



ORIGINAL ARTICLE

Reference equations for the 6-minute walk distance in healthy Portuguese subjects 18–70 years old



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Abstract

Introduction: Six-minute walk test (6MWT) is used for evaluating functional exercise capacity. To the best of our knowledge, there are no reference equations to predict six-minute walk distance (6MWD) for the Portuguese population. The aims of the present study were to measure anthropometric data and 6MWD in a sample of healthy Portuguese population, to establish reference equations to predict 6MWD and to compare our equations with those obtained by previously published studies.

Methods: We conducted an observational prospective study. We consecutively recruited 158 healthy 18–70 years old subjects from Porto district, who performed two 6MWTs using a standardized protocol. The best 6MWD was used for further analysis.

Results: The mean 6MWD was 627.8 m (SD = 73.3 m). The variables that were significantly associated with the 6MWD were age, sex, BMI and Δ HR (Heart Rate_{at the end of the test} – HR_{at rest}). We found three explanatory models for 6MWD, the best with an explanatory power of 38%: $6MWD = 721.7 - 1.6 \times \text{Age} - 4.0 \times \text{BMI} + 0.9 \times \Delta\text{HR} + 58.4 \times \text{Sex}$. We verified that 6MWD decreased 1.6 m per year of age, and 4.0 m per unit of BMI and increased 0.892 m per beat per minute. Moreover, on average, males walk 58.4 m more than females ($p < 0.001$). Applying equations from other studies to our population resulted in an overestimation or underestimation of the 6MWD.

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Conclusion: The present study was the first to describe the 6MWD in healthy Portuguese people aged 18–70 years old and to propose predictive equations. These can contribute to improving the evaluation of Caucasian Mediterranean patients with diseases that affect their functional capacity.

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Introduction

Timed walking tests have been used for a long time to evaluate functional exercise performance.^{1–4} The six-minute walk test (6MWT) is a safe, simple, submaximal test, for evaluating functional exercise capacity, assessing prognosis and evaluating response to treatment across a wide range of respiratory diseases^{4–15}; it reflects the capacity of the individual to perform activities of daily living.^{3,8–10} The six-minute walk distance (6MWD) is the primary outcome of the 6MWT, which is a reliable measure associated with death in some diseases.^{5–7,16–19} There is strong evidence of learning effect for the 6MWD when two or more 6MWT are conducted.^{1,6,7}

Demographic, anthropometric, clinical, psychological and physiological characteristics can affect the test performance.^{5,16} Since 6MWT is a self-paced test, the results are influenced by external factors such as energy expenditure, clinician's/investigator's encouragement and subject's motivation.^{4,9,10,15,16,20}

The American Thoracic Society (ATS) published the 6MWT guidelines, which aimed to standardize this procedure and encourage researchers to establish reference values for each population.^{5,11} During the last decade, several studies have elaborated 6MWT reference values,^{1,4,8–11,13–17,21–29} using different populations and 6MWT protocols.^{1,10,13,20} To the best of our knowledge, there are no reference equations for predicting 6MWD for the Portuguese population.

The aims of the present study were: to measure anthropometric data and 6MWD in a sample of healthy Portuguese population aged 18–70 years, according to the standardized approach provided by the ERS/ATS guidelines^{5,6}; to establish reference equations to predict 6MWD; and to compare the 6MWD obtained with our reference equations to those obtained using previously published equations.^{27,28}

Methodology

Study design and subjects

This was an observational, descriptive, prospective study, conducted in a Pulmonary Function Testing Laboratory, between January 2016 and December 2017.

We consecutively recruited 158 healthy subjects from 18 to 70 years old. All the subjects worked in the district of Porto. The birth place of the subjects was: Aveiro (10%), Braga (9%), Bragança (1%), Lisbon (7%), Portalegre (1%), Oporto (64%), Viana do Castelo (2%), Vila Real (3%) and unknown (3%). Most of the subjects were workers from a public hospital, students and workers at a local

medical school. An informative letter was prepared clarifying the objectives of the study and the conditions for participation. This letter was sent by email to the employees of the hospital and the medical school. Accompanying people and patients, who were in consultations or undergoing outpatient examinations at the hospital for reasons other than those determined in the exclusion criteria, were also invited to participate in the study. Approval of the study was obtained from the hospital ethics committee, and written informed consent was given from each healthy subject before participation in the study.

The data obtained from each participant before undergoing 6MWT were: gender, age, height, weight, smoking history, medication use, medical history, physical examination, chronic obstructive pulmonary disease (COPD) Diagnostic Questionnaire (CDQ).³⁰ The body mass index (BMI) was calculated by the standard formula.³¹

The exclusion criteria were: history of chronic disease that could influence the ability to perform physical exercises (e.g., impaired cognition, metabolic, cardiovascular, respiratory, neuromuscular or musculoskeletal diseases or use of walking aids); current or former-smokers; presence of respiratory symptoms, flu, or any other lung disease in the past 4 weeks; CDQ greater than 15,³⁰ resting blood pressures higher than 150/100 mmHg; resting heart rate (HR) higher than 100 beats per minute, BMI less than 18 kg/m² or greater than 30 kg/m², conditions that could affect walking, involvement in high competition sport; use of drugs that could affect muscle function and/or HR; ethnicity other than Caucasian.

Data collection

The data were collected by two respiratory registrars and all 6MWT were performed by the same cardiopulmonary technician.

Prior to the 6MWT, age was confirmed, medical history and physical examination were completed, height, weight and blood pressure were evaluated and the CDQ was filled-in.

6MWT

Each subject did two 6MWTs (6MWT1 and 6MWT2), with at least a 20-min rest between walks, according to the ERS/ATS guidelines.^{5,6} The 6MWTs were performed along a straight, flat, 30-m long corridor, with marks at 3 m intervals. The 6MWTs were monitored by a single operator who recorded the 6MWD at the same time. A standard explanation was provided just before the first 6MWT. During the test, oxygen

Table 1 Characteristics of the study subjects and 6MWT measures.

Characteristics	Total	Male	Female	<i>p</i> -Value*
Subjects				
Sex <i>n</i> (%)	158 (100.0)	69 (43.7)	89 (56.3)	–
Age (years-old) mean (SD)	39.0 (13.1)	37.9 (13.1)	39.8 (13.1)	0.357
Height (cm) mean (SD)	168.0 (9.6)	175.6 (7.1)	162.0 (6.5)	<0.001
Weight (kg) mean (SD)	67.5 (12.6)	75.8 (12.2)	61.1 (8.5)	<0.001
BMI (Kg/m ²) mean (SD)	23.8 (3.1)	24.5 (3.0)	23.3 (3.0)	0.011
6MWT				
6MWD1 (meters) mean (SD)	604.8 (68.6)	632.3 (67.3)	583.4 (62.0)	<0.001
6MWD2 (meters) mean (SD)	627.8 (73.6)	661.5 (66.1)	602.4 (69.0)	<0.001
Borg (dyspnea) before best 6MWT mean (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.2)	0.623
Borg (fatigue) before best 6MWT mean (SD)	0.2 (0.6)	0.2 (0.6)	0.2 (0.5)	0.860
Diastolic BP before best 6MWT (mmHg) mean (SD)	69.6 (10.7)	74.0 (9.1)	66.2 (10.6)	<0.001
Systolic BP before best 6MWT (mmHg) mean (SD)	118.6 (12.3)	123.1 (11.2)	115.3 (12.1)	<0.001
Best 6MWD (meters) mean (SD)	627.8 (73.3)	657.8 (70.7)	604.6 (66.8)	<0.001
ΔHR of best 6MWT (bpm) mean (SD)	45.2 (17.0)	45.3 (17.1)	45.1 (16.9)	0.996
% mHR after best 6MWT (%) mean (SD)	67.6 (10.0)	65.8 (10.4)	69.0 (9.5)	0.052
Borg (dyspnea) after best 6MWT mean (SD)	0.9 (1.2)	1.0 (1.2)	0.8 (1.2)	0.253
Borg (fatigue) after best 6MWT mean (SD)	1.1 (1.4)	1.3 (1.5)	0.9 (1.3)	0.106
Diastolic BP after best 6MWT (mmHg) mean (SD)	73.7 (10.8)	77.8 (9.6)	70.6 (10.7)	<0.001
Systolic BP after best 6MWT (mmHg) mean (SD)	131.7 (15.7)	134.7 (14.7)	129.4 (16.1)	0.036

The values in bold show significance of $p < 0.005$.

* *p*-Value between male and female subjects.

6MWT: six-minute walk test; 6MWD: six-minute walk distance; % mHR: percentage of the predicted maximum heart rate; BMI: body mass index; BP: blood pressure; BPM: beats per minute; cm: centimeters; HR: heart rate; ΔHR: difference between heart rate at the end and at the beginning of 6MWT; kg: kilograms; m: meters; SD: standard deviation.

saturation and HR were measured by wearable transcutaneous pulse oximetry (Oximeter Nonin WristOx 2™, model 3150, Nonin, Plymouth, MN, USA), already validated.³² If subjects experienced dizziness, leg cramps, chest pain or dyspnea, they were permitted to stop and rest. At the end of each minute, subjects were given feedback on the elapsed time and standardized encouragement in the form of statements. Before and after each 6MWT, pulse rate, blood pressure, oxygen saturation, and Borg value were recorded. Subjects were asked to indicate their level of dyspnea perception using a modified Borg scale.³³ The maximum predicted HR (mHR) was calculated as 220 minus age. The two distances walked by each subject were used for the learning effect analysis. The best 6MWD was used for the calculation of the reference equations. Measured 6MWD values were compared with predicted values using three reference equations devised for use in other populations.^{27,28}

Statistical analysis

Quantitative variables were reported as mean ± standard deviation (SD). Sexes were compared using paired samples Student's *t*-tests. Correlation between variables was assessed using Pearson's or Spearman's correlation coefficients. Several multiple regression models were studied; gender was included as a binary variable (female=0, male=1) and all remaining variables as continuous; age in classes was categorized through dummy variables, taking as reference class the youngest age ≤ 30. Collinearity was investigated based on the variable inflation factors.

Normality of the residuals was evaluated through the Kolmogorov–Smirnov test. Sample size was determined based on G*Power (version 3.1.9.3), for a power of 80% and taking into consideration the number of predictors. All statistics were calculated using the IBM SPSS Statistics (version 24.0) software. A *p*-value was declared as significant for $p < 0.05$.

Results

Demographic, anthropometric and 6MWT results

Of the 178 subjects recruited, 20 were excluded because of: smoking history ($n = 6$), CDQ greater than 15 ($n = 4$), involvement in high competition sport ($n = 4$), ethnicity other than Caucasian ($n = 3$), high blood pressure ($n = 2$) and personal history of respiratory disease ($n = 1$).

The characteristics of the healthy subjects and of the 6MWT measures are summarized in Table 1. There were significant differences between male and female subjects, with respect to anthropometric characteristics, since men were significantly taller, heavier and had higher BMI.

No subject prematurely finished or interrupted the test. The difference of the distance covered between 6MWT1 and 6MWT2 was 21.6 (SD=26.2) m (95% confidence interval [CI]: 17.4–25.7), suggesting a learning effect; for males 24.9 (SD=25.6) m (95% CI: 18.7–31.2), for females 19.0 (SD=26.6) m (95% CI: 13.4–24.6). The mean 6MWD was 627.8 (SD=73.3) m (range, 453–831 m), with significantly longer distances walked by males than females ($p < 0.001$).

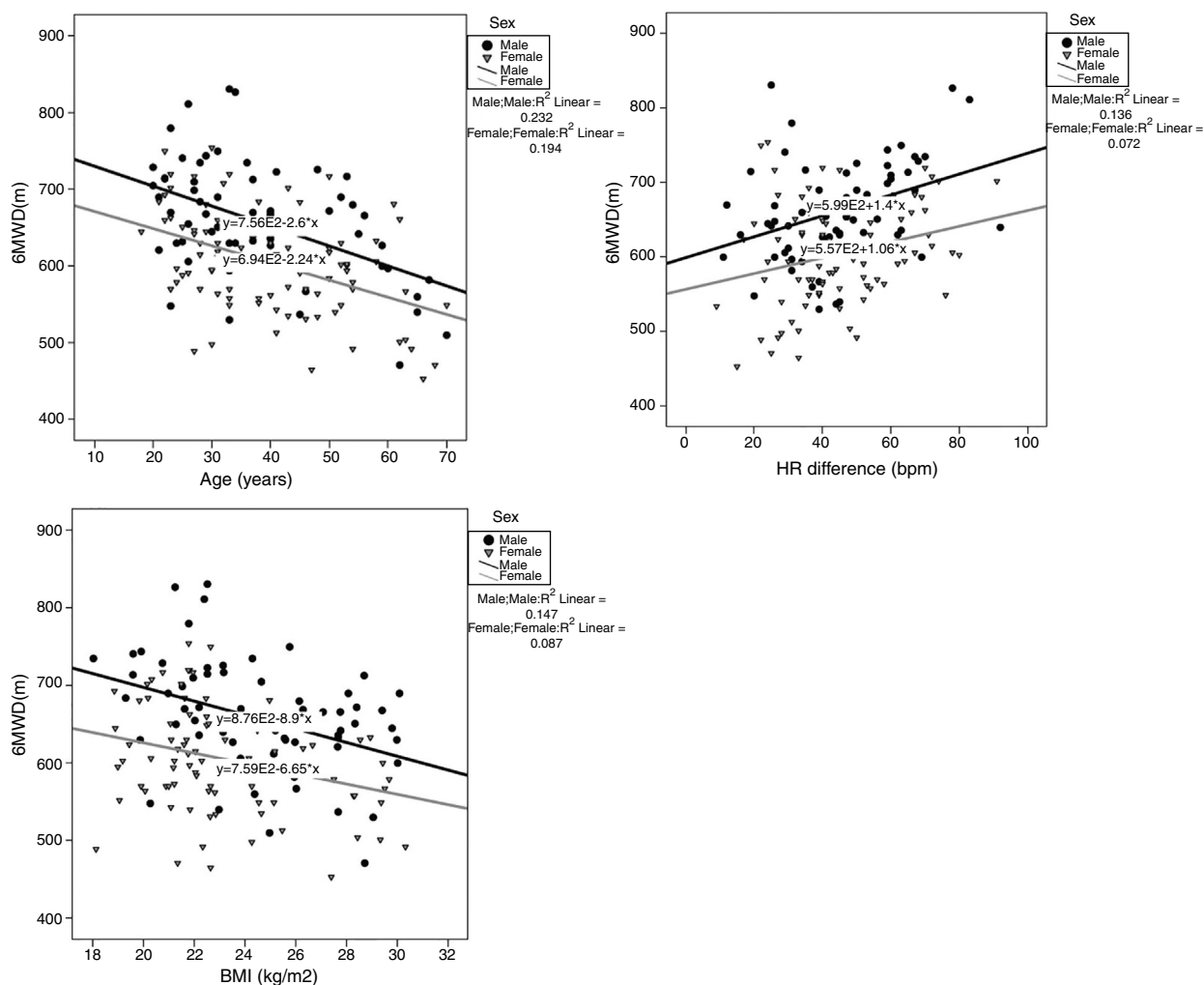


Figure 1 Correlation between age, BMI, Δ HR and 6MWD, per sex. 6MWD: six-minute walk distance; BMI: body mass index; Δ HR: difference between heart rate at the end and at the beginning of 6MWT.

Clinically significant oxygen desaturation was not observed during 6MWT.

Univariate and multiple regression analysis

Univariate regression models were developed to evaluate the most important relations between 6MWD and the explanatory variables recorded. The variables that were significantly associated with the 6MWD were: age, sex, BMI and Δ HR (Heart Rate_{at the end of the test} – HR_{at rest}) (Fig. 1).

Several multiple regression models were tested, and three explanatory models were found for 6MWD. The first (Table 2) has an explanatory power of 34%, being simpler since it can be applied only with demographic and anthropometric variables (sex, age and BMI).

$$6MWD = 787.2 - 2.0 \times \text{Age} - 4.4 \times \text{BMI} + 54.76 \times \text{Sex} \quad (1)$$

All regression coefficients were significant, and it can be observed that the 6MWD decreases with age (approximately -2 m per year of age) and BMI (approximately -4 m per unit of BMI) and that there is a difference in the walked distance between males and females (approximately, 55 m plus for males).

Refining the model with the introduction of Δ HR, we were able to increase the explanatory power to 38% which resulted in the second model (Table 2). From the multiple regression model 2, it can be concluded that the 6MWD decreases 1.6 m per each year of age, and 4.0 m with each unit of BMI. On the other hand, the distance increases 0.892 m per each beat per minute. Moreover, it can be seen that, on average, males walk 58.4 m more than females ($p < 0.001$). These findings are in line with the ones of model 1, apart from small variations in the regression coefficients.

$$6MWD = 721.7 - 1.6 \times \text{Age} - 4.0 \times \text{BMI} + 0.9 \times \Delta \text{HR} + 58.4 \times \text{Sex} \quad (2)$$

Regarding age range, per decade, it can be observed that the decrease in distance progresses with age; there was a significant difference with respect to the younger decade (≤ 30) from the age range 41–50 and ≥ 61 , and close to significance in the age range 51–60 (Table 3). Taking into consideration that the maximal distance walked declines with age, a third multiple regression model was developed where age was categorized in decades (Table 2). In this

Table 2 Multiple regression models 1, 2 and 3.

Model	Unstandardized coefficients	Standard error	p-Value	VIF
<i>Model 1</i>				
Constant	787.187	37.787	<0.001	
Age (years-old)	-2.025	0.395	<0.001	1.166
Sex (0-F; 1-M)	54.736	9.954	<0.001	1.069
BMI (kg/m ²)	-4.381	1.723	0.012	1.209
<i>Model 2</i>				
Constant	721.753	40.284	<0.001	
Age (years-old)	-1.606	0.394	<0.001	1.197
Sex (0-F; 1-M)	58.360	9.633	<0.001	1.075
BMI (kg/m ²)	-4.016	1.659	0.017	1.201
ΔHR (bpm)	0.891	0.278	0.002	1.041
<i>Model 3</i>				
Constant	690.436	41.365	<0.001	
Age (31–40 years-old) ^a	-18.661	12.189	0.128	1.441
Age (41–50 years-old) ^a	-37.310	13.834	0.008	1.351
Age (51–60 years-old) ^a	-27.321	16.421	0.098	1.406
Age (≥60 years-old) ^a	-76.525	19.836	<0.001	1.303
Sex (0-F; 1-M)	57.217	9.870	<0.001	1.114
BMI (kg/m ²)	-4.377	1.699	0.011	1.244
ΔHR (bpm)	0.895	0.283	0.002	1.064

^a Reference class for age is ≤30 years-old.

ΔHR: difference between heart rate at the end and at the beginning of 6MWT; BMI: body mass index; F: female; M: male; VIF: variable inflation factor.

Table 3 6MWD per age range.

Age range	Subjects n (%)	6MWD (m) Mean (SD)	95% CI
≤30	49 (31.0)	659.2 (68.7)	639.5–678.9
31–40	46 (29.1)	643.0 (67.0)	624.0–662.1
41–50	29 (18.4)	605.4 (67.0)	580.0–630.8
51–60	20 (12.7)	610.9 (53.3)	586.0–635.8
≥61	14 (8.9)	538.7 (68.3)	499.3–578.0
Total	158 (100.0)	627.8 (73.3)	616.3–639.3

6MWD: six-minute walk distance; CI: confidence interval; SD: standard deviation.

model the coefficients associated with sex, BMI and ΔHR were very similar to the previous models. For this model, the residuals were also well behaved.

For all regression models, multicollinearity was assessed by the Variable Inflation Factor (VIF), which were all below 2, indicating that multicollinearity was not a problem. Likewise, for all models the residuals are also well behaved, uniformly distributed around zero and approximately normal (Kolmogorov–Smirnov test, $p > 0.2$).

$$\begin{aligned}
 6MWD = & 690.4 - (18.6 \times \text{Age}_{31-40} + 37.3 \times \text{Age}_{41-50} \\
 & + 27.3 \times \text{Age}_{51-60} + \\
 & 76.5 \times \text{Age}_{\geq 61} - 4.4 \times \text{BMI} + 0.9 \times \Delta\text{HR} \\
 & \times 57.2 \times \text{Sex}
 \end{aligned} \quad (3)$$

Comparison with published regression equations

The regression equations from the models of *Gibbons et al.*²⁷ and *Britto et al.*²⁸ were developed on the same age range as our multiple regression model. Applying these equations to our data, showed that there was an overestimation of 157 meters with the *Gibbons* equation (only considering age and sex as explanatory variables),²⁷ an underestimation of approximately 12 meters with *Britto* Eq. (1) (which considers age, age,² sex and BMI),²⁸ and an overestimation of 1 meter with *Britto* Eq. (2) (which considers age, sex, height and ΔHR).²⁸

Discussion

To the best of our knowledge, the present study was the first to describe the 6MWD in healthy Caucasian Mediterranean people aged 18–70 years-old and to present predictive equations.

The 6MWT is one of the several modalities available for the objective evaluation of functional exercise capacity.⁵ In our sample of healthy adults, no spirometry was performed because only subjects who never smoked and without respiratory diseases were included after applying a COPD Diagnostic Questionnaire.³⁰ The original papers on reference values for the 6MWT (published in English) included: unhealthy individuals,²³ six papers with age ranges greater than 4 decades^{4,10,17,20,26,29} and only eight had more than 150 individuals.^{1,11,14,17,21,25,28,29} In the present study, the 158 healthy subjects were balanced both by sex and decades of age.

The 6MWD is influenced by learning effect,^{1,5-7,11} being large enough to be clinically important.⁵ In order to avoid bias caused by the learning effect in our study, two standardized tests were performed, and the best of both was used in the analysis. Our results showed that 6MWT2 was, on average, 3% better than 6MWT1. 6MWT2 was higher than documented in the study of *Casanova et al.*,¹¹ which included a population analysis of seven countries, but very similar to the data from 13 studies of COPD patients.⁷

There was a significant difference in the 6MWD between male and female, with men walking a greater distance than women. This may be due to the fact that men were significantly taller – a higher height is associated with a longer stride, which generates a longer distance.^{1,4,26,29} In addition, men have a greater absolute muscle strength and muscle mass.^{9,11,16}

The average 6MWD measured in this study was relatively shorter than those of Caucasian studies^{20,22,24,27} and longer than those of North and South American^{1,9,13-15,28} and Asian studies.^{16,17,26,29} The explanation for these differences may lie not only in racial and demographic differences, but also in 6MWT methodology.

Age, sex, BMI and Δ HR were the most important factors that significantly influenced the 6MWD of our healthy subjects. Age is a variable that significantly influenced 6MWD in almost all²⁹ previous studies on 6MWD reference equations. We found that age and BMI were negatively associated with the 6MWD. The negative association with age could be explained by the fact that muscle mass, muscle strength and maximal oxygen uptake gradually decreases with age.^{9,13,16} The six-minute walk work (6MWW) is the product of 6MWD and body weight. 6MWW increases with obesity; as a result, the obese walk shorter distances since changes in weight can significantly affect the energy requirement and, therefore, the amount of work performed.³⁴ In our study, we found that the Δ HR was significantly positively associated with 6MWD, which may be because Δ HR represents the level of effort the subject expended while performing the test,¹⁷ the subjects who tried harder walking more. Another measure for level of effort may be the percentage of mHR, which in our study was 67.6%, a value lower than that described by *Camarrì et al.* in a Caucasians study, where 6MWD was greater,²⁰ reinforcing the idea that less effort may have influenced outcomes.

In the present study, three equations were derived for 6MWD in a sample of healthy Portuguese population aged 18–70 years old. The first proposed model seems advantageous given its simplicity. We considered the second model (with explanatory power of 38%), to be the reference equation for the Portuguese population aged 18–70 years old. In agreement with the literature,^{1,4,8-11,13-17,20-28} we verified that there was a decrease of 6MWD with increase in age. Consequently, it seemed pertinent to propose the third model in which the age range, by decade, was included.

The use of predictive equations for 6MWD created for populations other than the one studied, was associated with errors on the predicted distances. The difference between the measured and predicted 6MWD values might be caused by multiple factors. A systematic review identified many published studies from 1998 to 2017 that included 6MWD prediction equations from healthy adults.^{1,4,9-11,13-17,20-22,24-29} These studies were conducted using a wide variety of populations and methodologies. *Casanova et al.*¹¹ studied a

population of 7 countries, including Spain. In spite of having included a Mediterranean population, the conclusions reached by this group was that there were wide regional and geographic differences not explained by the variables used to obtain the reference equations. Thus, considering that a single reference equation was generated for a population of 6 American and one Mediterranean countries, we do not consider this equation to be representative of Mediterranean population. We selected the regression equations from the models of *Gibbons et al.*²⁷ and *Britto et al.*,²⁸ because these studies included populations with an age range similar to our study population. Applying the *Gibbons* and *Britto* equations, we found that there was an overestimation with the first and an underestimation with the equation 1 of the second one. Further, our study adds to the evidence that the predictive equations derived from other populations^{27,28} would not apply to Portuguese population.

Our research had some limitations: our sample may not be representative of the entire Portuguese population (although subjects were selected consecutively on the basis of inclusion criteria); the sample size was sufficient to elaborate a reference equation, but it was a relatively small sample, in particular the age group over 60 years old for which this test is widely used and has a particular interest (rehabilitation and exercise capacities in clinical groups); we did not recruit underweight and obese people, our reference equations are not applicable to the subjects with $18 < \text{BMI} < 30 \text{ kg/m}^2$ and although we have excluded high competition athletes we haven't objectively measured physical activity. Despite the limitations, we found, for the first time, reference values for the 6MWD for Caucasian Mediterranean healthy population aged 18–70 years old.

Conclusion

The present study was the first to describe the 6MWD in healthy Portuguese people aged 18–70 years old and to propose predictive equations. Age, sex, BMI and Δ HR were the most significant predictors of the 6MWD and the regression equations explained approximately 34–38% of the variance in the 6MWD. We conclude that our equations can improve the evaluation of Caucasian Mediterranean patients with diseases that affect their functional capacity.

Author contributions

Conceptualization: Miguel Guimarães, Maria João Oliveira.
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Formal analysis: Pedro Oliveira.

Writing: Maria João Oliveira, Raquel Marçôa, Pedro oliveira.

Writing ± review & editing: Maria João Oliveira, Raquel Marçôa, Pedro Oliveira, José Moutinho, Inês Ladeira, Ricardo Lima and Miguel Guimarães.

Ethics statement

The protocol was approved by our ethics committee, and written informed consent was obtained from each patient prior to the study.

Statement of interest

None declared.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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