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**SMARTPHONE PEDOMETERS IN ADULTS WITH ASTHMA: A PRACTICAL APPROACH TO PHYSICAL
ACTIVITY ASSESSMENT? A PILOT VALIDATION STUDY**

Caroline Reilly¹, Antonis Stavropoulos Kalinoglou¹, Ian Clifton², Jim McKenna¹, Daniel Peckham³,
Oliver J. Price^{1*}

¹Leeds Beckett University, Carnegie School of Sport, Headingley Campus, Leeds, LS6 3QT United
Kingdom of Great Britain and Northern Ireland

²Leeds Teaching Hospitals NHS Trust, Department of Respiratory Medicine , Leeds, United Kingdom
of Great Britain and Northern Ireland

³University of Leeds Leeds Institute of Medical Research at St James's, Leeds , Leeds, United Kingdom
of Great Britain and Northern Ireland

*Corresponding Author: Email: o.price@leedsbeckett.ac.uk

Running title: Physical activity assessment in adults with asthma.

ABSTRACT

Purpose: The aim of this pilot validation study was to determine the accuracy of a smartphone (iPhone®) pedometer in adults with and without asthma. **Methods:** Ten adults with asthma and ten healthy controls underwent clinical assessment prior to completing two separate trials. **Phase 1.** standardised treadmill and self-paced walking tests. Total steps were recorded via: (i) Yamax Digiwalker™ SW800 pedometer positioned on the waistband, (ii) iPhone® pedometer positioned on the upper body, (iii) iPhone® pedometer positioned on the lower body and evaluated against a video-verified manual step-count. **Phase 2.** step-count was evaluated over seven-days during habitual free-living conditions via Yamax Digiwalker™ SW800 and iPhone® pedometers. **Results:** During treadmill walking, the iPhone® positioned on the lower body correlated strongly ($r = 0.96$) and produced the highest level of agreement (mean bias: -11 steps, LOA: -43 to 21 steps) in comparison to video-verified manual step-count. During self-paced walking, all devices provided an excellent step-count estimate. During free-living conditions, no difference was observed between the Yamax Digiwalker™ SW800 pedometer and iPhone® ($P = 0.10$) and a strong correlation ($r = 0.94$) and acceptable agreement (mean bias: -343, LOA: -1963 to 1276 steps) was observed. **Conclusion:** Our findings indicate that an in-built iPhone® pedometer offers a practical approach to physical activity assessment in adults with and without asthma. Future research is now required to further validate the precision of this approach and evaluate the efficacy and effectiveness of smartphone pedometers to monitor and promote physical activity when employed during medical consultation and/or clinical research trials.

Key words: Asthma, Exercise, Physical Activity, Pedometer, Step-count.

INTRODUCTION

Asthma is a chronic inflammatory airways disease associated with airway hyperresponsiveness, bronchoconstriction and variable respiratory symptoms such as cough, wheeze, and dyspnoea. The disease affects approximately 350-million people worldwide [1] and remains a major source of global economic and societal burden [2]. Despite clear guidelines and even in the context of adequate health care provision, control is often sub-optimal with asthma symptoms and exacerbations being common and under reported [3]. For the most part, asthma management strategies focus on pharmacological intervention with a stepwise approach to treatment escalation according to local, national and international guidelines [4]. While this approach is effective in most cases, the adverse side effects associated with long-term therapy can be significant [5, 6] and adjunctive treatments which can help improve asthma control and minimise complications should be considered when optimising care.

Physical activity has the potential of providing affordable and accessible adjunct approach to asthma management and related co-morbidities (e.g. obesity and cardiovascular disease etc.) with recent systematic reviews and meta-analyses reporting an association between the duration of activity, improved symptomology, slower lung function decline, higher functional capacity and lower systemic inflammation [7-9]. However, previous studies have relied primarily on patient recall when evaluating physical activity in people with airways disease (i.e. self-report and/or questionnaires) and this can be prone to both over and underestimation [10].

The optimal method of measuring physical activity currently remains debated [11]. Although objective devices such as accelerometers and pedometers (i.e. step-counters) are widely endorsed for assessment, they have substantial limitations. For example, measurement error can arise through participant reactivity (i.e. behaviour changes in response to being observed). Equally, the high associated cost of the technology often precludes implementation in physical activity promotion programmes (i.e. pulmonary rehabilitation) and large-scale clinical trials.

Over the past decade there have been dramatic advances in mobile technologies and an exponential growth in smartphone devices (>3.5 billion users worldwide) [12] with in-built activity sensors (i.e. functionality to monitor daily step-count) which provides a pragmatic alternative approach to physical activity assessment. Although the validity and application of smartphones pedometers have previously been reported in healthy cohorts [13], there are little data on their use in people with asthma to measure habitual physical activity (i.e. total distance covered and time spent active) which is often significantly reduced and may impact and/or be an indirect measure of asthma control [7].

The aim of this pilot validation study was therefore to determine the accuracy of a smartphone (Apple® iPhone - version 6 onwards) to quantify step-count in adults with and without asthma. We hypothesised that an in-built pedometer would provide a practical approach to physical activity assessment (i.e. valid step-count estimate) during laboratory and self-paced walking challenges and habitual free-living conditions.

METHODS

Study population and experimental design

Twenty adults (male: n = 12) were enrolled into the study; ten adults with a prior physician-based asthma diagnosis prescribed 'as-needed' reliever and daily low dose ICS maintenance therapy and ten asymptomatic healthy controls with no prior history of airways disease or inhaler medication use (matched for age, gender and body mass index (BMI)). At study entry, all participants completed pre-participation American College of Sports Medicine (ACSM) health screening [14] and underwent clinical assessment prior to completing two separate trials: treadmill and self-paced walking challenges (**Phase 1**) and habitual free-living conditions (**Phase 2**) (protocols detailed below). A standard Apple® iPhone (version 6 onwards) was used to quantify step-count for all trials. The study was approved by research ethics committee (ID: 61792) and all participants provided written informed consent. **Clinical assessment and baseline pulmonary function**

The Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) was completed by participants with asthma to evaluate symptom burden and disease specific health-related quality of life [15, 16]. The Dyspnoea-12 (D-12) questionnaire was employed to characterise the physical and affective aspects of breathlessness and to ensure healthy controls had an entirely normal D-12 score (i.e. confirming their asymptomatic status) [17]. Lung function was assessed by maximal forced flow-volume spirometry (MicroLoop ML3535; Cardinal Health, Basingstoke, UK) and airway inflammation was evaluated via fractional exhaled nitric oxide (FeNO) using a hand-held measuring device (NIOX VERO; Aerocrine AB, Stockholm, Sweden) with established reference values employed in accordance with international guidelines [18, 19] . Body composition was determined via bioelectrical impedance analysis (Tanita, 330ST, Japan).

Phase 1: Treadmill and self-paced walking challenges

Participants completed a standardised treadmill test (Woodway PPS55 Med, Germany) consisting of 3 x 3-minute stages at pre-determined speeds: low (2.5kph); moderate (5.0kph); high (7.5kph) at a 1% gradient, followed by a self-paced 1-km walking test around a 400m athletics track. For both

tests, total steps were recorded using the following devices: (i) Yamax Digiwalker™ SW800 pedometer positioned on the waistband, (ii) iPhone® pedometer positioned on the upper body (armband), (iii) iPhone® pedometer positioned on the lower body (trouser pocket) and evaluated against a video-verified manual step-count conducted by the investigator (CR).

Phase 2: Habitual free-living conditions

Total step-count was evaluated over a seven-day period during habitual free-living conditions via Yamax Digiwalker™ SW800 pedometer (criterion measure) and iPhone® pedometer. Participants were instructed to maintain their usual daily activities and were provided with a logbook to record hours spent active and total daily step-count. Participants were required to carry the devices on their person for a minimum of 10-hours per day [20].

Statistical analysis

Data are presented as mean (SD) or median (IQR) for continuous outcomes dependent on normality. An unpaired and paired samples *t*-test was employed to evaluate between and within group differences, respectively. Intra-class correlation coefficient (ICC) was calculated using a two-way mixed effect model with the mean single measure reported. Reproducibility was assessed (i.e. video-verified manual step-count vs. pedometer) using the method described by Bland and Altman with difference expressed as mean bias (i.e. mean difference between group measures) and upper and lower 95% limits of agreement [21]. Linear regression was conducted to evaluate proportional bias between mean differences in devices. Data was analysed using SPSS Statistics 24 statistical software package (SPSS Inc., Version 26, Chicago, IL) and GraphPad Prism Version 8.0 (GraphPad Software, San Diego, California, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Respiratory symptoms and baseline pulmonary function

Of the ten participants with asthma, five had an ACQ score >1 (i.e. indicating inadequate asthma control). Of these, three had an AQLQ score <6 (i.e. indicating impaired quality of life). Two participants with an ACQ score <1 (i.e. well-controlled asthma) had an AQLQ score <6 . The majority of participants (90%) had normal resting lung function with no evidence of expiratory airflow limitation (FEV_1 predicted $>80\%$ and $FEV_1/FVC >70\%$ predicted). Although participants with asthma had a lower FEV_1 % predicted ($P = 0.008$), no difference was observed for any other pulmonary function parameter. Clinical characteristics are presented in Table 1.

Phase 1: Treadmill walking challenge

No difference was observed in video-verified total manual step-count between participants with asthma (1018 ± 54 steps) and healthy controls (1038 ± 58 steps) ($P = 0.44$) and therefore group data was pooled for analysis (mean: 1028 ± 56 steps). The Yamax Digiwalker™ SW800 pedometer correlated poorly ($r = 0.37$) with video-verified total manual step-count and produced wide limits of agreement (mean bias: -74 steps, LOA: -203 to 55 steps) at the lowest walking speed (2.5kph) ($P < 0.0001$), yet provided an acceptable step-count estimate at moderate (5.0kph) and high (7.5kph) speeds.

In contrast, the iPhone® positioned on either the upper or lower body provided a valid step-count estimate across all walking speeds. Although the iPhone® under-reported for most test stages when compared with video-verified total manual step-count ($P < 0.05$), the absolute difference in step-count was negligible (range: -4 to -11 steps). For total step-count, the iPhone® (upper and lower) and Yamax Digiwalker™ SW800 pedometer had a percentage error of 2%, 1% and 8%, respectively. Specifically, the iPhone® positioned on the lower body (1017 ± 58 steps) correlated strongly ($r = 0.96$) and produced the highest level of agreement (mean bias: -11 steps, LOA: -43 to 21 steps) in comparison to video-verified manual step-count (Figure 1-3). Proportional bias was identified for

Yamax Digiwalker™ SW800 pedometer ($F = 11.47$, $P = 0.003$) but not for the iPhone® lower body ($F = 0.36$, $P = 0.56$) or iPhone® upper body ($F = 1.24$, $P = 0.28$) (Table 2).

Phase 1: Self-paced walking challenge

Visual inspection of the data indicated a significant outlier (>20% difference between devices and video-verified total manual step-count) and thus nineteen participants were included in the analysis (asthma: $n = 9$; healthy controls: $n = 10$). No significant difference was observed in video-verified total manual step-count between participants with asthma (1390 ± 168 steps) and healthy controls (1420 ± 131 steps) ($P = 0.67$) and therefore group data was pooled for analysis (mean: 1406 ± 146 steps). The iPhone® (upper and lower body) and Yamax Digiwalker™ SW800 pedometer had a percentage error of 1%, 0% and 1%, respectively. Although the strongest correlation ($r = 0.99$) and highest level of agreement was observed for iPhone® upper (mean bias: -4 steps, LOA: -49 to 41 steps), all devices provided an excellent step-count estimate during self-paced walking (Figure 4). Proportional bias was not identified for any of the devices: Yamax Digiwalker™ SW800 pedometer ($F = 0.02$, $P = 0.88$), iPhone® lower body ($F = 0.12$, $P = 0.74$), iPhone® upper ($F = 0.00$, $P = 0.96$) (Table 3).

Phase 2: Habitual free-living conditions

Over the seven-day period, visual inspection of the data indicated two significant outliers which corroborated with device non-compliance (as per logbook records) and thus eighteen participants were included in the analysis (asthma: $n = 8$; healthy controls: $n = 10$). No significant difference was observed in daily step-count (Yamax Digiwalker™ SW800 pedometer) between participants with asthma (7877 ± 2593 steps) and healthy controls (8809 ± 2326 steps) ($P = 0.43$) and therefore group data was pooled for analysis (mean: 8395 ± 2421 steps). No significant difference was observed between the Yamax Digiwalker™ SW800 pedometer and iPhone® ($P = 0.10$) and a strong correlation ($r = 0.94$) and acceptable agreement (mean bias: -343, LOA: -1963 to 1276 steps, error range: 4%) was observed. Importantly, analysing data from the 'best' day of the week (i.e. highest compliance as per logbook records) resulted in a stronger correlation ($r = 0.99$) and even closer limits of agreement (mean bias: -105, LOA: -946 to 736 steps, error range: 0.5%) between devices (Figure 5). Proportional

bias was identified for the 'best day' ($F = 5.18$, $P = 0.04$) but not for 'average days' ($F = 2.00$, $P = 0.18$) (Table 3).

DISCUSSION

The purpose of this pilot study was to evaluate the validity of modern smartphone technology for the assessment of physical activity in adults with and without asthma. In support of the initial hypothesis, our findings indicate that an in-built iPhone® pedometer provides an accurate step-count estimate during standardised treadmill and self-paced walking challenges and free-living conditions. The potential practical application of smartphone pedometers in the context of asthma management can therefore be considered three-fold. Firstly, as a simple approach to monitor or promote step-based physical activity during medical consultation (i.e. routine asthma review). Secondly, a reduction in physical activity may potentially represent an early marker of impending exacerbation that could be prevented through a self-management plan. Thirdly, as a research tool or outcome measure when utilised in clinical trials.

The measurement of physical activity is a complex task and thus the development and evaluation of scalable and low-cost methods of assessment remains an important research avenue [22]. In-keeping with previous comparable studies in healthy individuals [13, 23] the present study confirms that the iPhone® (positioned on either the upper or lower body) provides an accurate step-count estimate during a standardised laboratory-based treadmill challenge at slow (2.5kph), moderate (5.0kph) and high (7.5kph) walking speeds. Specifically, the iPhone® positioned on the lower body (i.e. trouser pocket) provided the closest agreement with video-verified manual total step-count, and importantly, either matched or outperformed the Yamax Digiwalker™ SW800 pedometer across all test stages.

It has previously been recommended that, to be considered 'research-grade' quality, pedometers should be within $\pm 1\%$ error range during standardised treadmill-based walking [24]. A key observation from this phase of the study was the significant step-count error (29%) for the Yamax

Digiwalker™ SW800 pedometer at the slowest walking speed (2.5kph). Many commercially available pedometers have a 'acceleration dependent' component, meaning they often underestimate step count at slower walking speeds [25-27]. In support of this concept, the error rate of the Yamax Digiwalker™ SW800 pedometer in the current study improved significantly during moderate (5.0kph) and high (7.5kph) walking speeds. Similarly, during self-paced walking (estimated average speed approximately 5.0kph) all devices demonstrated excellent agreement with video-verified manual step-count. Importantly, regardless of positioning - on either the upper or lower body - the iPhone® accurately captured step count across all walking speeds. This highlights the potential benefit of using smartphone technology in patients recognised to avoid moderate to vigorous intensity physical activity (e.g. people with airways disease) [28] or in cohorts with impaired mobility (i.e. elderly individuals +/- those with underlying musculoskeletal disorders) [29].

The evaluation of pedometers in a real-world setting is important to determine device validity according to the specific demands (i.e. walking speeds) of daily tasks. A previous comprehensive assessment of 13 models of electronic pedometers, over a 24-hour period, concluded that a $\pm 10\%$ variability was an acceptable error range during free-living conditions [30]. Specific to smartphone devices, Duncan et al. reported a significant under-estimation of steps when evaluating the iPhone® during free-living conditions in healthy individuals ($\pm 18\%$ error range in comparison to the Actigraph GT3X) [13]. In contrast, the iPhone® exceeded the $\pm 10\%$ criterion [30] (4% error range in comparison to the Yamax Digiwalker™ SW800 pedometer) in the current study and improved further when selecting the 'best day' according to participant compliance over a seven-day period (<1% error range). Although the disparity between studies remains unclear, our data indicate that, with optimal compliance (i.e. verifying time spent active with logbook records), the iPhone® pedometer can be considered a valid method to quantify habitual physical activity. Furthermore, using modern smartphone pedometers for this purpose may reduce the impact of participant reactivity given most people typically carry their device with them throughout the day. In addition, having reliable and accurate instruments to-hand, potentially helps patients to become powerful agents in behavioural

self-management of their condition. Importantly, in-built smartphone pedometers report accurate scores, minute-by-minute, thus encouraging positive self-surveillance and habit formation.

Methodological considerations and future research

The present study has two key strengths. Firstly, the iPhone® pedometer was evaluated in both standardised and free-living conditions. Secondly, our results are directly compared to those of an asymptomatic group of healthy controls. It is important to recognise, however, that despite our encouraging findings, due to the current lack of a gold-standard comparator, evaluating the validity of *any* novel physical activity assessment method remains a challenge [11]. Although video-verified manual step-count was utilised to verify the accuracy of our data during laboratory and field-based walking challenges, a degree of measurement error is inevitable when evaluating step-count during habitual free-living conditions. In addition, the current study focused exclusively on the iPhone® pedometer (on the basis that it currently exceeds over half of the total smartphone UK market share [31]) in a modest sample size and thus a logical extension of this work is to consider inter-device variability according to different smartphone brands/models and mobile operating systems in a large asthma cohort (i.e. factoring activity profiles according to disease severity and sub-types). Notwithstanding these limitations, our data provides the first evidence to suggest that in-built smartphone pedometers provide a reliable means of estimating step-count in adults with asthma. From a practical perspective, they may therefore be used in future prospective research trials and/or retrospective analysis of clinical records to determine the association between physical activity and asthma control and/or efficacy of physical activity promotion or behaviour change programmes. This is particularly pertinent at present due to the SARS-CoV-2 pandemic where shielding and self isolation has had a negative impact on physical engagement for ‘high-risk’ groups and urgent need for remote monitoring.

Conclusion

In summary, our findings indicate that an in-built iPhone® pedometer offers a practical approach to physical activity assessment (i.e. valid step-count estimate under varying conditions) in adults with and without asthma. Future research is now required to further validate the precision of this approach and evaluate the efficacy and effectiveness of smartphone pedometers to monitor and promote physical activity when employed during medical consultation and/or clinical research trials.

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Nil relevant.

COMPETING INTERESTS

The authors have no real or perceived conflict of interest in respect of this manuscript.

CONTRIBUTION STATEMENT

CR, ASK, IC, OP designed the study. CR acquired the data. CR, ASK, OP interpreted the data. CR, ASK, IC, JM, DP, OP were involved in drafting and critical revision of manuscript; and final approval of the version to be published.

GUARANTOR STATEMENT

OP confirms full responsibility for the content of the manuscript.

TABLE HEADINGS

Table 1. Clinical characteristics and baseline lung function.

	Healthy	Asthma	Total
Age (years)	23 (9)	23 (7)	23 (8)
Sex (M:F)	6 : 4	6 : 4	12 : 8
Height (cm)	172 (10.3)	175.3 (8.8)	173.6 (9.5)
Weight (kg)	74.3 (12.3)	75.4 (11.1)	74.9 (11.4)
BMI (kg/m ²)	25.0 (2.5)	24.5 (2.8)	24.7 (2.6)
Blood pressure (mmHg)			
Systolic	121 (6)	123 (9)	122 (7)
Diastolic	73 (9)	75 (9)	74 (8)
Resting heart rate (bpm)	70 (14)	71 (13)	71 (13)
Fat (%)	20.5 (8.1)	19.7 (7.2)	20.1 (7.5)
Fat mass (kg)	16.0 (7.0)	14.8 (6.0)	15.4 (6.4)
Fat free mass (kg)	60.3 (13.7)	60.4 (10.5)	60.3 (11.9)
FEV ₁ (L)	4.0 (0.8)	3.6 (0.6)	3.7 (0.7)
FEV ₁ (%) predicted	104 (8)	90 (12.7)*	97 (12.7)
FVC (L)	4.6 (1.3)	4.6 (0.90)	4.6 (1.1)
FVC (%) predicted	104 (8.1)	97 (8.9)	100 (9.1)
FEV ₁ /FVC (%)	87 (8.5)	79 (12)	83 (10.9)
PEF (l/min)	531.9 (126.3)	487.5 (92.1)	509.7 (109.9)
PEF (%)	101.8 (11.8)	97 (11.5)	99.5 (11.6)
FeNO (ppb)	20 [13 - 32]	36 [19 - 72]	21 [19 - 47]
ACQ	-	1.1 [0.7 - 1.0]	-
AQLQ	-	6.1 [5.4 - 6.2]	-
D-12	0	5.5 [1.0 - 10.3]	-

Data presented as mean (SD) and median [IQR]. Definitions of abbreviations: FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; FeNO, fractional exhaled nitric oxide; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; D-12, Dyspnoea-12. *Denotes significant difference between groups (P<0.05).

Table 2. Total step-count during standardised treadmill walking.

Device (speed)	Step-count	Paired t test P-value	ICC	Mean bias	LOA	Regression	
						F-value	P-value
Video-verified manual step-count (2.5kph)	253 (18)	-					
iPhone® upper	242 (42)	0.24	0.33	-11	-89 to 67	16.76	0.00
iPhone® lower	253 (21)	0.99	0.77	0	-27 to 27	0.88	0.36
Yamax Digiwalker™ SW800	179 (70)	<0.0001	0.37	-74	-203 to 55	65.0	<0.0001
Video-verified manual step-count (5.0kph)	337 (17)	-					
iPhone® upper	336 (18)	0.86	0.88	-1	-17 to 16	0.20	0.59
iPhone® lower	333 (16)	0.003	0.96	-4	-14 to 6	0.88	0.36
Yamax Digiwalker™ SW800	329 (28)	0.23	0.40	-8	-59 to 44	5.77	0.03
Video-verified manual step-count (7.5kph)	439 (29)	-					
iPhone® upper	431 (30)	0.009	0.91	-8	-33 to 17	0.05	0.83
iPhone® lower	430 (35)	0.009	0.93	-9	-33 to 17	3.95	0.06
Yamax Digiwalker™ SW800	433 (31)	0.004	0.97	-6	-20 to 9	0.69	0.42
Video-verified manual step-count (total)	1028 (56)	-					
iPhone® upper	1009 (67)	0.08	0.74	-19	-108 to 70	1.24	0.28
iPhone® lower	1017 (58)	0.006	0.96	-11	-43 to 21	0.36	0.56
Yamax Digiwalker™ SW800	942 (99)	<0.0001	0.66	-86	-233 to 60	11.47	0.00

Definitions of abbreviations: ICC, intraclass correlation coefficient; LOA, limits of agreement.

Table 3. Total step-count during self-paced walking and habitual free-living conditions.

Device	Step-count	Paired <i>t</i> test	ICC	Mean bias	LOA	Regression	
		P-value				F-value	P-value
1-km self-paced walking test							
Video-verified manual step-count							
iPhone® upper	1406 (146)	0.45	0.99	-4	-49 to 41	0.00	0.96
iPhone® lower	1402 (146)	0.06	0.98	-13	-67 to 42	0.12	0.74
Yamax Digiwalker™ SW800	1393 (149)	0.08	0.98	-12	-66 to 43	0.02	0.88
Habitual free-living conditions							
Average days							
Yamax Digiwalker™ SW800	8395 (2421)	0.10	0.94	-343	-1963 to 1276	2.00	0.18
iPhone®	8051 (2149)						
Best day							
Yamax Digiwalker™ SW800	9706 (3712)	0.31	0.99	-105	-946 to 736	5.18	0.04
iPhone®	9601 (3500)						

Definitions of abbreviations: ICC, intraclass correlation coefficient; LOA, limits of agreement.

FIGURE CAPTIONS

Figure 1. Bland-Altman plots for iPhone® upper body: (a) 2.5kph, (b) 5.0 kph, (c) 7.5 kph and (d) total steps during a standardised treadmill walking test. Closed black circles denote healthy controls; open circles denote adults with asthma.

Figure 2: Bland-Altman plots for iPhone® lower body: (a) 2.5kph, (b) 5.0 kph, (c) 7.5 kph and (d) total steps during a standardised treadmill walking test. Closed black circles denote healthy controls; open circles denote adults with asthma.

Figure 3: Bland-Altman plots for Yamax Digiwalker™ SW800: (a) 2.5kph, (b) 5.0 kph, (c) 7.5 kph and (d) total steps during a standardised treadmill walking test. Closed black circles denote healthy controls; open circles denote adults with asthma.

Figure 4. Bland Altman plots from 1-km self-paced walking test: (a) iPhone® upper body, (b) iPhone® lower body and (c) Yamax Digiwalker™ SW800. Closed black circles denote healthy controls; open circles denote adults with asthma.

Figure 5. Bland-Altman plots ~~with 95% limits of agreement~~ from 7-day free living assessment for Yamax Digiwalker™ SW800 versus iPhone®: (a) average day and (b) best day. Closed black circles denote healthy controls; open circles denote adults with asthma.

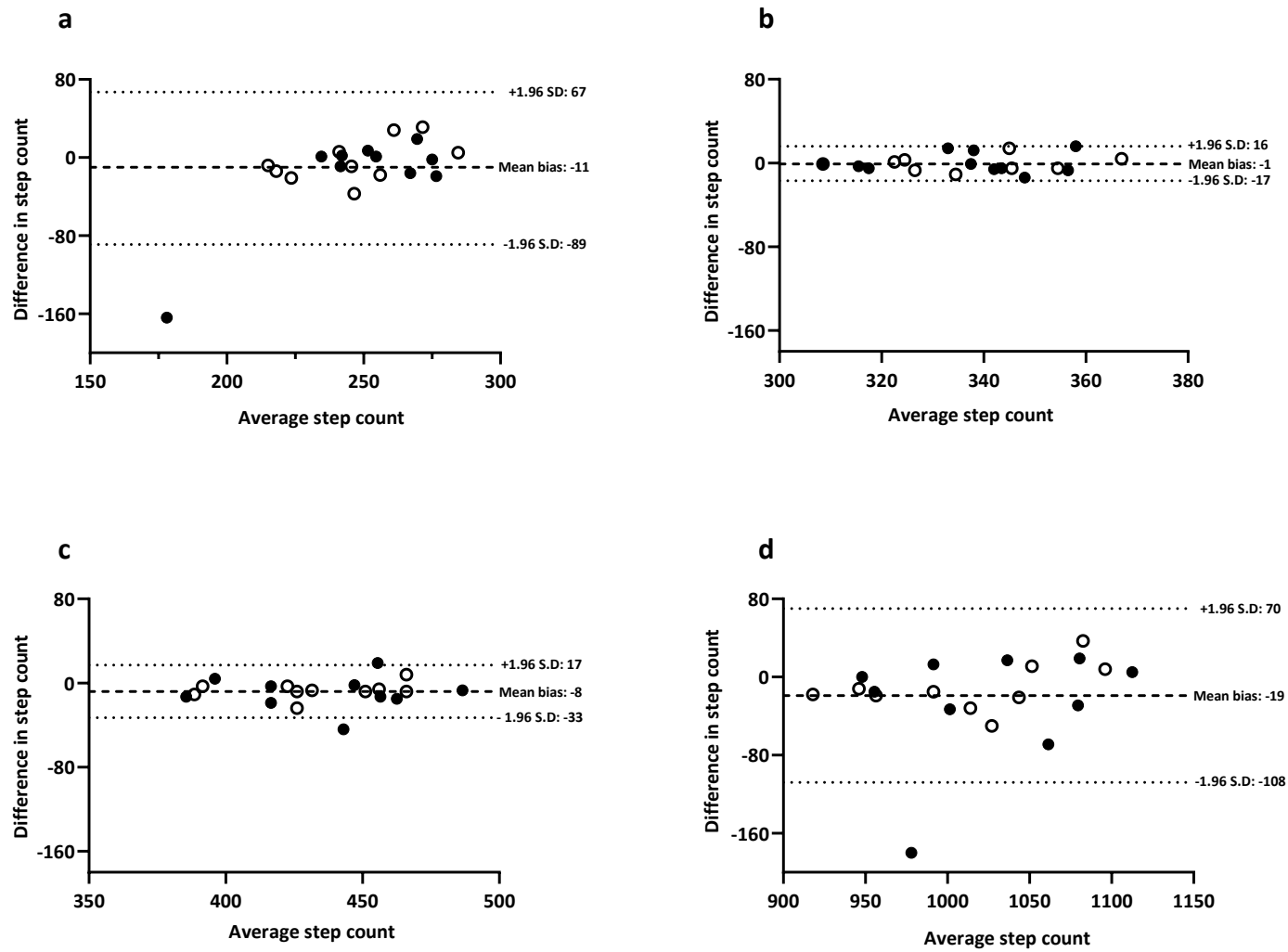


Figure 1.

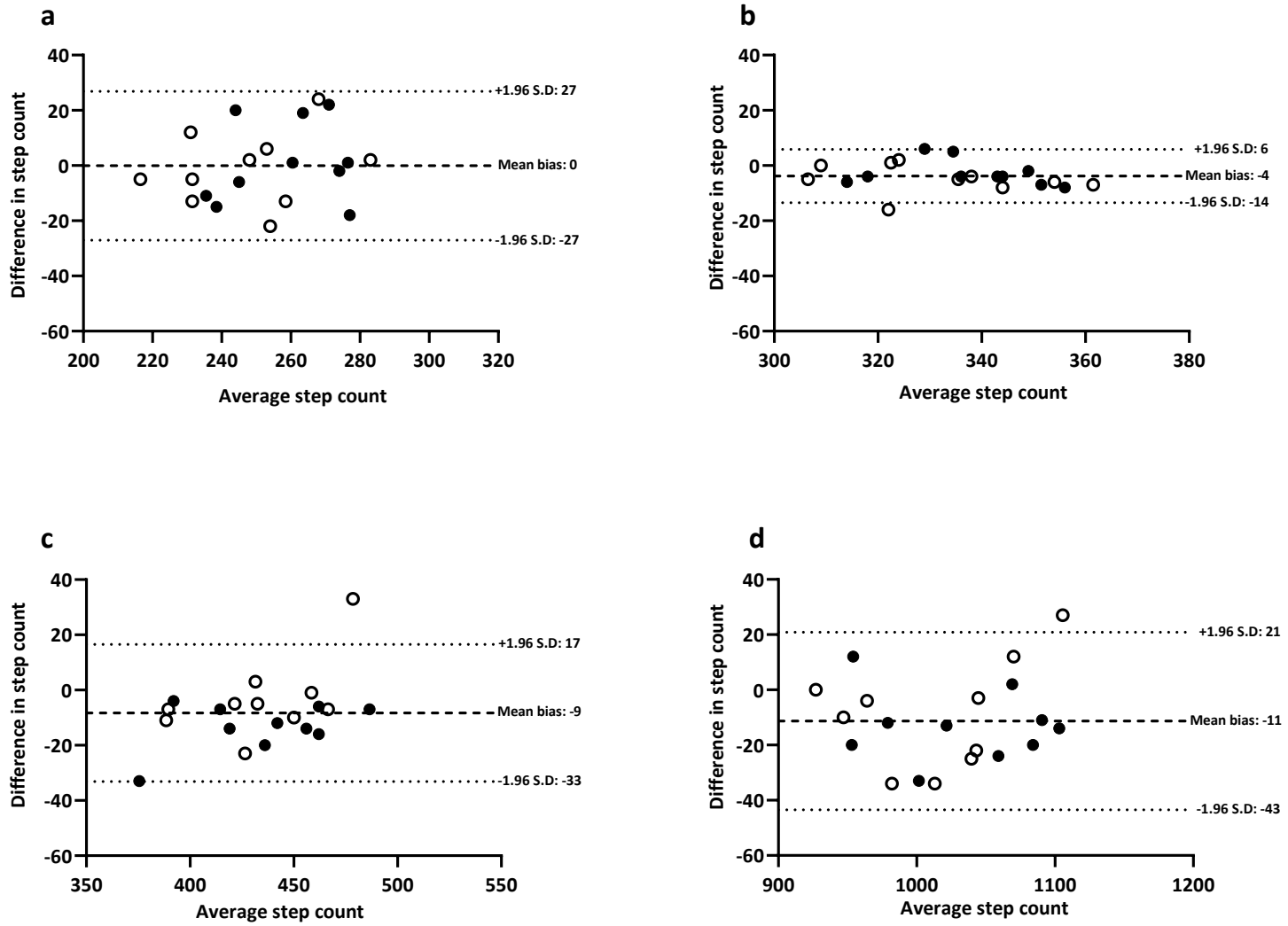


Figure 2.

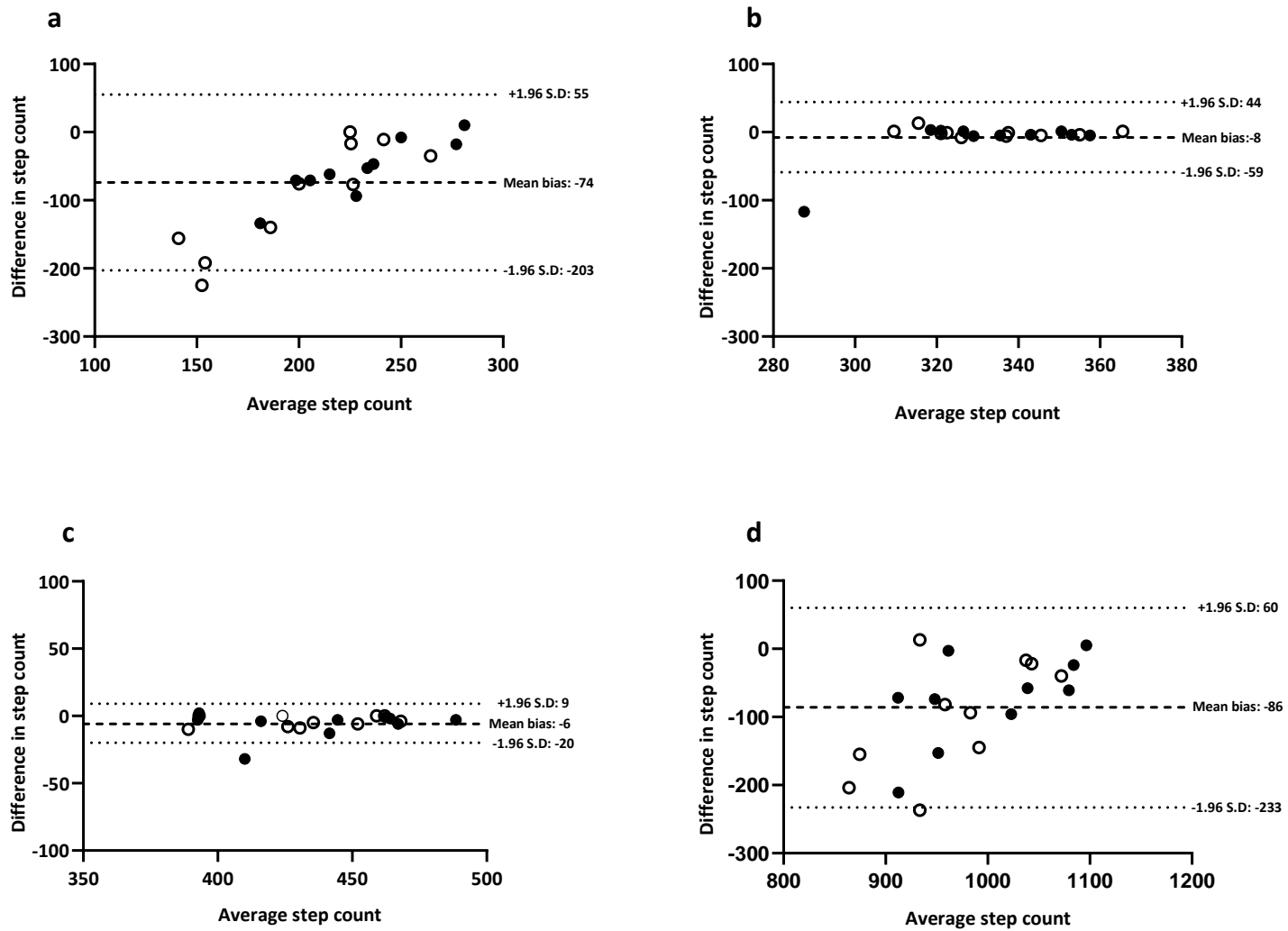
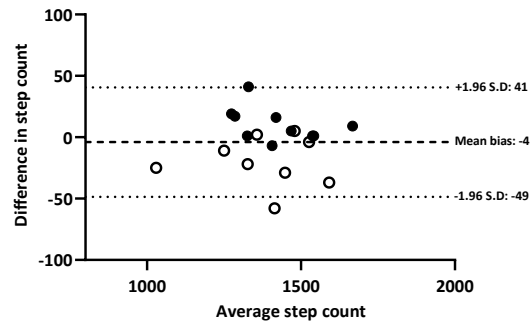
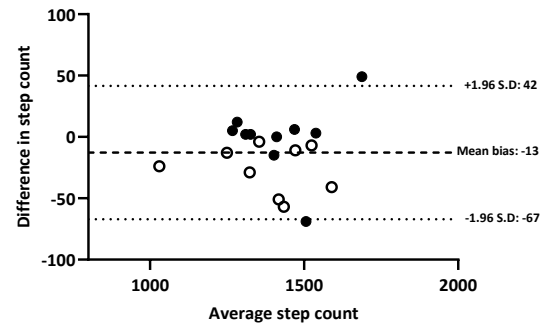


Figure 3.

a



b



c

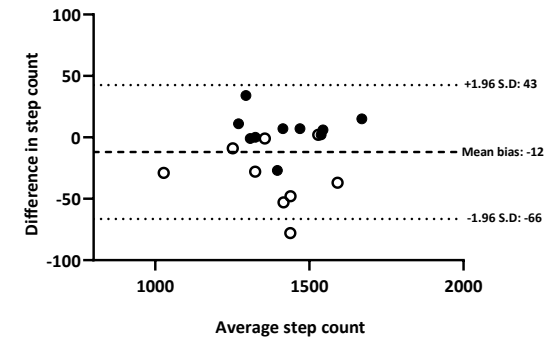
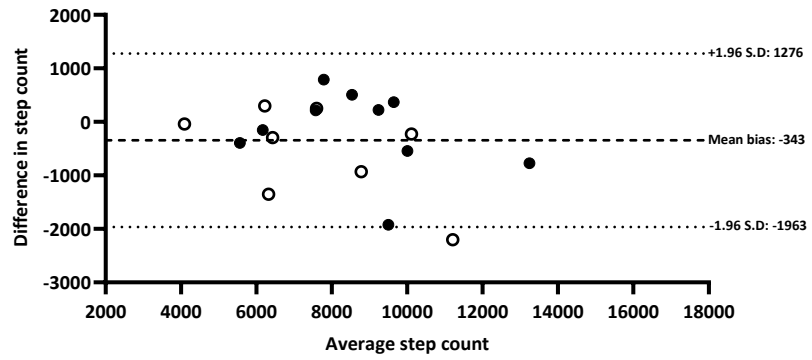
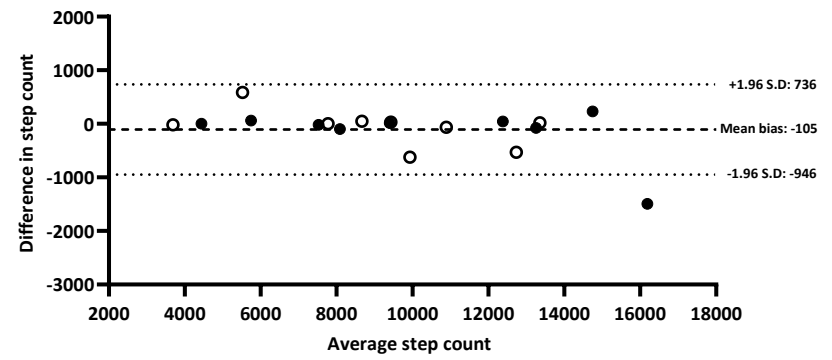


Figure 4.

a



b



Figure

5.

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