daily steps at one year post-stroke is displayed in Table 2. Participants with <6000 daily steps at one year had slower walking speeds, less walking endurance, greater lower extremity impairment, greater balance impairment, less balance confidence, greater self-reported mobility limitations and an increased initial stroke severity at two months post-stroke as compared to those with $\geq$6000 daily steps. The step count with the highest *J* value was 1632 steps, which had a corresponding sensitivity of 86% and specificity of 54% (Table 3).

DISCUSSION

The present study utilized longitudinal data from the LEAPS trial to determine which factors present early after stroke were predictive of future PA (i.e. daily steps). A total of 18 nonmodifiable and modifiable factors were examined as potential predictors of daily steps at one year post-stroke, nine of which had significant associations with daily steps. However, only daily steps and Berg Balance Scale score at two months post-stroke remained in the final prediction model, which accounted for 39% of the variance in daily steps at one year post-stroke.

Previous research examining prediction, rather than association, of PA post-stroke is limited. A recent study examined daily steps in people with stroke after discharge from inpatient rehabilitation and again three months later.[111] Predictors of daily steps at follow up included self-selected walking speed and balance. A separate twelve month exercise intervention study found that walking endurance, balance and health related quality of life explained 33% of the variance in daily steps one year later.[112] While an R^2 value of 33% is similar to our 39%, the previous study involved individuals with chronic stroke as opposed to our study which followed individuals from the subacute (i.e. between two weeks and six months post-stroke) to chronic (i.e. $\geq$six months post-stroke) phase of stroke.[113] While walking ability can be improved years after stroke onset,[114] the majority of recovery happens within the first six months.[115] Thus, for providers treating individuals with stroke in the sub-acute phase, our results may be more pertinent. Clearly, evidence supports assessment of both walking ability and balance early and often during stroke recovery. However, if PA is the primary outcome of interest, our results indicate that there is no greater predictor of future PA levels than PA levels at two months post-stroke, and therefore PA levels should be assessed to gain insight into future PA. Fortunately, assessment of PA and specifically steps, is becoming easier with the use of commercially available wearables[116] that provide users with a single metric that may be used to set goals and track progress with PA.

While participants' balance scores explained only an additional 3% of the variance in daily steps at one year post-stroke, balance is consistently related to daily steps post-stroke and therefore important to assess. Numerous studies have found that greater balance is related to greater PA, including daily steps.[111,112,117,118] In our sample, participants who did not reach at least 6000 daily steps at one year post-stroke, had poorer balance scores (median of 39/56) than those who did reach 6000 steps (median of 46/56). Both elderly adults and individuals with acute stroke who score <45 on the Berg Balance Scale are at a heightened risk for falls[119] and this could have negatively impacted PA levels. Previous falls and a fear of falling are associated with reduced daily steps in older adults.[120] This finding is supported by decreased balance confidence scores observed for participants with less than 6000 daily steps. Collectively, balance is an important metric to measure after stroke, not only to assess fall risk but also to gain additional insight into future PA levels.

PA is immensely beneficial in all stages of stroke recovery, with performance of additional PA providing additional health benefits.[121] Despite this, nearly three fourths of our participants obtained <6000 daily steps at one year-post stroke. The daily step count found in the present study is consistent with other literature[28] but also surprising considering our participants engaged in 36 sessions of supervised, structured and progressive exercise. While the majority (52%) of participants in the LEAPS trial had clinically meaningful improvements in daily steps (regardless of group allocation),[16] the intervention's main purpose was to increase walking ability (chiefly, walking speed) not daily walking behavior. There is growing evidence that combining aerobic exercise (i.e. walking) with a behavioral change intervention improves PA levels after stroke.[32] These findings however, remain to be seen in the acute and subacute phases of rehabilitation, where providers are focused on restoring patient function, rather than improving overall fitness or PA levels.[122] For providers working with individuals in the subacute phase of stroke, encouraging ≥1632 daily steps can serve as a preliminary target that corresponds to reaching ≥6000 daily steps at one year. Future research examining the utility of ≥1632 daily steps will be required to support or refute our findings, followed by interventions to determine if achieving 1632 daily steps is feasible and effective at improving health after stroke.

Daily step counts can provide valuable insight into future health outcomes but much of our understanding comes from populations without cardiovascular disease. For example, in adults at risk for type 2 diabetes, increasing daily steps by 2000 was associated with an 8% reduction in cardiovascular events.[66] To our knowledge, only one study to date has examined the relationship between step count and subsequent cardiovascular events in people with stroke. Kono et al[85] assessed participants' daily steps at three months and again at three years post-stroke and found that 6000 daily steps was predictive of future cardiovascular events. Their sample, however, consisted of higher functioning individuals with mild disability. In contrast, the present sample consisted of participants with a variety of functional levels and only followed participants up to one year-poststroke. As a result, long-term outcomes such as cardiovascular events could not be assessed. Additional longitudinal studies with longer follow up periods will be required to determine the role daily steps play in terms of subsequent stroke risk, which is a stroke research priority.[123]

Strengths & Limitations

A major strength of the present study is the large sample size, which allowed adequate power to examine numerous predictors of PA. Additional strengths include the use of an objective activity monitor to measure steps and assessment of individuals with moderate to severe gait impairments (i.e. gait speed $\leq$0.8m/s). Still, the present study has several limitations. For one, potential predictors of PA were limited to those collected in the LEAPS trial. Factors known to be associated with PA such as motivation[111] or fatigue[124] were not examined, nor were qualitative components such as outcomes expectations or social support.[125] Additional details on what precluded participants from performing more PA may help guide interventions. In addition, our findings only apply to participants who adhered to wearing the activity monitor at both two months and one year post-stroke. Previous research using data from the LEAPS trial found that adherence to wearing the activity monitor was reduced in younger participants with reduced balance confidence and walking endurance.[93] Because of non-adherence, the original LEAPS sample size of 408 was reduced to 206 for the current analysis. Finally, we chose 6000 daily steps as a metric of a positive outcome (i.e. reduced risk of subsequent cardiovascular event) but this number was based on a single study. Thus, our resulting threshold of 1632 daily steps (at two months post-stroke) that corresponds to obtaining $\geq$ 6000 steps at one year post-stroke should be used with caution.

CONCLUSION

In summary, the present study found that the strongest predictors of daily steps at one year post-stroke were daily steps and Berg Balance Scale scores assessed at two-months post-stroke. When working with individuals with stroke in the subacute phase, promotion of daily walking, in addition to targeted balance interventions, may lead to future increases in PA. Though there is no consensus as to how many daily steps people with stroke should be taking, a preliminary target for those two months post-stroke is at least 1632 steps per day. Further research examining daily steps in people with stroke is needed to determine effective methods of increasing walking and the role daily steps play in health outcomes.

Table 3.1 Participant Descriptors At Two Months Post-Stroke[a]

Descriptor	Participants (N=206)[b]
Age, years, mean (SD)	63 (12.7)
Male, n (%)	118 (57.3)
Non-Hispanic White, n (%)	101 (49)
Married, n (%)	128 (62.1)
Employed at least part time, n (%)	104 (50.5)
Completed at least some college, n (%)	117 (56.8)
Self-selected walking speed, m/s	0.42 [0, 0.78] (0.37)
Fast walking speed, m/s	0.55 [0, 1.22] (0.49)
Walking endurance (Six Minute Walk Test), m	136.5 [0, 315] (113.5)
Cardiorespiratory fitness (maximal exercise test), test duration, minutes	24.9 [0, 60] (30.5)
Daily steps, mean (SD)	2922 (2749)
Motor function (Lower extremity Fugl-Meyer)	26 [8, 34] (9.19)
Balance (Berg Balance Scale)	41 [0, 56] (18)
Balance confidence (Activities Specific Balance Confidence Scale), %	48.5 [0, 100] (34.1)
Participant-reported mobility (Stroke Impact Scale)	61.1 [2.78, 100] (97.22)

Participant-reported participation (Stroke Impact Scale)	43.75 [0, 100] (32.03)
Patient Health Questionnaire (PHQ-9)[106]	3 [0, 24] (5)
Initial stroke severity (NIHSS)	6 [0, 20] (5)
Activity monitor wear time, hours, mean (SD)	20.8 (4.8)

Abbreviations: m/s, meters per second; m, meters; NIHSS, National Institutes of Health Stroke Scale

[a] Data presented as median [minimum, maximum] (IQR) unless otherwise stated

[b] One outlier with 29864 steps at one year (more than 5 standard deviations from mean of 4551 steps) was excluded from analysis.

Table 3.2 Comparison of Descriptors At Two Months Post-Stroke Between Those With <6000 and ≥6000 Daily Steps At One Year Post-Stroke.[a]

Descriptor	Participants With <6000 Daily Steps (n=149)	Participants With ≥6000 Daily Steps (n=57)	*P*
Age, years, mean (SD)	64 (13)	61 (12)	0.151[b]
Male, n (%)	82 (55)	36 (63)	0.292[c]
Non-Hispanic White, n (%)	75 (50)	26 (46)	0.544[c]
Married, n (%)	89 (60)	39 (68)	0.250[c]
Employed at least part time, n (%)	71 (48)	33 (58)	0.188[c]
Completed at least some college, n (%)	84 (56)	33 (58)	0.844[c]
Self-selected walking speed, m/s	0.38 [0, 0.78] (0.38)	0.49 [0.10, 0.77] (0.30)	**0.001[b]**
Fast walking speed, m/s	0.49 [0, 1.11] (0.50)	0.71 [0.14, 1.22] (0.40)	**<0.001[b]**
Walking endurance (Six Minute Walk Test), m	121 [0, 315] (103)	178 [0, 306] (108)	**<0.001[d]**
Cardiorespiratory fitness (maximal exercise test), test duration, minutes	25 [0, 60] (27)	24 [0, 55] (34)	0.235[d]

Daily steps at two months post-stroke, mean (SD)	2218 (2151)	4761 (3267)	**<0.001**[b]
Daily steps at one year post-stroke, mean (SD)	2870 (1704)	8503 (2059)	**<0.001**[b]
Motor function (Lower extremity Fugl-Meyer)	25 [9, 34] (10)	27 [8, 34] (8)	**0.036**[d]
Balance (Berg Balance Scale)	39 [0, 56] (18)	46 [21, 55] (12)	**<0.001**[d]
Balance confidence (Activities Specific Balance Confidence Scale), %	44 [0, 99] (33)	57 [6, 100] (41))	**0.020**[d]
Participant-reported mobility (Stroke Impact Scale)	61 [3, 100] (28)	67 [8, 100] (26)	**0.043**[d]
Participant-reported participation (Stroke Impact Scale)	44 [0, 100] (34)	44 [6, 100] (30)	0.838[d]
Patient Health Questionnaire (PHQ-9)[106]	3 [0, 24] (6)	2 [0, 18] (5)	0.664[d]
Initial stroke severity (NIHSS)	7 [0, 20] (4)	5 [0, 19] (4)	**0.017**[d]
Activity monitor wear time, hours, mean (SD)	21.1 (4.7)	20.1 (5.2)	0.170[b]

Abbreviations: m/s, meters per second; m, meters; NIHSS, National Institutes of Health Stroke Scale

[a] Data presented as median (minimum, maximum) unless otherwise stated. Boldface indicates significant at $p \leq 0.05$.

[b] Independent samples t-test, 2-sided

[c] Pearson Chi-Square, 2-sided

[d] Independent samples, Mann-Whitney U test.

Table 3.3 Accuracy of Daily Step Count At Two-Months Post-Stroke To Classify Who Will Reach >6000 Steps At One Year Post-Stroke.[a]

Threshold	AUC[b] (95% CI)	Sensitivity	Specificity	+LR (95% CI)	-LR (95% CI)
Daily Steps 1632	**0.76 (0.69 to 0.83)**	86%	54%	1.86 (1.52 to 2.27)	0.26 (0.13 to 0.50)

Abbreviations: AUC, area under the receiver operating characteristics curve; 95% CI, 95% confidence interval; +LR, positive likelihood ratio; -LR, negative likelihood ratio

[a] Using the daily step count threshold of 1632 steps correctly classified 86% (sensitivity) of participants who obtained >6000 daily steps at one year post-stroke and 54% (specificity) of participants who did not. Participants who obtained >6000 steps at one year were between 1.52 and 2.27 times more likely to average at least 1632 steps at two months post-stroke compared to those who did not obtain 6000 steps. Boldface indicates significant at p <0.001.

[b] An AUC value of 1.0 indicates a perfect diagnostic test, whereas an AUC of 0.5 is equal to chance.

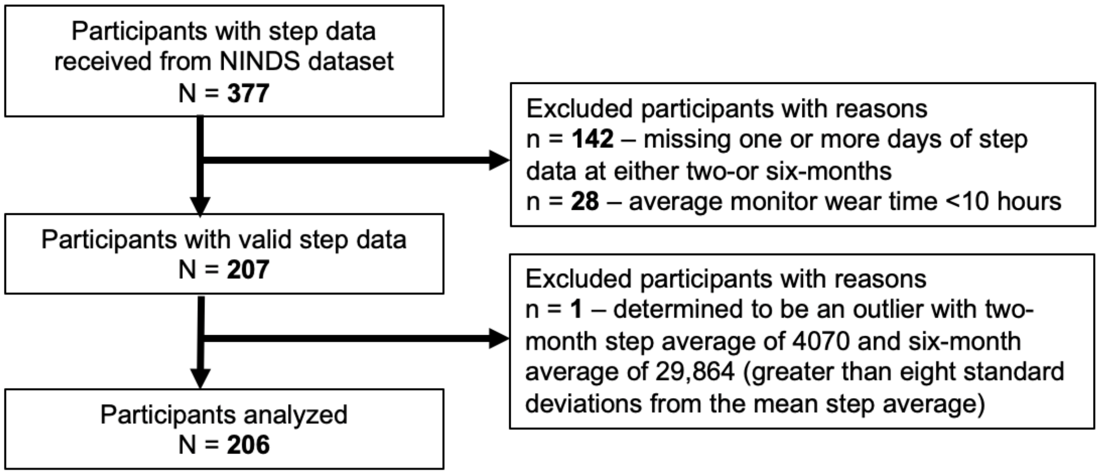

Figure 3.1 Flow Diagram of Participant Data

Abbreviations: NINDS, National Institute of Neurologic Disorders and Stroke.

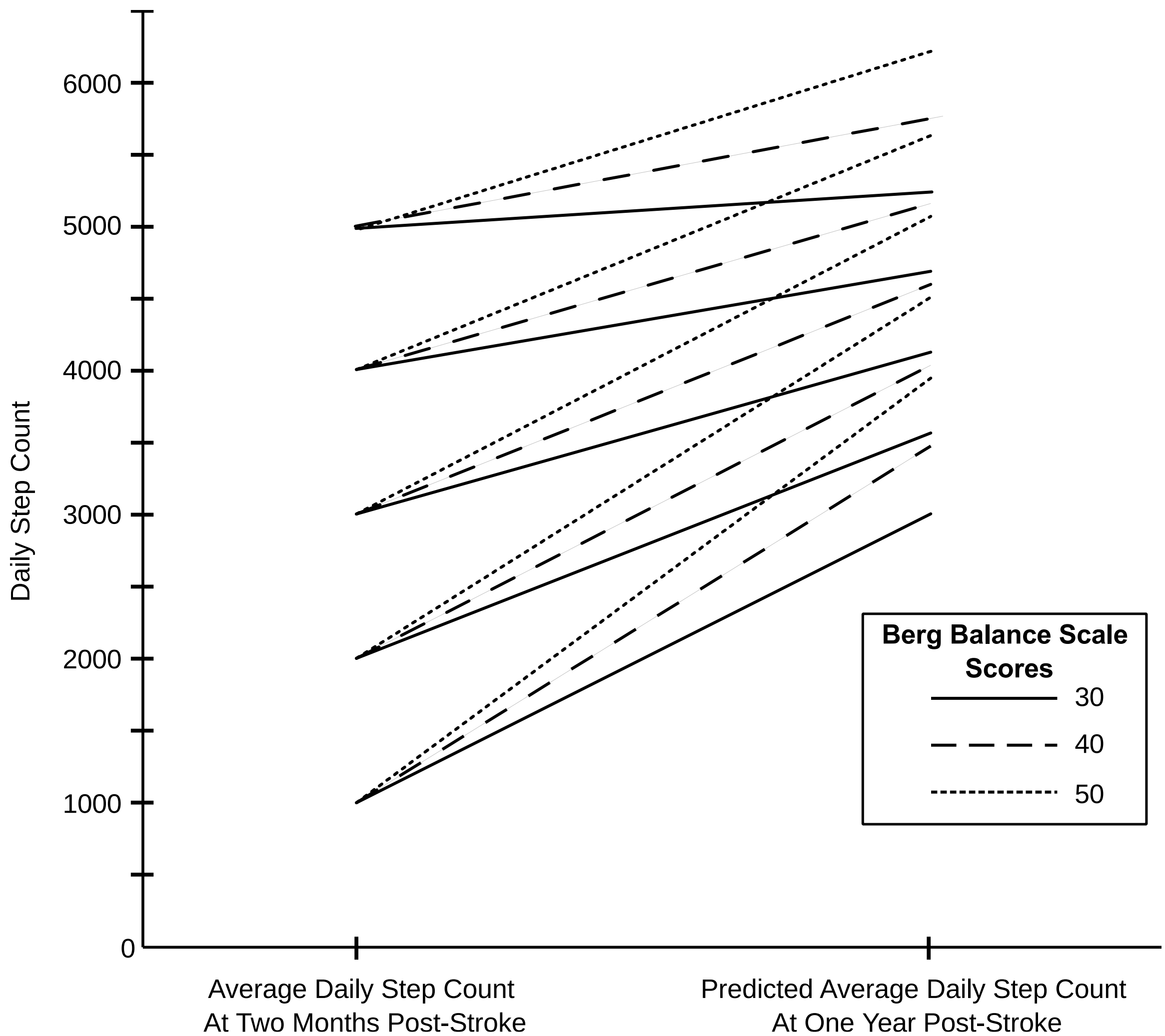

Figure 3.2 Predicted Average Daily Steps At One Year Post-Stroke Based On Steps At Two Months and Berg Balance Scale Score.

Figure depicts arbitrary daily step counts and Berg Balance Scale scores at two months post-stroke and how these factors may predict daily steps at one year. Figure provides a hypothetical example of the regression equation:
Predicted daily steps at one year-post stroke=
1031 +0.56(daily steps at two months post-stroke)+47(Berg Balance Scale score)

CHAPTER 4: EXAMINATION OF DAILY STEPS IN PEOPLE WITH PARKINSON'S DISEASE & STROKE

Overall, there is little evidence to guide daily step recommendations for those with PD or stroke. For pwPD or stroke, the aforementioned studies (Chapters 2 and 3) identified daily step counts associated with health outcomes (meeting PA guidelines for pwPD and obtaining ≥6000 and perhaps reducing risk of cardiovascular events for those with stroke). Collectively, results from both studies can be used to inform future interventions aimed at improving PA for both groups.

Daily Steps In People With Parkinson's Disease

For people newly diagnosed with PD, PA can reduce symptoms and disease progression. Results from our study found that individuals taking at least 4200 daily steps were much more likely to meet PA guidelines compared to those who took less than 4200 daily steps. Thus, a step count of 4200 steps per day can be used as a starting point for when a newly diagnosed individual asks, "how much should I walk?" A step count of 4200 daily steps may also be more realistic for individuals with greater disability who may not be able to engage in long, intense bouts of PA. While translating PA guidelines (150 minutes of moderate-intensity aerobic activity) into steps is salient for those who accumulate most of their PA from walking, PA guidelines are backed by a larger body of evidence than daily step counts. Thus, at this time it would be inappropriate to simply replace PA guidelines with step guidelines. Our recommendation of 4200 daily steps will need to be tested, preferably in longitudinal studies, to determine its role in long term health outcomes including disease progression, cardiovascular events and mortality.

Recruitment of physically inactive individuals into an exercise intervention can be difficult, as was found with our study in Chapter 2 (75% of participants were meeting PA guidelines at baseline). Using the entire sample of participants with de novo PD (n=110), other authors found no differences in daily steps at the six month assessment.[14] Authors went on to suggest that those allocated to an exercise group (i.e. high or moderate-intensity treadmill exercise) may have reduced the number of steps taken outside the intervention so that average daily steps remained unchanged. Our study examined daily steps in the least active individuals (i.e. those with the least steps) and found that for those in the high-intensity group, there was indeed a significant increase in both steps and MVPA. This finding would have gone undetected if not for closer inspection of the least active participants, who arguably stand to benefit the most form increasing PA levels. There is overwhelming evidence of a dose-response relationship in terms of PA and health benefits. Thus, even small increases in PA, including daily steps, are likely beneficial and should be examined.

Daily Steps In People With Stroke

Using a sample of 206 individuals who were two months post-stroke, we found that daily steps and balance were the strongest predictors of PA at one year post-stroke. While many previous studies found associations between physical function and PA, our study represents the largest longitudinal examination of the predictors of PA. Our results suggest that targeting PA (e.g. daily walking) and balance at two months post-stroke may lead to higher amounts of PA at one year. While walking is the predominant intervention employed in rehabilitation early after stroke, much of the intervention is focused on the quality of gait, with little to no attention paid to community walking or overall PA levels. At first glance, our findings seem obvious: in order to walk more in the future, you should walk more now. However, our study is the first to explicitly determine that PA early after stroke predicts future PA. This information may be valuable to providers working with individuals early after stroke and may prompt the initiation of behavioral change interventions, alongside standard rehabilitation, to improve PA and subsequent health of people living with stroke.

While we determined that 1632 steps at two months post-stroke was the optimal step count for determining who would reach $\geq$6000 daily steps at one year, with a sensitivity of 86%, the step count should be used cautiously. At each assessment period, steps were only monitored for two consecutive days and thus provide a small window in which to view PA. It is possible that our determined step count would have been different if data were collected for a longer period of time. Future longitudinal studies, employing repeated assessments, may provide a more accurate account of daily stepping after stroke and better inform future PA recommendations. Overall, few participants (~28%) in our sample obtained $\geq$6000 daily steps at one year. This finding reinstates the need for interventions designed to increase PA in all stages of stroke.

Future Directions

Using two large and publicly available datasets, the two aforementioned studies provided meaningful insight into daily step counts in two groups of people (pwPD and people with stroke) who face an increased risk for further disability and death due to physical inactivity. The daily step thresholds determined in the proposed studies may be used as preliminary targets for interventions aimed at improving PA in pwPD and stroke. Subsequently, future research can begin to use findings from the proposed studies to better describe daily step counts and their relationship to overall health and wellbeing. Nevertheless, there is a dire need for interventions that successfully increase the PA levels in both pwPD and stroke. These interventions may begin to elucidate the relationship between daily steps and health outcomes such as cardiovascular events, hospitalizations and/or mortality, and improve our understanding of the true value of daily steps.

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