The first reference equations for the six-minute walk distance over a 10 metre course

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Online supplement ("Web only file")

METHODS

Study population

Healthy Caucasian subjects who volunteered to participate (n = 194) in a cross-sectional study were recruited by the researchers (EB and IM) in southern and central regions of the Netherlands. The population in this study was recruited by means of snowball sampling: the researcher sampled an initial group of people relevant to the research question, and these sampled participants proposed other participants from among their colleagues (at Maastricht University), family members of colleagues, inhabitants of homes for the elderly and participants of exercise and cycle teams for people aged 50+, who had characteristics relevant to the research.(1) Subjects who were free from injury and who had no history of hospitalization or chronic disease, influencing their exercise capacity during the 6MWT, were asked to participate.

Both sedentary as well as (highly) active subjects, smokers, non-smokers and ex-smokers were asked to participate. All subjects performed the 6MWT for the first time in their lives. The number of subjects, included after screening, needed to achieve reliable prediction in this study is at least 170 (in this study the rule of thumb for regression models is considered to give the minimum number of subjects needed: *N = 10* number of independent factors = 10*17 = 170*) (2, 3). All subjects were required to give written informed consent prior to the screening.

Any necessary ethics committee approval was secured for the study reported, checked with the institutional ethics committee (METC Atrium-Orbis-Zuyd, 13-N-91) and all healthy volunteers received written and verbal information about the aim of the project and were required to give written informed consent prior to the screening.

Screening

Prior to the 6MWT all participants were screened by one researcher (EB) during intake. Participants completed a health status questionnaire to ensure good health, defined as: having no walking problems and no history of lung cancer, any respiratory disease (apart from seasonal allergic rhinitis at other moments than the test moment), lung surgery, stroke, angina pectoris, myocardial infarction, any heart disease, heart surgery and not using the following medication: anti-arrhythmic, any long-acting or short-acting bronchodilator, inhaled corticosteroids, mucolytica or antibiotics. Heart rate, resting diastolic and systolic blood pressure were measured twice on both arms with a digital blood pressure monitor (A&D Medical, UA-767 Plus30). Subjects with hypertension were allowed to participate in the case of a stable and medically controlled condition and no blood pressure over 180/100 mmHg or resting heart rate over 120. All subjects who did not meet former criteria were excluded. Spirometry was performed by one researcher (EB) using a Spirobank and WinspiroPRO software to measure forced vital capacity (FVC), expiratory volume in one second (FEV_1) and Tiffeneau index (FEV_1/FVC) according to the GOLD and ATS/ERS guidelines for spirometry (4). The results in litres were referred to the predicted litres as reported by Quanjer and colleagues (5). If FVC or FEV_1 was <80% of the predicted value, subjects were excluded from further testing and referred to a pulmonologist (4).

Sex, age, height and body weight were measured. Variables that were noted to record smoking history were number of cigarettes, years of smoking and current smoking. To score intensity and frequency of physical activity in daily life the Physical Activity Questionnaire was used, scoring 0-3 = insufficiently active, 4 ≥ = sufficiently active (6, 7).

Six-minute walk test

Participants were asked to wear comfortable clothes and shoes. All tests were performed between 08:00 and 20:00 hours in a quiet indoor hallway with a flat and straight floor with marks at one metre intervals. Subjects were instructed to walk up and down over a straight 10-metre course. Two traffic cones marked the turning points at nine metre, allowing for a circular turn of one metre. To achieve familiarisation and to allow for the learning effect, the test was repeated after a rest period of at least 15 minutes.(8, 9) Participants were asked to walk at their own pace, while attempting to cover as much ground as possible within the allotted six minutes (10). Participants were allowed to turn in either direction, whatever they preferred, because research shows that turning direction seems to have no significant influence on the distance coverd (11, 12). Researchers encouraged subjects every minute to continue walking and informed them of the time elapsed, using standardised phrases (10). Participants were allowed to stop and rest during the test, but were instructed to continue the test as soon as possible. Transcutaneous oxygen saturation (SpO_2), heart rate, dyspnea and fatigue were assessed at rest (after sitting for at least 15 minutes, preceding the 6MWT) and directly after testing, with a finger pulse oximeter (Onyx 9500[1]) and the modified Borg scale ranging from zero (nothing at all) to ten (very, very severe) (13). All tests were supervised by the same researcher (EB). 6MWD was defined as the greatest distance achieved from the two tests, i.e. the better test .(10)

[1] The Nonin Medical's Onyx Model 9500 Finger Pulse Oximeter displays an average heart rate after two pulses.

Statistical analysis

Data were presented as means±SDs and medians (5^{th}-95^{th} percentiles). At a minimal statistical power of 80%, p-values below 0.05 were considered to be significant. Univariate correlation coefficients between 6MWD and continuous subject characteristics and between subject characteristics were calculated by Pearson single correlation coefficients. Variables that were significantly independently associated with the 6MWD (two-tailed, $\alpha=0.05$) were entered into a hierarchical and stepwise (backward) multiple regression analysis to evaluate independent variables explaining the variance in the 6MWD and to create a model predicting 6MWD.(14)

Change scores (change HR, change SpO_2, change Borg dyspnea, change Borg fatigue) were determined as the score directly after the test minus the score at rest before the test (preceded by a resting period of minimal 15 minutes). Pack years, to equally determine lifetime tobacco exposure with one value, were calculated as: number of cigarettes per day / 20 cigarettes (one pack) * number of years smoking. One cigarette contains one gram tobacco, one pack pipe tobacco (of 50 grams) will therefore be substituted by 50 cigarettes and one cigar (of approximately 4 grams) by 4 cigarettes (15). The habit that cigars and pipe tobacco are sometimes not inhaled is left out of consideration in these calculations. When a subject gave an estimate of the amount of cigarettes smoked, the highest value mentioned by the person was noted.

A sex-specific lower limit of normal (LLN) was calculated as the 5^{th} percentile of the data. In the absence of predefined cut-offs for 6MWD on clinical grounds and the utilization of the 5^{th} percentile in previous studies on 6MWD reference equations, the statistical delineation of normal is assumed to fall within 1.64 standard errors of the estimate (16, 17).

RESULTS

Additional statistical comments

Subjects' characteristics, summarised in Table 2, were comparable to healthy people (the majority was sufficiently physical active, had normal blood pressure and showed no substantial increase in dyspnoea and fatigue). Age was distributed normally, as well for the 181 participants as for male and female separately. The FVC and the 6MWD were distributed normally. All other variables were slightly skewed to the left. On average, subjects walked 578±108m on the better 6MWT. Walk distance varied 287 to 852m. Most subjects (86%) performed better on the second test, which was on average 30±33m or 6±6% better than the first test (p < 00.1). The 6MWD in male was 625±120m in contrast to 554±94m in female, with a statistically significant difference of 70±16m (t = 4.34, p < 0.001).

In multiple regression analysis all significantly independently correlating variables were entered. Variables were added by hierarchical method and stepwise backward method combined, based on the substantive theoretical importance of these variables. The variables age, gender and either BMI or "weight and height" were added in their order of importance by means of blockwise entry, based on previous studies.(17) The remaining variables lung functions, smoking, physical activity, and changes in HR, experienced dyspnoea and fatigue were added stepwise backward to check their influence on 6MWD prediction in an explorative way. In the overall regression model (N = 181) age alone explained 50% of the variance in 6MWD. Sex and BMI explained an additional 6.1% and 3.2%, respectively. Apart from these demographic and anthropometric factors that were retained in the model on a theoretical and statistical basis, three additional variables contributed significantly to the variance in 6MWD: change in heart rate (10.2%), physical activity (2.7%) and FEV_1 (2.3%). Apart from change in heart rate, the additional variables were considered but not retained in the model due to lack of theoretical basis in combination with the small contribution to explained variance. Figure 1 shows a comparison of measured and predicted 6MWD determined by the following overall model (N = 181): 6MWD (m) = 1,158.68 – (6.10*age) – (5.86*BMI) – (59.61*sex), where males = 0 and females = 1. A clear difference exists between the directions of the slopes for male versus female. Since the number of participants per sex-group is still sufficient (male: N = 62, female: N = 119), based on the variables that were retained in the model, sex-specific reference equations were calculated.

Residual statistics showed no cause for concern; no significant outliers and the sample appeared to conform to what was expected for a fairly accurate model (*highest standardised residual of 2.818 < 3, only 1% of the sample had a value greater than 2.5 and only 3% had a value greater than 2*) (14). No influential cases were identified according to Cook's distance (*highest value of Cook's distance of 0.271 < 1*). Although, with respect to the cut-off for the Mahalanobis distances (18) and the average leverage values (2* 0.022), one influential case seemed problematic. However, when running the regression analysis without the potential influential cases the differences between the *b*-coefficients in the regression equations were small enough not to exclude one of the cases from the final analysis (*all standardised DFBeta values < 1*). Overall, the models appear to be fairly reliable without undue influence of any subset of cases (14, 18).

None of the assumptions of multiple regression analysis was violated. Based on a correlation matrix, there was little chance for multicollinearity (*all* $r < 0.69$), except for the correlation between FVC and FEV_1 ($r = 0.933$). Therefore only one of the two variables was entered in the model based on a theoretical basis, yet was not retained in the final model. Furthermore, lung function variables were expressed in absolute numbers (litres) and not in percentages of predicted, because the calculation of predicted lung functions already incorporates sex, age and height. In accordance with the correlation matrix, the eigenvalues or the variance inflation factor showed no concern for biased regression (*largest VIF of 1.430* < 10 *and smallest value of tolerance of 0.699* > 0.2). The standardised residuals in the model were independent (*Durbin-Watson* $2.5 > 1.602 > 1.5$) and random, normally distributed with a mean of zero ($D(181) = 0.05$, $p > 0.2$). Finally plots of standardised residuals against standardised predictive values seemed to justify the assumptions of linearity and homoscedasticity. Consequently, the models generalise very well, because the cross-validity of these models is very good, both in male (*adjusted* $r^2 = 0.521$ *versus observed* $r^2 = 0.537$ for the basic model and *adjusted* $r^2 = 0.616$ *versus observed* $r^2 = 0.635$ for the extended model) and in female (*adjusted* $r^2 = 0.579$ *versus observed* $r^2 = 0.586$ for the basic model and *adjusted* $r^2 = 0.699$ *versus observed* $r^2 = 0.707$ for the extended model) (14). For generalisability, the range of each factor in the study population should be taken into account (Table S2). For people with an extreme low or high BMI (5^{th} and 95^{th} percentiles: 21.6-32.7) or high age (>90 years), the outcome of the reference equation should be interpreted with caution.

In the multiple regression analysis, the variables age, gender and either BMI or “weight and height” were added by means of a hierarchical method, based on the substantive theoretical importance of these variables (17, 19), whereas the other variables were added exploratively by means of a stepwise backward method. When, in an additional analysis, all variables were added stepwise to create a complete explorative model, age, gender and BMI were still retained as most prominent variables. This indicates that the theoretical assumptions that were made in this study, regarding the importance of predictors, were in agreement with our dataset.

When adding “weight and height” to the basic model instead of BMI, only slight, but no statistically significant changes were noted ($r^2 = 0.540, F = 22.70, p < 0.001$ versus $r^2 = 0.537, F = 34.17, p < 0.001$ for male and $r^2 = 0.585, F = 53.93, p < 0.001$ versus $r^2 = 0.586, F = 81.99, p < 0.001$ for female), meaning either can be used. Here the single variable BMI was chosen.

ELABORATION ON DISCUSSION ITEMS

The significant contribution of HR was in line with three previous studies.(20-22) However, because these studies used a percentage of age-predicted maximal heart rate (HRmax%predicted), there may be double correction for the variable age. Therefore, our study included only absolute values.

Some considerations need to be made regarding the use of HRchange as a predictor in the reference equation. Firstly, change in heart rate does not only depend on age ($r = -0.503, p < 0.001$) but also on the participant’s motivation to perform well on the test. However, all participants confirmed that they had given everything they could during the tests and all participants were equally motivated by the researcher according to the ATS-standard.(10) In addition, the maximum heart rate achieved in the healthy subjects in this study was on average 77%±14% of predicted HRmax (220-age) during the better test of two. This confirms that the 6MWT was actually received as a submaximal test. These results show similarity to the percentage of age-predicted HRmax reported by Troosters and colleagues (77% during the better test of two).(23) They are somewhat lower than the percentages by Camarri and colleagues (87% during the better test of three).(24) and by Kervio and colleagues (86% during the better test of two),(25) but higher than the percentage by Enright and colleague (<65% during the first and only test).(17)

Secondly, the explained variance of 6MWD in the extended equations (including HRchange) should be interpreted with some caution when symptoms, such as dyspnoea in patients with COPD, fatigue in peripheral muscles or musculoskeletal pain, limit test performance.

Thirdly, because a change score of heart rate (the difference between HR directly after the test minus the score at rest before the test) was used in the equations, standardisation of the measurement should be maintained. Here, baseline HR measuement was preceded by a resting period of minimal 15 minutes (sitting) and subjects drank water only, no coffee or thea, within two hours before the test.

Fourthly, the extended equations should be used with some caution in patients with chronic illness using medication that affects the relation between external physical load and HR, like beta-adrenergic blocking agents. In such cases, the equation including HRchange will be unreliable. Medication for anxiety disorders or beta-adrenergic bronchodilators are more likely to influence resting HR than HRchange, but in the case of chronic use of beta-adrenergic bronchodilators that can cause ventricular tachycardia one should better avoid the extended equation.

All subjects using beta-adrenergic blocking agents or bronchodilators were excluded from this study. Those subjects who had stable hypertension, used diuretic, anticoagulant or antihypertensive medication and had no blood pressure over 180/100 mmHg. Consequently, these participants showed a decreased baseline HR and end HR. However, HRchange corrected for the absolute increased values and was not significantly different from HRchange in the subset of subjects without hypertension and/or related medication ($t = 1.484$, $p = 0.139$). These findings correspond with a study by Kervio and colleagues where HR at the start and at the end of the 6MWT also was decreased in patients with chronic heart failure under optimal drug treatment compared to healthy subjects, whereas HRchange showed no difference between the groups.(26)

The small significant association of 6MWD with absolute resting pulmonary functions was in agreement with a recent study in patients with COPD.(27) FEV_1 was not retained in the final model because it's predictive value for 6MWD (2.3% explained variance) lacks evidence in the literature. Other studies suggested that part of the unexplained variance in 6MWD could be contributed to patient characteristics like physical activity in daily life or the effects of smoking.(20, 24) The present study added these variables in an explorative way in regression analysis. Although a negative association between pack years and 6MWD was hypothesised, no statistically significant association was supported by the data. This finding is consistent with other studies that failed to show an association between carboxyhemoglobin (COHb) levels or pack years and 6MWD,(23, 24) probably because the participants had lung functions within the normal range (FVC $\geq$ 80% and $FEV_1 \geq$ 80% of predicted). Physical activity was a significant predictor of 6MWD, but was not retained in the final model because it explained only 2.7% of the variance in 6MWD. Other studies support the lack of influence of self-reported daily physical activity.(8, 20, 23, 24)

Not all predictors in the equation were normally distributed (BMI and HRchange). The most important assumption of multiple regression analysis is that the residuals in the model are random, normally distributed variables with a mean of zero. This assumption was met in the analysis. (14)

The expectation that the predicted 6MWD in this study is lower than the predicted 6MWD from reference equations in other studies, using longer walking courses, was confirmed. For example a woman 70 years of age, 65kg, 168cm, HRchange of 30 bmp, a HRmax of 116 bpm and a HRmax%predicted of 77%, has a predicted 6MWD of 544m (according to the basic model in Table 4). As expected, the predicted walk distances increased when calculated with the prediction models by Gibbons and colleagues (+41m), Hill and colleagues (+42m), Troosters and colleagues (+48m) and Jenkins and colleagues (+93m).(8, 22, 23, 28) But, there was a decrease when compared to the prediction models by Casanova and colleagues (-249 m) and Enright and colleague (-76m), which might be explained by race difference or a reduced maximum heart rate achieved in the study subjects.(17, 20) The decrease compared to the model by Chetta and colleagues (-51m) can probably be explained by the much younger subjects included in that study (20-50 yr) compared to this study (40-90yr).(29)

This study had some limitations. Firstly, participants were not a pure random sample from the population of adults. The non-probability sampling technique to recruit healthy study subjects was necessary to locate potential subjects, because especially older people without any heart or lung complaints and no walking disabilities are a relatively small subgroup of Western populations. However, the subjects represented all age groups with age as a normally distributed factor, balanced by sex. Geographic variations in normal 6MWD appear to exist. Although, the skewed distribution of sex (66% female) represents the current male-female ratio in elderly in western countries, gender-specific reference-equations were provided.(30, 31) Secondly, about 45% of the variance in 6MWD remained unexplained by the basic model and 34% remained unexplained by the extended model. Other potential variables not included in this study may improve the variance in 6MWD. For example mood, attitude, motivation and psychological characteristics, as these also seem to affect 6MWD in older people.(32, 33) This study aimed for a practical solution to provide health care providers with a reference equation for the 6MWT over a 10m-course that is simple, efficient and easy to implement in clinical practice. As it stands, both models in this study explain more variance than most previous studies with Caucasian subjects (ranging from r^2 *= 0.20 to 0.66* (8, 17, 20, 22, 23, 28, 29, 32)) and include all the factors that have shown a strong and independent association with the 6MWD.

Since the majority of patients with cardiopulmonary pathologies and other chronic diseases are over 40 years of age, the prediction models may be applicable to a wide range of patients with diseases like COPD, heart failure, rheumatoid arthritis and neuromuscular disease and is generalisable to different countries.

Finally, urgency of reference equations for the 6MWT over a 10m-course does not only represent the Dutch situation, as it also applies to other countries such as Germany, England, the United States of America, Australia and Scandinavian countries.(34, 35)

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Table S1 Reasons for exclusion from the healthy study population (n=194), resulting from the screening

Variable	**n excluded**
FVC and/or FEV_1 was <80% of predicted	4
A diagnosis of asthma and FVC and/or FEV_1 <80% of predicted	1
Non-controlled blood pressure (216/122 and 200/107 respectively)	2
Using anti-arrhythmic medication	2
Using long acting bronchodilator without a medical diagnosis	1
History of TIA with neurological impairment in one leg, influencing walking speed	1
History of myocardial infarction and heart surgery	1
Having a pacemaker	1

Definition of abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; TIA = transient ischemic attack.

Table S2 Demographic and functional characteristics of study subjects

Characteristics (n=181)	**n (%) or mean±SD and median (5^{th}-95^{th} percentile)**	
Sex (M)	62 (34)	
Age (years)	63.5±11.6	
40-49, sex (M)	25 (14), 6 (24)	
50-59, sex (M)	42 (23), 23 (55)	
60-69, sex (M)	60 (33), 17 (28)	
70-79, sex (M)	39 (22), 11 (28)	
80-90, sex (M)	15 (8), 5 (33)	
Height (cm)	168.2±98.5	167.4 (153.4-185.9)
Weight (kg)	74.4±12.7	72.5 (57.0-99.0)
BMI (kg/m^2)	26.2±3.4	25.7 (21.6-32.7)
FVC (L)	3.9±1.2	
FEV_1 (L)	2.9±0.9	
Smoking (pack years)	7.4±12.6	0.6 (0.0-33.0)
Physical activity		
level (0-8)	4.1±2.0	4.0 (1.0-8.0)
sufficient	123 (68)	
Systolic blood pressure (mmHg)	140.2±20.5	137.0 (113.1-176.0)
Diastolic blood pressure (mmHg)	79.8±10.4	79.0 (66.0-99.8)
Baseline heart rate (bpm)	80.8±12.0	80.0 (60.0-102.0)
Change* heart rate (bpm)	39.9±20.8	35.0 (13.1-78.9)
Baseline SpO_2 (%)	97.4±1.3	98.0 (95.0-99.0)
Change* SpO_2 (%)	-1.0±2.6	-1.0 (-4.0-1.0)
Baseline Borg dyspnoea (0-10)	0.3±0.6	0.0 (0.0-2.0)
Change* Borg dyspnoea (0-10)	1.3±1.3	1.0 (0.0-3.5)
Baseline Borg fatigue (0-10)	0.5±0.9	0.0 (0.0-3.0)
Change* Borg fatigue (0-10)	1.0±1.2	1.0 (0.0-3.0)

Definition of abbreviations: M = male; BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; SpO_2 = transcutaneous oxygen saturation. Physical activity was measured by two questions assessing the frequency of 20 minutes vigorous and 30 minutes moderate intensity physical activity in a "usual" week resulting in a total score (0-8). A score of ≥4 is considered to represent sufficient physical activity.(6) *Change scores are based on the better walk test over a 10m-course.

Table S3 Univariate correlation coefficients (Pearson's *r*) between 6MWD and continuous subject variables.

Variable	**6MWD (m)**	**p-value**
Age (years)	-0.704	0.001
Height (cm)	0.378	0.001
Weight (kg)	0.074	0.320
BMI (kg/m^2)	-0.265	0.001
FVC (L)	0.614	0.001
FEV_1 (L)	0.641	0.001
Smoking (pack years)	-0.169	0.023
PA (level)	0.333	0.001
Baseline HR (bpm)	0.002	0.980
Change HR (bpm)	0.645	0.001
Baseline SpO_2 (%)	0.083	0.268
Change SpO_2 (%)	-0.007	0.924
Baseline Borg dyspnoea	-0.099	0.186
Change Borg dyspnoea	0.164	0.027
Baseline Borg fatigue	-0.333	0.655
Change Borg fatigue	0.152	0.041

Definition of abbreviations: 6MWD = six-minute walk distance; BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; PA = Physical Activity; HR = heart rate; SpO_2= transcutaneous oxygen saturation.

Figure legends:

Figure S1 Comparison of measured and predicted 6MWD by the overall regression model (N = 181), differentiated by sex. The difference between the directions of the slopes for male versus female was statistically significant ($p < 0.001$).