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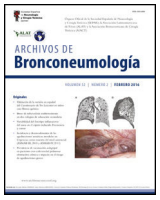

Original Article

Development and Comparison of Reference Equations for the Six-Minute Walk Test in Spanish Healthy Adults Aged 45–85 Years

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ABSTRACT

Objectives: (i) To develop sex-specific reference equations to predict distance walked (6MWD) in the 6-minute walk test (6MWT), in healthy subjects aged 45–85 years, from different geographic areas of Spain; and (ii) to compare developed equations with previously published in a large sample of COPD patients.

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Methods: First, a cross-sectional multicentre sample of randomly selected healthy subjects from 17 Spanish hospitals and universities performed two 6MWT. Linear regression and fractional polynomial modelling were used to develop the equations. Second, the developed equations were applied to 715 COPD patients from Spanish primary care centres and hospitals, and the % predicted 6MWD obtained was compared with previously published equations using Dunnett's multiple comparisons test.
Results: 568 healthy subjects were included (51% females, mean (SD) age 62 (11) years), walked a 6MWD of 615 (113) and 557 (93) m in males and females, respectively. The developed equations included age, weight and height, and explained 43% and 51% of the 6MWD variance for males and females, respectively. In the COPD sample (n = 715, 14% females, 68 (9) years, FEV_1 61 (18) % predicted, 6MWD 464 (97) m), only 1 out of 9 previously published equations for males, and 6 out of 9 for females predicted 6MWD values similar to those of the newly developed Spanish reference equations.
Conclusions: The newly developed reference equations provide a more valid prediction of 6MWD in Spanish adults with COPD compared to previously published equations. We suggest their use in future research and clinical practice for the Spanish adult population.

Introduction

The 6-minute walk test (6MWT) is a submaximal exercise test, commonly used and valid to assess functional exercise capacity in individuals with chronic respiratory diseases (CRD) in both clinical practice and research settings.[1–3] It is well standardised, cost-effective, reproducible, and reliable.[1,3,4] The test involves walking as far as possible for six minutes. The distance walked (6MWD) better reflects the activities of daily life than other exercise tests, because walking is more closely aligned with the physical demands of daily life activities.[2,5] Moreover, the 6MWD has been demonstrated to have prognostic value for mortality and disease progression in CRD[6–9] and to be responsive to several interventions, including exercise training,[10,11] lung surgery,[12,13] and pharmacological treatment.[14] Nevertheless, its interpretation remains inadequate in consideration of the global human diversity.[15]

The accurate interpretation of the 6MWT relies on expressing test results as a percentage of the expected value (%6MWD), employing reference equations.[1] This 'percent predicted' approach allows for a precise assessment of functional limitation in individual patients and facilitates meaningful comparisons among groups with varying characteristics. To date, based on a literature search in PubMed, more than thirty 6MWD reference equations have been published, but their use and applicability remain suboptimal due to the diverse quality of their development and the lack of representation of certain population groups. The main methodological flaws include the reliance on convenience[16,17] or small samples,[16–19] which can lead to inaccuracies in predicted values compared to those in the source population. Moreover, two reference equations were generated using data from a single test,[20,21] rather than considering results from two tests, as recommended by guidelines. This has resulted in an underestimation of predicted values, as the learning effect was not considered. Finally, most of the early-developed and commonly used equations have been derived from populations in Northern Europe,[16] North America,[20,21] Canada[17,18,22] or Australia.[23] These equations exhibit geographical, anthropometric and cultural characteristics unique to those regions, which limits their direct comparability with populations from Southern Europe, South America, or Asia. Indeed, the utilisation of equations developed for other populations may result in the misinterpretation of functional capacity levels.[1] For instance, Andrianopoulos et al. applied 22 distinct 6MWT reference equations to a data set of 2757 individuals with chronic obstructive pulmonary disease (COPD), and observed a considerably discrepancy in the estimated 6MWD (ranging from 60.8% to 94.5% of the predicted value), despite the inclusion of similar characteristics (age, sex, height, weight or BMI) in the equations.[24] As another example, a previous study on COPD patients from Spain found that more than 25% of patients with severe spirometric values presented 6MWD values exceeding 100% of the predicted value.[25] Consequently, the recommendations of the technical standard from the European Respiratory Society/American Thoracic Society (ERS/ATS) stipulate that the selection for the 6MWD equations should be specific to the region of the population that intends to assess.[1,24]

Therefore, the objective of this study was to develop sex-specific reference equations to predict the 6MWD for the Spanish population, using a large random sample of 45–85 years old healthy subjects from different geographic areas of Spain. In addition, the developed equations in this study were compared with the 6MWD equations previously published in a large sample of Spanish COPD patients.

Methods

For the development of Spanish reference equations, a cross-sectional multicentre study was conducted in 17 hospitals and universities across 9 autonomous communities in Spain. The study employed a stratified random sampling approach from an initial candidate pool identified through convenience sampling. Specifically, investigators implemented a broad outreach strategy within their networks—targeting employees of participating universities and hospitals, along with their families and friends, current and former students, and attendees of senior community centres—to compile a list of over 1000 potential candidates. This list was then stratified by sex (male and female), geographic region (Andalusia, Aragon, Asturias, Catalonia, Galicia, Balearic Islands, Canary Islands, Madrid, and Murcia), and age groups (45–55, 56–65, 66–75, 76–85 years). Candidates within each stratum were randomly ordered and contacted sequentially until the required minimum participant count per stratum was reached (see sample size estimation below). Inclusion criteria were as follows: males and females aged 45–85 years; and residents in the geographical areas of the participating centres for the majority of the last 12 months. The exclusion criteria considered individuals with musculoskeletal, neurological, cognitive, visual or hearing disorders that preclude the performance of the 6MWT; with CRD or heart failure who have been diagnosed or are undergoing specific treatment; with haemodynamic instability (indicated by a resting heart rate (HR) exceeding 120 beats per minute (bpm), or high resting blood pressure (systolic > 200 mmHg, diastolic > 120 mmHg)); who had smoked more than 10 pack-years; who were pregnant; who were morbid obese (body mass index (BMI) > 40 kg/m^2); athletes or individuals engaged in highly rig-

orous training; and those belonging to ethnic groups other than Caucasian.

The study was approved by the Human Research Ethics Committees at each participating centre. All subjects provided written informed consent.

The 6MWT was conducted in accordance with the ATS guidelines[4] at all participating centres. Each subject was required to complete two attempts on the same day, with a minimum of 30 min of rest in between. Participants were instructed to refrain from engaging in moderate-to-vigorous physical activity on the day of the 6MWT. The test was conducted in an enclosed corridor, a long and flat course delineated by signalling cones with a recommended length of 30 m. In the event that a 30-m corridor was not available, the minimum required distance was 20 m. Subjects were encouraged at regular intervals throughout the test using the standardised phrases. The following data were obtained: the longest 6MWD (the primary outcome of the study), and heart rate (HR), dyspnoea and leg fatigue (measured using the modified Borg scale) before and after the 6MWT. The percentage of the predicted maximal HR (HRmax) was calculated as follows: "(peak HR during the best 6MWT/HRmax) × 100", where HRmax was obtained using the formula proposed by Nes et al. "HRmax = 211 − (0.64 × age)".[26]

The data set comprised information on sociodemographic characteristics (sex, age, geographic origin, and marital and working status), smoking habits, self-reported chronic conditions, weight and height on a calibrated scale, resting blood pressure, and regular physical activity (assessed using the International Physical Activity Questionnaire (IPAQ), long version).[27] To minimise the inclusion of subjects with pre-clinical conditions, an exhaustive and standardised data collection of current medication was conducted by health professionals.

A quality control protocol was implemented to ensure the consistency and homogeneity between sites (including standardising the procedures for the 6MWT and data collection, training sessions, a pilot study with two to four subjects per site, and quality control visits by an external expert).

For the application of Spanish reference equations and comparison with previous 6MWD published equations, the baseline data from all participants in two previous COPD studies conducted in Spain were pooled: the primary care- and hospital-based Urban Training[30] and the hospital-based PAC-COPD studies.[31] Further details of these studies have been previously published.[30,31]

The sociodemographic characteristics (age, height, and weight) and clinical and functional parameters (forced spirometric values, modified Medical Research Council (mMRC) dyspnoea scale, and 6MWD), as previously published,[30,31] were obtained.

We identified all 6MWD reference equations published in PubMed up to 2023 and excluded those that: (i) included physical activity level as a predictor (because this is not standard information collected in clinical practice), (ii) included baseline or peak HR as predictors (because they have a direct relation with the functional capacity), (iii) were developed in children, adolescents or only in older adults; (iv) were developed in heterogeneous populations regarding ethnic group or cultural habits; (v) and those that had never been used in a published manuscript nor reported as being used by any of the study authors.

Statistical Analysis

The estimation of the sample size, using the methodology for developing multivariable prediction models presented by Riley et al.,[28] suggested that 237 subjects per group (i.e., sex) would be required, based on a R-squared value of 0.66[16] from a previous model, assuming a mean and standard deviation (SD) of 631 (93) m in the 6MWT,[16] and estimating the number of parameters included in the model to be three. Given the stratified sampling strategy by geographic area and age group (total strata = 9 areas × 4 age groups = 36 strata), each recruitment site had to recruit 6–7 subjects. To simplify recruitment and ensure a sufficiently large and diverse sample, sites were instructed to enrol between 5 and 10 participants per stratum.

The baseline characteristics of the sample are presented as mean and SD, median and 25th and 75th percentile (P_{25-75}), and number and percentage (%), according to the distribution of each variable. All analyses were conducted separately for males and females. To develop the reference equations, a multiple linear regression model was build using the best 6MWD as the outcome variable and considering age, height, weight, and BMI as predictors. Fractional polynomial (FP) modelling was employed to identify non-linear associations and to ascertain the optimal transformations (logarithmic, square, cubic, or reciprocal) for each predictor.[29] The fit of the models was evaluated by examining the predicted values plotted against the residuals and the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) as a criterion for model selection. A quantile regression model was estimated to establish the lower limit of normality (LLN). As a secondary analysis, the length of the corridor (in 3 categories: 30 (reference group), 25 and 20 m) was added as a predictor.

The %6MWD was calculated using the equations developed in our study (as a reference category), and it was compared with those obtained from previously published equations[16,20,21,23,32–34] by means of the Dunnett's multiple comparisons test.

All statistical analyses were conducted using Stata statistical software programme (version 14; Stata Corp LP; College Station, Texas, USA).

Results

From 577 adult participants that were screened, 9 were excluded due to the presence of chronic conditions that could impact the 6MWT performance (including diagnosis of asthma, use of bronchodilators, osteoarthritis in the feet, and the presence of morbid obesity). The 568 healthy adults included (Table 1) were 51% female, had mean (SD) age of 62 (11) years old, most were active workers and the prevalence of chronic disease was relatively low, except for systemic arterial hypertension and hypercholesterolemia (approximately 30% each). No differences were observed between males and females in terms of geographical distribution, sociodemographic characteristics or clinical variables.

A total of 418 (74%) participants walked a longer distance in the second 6MWT compared to in the first attempt, with a learning effect observed in both males and females (mean difference (95% CI) 15 (12–18) m and 13 (9–17) m, respectively). Table 2 presents the characteristics of the 6MWTs stratified by sex.

With regard to the length of the corridor, 61% of the sample completed the 6MWT in a 30-m walkway, 26% in a 25-m walkway and 13% in a 20-m walkaway. In the whole group, there were statistically significant differences in the 6MWD performed in a 30-m versus a less than 30-m walkway (596 (109) vs 568 (102) m, $p < 0.005$, respectively). This difference remains significant in males (634 (108) vs 587 (116) m, $p < 0.001$), but no significant differences were observed in females (562 (99) vs 549 (82) m, $p = 0.274$).

Table 3 shows the models that best explained the higher proportion of variance in 6MWD (R^2 43% in males and 51% in females). In males, 6MWD was found to be linearly related to age and weight, but not to height. In females, 6MWD was related linearly to weight and not linearly to age, but not to height. Table 4 presents the developed reference equations and the LLN for 6MWD predicted values, both for males and females.

In the secondary analysis, which included the length of the corridor as a predictor, we observed a significant effect of corridor

Table 1
Characteristics of the Sample Used for the Development of the 6-Min Walking Distance Reference Equations Stratified by Sex.

	Males (n = 277)	Females (n = 291)
Age, years	62 (11)	62 (11)
Categories of age		
45–55 years	97 [35]	98 [34]
56–65 years	67 [24]	74 [25]
66–75 years	66 [24]	75 [26]
76–85 years	47 [17]	44 [15]
Geographical distribution		
Andalusia	24 [8]	24 [8]
Aragon	13 [5]	17 [6]
Asturias	18 [7]	18 [6]
Catalonia	88 [32]	103 [36]
Galicia	25 [9]	21 [7]
Balearic Islands	24 [8]	32 [11]
Canary Islands	14 [5]	7 [2]
Madrid	53 [19]	49 [17]
Murcia	18 [7]	20 [7]
Marital status		
Single	18 [7]	27 [9]
Married or living together	229 [83]	182 [63]
Widower	13 [5]	56 [19]
Divorced	16 [6]	25 [9]
Working status		
Active	141 [51]	123 [42]
Inactive	6 [2]	48 [17]
Retired	129 [47]	119 [41]
Height, cm	171.2 (7.5)	158.0 (6.2)
Weight, kg	81.0 (11.7)	66.3 (10.1)
BMI, kg/m²	27.6 (3.3)	26.6 (4.2)
Systolic BP, mmHg	125 (14)	120 (16)
Diastolic BP, mmHg	76 (8)	73 (9)
Smoking habit		
Current	36 [13]	36 [12]
Occasional	8 [3]	11 [4]
Former	131 [47]	82 [28]
Non-smoker	101 [37]	161 [56]
Chronic conditions, yes		
Systemic hypertension	100 [36]	92 [32]
Myocardial infarction	3 [1]	1 [0.3]
Other cardiovascular event	17 [6]	12 [4]
Stroke	8 [3]	3 [1]
Diabetes	24 [9]	20 [7]
Cholesterol	82 [30]	88 [30]
Cataracts	40 [14]	43 [15]
Cancer	18 [7]	14 [5]
Anxiety/depression	18 [7]	51 [18]
Allergy	29 [11]	41 [14]
Asthma	4 [1]	4 [1]
Chronic bronchitis	3 [1]	3 [1]
Osteoporosis	6 [2]	54 [19]
Anaemia	5 [2]	16 [6]
Physical activity (IPAQ)		
Total time walking, min/day	90 (40–130)	90 (45–150)
Total time in moderate PA, min/day	90 (30–210)	120 (60–240)
Total time in vigorous PA, min/day	0 (0–60)	0 (0–30)
Total time sited, min/day	300 (214–429)	257 (180–377)

Data is presented as mean (SD), n [%] or median ($P25$–$P75$).
Abbreviations: BMI, body mass index; BP, blood pressure; IPAQ, international physical activity questionnaire; PA, physical activity.

length. We therefore constructed reference equations by sex for 25 and 20-m walkaways (Supplemental material, Table S1).

A total of 715 Spanish patients with COPD (633 males and 82 females) were included, with a mean age of 68 (9) years, FEV_1 of 61 (18) % predicted, and mean 6MWD of 464 (97) m (Table 5). Fig. 1 shows discrepancies in the application of the 6MWT equations, particularly for males, while discrepancies are less pronounced for

Table 2
Characteristics of the 6-Min Walk Tests Stratified by Sex.

	Males (n = 277)	Females (n = 291)
6MWD in first attempt, metres	597 (110)	540 (94)
6MWD in second attempt, metres	612 (112)*	553 (93)*
Characteristics of the best 6MWT (longer 6MWD)		
6MWD, metres	615 (113)	557 (93)
HR at rest, bpm	76 (11)	76 (12)
HR at end, bpm	124 (23)	124 (19)
HRmax, %predicted	72 (12)	72 (11)
Dyspnoea at rest, modified Borg scale	0 (0–3)	0 (0–3)
Dyspnoea at end, modified Borg scale	2 (0–8)	2 (0–7)
Leg fatigue at rest, modified Borg scale	0 (0–5)	0 (0–5)
Leg fatigue at end, modified Borg scale	2 (0–7)	1 (0–7)

Data is presented mean (SD)/median (min–max).
Abbreviations: HR, heart rate; bpm, beats per minute; 6MWD, six minute walk distance; 6MWT, six minute walk test.
* p-Value first vs. second 6MWT $p < 0.001$.

Table 3
Predictive Model for 6-Min Walking Distance in the Healthy Spanish Subjects for (a) Males (b) and Females.

(a) Males

	Coefficient	95% CI	p-Value	Partial R^2
Constant	−5228	−9412 to −1044	0.015	–
Age (years)	−5.516	−6.518 to −4.514	<0.001	0.36
Weight (kg)	−1.895	−2.953 to −0.837	<0.001	0.01
Height (cm)	69.420	20.802 to 118.038	0.005	0.16
Height² (cm²)	−0.189	−0.330 to −0.047	0.009	0.15

(b) Females

	Coefficient	95% CI	p-Value	Partial R^2
Constant	675	494 to 856	<0.001	–
Age (years)	2.962	−1.493 to 7.416	0.192	0.47
Age³ (years³)	−0.00071	−0.00106 to −0.00035	<0.001	0.48
Weight (kg)	−1.771	−2.530 to −1.013	<0.001	0.05

Table 4
Reference Equations Developed for 6MWD for Males and Females in the Spanish Population.

Males:
$6MWD = -5228 - (5.516 \times age_{yrs}) - (1.895 \times weight_{kg}) + (69.420 \times height_{cm}) - (0.189 \times height^2)$
Total $R^2 = 0.43$
$LLN = 904 - (7.172 \times age)$

Females:
$6MWD = 675 + (2.962 \times age_{yrs}) - (0.00071 \times age^3) - (1.771 \times weight_{kg})$
Total $R^2 = 0.51$
$LLN = 589 - (0.0006 \times age^3)$

Abbreviations: 6MWD, six-minute walk distance; LLN, lower limit of normality.

Table 5
Characteristics of Spanish COPD Patients From the Urban Training and PAC-COPD Studies.

	All Subjects (n = 715)	Males (n = 633)	Females (n = 82)
Age, years	68 (9)	69 (8)	64 (9)
Height, cm	164.8 (14.9)	165.7 (6.4)	157.4 (6.0)
Weight, kg	76.9 (14.5)	78.3 (14.4)	66.5 (14.2)
BMI, kg/m²	28.3 (4.8)	28.5 (4.6)	26.9 (5.8)
FEV_1, % predicted	55.0 (17.1)	54.2 (16.9)	61.3 (17.8)
FEV_1/FVC	53.6 (11.9)	53.6 (11.9)	53.2 (12.0)
mMRC dyspnoea scale	1 (1–2)	1 (1–2)	1 (0–2)
6MWD, m	464 (97)	466 (96)	452 (104)

Data is presented mean (SD)/median (min–max).
Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; mMRC, modified Medical Research Council; 6MWD, six minute walk distance.

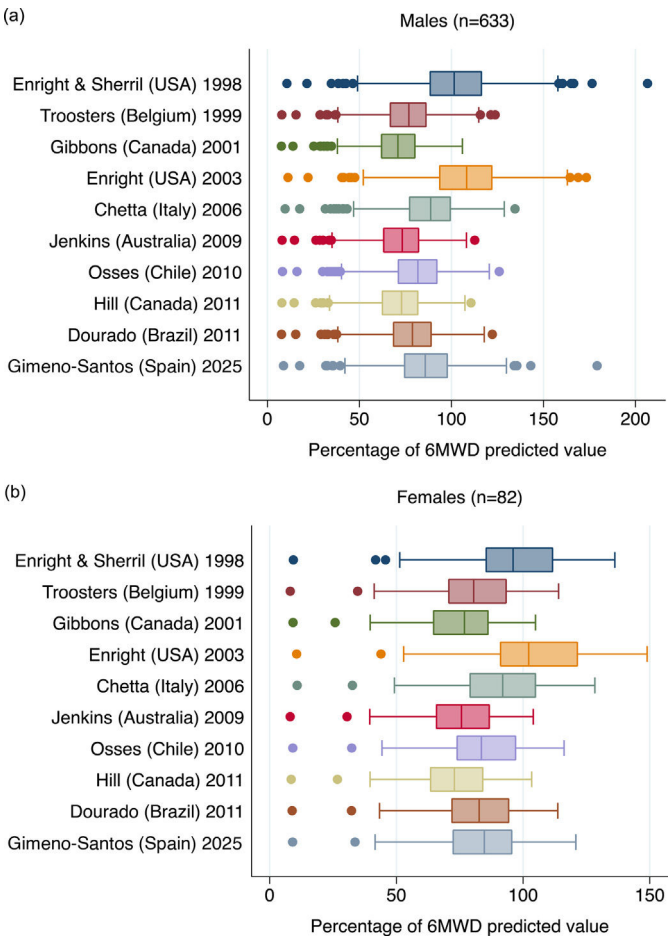

Fig. 1. Distribution of percentage of 6-min walk distance (6MWD) predicted values by using 9 published prediction equations and the one developed in this study (Gimeno-Santos) applied to patients with COPD from the primary case-based Urban Training and the hospital-based PAC-COPD studies (a) $n = 633$ males and (b) $n = 82$ females.

females. In particular, in males, 2 out of 9 equations[20,21] resulted in higher predicted values of 6MWD (overestimation) than the equation developed in our study (all $p < 0.001$), while 6 out of 9 equations[16,23,32,33] resulted in lower predictions (underestimation) (all $p < 0.001$) (Table 6). Only one equation[34] predicted similar 6MWD values to those in our equation. In females, the same 2 equations[20,21] that overestimated 6MWD in males also resulted in an overestimation in females ($p \leq 0.05$). Conversely, only 1 equation[18] underestimated ($p < 0.05$), while 6 equations predicted similar %6MWD.[16,17,23,32–34]

Discussion

This is the first study that provides 6MWD sex-specific reference equations for the Spanish population, as developed from a large sample of healthy subjects between the ages of 45 and 85 from 9 autonomous communities on the Spanish peninsula and the Balearic and Canary Islands. This approach ensured the representation of the country's heterogeneity. The application of these equations to a large Spanish sample of people with COPD yielded statistically different 6MWD predicted values than those obtained using existing equations, suggesting the previous equations do not fit the Spanish COPD population. As anticipated, demographic and anthropometric variables significantly influenced the 6MWD, accounting for a considerable proportion of the variability observed in the here developed equations (43% in males and 51% in females).

Table 6
Comparison of Percentage of 6MWD Predicted Values by Using 9 Published Prediction Equations Versus the One Developed in This Study (Gimeno-Santos) Over a Data Set of Spanish Patients With COPD From the Urban Training and PAC-COPD Studies (a) $n = 633$ Males and (b) $n = 82$ Females.

(a) Males

Equation	Country	Mean Difference %6MWD (95% CI)	*p*-Value
Enright & Sherril (1998)	USA	17 (14 to 19)	<0.001
Troosters (1999)	Belgium	−9 (−12 to −7)	<0.001
Gibbons (2001)	Canada	−15 (−18 to −13)	<0.001
Enright (2003)	USA	22 (19 to 24)	<0.001
Chetta (2006)	Italy	2 (−0.4 to 5)	0.135
Jenkins (2009)	Australia	−13 (−16 to −10)	<0.001
Osses (2010)	Chile	−5 (−7 to −2)	<0.001
Hill (2011)	Canada	−13 (−16 to −11)	<0.001
Dourado (2011)	Brazil	−7 (−10 to −5)	<0.001

(b) Females

Equation	Country	Mean Difference %6MWD (95% CI)	*p*-Value
Enright & Sherril (1998)	USA	13 (8 to 21)	<0.001
Troosters (1999)	Belgium	−3 (−11 to −5)	0.948
Gibbons (2001)	Canada	−8 (−16 to 0.2)	0.057
Enright (2003)	USA	21 (13 to 29)	<0.001
Chetta (2006)	Italy	8 (0 to 16)	0.050
Jenkins (2009)	Australia	−7 (−16 to 0.7)	0.088
Osses (2010)	Chile	0.6 (−7 to 9)	1.000
Hill (2011)	Canada	−10 (−18 to −2)	0.010
Dourado (2011)	Brazil	−0.6 (−9 to 8)	1.000

Abbreviations: 6MWD, six-minute walk distance.

In contrast with previous published equations,[16,33,34] but in agreement with others,[20,21,23,32] the factors that affect 6MWD were different for males and for females. This emphasises the need for specific equations developed for each sex.

Our reference equation for 6MWD in females did not include height, differing from both the male-specific equations we developed and many of the previously published 6MWD reference equations. Height is often considered as a determinant of 6MWD because it is a surrogate of the walking stride length. However, in our female models, adding height neither improved the cumulative R^2 nor was it statistically significant ($p = 0.124$). Two potential reasons for our findings could be (i) low height variability in our female sample and (ii) multicollinearity due to correlations between height and other included variables (i.e., weight). Nonetheless, neither of these explanations holds true in our analysis. Regardless of the explanation, our findings align with some previous reference equations[16,17] which also excluded height in their models.

Previous studies have identified handgrip strength,[33] the percentage of predicted HRmax,[18,22] the difference between the HR at rest and HR at the end of the test[35] and self-reported level of physical activity[36] as predictors of 6MWD. Nevertheless, the incorporation of these variables may present challenges to the application of equations in clinical settings. It would be necessary to perform a prior strength grip measurement or a physical activity questionnaire assessment, which are both time-consuming and not feasible in clinical context. Furthermore, the incorporation of physiological variables, such as HR, may influence the interpretation of the results in patients undergoing pharmacological treatments that alter cardiovascular response (e.g., beta-blockers or short-acting beta-2 adrenergic agonists) or in individuals with cardiopulmonary diseases exhibiting an abnormal response to the exercise.

We found that, particularly in males but also in females, the %6MWD values obtained from our equations differed significantly from those obtained from previously developed and commonly used equations, also in our region. This discrepancy can be attributed to several factors.

Some of these equations were developed in geographical areas where people engage in less physical activity than in Spain.[37] It is well-established that physical activity and exercise capacity, while distinct, are closely interrelated. Both are beneficial in general population and in individuals with chronic conditions.[37,38] Additionally, inequality in physical activity distribution is evident across middle- and high-income countries.[37] These disparities suggest that sociodemographic, climatic and cultural factors can significantly influence physical activity habits across countries, therefore, impacting the exercise capacity and performance in assessments such as the 6MWT. For example, Central European and North American regions tend to engage in less daily physical activity compared to Mediterranean countries, such as Spain.[39] Factors like a less active lifestyle, higher rates of sedentary work, and urban living patterns contribute to poor functional capacity and may reduce the 6MWD achieved by these populations in reference tests.

Additionally, there are anthropometric differences[40] and methodological differences in the 6MWT protocol (i.e., encouragement every 30 s or based on a single attempt).[41] Interestingly, the greater variability observed in our COPD population with predictions from by Enright's equations,[20,21] which are based on a single attempt, supports the importance of conducting two tests to account for the learning effect and reduce random error, as recommended per standard technical guidelines.[1,3]

It is our intention that these equations will be made available for their use in research and clinical practice, not only for the Spanish population, but also for the wider Mediterranean and South European area, with whom there are shared geographic, climatic, and cultural characteristics.[42] It is noteworthy that a set of equations had been recently developed from a Mediterranean area (Italy),[36] where the level of physical activity was used as a dichotomous variable to obtain the predictive value for the 6MWD. However, as it was stated above, this may hinder its applicability for clinical practice.

A limitation of the present study is that the participants were included or excluded based on a self-report of chronic conditions. This may have resulted in the inclusion of participants with pre-clinical and/or undiagnosed diseases. Nevertheless, the standardised application of recruitment criteria, including a physical examination and the revision of active treatment by health professionals, may have reduced the likelihood of this occurring.

A second limitation arises from the fact that different lengths of the corridor were employed in several sites, which may have influenced the distance walked and, consequently, the accuracy of our equations. However, we adhered rigorously to the standardised procedures of the test and established 20 m as the shorter distance permitted in the study. It is crucial to highlight that utilising a range of corridor lengths (20, 25 and 30 m) provides insights that are more aligned with real-world settings. In certain locations, conducting a 6MWT in a 30-m-long corridor could be impractical. The current technical standard for field walking tests states that the difference in the 6MWD is unimportant when the test is carried out on tracks longer than 15 m.[1] Nevertheless, recent studies have shown that the length of the corridor may have a significant impact on 6MWD in COPD.[43,44] Our findings highlight that in healthy adults, the 6MWD also varies according to corridor length, consistent with previous research in this population (adults aged $\geq$ 18 years).[45–47] This has significant implications for conducting the 6MWT, emphasising the need to adhere to technical standards in both clinical and research settings,[1] especially in multicenter studies. Furthermore, considering corridor length is crucial for ensuring comparability with previously published studies and maintaining alignment with the conditions under which reference equations were originally developed.[1,3] Therefore, we conducted a secondary analysis to develop sex-specific equations for 20- and 25-m corridors. This will permit the prediction of the 6MWD in those clinical settings where a 30-m corridor is not available, which is a strength of the study.

Finally, one could argue that the male-to-female ratio used in applying our equations to a COPD sample does not match the current sex distribution of COPD cases. It is important to note that the ratios in both Urban Training and PAC-COPD studies (with recruitment in 2013 and 2004–2006, respectively) were consisted with the COPD sex-distribution reported in epidemiological studies at that time.[48] However, this sex ratio difference should not affect the observed discrepancies in predicted walking distances compared to previous 6MWD reference equations.

The study also has notable strengths. Firstly, the random selection of the sample from a larger pool of volunteers who met the specified criteria. This approach enabled the generation of reference equations for the 6MWD that are highly representative of the study population. Secondly, the representativeness of the different regions of Spain (volunteers were recruited from 9 different autonomous communities) is noteworthy, given the considerable heterogeneity in weather, environment and traditions across these regions. Thirdly, the data collection and analysis were conducted in a methodologically robust manner, including the use of fractional polynomials[29] to preserve the continuous nature of the predictor variables when their relationship with 6MWD was non-linear, a process that could not be achieved with linear regression or spline models. Finally, the assessors underwent standardised training, and the quality control was carried on strictly by the same investigator at each site to ensure the consistency and homogeneity between them.

In conclusion, two 6MWD reference equations have been developed, one for males and one for females, which allow for the valid prediction of the functional exercise capacity of adults and older adults from the Spanish region. These equations are likely to be useful for the prediction of the 6MWD of healthy subjects and patients with chronic respiratory diseases, or even with other chronic conditions (e.g., cardiovascular or metabolic) from similar regions with regard to geography, climate and cultural habits, such as the Mediterranean and South Europe areas.

Contribution of Each Author

All authors meet the authorship criteria and (i) contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (ii) drafted the work or reviewing it critically for important intellectual content; (iii) approved the final version of the manuscript to be published; (iv) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Artificial Intelligence Involvement

None of the material has been partially or totally produced with the help of any artificial intelligence software or tool.

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Conflicts of Interest

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2025.01.005.

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