

Running Title: Energy Expenditure & Down Syndrome

Prediction of Energy Expenditure during Walking in Adults with Down Syndrome

## 1   **Abstract**

2   *Background* When developing walking programs for improving health in adults with Down  
3   syndrome (DS), physical activity professionals are in need of an equation for predicting energy  
4   expenditure. We therefore developed and cross-validated an equation for predicting the rate of  
5   oxygen uptake ( $\text{VO}_2$ ; an index of energy expenditure) for adults with and without DS.

6   *Method* A total of 469  $\text{VO}_2$  observations during walking across different speeds were available  
7   from 54 adults with DS and 61 adults without DS.

8   *Results* Significant predictors of  $\text{VO}_2$  were speed, speed square, group, and group by speed  
9   interaction. Separate models for each group showed that speed and its square significantly  
10   predicted  $\text{VO}_2$ . Absolute percent error was small and did not differ between groups.

11   *Conclusion* Adults with DS have different  $\text{VO}_2$  response to walking speed from persons without  
12   DS.  $\text{VO}_2$  is predicted from speed with acceptable accuracy for persons with DS.

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16   Keywords: physical activity, exercise, Down syndrome, gait, energy expenditure, metabolism

## 1    **Introduction**

2            Adults with Down syndrome (DS) experience health disparities. They have earlier  
3    mortality than the general population (Presson et al., 2013; Yang, Rasmussen, & Friedman,  
4    2002). They also have very high obesity rates, very low cardiovascular and muscular fitness,  
5    functional limitations, and a set of other preventable secondary conditions (Carmeli, Kessel, Bar-  
6    Chad, & Merrick, 2004; Croce, Pitetti, Horvat, & Miller, 1996; Fernhall et al., 1996; Pikora et  
7    al., 2014; Stancliffe et al., 2011). Physical activity is an important means of improving the health  
8    of adults with DS (Mendonca, Pereira, & Fernhall, 2010; US Department of Health and Human  
9    Services, 2002, 2008). However, most adults with DS do not meet the recommendations for  
10   health-promoting physical activity (Draheim, Williams, & McCubbin, 2002; Heller, Hsieh, &  
11   Rimmer, 2002; Phillips & Holland, 2011). The most common physical activity among adults  
12   with DS is walking (Draheim et al., 2002; Heller et al., 2002). Walking programs are essential  
13   for promoting health in persons with and without disabilities (US Department of Health and  
14   Human Services, 2008). Physical activity specialists must carefully design walking programs in  
15   order to maximize health benefits in adults with DS. The selection of appropriate intensities,  
16   especially of moderate-to-vigorous levels, is important if participants are expected to meet  
17   physical activity recommendations and improve their fitness (American College of Sports  
18   Medicine, 2014; US Department of Health and Human Services, 2008).

19           When selecting appropriate walking intensities, physical activity professionals use  
20   equations that estimate the rate of oxygen uptake ( $\text{VO}_2$ ) from walking speed.  $\text{VO}_2$  reflects the  
21   energy expenditure and is commonly used to classify the intensity of activity; for example,  
22   activities eliciting a  $\text{VO}_2$  between 10.5 and 20.99  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  is considered of moderate  
23   intensity and activities eliciting 21.0  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  or higher are considered vigorous. A widely

used formula that estimates  $\text{VO}_2$  from walking speed is the one endorsed by the American College of Sports Medicine (ACSM) (American College of Sports Medicine, 2014). This equation, however, has been developed for people without disabilities and, not surprisingly, underestimates the  $\text{VO}_2$  during walking in adults with DS (Agiovlasitis, Motl, Ranadive, et al., 2011). These individuals have higher  $\text{VO}_2$  during walking—especially at faster speeds—than individuals without DS likely because of altered gait patterns (Agiovlasitis, McCubbin, Yun, Widrick, & Pavol, 2015). This may result from deficits in motor control, joint laxity, and muscle hypotonia, all of which are associated with DS (Bull & Committee on Genetics, 2011; Pinter, Eliez, Schmitt, Capone, & Reiss, 2001; Rigoldi et al., 2009). Additionally, previously reported low aerobic fitness and mitochondrial dysfunction in persons with DS may contribute to their higher  $\text{VO}_2$  during walking (Fernhall et al., 1996; Helguera et al., 2013; Sawyer et al., 2010).

Past research, with a small number of participants, attempted to develop an equation for predicting  $\text{VO}_2$  from walking speed in adults with and without DS (Agiovlasitis, Motl, Ranadive, et al., 2011). There is a need to develop a prediction equation in larger and more representative samples because DS is a chromosomal disorder that results in wide diversity of physiologic complications (Bull & Committee on Genetics, 2011). In addition, that previously-developed equation used over-ground walking and the equation may not apply to treadmill walking—a common mode of exercise in rehabilitation and fitness settings. Some past research in persons without disabilities has found that the energy cost of walking is higher on the treadmill than over-ground (Berryman et al., 2012; Dasilva et al., 2011; Parvataneni, Ploeg, Olney, & Brouwer, 2009). Whether equations for predicting  $\text{VO}_2$  in adults with DS should be different for over-ground and treadmill walking is not known.

The present study involved secondary analysis of combined data from three different previous research projects on walking economy in adults with DS (References removed for blind review). The purpose was to confirm that the relationship between  $\text{VO}_2$  and walking speed differs between adults with DS and adults without DS or any other disability. We also attempted to develop an equation for predicting  $\text{VO}_2$  from walking speed for adults with DS using the largest data set to date in order to improve generalizability. Furthermore, we examined if walking mode (treadmill vs. over-ground) contributes to prediction of  $\text{VO}_2$ . Finally, we evaluated the accuracy of prediction models for adults with and without DS using the leave-one-participant out cross-validation procedure.

## Methods

### Participants

We compiled de-identified data from three previous studies that included adults with and without DS from three different geographical regions (References removed for blind review). Study 1 was conducted in Northwestern U.S. and included 15 adults with DS (7 women) and 15 adults without DS (7 women). Study 2 was conducted in Midwestern U.S. and participants were 18 adults with DS (10 women) and 22 adults without DS (13 women). Study 3 was conducted in Portugal and participants were 21 adults with DS (6 women) and 24 adults without DS (6 women). Consequently, the sample for the present study included 54 adults with DS (23 women and 31 men) and 61 adults without DS or any other disability (26 women and 35 men). Participants with DS were recruited via group homes, vocational rehabilitation centers, community-based physical activity programs, and contacts from previous research. Participants without DS were recruited from the local communities in an attempt to match the age and sex

profiles of those with DS. All participants with DS had the cognitive ability to understand the protocols and follow instructions. Seven participants with DS had congenital heart defects corrected with surgery in childhood; however, all had medical approval to participate in physical activity programs. Otherwise, all participants with and without DS had good general health, did not smoke, and did not have mobility limitations. Independent-samples *t*-tests showed that participants with and without DS did not differ significantly in mean age (DS:  $29 \pm 8$ ; non-DS:  $30 \pm 8$  y;  $p = 0.405$ ), body mass (DS:  $69.3 \pm 13.3$ ; non-DS:  $73.2 \pm 17.8$  kg;  $p = 0.187$ ), or resting  $\text{VO}_2$  (DS:  $3.8 \pm 0.8$ ; non-DS:  $3.9 \pm 0.7$  ml·kg<sup>-1</sup>·min<sup>-1</sup>;  $p = 0.835$ ). Adults with DS had shorter height (DS:  $152.5 \pm 8.3$ ; non-DS:  $172.1 \pm 8.7$  cm;  $p < 0.001$ ) and had higher body mass index (BMI; DS:  $29.8 \pm 5.6$ ; non-DS:  $24.6 \pm 5.2$  kg·m<sup>-2</sup>;  $p < 0.001$ ) than those without DS. This study was conducted in full accordance with the World Medical Association Declaration of Helsinki of 2002. The Institutional Review Board at each site approved the procedures. All participants with and without DS, as well as the legal guardians of those with DS provided informed consent.

## Procedures

The methodology of each study has been described in detail elsewhere (References removed for blind review). In brief, participants with and without DS in each study became thoroughly familiar with the procedures in 1-4 separate sessions and then attended a data collection session.

Participants with and without DS in study 1 performed six treadmill walking trials, each 6 min in duration, at predetermined dimensionless speeds of 0.1, 0.2, 0.3, 0.4, 0.5, and 0.6. Dimensionless speed accounts for differences in leg length between people. Absolute walking speeds for these six trials for participants with DS were 0.3, 0.5, 0.8, 1.1, 1.3, and 1.6 m·s<sup>-1</sup>,

1    whereas for participants without DS 0.3, 0.6, 0.9, 1.2, 1.5, and 1.7 m·s<sup>-1</sup>. One participant with DS  
 2    from study 1 was unable to maintain the fastest walking trial without handrail support for its full  
 3    duration and this trial was not included in the analysis. Participants in study 2 performed five  
 4    over-ground walking trials, each lasting 6 min. The trials took place indoors in a quiet  
 5    rectangular hallway with a perimeter of 90 m. The speed was set by a researcher who walked ~1  
 6    m in front of the participant and rolled a distance-measuring wheel (MP301DM, Keson, Aurora,  
 7    IL). The measuring wheel was furnished with a cycle computer (Velo 8, Cateye, Osaka, Japan)  
 8    that displayed instantaneous speed. Target speeds for these trials were 0.50, 0.75, 1.00, 1.25, and  
 9    1.50 m·s<sup>-1</sup>. Actual average walking speeds determined from the distance covered over the 6 min  
 10   of each trial were 0.51, 0.76, 1.01, 1.26, and 1.51 m·s<sup>-1</sup> for participants with and without DS  
 11   combined. Participants in study 3 performed four treadmill walking trials each lasting 5 min.  
 12   Two of these trials were conducted at 0.69 and 1.25 m·s<sup>-1</sup> with 0% incline. The remaining two  
 13   were performed at 1.25 m·s<sup>-1</sup>, one with 2.5% and the other with 5% incline. For the present  
 14   study, we focused on level walking and did not consider trials with incline. There were a total of  
 15   221 data points for adults with DS and 248 data points for adults without DS available for the  
 16   present analysis.

17       For all studies, data collection occurred in temperatures between 21 and 24 °C and  
 18   relative humidity of ~50%. Participants avoided food and caffeine for 2-4 hours and exercise for  
 19   3-24 hours prior to testing. VO<sub>2</sub> during the walking trials was measured with open-circuit  
 20   spirometry (Study 1: TrueMax 2400, Parvo Medics, Salt Lake City, UT; Study 2: K4b<sup>2</sup>, Cosmed,  
 21   Italy; Study 3: Quark b<sup>2</sup>, Cosmed, Italy). These systems were calibrated prior to each data  
 22   collection section. The VO<sub>2</sub> was determined in ml·kg<sup>-1</sup>·min<sup>-1</sup> as the average over the last 3 min  
 23   of each walking trial to ensure that participants reached steady state.

## Prediction of Oxygen Uptake

We examined the responses of  $\text{VO}_2$  to walking speed in adults with and without DS with hierarchical linear modeling. This approach to regression was used to account for the multiple measurements obtained from each participant—unlike traditional regression, the assumptions of independent observations and missing data are not issues in hierarchical linear modeling (Snijders & Bosker, 1999). The dependent variable was  $\text{VO}_2$  ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) during walking. Independent variables (fixed effects) were walking speed ( $\text{m} \cdot \text{s}^{-1}$ ), the square of speed, group (DS vs. non-DS), the group-by-speed interaction, and walking mode (treadmill vs. over-ground). We also considered BMI as an independent variable because it differed between groups. Potential random effects were the intercepts and slopes of the  $\text{VO}_2$  to walking speed relationship across participants. Each parameter was included in the regression model based on the difference in -2 log-likelihood against a  $\chi^2$  distribution with 1 degree of freedom. Upon significant group-by-speed interaction, we developed separate models for each group. Predictors in these models were all parameters of the combined-groups regression model, except group and the group-by-speed interaction.

## Cross-validation of Prediction Models

We then attempted to cross-validate the separate-group regression models, using the leave-one-participant-out approach (Staudenmayer, Zhu, & Catellier, 2012). Specifically, the model for each group was run on the data from all participants in that group except one. The resulting regression coefficients were then used to predict the  $\text{VO}_2$  data points for the left-out participant. This process was repeated until the data from all participants were considered for cross-validation, resulting in obtaining the estimated  $\text{VO}_2$  for each participant. As a component



of this method, we also determined the absolute percent error for the left-out participant as the absolute value of  $[(\text{actual VO}_2 - \text{estimated VO}_2) / \text{actual VO}_2] \times 100$ . The difference in absolute percent error across speeds between adults with and without DS was evaluated with an independent-samples *t*-test. Finally, we evaluated the agreement between actual and estimated VO<sub>2</sub> for left-out participants with Bland-Altman plots (Bland & Altman, 1999). Statistical analyses were run in SPSS Statistics 23 (IBM Corp., Armonk, NY) and the alpha level was 0.05.

## Results

### Prediction of Oxygen Uptake

Hierarchical linear modeling indicated that the relationship between VO<sub>2</sub> and walking speed differed between persons with and without DS. Random intercepts and random slopes significantly contributed to the model ( $p < 0.001$ ). Significant predictors of VO<sub>2</sub> were speed, the square of speed, group (DS vs. non-DS), and the group-by-speed interaction ( $p < 0.001$ ;  $R^2 = 0.82$ ; Table 1). Walking mode (treadmill vs. over-ground) and BMI were not significant predictors. The group-by-speed interaction was further analyzed with separate models for each group with random intercepts and slopes. For persons with DS, speed and its square significantly predicted VO<sub>2</sub>, whereas for persons without DS only speed square significantly predicted VO<sub>2</sub> ( $p \leq 0.001$ ;  $R^2 = 0.83$  and  $0.77$  for adults with and without DS, respectively; Table 2 and Figure 1).

For adults with DS, the prediction equation was:  $\text{VO}_2 = 7.713 - (3.477 \times \text{walking speed}) + (7.911 \times \text{Walking Speed}^2)$ ; VO<sub>2</sub> is in ml·kg<sup>-1</sup>·min<sup>-1</sup>; walking speed is in m·s<sup>-1</sup>; and walking speed<sup>2</sup> is in (m·s<sup>-1</sup>)<sup>2</sup>

For adults without DS, the prediction equation was:  $VO_2 = 6.951 - (0.736 \times \text{walking speed}) + (3.560 \times \text{Walking Speed}^2)$ ;  $VO_2$  is in  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; walking speed is in  $\text{m} \cdot \text{s}^{-1}$ ; and walking speed<sup>2</sup> is in  $(\text{m} \cdot \text{s}^{-1})^2$

#### Cross-validation

Using the leave-one-participant-out cross-validation procedure, we found that mean absolute percent error across speeds did not differ between adults with and without DS ( $13.0 \pm 9.3\%$  and  $11.9 \pm 8.2\%$ , respectively;  $p = 0.16$ ). Bland-Altman plots showed that the difference between actual and predicted  $VO_2$  was on average nearly zero for each group (DS:  $-0.36 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; non-DS:  $-0.33 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; Figure 2) and that there was no systematic over- or under-estimation. However, agreement error had somewhat greater 95% confidence intervals for adults with than without DS ( $7.66$  and  $5.17 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively), indicating somewhat lower predictability of individual  $VO_2$  values in adults with DS.

## Discussion

In the present study, we examined differences in the relationship between  $VO_2$  and walking speed between adults with and without DS with the largest sample to date. We also developed specific  $VO_2$  prediction equations for adults with and without DS and further evaluated their accuracy using the leave-one-participant-out cross-validation method. We found that the relationship between  $VO_2$  and walking speed was steeper in adults with than without DS. Furthermore, the prediction equation for adults with DS had acceptable accuracy. These results have implications for designing health-promoting physical activity programs for adults with DS with profiles similar to the participants with DS of the present study.

With the results of the combined-groups regression, we confirmed that, compared to adults without DS, those with DS have a steeper response of  $\text{VO}_2$  to walking speed and their  $\text{VO}_2$  is higher, especially at fast speeds. Previous research has shown that, after controlling for the effect of speed, differences in gait patterns between adults with and without DS accounted for 74% of the difference in  $\text{VO}_2$  between groups (Agiouvasitis et al., 2015). In that research, the following gait variables were identified as contributors to the between-group difference in  $\text{VO}_2$ : mediolateral motion of the body's center of mass (COM); variability in anteroposterior COM velocity; step width variability; and step length variability. All of these variables are greater in adults with than without DS, especially during faster walking (Agiouvasitis, McCubbin, Yun, Mpitsos, & Pavol, 2009). Such gait alterations are consistent with less precise control of body dynamics and greater difficulty in maintaining balance during walking (Kuo, 2007). In turn, this may result from the documented deficits of the cerebellum, muscle hypotonia, and ligamentous laxity of persons with DS (Bull & Committee on Genetics, 2011; Pinter et al., 2001; Rigoldi et al., 2009). Although gait variables seem to account for most of difference in  $\text{VO}_2$  attributable to DS, there are additional contributors inherent in DS. Possible factors may include co-activation of agonist-antagonist muscle groups, mitochondrial dysfunction, and very low aerobic fitness, all of which have been documented in adults or children with DS (Fernhall et al., 1996; Helguera et al., 2013; Ulrich, Haehl, Buzzi, Kubo, & Holt, 2004). In support of the role of aerobic fitness, past research has found that exercise training that increases fitness also improves walking economy in adults with DS (Mendonca, Pereira, & Fernhall, 2011). All these factors, inherent to DS, may collectively increase the energy expenditure during walking, especially at fast speeds.

The combined-groups model of the present study explained 82% of the variance in  $\text{VO}_2$  between people across groups. Thus, in addition to DS and walking speed, other factors account

1 for the remaining 18% of the variance between people. Our analysis showed that walking mode  
2 (treadmill vs. over-ground) does not explain a significant portion of the variance. This is  
3 supported by previous research showing very similar biomechanics between treadmill and over-  
4 ground walking (Lee & Hidler, 2008). Other research, however, has found that people walk with  
5 higher  $\text{VO}_2$  on the treadmill than over-ground (Berryman et al., 2012; Dasilva et al., 2011;  
6 Parvataneni et al., 2009). It is difficult to reconcile our results with those previous findings.  
7 Differences in the amount of practice time with treadmill walking between studies may be at  
8 play. The main difference is that our study included people with and without DS, whereas  
9 previous studies were focused on young or older adults without disabilities. It is therefore  
10 possible that variability between people—especially those with DS—may overlap with the  
11 variability attributable to the potential impact of treadmill walking. Research in this area is  
12 needed. Nevertheless, other factors—not measured herein—likely contribute to the unexplained  
13 variance of the combined-groups model. Still, the model with walking speed and DS explained a  
14 very large proportion of the variance in  $\text{VO}_2$ .

15 We also developed formulas for predicting  $\text{VO}_2$  during walking separately for adults with  
16 and without DS. As for the combined-groups model, explained variance was high (and somewhat  
17 higher for the DS group), suggesting that these models have predictive value. Indeed, when we  
18 examined the accuracy of the models with the leave-one-participant-out cross-validation  
19 approach, we found that absolute error was relatively small and not statistically different between  
20 groups. Furthermore, the Bland-Altman plots showed no systematic over- or under-prediction in  
21 adults with and without DS. However, the plots showed that predictability of individual scores  
22 was somewhat higher for adults with than without DS. Similar findings have been previously  
23 observed in prediction models for persons with and without DS (Agiouvasitis, Motl, Fahs, et al.,

2011; Agiovlasitis, Motl, Ranadive, et al., 2011; Agiovlasitis, Pitetti, Guerra, & Fernhall, 2011). This is generally expected because DS is a condition that can impact physiological systems in diverse ways and to a different extent between people (Bull & Committee on Genetics, 2011). Thus, our results indicate a need to consider other variables—not measured in our study—for capturing the variability in  $\text{VO}_2$  responses among individuals with DS; one such predictor could possibly be an index of mobility difficulties as it has been previously found in adults with Multiple Sclerosis (Agiovlasitis, Sandroff, & Motl, 2016). Nonetheless, the accuracy of the models was high and the equations appear valid for practice.

Physical activity and health promotion professionals may use the present equations for developing exercise programs and for monitoring physical activity in adults with DS with profiles similar to those of the present participants with DS. Professionals may prescribe walking that allows individuals to reach a certain  $\text{VO}_2$  level—our recommendation is that this level be expressed relative to  $\text{VO}_{2\text{peak}}$  which is very low in adults with DS (Fernhall et al., 1996). With appropriate conversions (American College of Sports Medicine, 2014), the formula could also be used to estimate the caloric expenditure of walking, allowing professionals to monitor the effectiveness of walking programs for weight control. Of course, this assumes that generalized conversions to calories apply to adults with DS, but this has not been examined empirically. In addition, the present equation may allow exercise professionals to monitor whether adults with DS perform the recommended amount of moderate-to-vigorous physical activity. The equation could be incorporated in the analysis of physical activity data collected with monitors such as pedometers or accelerometers, which allow for reasonable estimation of walking speed.

The present study had several limitations. First, we did not measure physical activity and physical fitness levels which could possibly account for some of the difference in  $\text{VO}_2$  between

1 participants with and without DS. Second, all participants had functional profiles that allowed  
2 them to complete the protocol; thus, the prediction equations may not generalize to participants  
3 with lower functional profiles. Third, we only included persons with DS in good general health  
4 and without mobility limitations; thus, our results may not generalize to persons with DS with  
5 mobility problems or morbidities such as thyroid dysfunction and diabetes.

6 This study also had several strengths. First, we employed the largest sample size on  
7 walking economy in persons with DS to date. Second, this was a multi-site study which may  
8 have resulted in a sample more representative of the population of adults with DS and in  
9 increased generalizability of the findings. Third, we included data points across different speeds  
10 that ranged from slow to fast. Fourth, we developed equations using hierarchical linear modeling  
11 which accounts for the possibility of correlated observations from the same participant (Snijders  
12 & Bosker, 1999). Finally, we cross-validated the equations using the leave-one-participant-out  
13 method which increases confidence in the external validity of the findings.

14 In conclusion, adults with DS have a steeper response of  $\text{VO}_2$  to increased walking speed,  
15 and their  $\text{VO}_2$  is higher compared to adults without DS, especially at fast speeds. A population-  
16 specific formula for predicting  $\text{VO}_2$  from speed during level walking in adults with DS has  
17 acceptable accuracy. Physical activity specialists may use this formula for designing exercise  
18 programs for adults with DS.

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8

## 1 Table 1

2 Hierarchical regression model predicting rate of oxygen uptake ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) during walking in  
 3 adults with and without Down syndrome

	b	SE
Intercept *	8.298	0.329
Walking Speed [ $\text{m} \cdot \text{s}^{-1}$ ] *	-4.092	0.636
Group [1=DS; 0=non-DS] *	-2.455	0.299
Walking speed $\times$ Group [ $\text{m} \cdot \text{s}^{-1}$ ] *	5.354	0.326
Walking Speed <sup>2</sup> [ $(\text{m} \cdot \text{s}^{-1})^2$ ] *	5.326	0.300

4 Note: b = unstandardized coefficient; SE = standard error; \* =  $p < 0.001$ ;  $R^2 = 0.82$ .

5

1 Table 2  
 2 Separate-group hierarchical regression models predicting rate of oxygen uptake ( $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )  
 3 during walking for adults with Down syndrome (DS) and adults without Down syndrome (non-  
 4 DS)

	DS		non-DS	
	b	SE	b	SE
Intercept	7.713*	0.461	6.951*	0.269
Walking Speed [ $\text{m}\cdot\text{s}^{-1}$ ]	-3.477*	1.031	-0.736	0.483
Walking Speed <sup>2</sup> [ $(\text{m}\cdot\text{s}^{-1})^2$ ]	7.911*	.529	3.560*	0.232

5 Note: b = unstandardized coefficient; SE = standard error; \* =  $p \leq 0.001$ ;  $R^2 = 0.83$  and  $0.77$  for  
 6 DS and non-DS groups, respectively.

## Figure Legends

Figure 1. Response of rate of oxygen uptake ( $\text{VO}_2$ ) to walking speed in adults with Down syndrome (DS) and adults without Down syndrome (non-DS). Solid lines are mean regressions using the coefficients of the separate-group models.

Figure 2. Bland-Altman plots of the difference between actual rate of oxygen uptake ( $\text{VO}_2$ ) and  $\text{VO}_2$  estimated by the separate-group models as a function of actual  $\text{VO}_2$  in adults with Down syndrome (DS) and adults without Down syndrome (non-DS). The difference shown is that for each left-out participant in the cross-validation procedure. Solid and dotted lines are means and 95% limits of agreement, respectively.