Physical exercise in patients with hematological malignancies

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2011

document version
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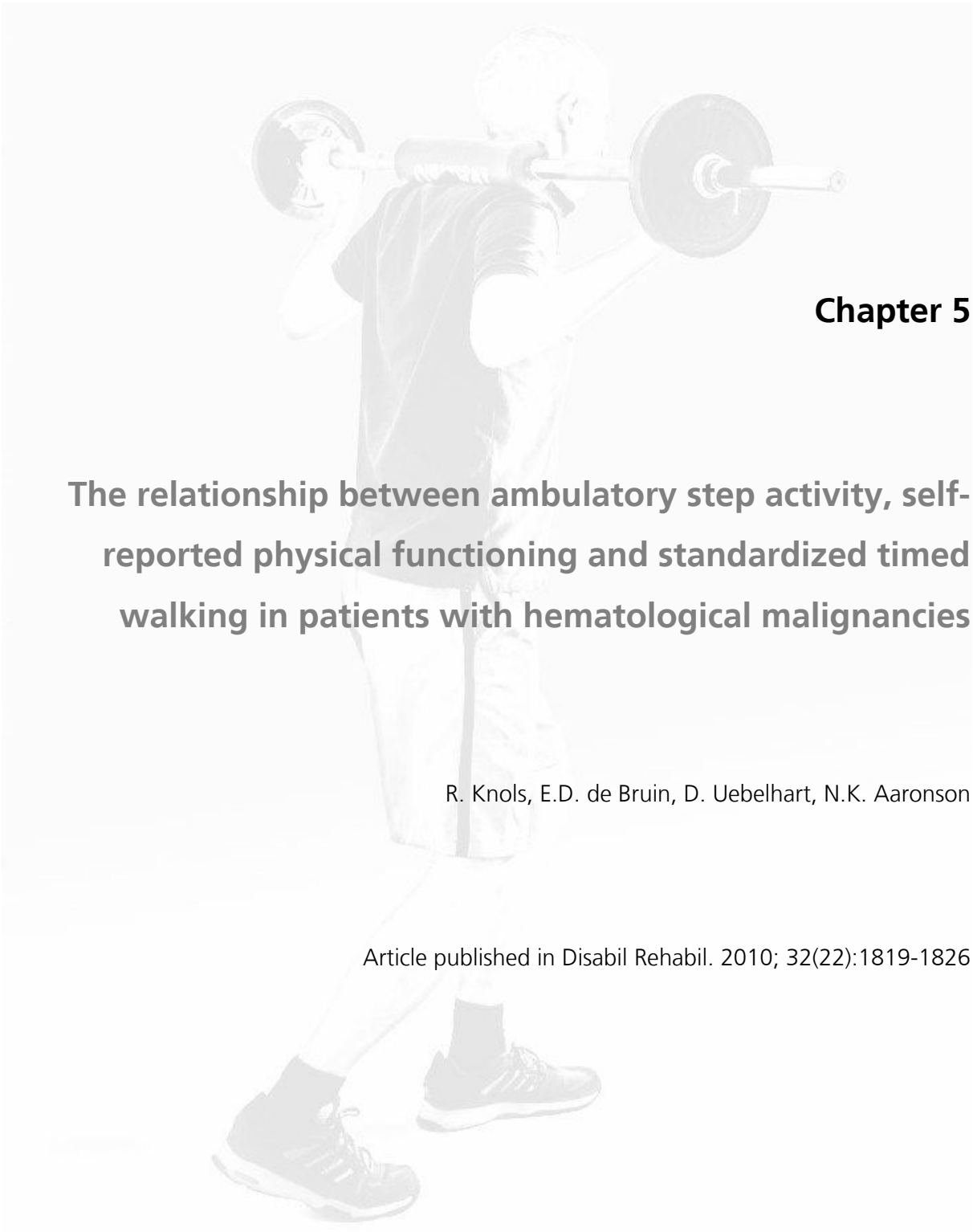

Chapter 5

The relationship between ambulatory step activity, self-reported physical functioning and standardized timed walking in patients with hematological malignancies

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Article published in Disabil Rehabil. 2010; 32(22):1819-1826

Summary

Purpose

This cross-sectional study investigated the degree of association between the results of ambulatory step activity monitoring (SAM), self-reported physical functioning (SRPF) and the 6-minute standardized walking test (6-MWT) in cancer patients with hematological malignancies.

Method

Assessments of ambulatory SAM, SRPF and 6-MWT were assessed in 102 patients up to 122 days (mean 78 $\pm$ 35) after hematopoietic stem cell transplantation (HSCT). To determine the association between measures of walking, the Pearson product moment correlation coefficient (r) including the 95% CI and the r^2 were calculated. Simple linear regression analyses were performed to estimate the ambulatory step activity from SRPF and the 6-MWT.

Results

The average age was 47 years ($\pm$12) and body mass index 23.4 ($\pm$4). The correlations were low between ambulatory SAM outputs and SRPF (ranging from -0.32 to 0.34, $p<0.01$), and very low between SAM outputs and 6-MWT, (ranging from 0.21 to 0.24). The correlation between SRPF and the 6-MWT was low (0.33, $p<0.01$). The 95% CIs were quite narrow around r. The shared variance (r^2) between the SAM and SPPF ranged between 4% and 11%, and the shared variance between the SAM and 6-MWT ranged between 0.5% and 18%. Linear regression yielded weak relationships and large standard errors of estimate between the SAM, SRPF and 6-MWT.

Conclusions

Self-reported physical functioning and the 6-minute standardized walking test do not reflect daily walking activity. In clinical use (e.g., to evaluate the effects of a rehabilitation program), ambulatory step activity outputs can be considered as an additional outcome to assess day-to-day walking activity in hematological cancer patients after HSCT.

Introduction

Haematopoietic stem cell transplantation (HSCT) can be a life-saving procedure in a number of haematologic diseases [1,2]. However, the toxicity associated with HSCT can have a significant impact on patients' functional health and symptom burden, even long after treatment has been completed [3,4]. Physical exercise interventions have been developed to reduce the debilitating treatment-related symptoms (e.g., pain, nausea, fatigue, loss of physical performance) in HSCT patients [5]. Beneficial effects have been reported for aerobic capacity, immunological function, muscle strength, fatigue and health-related quality of life [6-9]. However, only a few studies have investigated the effects of physical exercise on physical functioning [8,10,11], defined as the ability to conduct a variety of activities ranging from self-care to more challenging and vigorous activities that require increasing degrees of mobility, strength or endurance [4].

A range of tests are available to assess physical functioning in patients with chronic diseases [12]. The two basic approaches are self-report (i.e., questionnaire-based assessments) and performance-based, or laboratory-based measures [13]. Questionnaire-based assessments are designed to capture the individual's subjective ratings of his or her physical functioning, and are premised on the belief that the patient's perception is important if not essential in evaluating health and response to treatment [13]. Questionnaire-based assessments, however, have the drawback that they depend on the accuracy of the patient's perception, cognition and communication [14,15].

Performance-based or laboratory-based measures involve direct therapist or researcher observation and grading of the patient's physical activity level [14]. One of the potential disadvantages of such performance-based measures is that they may capture best performance at a single point in time rather than usual, daily performance [14]. The level of effort exerted during a walking test performed under standardized conditions may differ from that required or attempted in daily life [16]. Usual performance or daily activity can be reliably assessed by microprocessor-based accelerometers [17]. This relatively new approach has the potential to provide a more accurate estimate of how much patients actually walk in their day-to-day life [14,18].

Several studies have investigated the association between questionnaire-based assessments, standardized performance tests and usual performance assessments in patients with chronic diseases. A low to moderate association ($r = 0.42$, $p < 0.05$) was observed between standardized timed walking and an ambulatory activity monitor in post-poliomyelitis patients [16]. Moderate associations were observed between standardized timed walking and ambulatory walking activity in stroke patients ($r = 0.51$ to 0.73, $p < 0.01$ [14] and $r = 0.6$ to 0.73, $p < 0.001$) [19]. Moderate associations were also observed between a 6-minute walking test and daily walking activity in patients with chronic obstructive pulmonary disease ($r = 0.60$,

p< 0.05 [20] and r = 0.67, p< 0.01) [21] and in patients with chronic heart failure (r = 0.68, p< 0.001), respectively [22]. An almost perfect association was observed between standardized timed walking and an ambulatory activity monitoring in patients with chronic heart failure (r = 0.91, p< 0.001) [23]. A low association was reported between an ambulatory activity monitor and the questionnaire-based assessment of veterans using the RAND 36-item Health Survey (r = 0.29, p = 0.002) [21]. Moderate to strong associations have been reported between self-reported physical functioning (the SF-36 Health Survey) and ambulatory walking activity (r = -0.39 to 0.49, p< 0.01) in men with diabetes [13] and in patients with osteoarthritis r=0.5/0.6, p<0.01).[24] In one report, the physical activity values from the accelerometer correlated moderately with the Minnesota Leisure Time Physical Activity Questionnaire (r = 0.33; P < 0.01) [25]. No significant associations were reported between the 6-minute walking test and an ambulatory activity monitor in older adults residing in continuing care retirement communities [26] or in patients with peripheral arterial disease (p >.05) [27]. No significant associations were observed between the Physical Activity Scale for the Elderly (PASE) and an ambulatory activity monitor in older adults residing in continuing care retirement communities [26]. Similarly, ambulatory activity monitoring did not correlate significantly with self-reported functional status in patients with chronic obstructive pulmonary disease [20].

To the best of our knowledge, only one previous report has investigated the relationship between ambulatory step activity monitoring, self-reported physical functioning and the 6-minute standardized walking test in cancer patients [28]. There was moderate agreement between the 7-Day Physical Activity Recall and the accelerometer with longitudinal serial correlation coefficients of 0.54 (baseline), 0.24 (year 1), and 0.53 (year 2), all p-values <0.01.

To summarize, the association observed between self-reported physical functioning, standardized timed walking and the outputs of ambulatory step activity varies from none to almost perfect in studies of various chronic disease populations. Only one study has investigated this issue in cancer patients, and none among HSCT patients. The aim of the current study was to determine the degree of association between self-reported physical functioning, standardized timed walking and the outputs of ambulatory step activity monitoring among outpatients with hematological malignancies recovering from HSCT.

Methods

Participants

This study presents a cross-sectional analysis of baseline data collected from a subset of 117 ambulatory hematological patients after completion of HSCT at the University Hospital Zurich and the Cantonal Hospital of St. Gallen, Switzerland. These baseline data were collected before the patients were randomized between an ambulatory physical exercise intervention and a usual care (i.e., non-exercising) control group. Adult patients were considered eligible for the

study if they had completed their HSCT treatment. Patients were excluded from the study in case of graft versus host disease (GVHD) except for grade I not requiring treatment, painful joints, instable osteolyses, chronic pain, lesions of the central or peripheral nervous system, uncontrolled cardiovascular disease, thyroid disease or diabetes. The study was approved by the local ethical committee. All patients provided written informed consent.

Measurements

Ambulatory step activity levels were assessed with the Step Activity Monitor 3 (SAM3, Cymatech Corporation, Seattle, WA, USA). The patients were instructed to wear the SAM3 for seven consecutive days. Activity monitoring over a 7-day period has previously been found to result in reliable and representative measures of an individual's movements on a day-to-day basis [17]. All participants were instructed to leave the SAM3 on the ankle if they had to rest or lay down during the day and to perform their daily activities as usual. The parameters assessed by the SAM3 for this study were: (1) 'average steps/day', (2) percentage time 'with no step rate', 'at low step rate' (between 15 and 40 steps/min.), at 'moderate step rate`(between 40 and 75 steps/min.), and at 'high step rate' (more than 75 steps/min.), and (3) the 'peak activity index' (calculated by ranking all minutes of the day according to the cadence, and then taking the highest 30 values) [13]. The accuracy of the SAM3 has consistently been reported to be over 98% [18]. The test-retest reliability, as measured by ICCs for two consecutive 7-day recordings including the 95% CI for total steps and peak activity, was 0.90 (95% CI, 0.75-0.98) and 0.85 (95% CI, 0.66-0.94), respectively [17].

Walking distance was assessed with the 6-minute walking test. This test is a widely used, reliable (ICC=.98), sub-maximal exercise test that assesses the physiologic and functional status in cancer patients [29].

Self-reported physical function was assessed with the 'physical function' scale (5 items) of the EORTC Core Quality-of-Life Questionnaire (EORTC QLQ-C30, version 3). This questionnaire is a widely used, cancer-specific, patient-based and self-administered instrument. The EORTC QLQ-C30 has demonstrated validity and reliability when used among a wide range of cancer patient populations in a range of languages, including German [30,31]. The internal consistency (Cronbach's alpha) and the test-retest reliability (Pearson's correlation coefficient) of the physical functioning subscale are 0.81 and 0.91, respectively [32]. The scale items have four response choices ranging from 1 ("not at all") to 4 ("very much"). Following standard procedures, the physical function scale score was linearly transformed to a 0 to 100 scale, with a higher score representing a better level of functioning [33]. The patients were asked to report their physical functioning over the last seven days.

Measurement procedure

All patients underwent a standardized 6-minute walking test and completed the EORTC QLQ-C30 questionnaire at the same point of time during the day (late morning or early afternoon). Subsequently, patients were instructed to wear the SAM3 for seven consecutive days, excluding sleeping time. All participants were instructed to leave the SAM3 on the ankle if they had to rest or lay down during the day, and to perform their daily activities as usual. After seven days, the participants returned the SAM3 to the study centre in a pre-paid envelope. The SAM3 data were downloaded into a database.

Descriptive measures

Height was assessed to the nearest 0.5 cm with a wall fixed tape measure. Weight was assessed to the nearest 0.5 kg (SECA weighting machine, Model 791). Diagnosis and staging, type of donor, total body irradiation for patients with allogeneic transplantation, concomitant disease, time interval between hematological cancer diagnosis and walking assessment disease are described in Table 1.

Statistical analyses

Normality of the data was tested with the Kolmogorov-Smirnov test. Descriptive results are expressed as mean $\pm$ SD and range (Table 1). Baseline step activity outputs, health-related quality of life scores and standardised timed walking measures are presented in Table II. The level of association between the variables of interest was assessed using the Pearson product moment correlation coefficient for normally distributed variables (Table 3). A correlation above 0.9 was interpreted as very high, 0.7 to 0.89 as high, 0.5 to 0.69 as moderate, 0.30 to 0.49 as low and less than 0.29 as very low or negligible [34]. The 95% CI intervals around the Pearson product moment correlation coefficient (r) and the R squared (r^2) were calculated. Simple linear regression analyses, including the standard error of estimate, were performed to determine the relationships between the measures of walking activity. A p value of 0.05 was used to define statistical significance.

All statistical analyses were performed using SPSS 17.

Results

One hundred and seventeen patients were eligible and agreed to participate. Fifteen patients (12.8%) were excluded from the analyses due to missing data, resulting in a final study sample of 102 patients (42 women and 60 men). The study sample consisted of 35 patients with leukaemia, 30 with lymphoma, 33 with multiple myeloma and 4 with osteomyelofibrosis. The average age was 47 years ($\pm$12) and body mass index 23.4 ($\pm$4). Patients were included into

the study and performed the walking assessments between 22 and 122 days after completion of treatment (mean 78 days, SD 35 days) (Table 1). All outcomes were distributed normally.

The correlations were low (Table 3) between ambulatory step activity outputs and self-reported physical function (ranging from -0.32 to 0.34, $p<0.01$), and very low (Table 5) between ambulatory step activity outputs and the 6-minute walking test (ranging from 0.21 to 0.24). The correlation between self-reported physical function and the 6-minute walking test was also low (0.33, $p<0.01$). The 95% CIs around the r of the walking measures were quite narrow (Tables 3 and 5). The shared variance (r^2) between the ambulatory walking activity and self-reported physical function varied between 4% and 11% (Table 3). The shared variance between the ambulatory walking activity and the 6-minute walking test varied between 0.5% and 18% (Table 5).

All variables in the regression model for ambulatory walking activity and self-reported physical function remained statistically significant, except for the 'percentage of time at high step rate' ($p>0.05$, Table 4).

The standard error of estimate for ambulatory step activity and self-reported function was 1783 steps/day and 7.12 for peak activity. For the percentages of time with different walking intensities, the standard errors of estimate varied between 1.40% and 6.30% (Table 4). The standard error of estimate between ambulatory step activity and 6-minute walking test was 1852 steps/day and 7.12 for peak activity (Table 6). For the percentages of time with different walking intensities, the standard errors of estimate varied between 1.42% and 6.56% (Table 6).

The associations between the other multi-item scales (four functional scales (role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting), and the global health and quality of life scale) of the EORTC QLQ-C30, the daily ambulatory steps and the 6-minute walking test were determined. These calculations yielded low and mostly non-significant correlations varying between -.267 and .282 (data not presented).

Discussion

The results of this study indicate that ambulatory daily activity as measured with a step activity monitor does not correlate significantly or has only a weak correlation with a standardized walking test or with self-reported physical functioning (the EORTC QLQ-C30 physical functioning scale). Only 11% of the variability in daily walking activity was explained by self-reported physical function and 18% by the 6-minute walking test. The standard errors of estimate, which can be used to estimate the daily ambulatory activity from self-reported physical function and the 6-minute walking test, were large.

The assessment of mobility can be related to the World Health Organization International Classification of Functioning, Disability and Health (ICF) [35]. Central concepts of the ICF are

participation or performance, describing what an individual does in his environment, and activity, also referred to as capacity or the ability to execute a task or action. It is, thus, possible to make a distinction between three conceptually distinct levels of physical activity: self-reported (questions about functioning), experimental (physical performance) and enacted functioning (physical activity) [36]. Discordance can exist between what people say they can do, are able to do in standard physical performance tests and what they actually do. Such discordance is evidenced in the results of our study.

With the improvement of prognosis in hematological malignancies, programs to improve physical health through walking and other forms of physical activity may become an increasingly important component in continuing care programs [11,17]. Ultimately, the choice of which instrument or method is the best to assess patients' level of physical activity is a function of the research question, participant burden and available resources to the researcher or the practitioner [37]. The results of this study indicate that the SAM represents an additional approach to assessing in more detail the physical activity behaviour of the HSCT patient group, that it does not cause unnecessary or excessive discomfort to the patients, and that it contributes information independent of that provided by self-report measures and in-clinic performance tests.

Several possible limitations of the present study should be noted. First, due to the cross-sectional design, it was not possible to determine the degree of association in change scores derived from the three types of measures investigated. Second, the step activity monitor data for 15 patients (13% of the sample) had to be excluded from the analysis due to missing data (i.e., non-adherence with the continued use of the step activity monitor for seven consecutive days). Third, the data used in this study were based on baseline values obtained from HSCT patients who had agreed to take part in a randomized controlled trial investigating the effectiveness of a physical exercise programme. Patients who were either not eligible or not interested in participating in the trial were not included in this study. Those patients who did participate may represent a 'more active' or 'healthier' group of HSCT patients. Fourth, there was a fair degree of variability in the time at which the assessments took place in relation to the completion of treatment. Some patients had more time to recover from the side effects of high-dose chemotherapy than others (Table 1). This may have influenced the variation observed in the day to-day walking activity. Finally, the 95% CIs around the r indicated a relatively low degree of variability for the measures of walking activity measures; however, factors such as concomitant disease and staging may have biased the estimates of walking activity.

Conclusions

The use of step activity monitors adds additional and relatively independent information to that obtained from self-report measures of physical functioning and clinic-based performance tests for evaluating the physical activity level of patients who have undergone HSCT. The use of such daily monitors is feasible, although attention needs to be paid to ensuring high levels of compliance with the use of such devices over an extended period of time (e.g., seven days).

Table 1. Baseline demographic and medical data, step activity outputs, self-reported physical function and standardized timed walking

Demographic variables	Mean (SD) Range
Age (years)	47 (12) 23 to 75
Height (cm)	173.8 (9.3) *152 to 197*
Weight	71.9 (13.7) *38 to 109*
BMI (kg/m^2)	23.4 (4.0) 15 to 34
Time interval between HSCT and assessments of walking activity (days)	78 (35) 22 to 122
*Diagnosis and staging**	n (%)
AML	24 (23.5)
In remission before HSCT	17 (70.8)
CLL	10 (9.8)
Chronic phase before HSCT	7 (6.9)
Accelerated phase before HSCT	3 (2.9)
ALL	1 (100)
In remission before HSCT	1 (100)
Hodgkin	12 (11.8)
II	7 (6.9)
III	2 (2.0)
IV	3 (2.9)
NHL	18 (17.6)
I	2 (2.0)
II	11 (10.8)
IV	5 (4.9)
Multiple Myeloma	33 (32.4)
II	9 (8.8)
III	24 (23.5)
Osteomyelofibrosis	4 (3.9)

n=102; female 42 (41%), male 60 (59%). Abbreviations: HSCT; Hematopoietic stem cell transplantation, AML; Acute myeloid leukaemia, CLL; Chronic lymphoid leukaemia; ALL; Acute lymphoid leukaemia, NHL; Non-Hodgkin lymphoma, * For detailed information concerning diseases and staging see [38].

Table 1. Baseline demographic and medical data, step activity outputs, self-reported physical function and standardized timed walking (continued)

Demographic variables	Mean (SD) Range
Donor	n (%)
Allogeneic	
Unrelated donor	22 (21.6)
Related donor	16 (15.7)
Autologous	
ASCT 1x	46 (45.1)
ASCT 2x	18 (17.6)
Total body irradiation for allogeneic transplants	n (%)
Tbi	25 (65.8)
No Tbi	13 (34.2)
Time interval between hematological cancer diagnosis and walking assessment	n (%)
0-6 months	3 (2.9)
6-12 months	23 (22.5)
1-2 years	45 (44.1)
2-5 years	17 (16.7)
> 5 years	14 (13.7)
Concomitant disease	n (%)
0	11(10.8)
1	27 (26.5)
2	24 (23.5)
3	17 (16.7)
>3	23 (22.5)

n=102; female 42 (41%), male 60 (59%). Abbreviations: ASCT; Autologous stem cell transplantation, TBI; Total body irradiation.

Table 2. Baseline step activity outputs, Health related quality of life scores and standardized timed walking

Outcome	**Mean (SD) Range**
SAM: Average steps/day	4684 (1884) *897 to 11744*
SAM: Percentage of time with no step rate	75.3 (6.6) *52.4 to 93.2*
SAM: Percentage of time at low step rate (Between 15 and 40 steps / min.)	14.8 (3.8) *5.1 to 25*
SAM: Percentage of time at moderate step rate (Between 40 steps and 75 steps / min.)	7.0 (3.2) *1.5 to 21.3*
SAM: Percentage of time at high step rate (> 75 steps / min.)	2.1 (1.4) *0.1 to 7.6*
SAM: Peak activity index	41.8 (7.3) *18.6 to 58.2*
EORTC QLQ-C30: Self-reported physical function	71.2 (17.0) *20 to 100*
STW: 6 minute walking test (meters)	575.8 (87.4) *205 to 788*

n=102; female 42 (41%), male 60 (59%). Abbreviations: SAM; Ambulatory step activity monitoring, EORTC QLQ C-30, Quality of life questionnaire, STW; Standardized timed walking.

Table 3: Correlations between step activity outputs and self-reported physical function

Association	r	95% CI	r^2
ASD / SRPF	.34*	.16 to .58	.11
% no step / SRPF	-.32*	-.49 to -.13	.10
% low step / SRPF	0.20#	.01 to .04	.04
% moderate step / SRPF	0.33*	.15 to .50	.11
% high step / SRPF	0.27*	.08 to .44	.07
PAI / SRPF	0.24#	.05 to .42	.06

# p< 0.05, * p<0.01. Abbreviations: ASD; average steps/day, SRPF; self-reported physical function, r; Pearson product moment correlation coefficient, r^2; r square, % no step; percentage of time with no step rate, % low step; percentage of time at low step rate, % moderate step; percentage of time at moderate step rate, % high step; percentage of time at high step rate, PAI; peak activity index.

Table 4: Results of simple linear regression for step activity outputs and self-reported physical function

Model	Unst. cft		St. cft	t	p	St. err. estim
	B	St.e	Beta			
ASD (constant)	2007	765.51		2.62	.010	
			.34			1783
SRPF	37.66	10.46		3.60	.001	
% no step (constant)	85.04	2.71		31.42	.000	
			-.32			6.30
SRPF	-.12	0.04		-3.34	.001	
% low step (constant)	11.48	1.61		7.10	.000	
			.20			3.76
SRPF	.046	.022		2.09	.040	
% moderate step (constant)	2.60	1.32		1.97	.051	
			.33			3.06
SRPF	0.62	.018		3.45	.001	
% high step (constant)	0.43	.601		.71	.481	
			.27			1.40
SRPF	0.23	.008		2.81	.006	
Peak activity index (constant)	34.53	3.06		11.29	.000	
			.24			7.12
SRPF	.10	.04		2.45	.016	

Abbreviations: ASD; average steps/day, SRPF; self-reported physical function, % no step; percentage of time with no step rate, % low step; percentage of time at low step rate, % moderate step; percentage of time at moderate step rate, % high step; percentage of time at high step rate, PAI; peak activity index, Unst.cft; unstandardized coefficients, St.e; standard error, st.cft; standardized coefficients, p; p-value, st. err. estim; standard error of estimate.

Table 5: Correlations between step activity outputs and the 6-minute walking test

Association	r	95% CI	r^2
ASD / 6MWT	0.21#	.02 to .04	.04
% no step / 6 MWT	-.16ns	-.35 to -.04	.03
% low step / 6 MWT	.07ns	-.13 to .27	.005
% moderate step / 6 MWT	.14ns	-.06 to .33	.18
% high step / 6MWT	0.21#	.02 to .39	.04
PAI / 6 MWT	0.24#	.05 to .42	.06

# p< 0.05, * p<0.01. Abbreviations: r; Pearson product moment correlation coefficient, r^2; r- square, ASD; average steps/day, 6MWT; 6-minute walking test, % no step; percentage of time with no step rate, % low step; percentage of time at low step rate, % moderate step; percentage of time at moderate step rate, % high step; percentage of time at high step rate, PAI; peak activity index

Table 6: Results of simple linear regression for step activity outputs and 6-MWT

Model	unst. cft		st. cft	t	p	st. err. estim
	B	St.e	Beta			
ASD (constant)	2104.91	1228.14	.21	1.71	.090	1852
6-MWT	4.48	2.11		2.13	.036	
% no step (constant)	83.30	4.35	-.16	19.17	.000	6.56
6-MWT	-.01	.007		-1.64	.104	
% low step (constant)	13.00	2.54	.07	5.12	.000	3.83
6-MWT	.003	.004		.697	.487	
% moderate step (constant)	4.13	2.13	.14	1.40	.055	3.21
6-MWT	.005	.004		1.37	.174	
% high step (constant)	.058	.942	.21	.062	.951	1.42
6-MWT	.003	.002		2.16	.033	
Peak activity index (constant)	30.48	4.72	.24	6.54	.000	7.12
6-MWT	.020	.008		2.43	.017	

Abbreviations: ASD; average steps/day, 6-MWT; 6-minute walking test, % no step; percentage of time with no step rate, % low step; percentage of time at low step rate, % moderate step; percentage of time at moderate step rate, % high step; percentage of time at high step rate, PAI; peak activity index, Unst.cft; unstandardized coefficients, St.e; standard error, st.cft; standardized coefficients, p; p-value, st. err. estim; standard error of estimate.

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