Supplementary material

ß2-Adrenergic Agonists do not improve Physical Performance in Healthy Individuals

METHODS

The current systematic review and meta-analysis was previously registered on PROSPERO, with the registration number CRD42018112905.

The search for studies that potentially matched the inclusion criteria was performed independently by two authors. Five electronic databases, namely PubMed, Scopus, Science Direct, ISI Web of Science and Cochrane Library, were searched from inception to 31st December 2018. The PubMed search strategy served as a reference for the development of the search strategies for the remaining databases. The databases were systematically searched using the following search terms combined with Boolean operators: "adrenergic beta-agonists", "athletic performance", “doping”, "physical endurance", "muscle strength". Discrepancies were resolved through discussion with the involvement of a third author when necessary.

Inclusion Criteria

- Types of Studies

We included all randomized, controlled (crossover and parallel) studies that assessed the effect of ß2-agonists on physical performance in healthy, non-asthmatic individuals. The characteristics of the included studies are presented in Table S1.

- Types of participants

We included studies performed in healthy, non-asthmatic individuals over 18 years old (both male and female). Regarding performance level, we included elite athletes, recreational athletes and non-athletic people alike. We looked for studies that mentioned the level and intensity of sports participation, the training level (maximal oxygen consumption [VO_{2max}]) and the type of sport at inclusion. Athletes were considered to be highly trained if their maximal oxygen uptake (VO_{2max}) was above 55 mL/kg/min (females) or 60 mL/kg/min (males).

- Types of intervention

Any short- or long-acting inhaled or systemic ß2-agonist, whose use was single or multiple administrations, was considered.

- Types of outcome measures

We included studies with the following types of outcome measures:

1) VO_{2max} in $L.min^{-1}$ or $ml.\ kg^{-1}.min^{-1}$ determined with a maximal exercise test on a treadmill or cycle ergometer;
2) Endurance time(s) to exhaustion (TTE) during an exercise test at a predetermined percentage of VO_{2max}.
3) Duration time(s) of a time trial; cycling economy (W/L of O_2), in which a certain distance has to be covered or a certain amount of work has to be delivered;
4) Peak power (W or W/kg); mean power (W); force (N or N/kg); velocity (rpm); time to peak power (s) and fatigue index (%) during a Wingate test;
5) Maximal voluntary isometric contraction of muscles (N);
6) Agility (S).

Exclusion Criteria

We excluded studies including participants with any disease, as well as studies in which participants used any other medication concomitantly (except oral contraception in women). Studies performed in children or adolescents under 18 years old and studies performed on laboratory animals (i.e., rats, mice, etc.) were excluded. Studies including clenbuterol were also excluded since this drug is defined as an anabolic agent and not as a ß2-agonist by the WADA [1].

Data Extraction and Management

All data were independently extracted by two review authors. The discrepancies were resolved through discussion and involvement of a third review author, when necessary. Data extraction included article references (i.e. author, title and date), study design, study population (i.e. number of subjects, sex, age, type of sport, intensity level and training level) and intervention (i.e. substance, administration, dose).

Assessment of Risk of Bias in Included Studies

Two reviewers independently assessed the risk of bias of the included studies, considering the tool "Cochrane Collaboration tool for assessing risk of bias" and the respective criteria for judging the risk of bias in the assessment tool "Risk of bias" [2]. Disagreements between the authors' risk of bias analysis were resolved through discussion, with the involvement of a third

review author, when necessary. The risk of bias graph of the included studies is presented in Figure S2.

2.6.Statistical methods

The statistical analysis of the extracted data from included studies was performed using Comprehensive MetaAnalysis software, version 3.3.

Bearing in mind that all studies had paired samples (pre-post substance administration or placebo; substance administration or placebo on the same subjects) and since none provided the correlation coefficient value between paired samples or enough data to allow its determination, this value was assumed as zero. This strategy implied higher variance and less relevance of the studies included in the meta-analysis since the correlation value is never negative in paired sample studies. The heterogeneity between studies was assessed by both the Cochran Q Test and heterogeneity index (effect variations), I^2.

A sensitivity analysis was performed to understand the imputation effect of the correlation coefficient value on studies that did not provide data to calculate this value. Therefore, the zero value was compared with the weighted average of coefficient correlation values, calculated from the studies which allowed it.

TABLES

Table S1. Characteristics of the studies included in this systematic review.

Author; Date	Design	Study Population			Intervention	Primary Outcome Measures
		Number; Sex; Age (years) ± SD	Type of Sport	Performance Level (VO_{2max} mL/kg/min)	Substance (s); Dose/Dosage; Type of Administration	
Altarawneh, M M; 2016 [3]	C	7; M; 23±6	Soccer; Gym; Swimming	57±12.9	Salbutamol; 1000μg; I	Arterial potassium concentration during and after continuous high-intensity exercise
Beloka, S P; 2011 [4]	C	23; M; 23±2.3	NS	#	Salbutamol; 10μg/min; 20μg/min; IV	MIC; Cardiopulmonary exercise and strength test variables
Carlsen, K H; 1997 [5]	C	18; M; 22.9±6.34	Ski Cross Country; Biathlon	>63.1 *	Salbutamol(800μg); Salmeterol(50μg); I	$VO_{2má}$; Running TTE during max. exercise test
Carlsen, K H; 2001 [6]	C	24; M; 25±2.8	Ski Cross Country; Orienteering; Basketball; Soccer; Skating; Rowing	25±1.5mL	Formoterol; 9μg; I	VO_{2max}; Running TTE at 105% VO_{2max}
Caruso, J F; 1995 [7]	P	13(M); 21.4±3.3; 9(F); 21.4±1.8	NS	#	Salbutamol; 16mg/day for 6 weeks; O	Isokinetic force of the knee extensors
Caruso, J F; 2005 [8]	P	22; M; 18-22	Resistance exercises	#	Salbutamol; 16mg/day for 3 weeks; O	Isokinetic force of elbow and knee flexors and extensors
Collomp, K; 2000a [9]	C	8; M; 23.4±0.8	Cycling; Running	55±1.7	Salbutamol; 12mg/day for 3 weeks; O	TTE at 80-85% VO_{2max}
Collomp, K; 2000b [10]	C	9; M; 24.6±3.9	Cycling; Running	55.5±1.6	Salbutamol; 6mg; O	TTE at 80-85% VO_{2max} in cycling
Collomp, K; 2002 [11]	C	8; M; 26±5.9	NS	54.4±2.2	Salbutamol; 6mg; O	TTE at 90% VO_{2max} in cycling

Collomp, K; 2005 [12]	C	13; M; 31.2±5.8	Weightlifting	#	Salbutamol; 4mg; O	30s-Wingate Test
Decorte, N; 2008 [13]	3-way C	14; M; 23.3±3.2	NS	#	Salbutamol; 200μg; 800μg; I	Quadriceps muscle strength measured during maximal voluntary contraction; Magnetic stimulation of the femoral nerve
Decorte, N; 2013 [14]	3-way C	11; M; 33±6	Cycling; Triathlon; Running	74±4 *	Salbutamol; 200μg; 800μg; I	Fatigue Test (Quadriceps)
Decorte, N; 2015 [15]	2-way C	12; M; 28±6	NS	47±15	Salbutamol; 4mg; O	Incremental cycling test; Plantar flexion protocol; Muscle metabolism assessed by spectroscopy
Dickinson, J; 2014 [16]	P	16; M; 20.1±1.6	Soccer; Running; Cycling; Boxing; Kickboxing; Rugby; Fitness; Sneakers	#	Salbutamol; 1600μg; I	Peak consumption O_2; Time Trial Time 3-km
Elers, J; 2012 [17]	C	9; M; 27±5	Triathlon; Soccer; Cycling	#	Salbutamol; 0.2mg; I	Blood gases and metabolites during stress testing
Fleck, S J;1993 [18]	C	21; M; 23.8±1.1	Cycling	#	Salbutamol; 360μg; I	Maximum Power
Gong, H J; 1988 [19]	C	14(M); 1(F); 23±5	Cycling; Triathlon	61±4 *	Salbutamol; 180μg; I	VO_{2max} after 60 minutes of exercise and running to exhaustion; Ozone or filtered air exposure
Goubault, C; 2001 [20]	3-way C	12; M; 23±2	Triathlon	57.9±5.1	Salbutamol; 200μg; 800μg; I	TTE at 85% VO_{2max}
Heir, T; 1995 [21]	C	17; M; 18-30	Ski Cross Country; Running; Orienteering	>70 *	Salbutamol; 50μg/kg; I	VO_{2max}; Running TTE at 110% VO_{2max}
Hostrup, M; 2014 [22]	C	9; M; 24.3±1.1	Cycling; Running	58.9±3.1	Terbutaline; 15mg; I	MVIC; 30s-Wingate test; Time Trial Performance: 100-kcal
Hostrup, M; 2015 [23]	P	18; M;	NS	Terbutaline: 55±2 Placebo: 57±2	Terbutaline; 5mg/30kg for 4 weeks; O	Muscle strength and power in a cycle ergometer exercise

Hostrup, M; 2016 [24]	P	20; M; 25.9±1.4	Cycling; Mountaineering; Triathlon	69.4±1.8 *	Salbutamol; 8mg; O	MVQC; Isometric mass resistance of deltoids; 3-Wingate test; 110% VO_{2max} performance
Kalsen, A; 2014a [25]	C	9; M; 24.3±1.1	NS	58.9±3.1	Terbutaline; 15mg; I	Time to 300 kcal exhaustion on a cycle ergometer
Kalsen, A; 2014b [26]	C	13(M); 4(F)	Swimming	#	Salbutamol (1600µg); Formoterol (36µg); Salmeterol (200µg) I	MVIC; Sprint performance in a 110% VO_{2max} exhaust test
Kalsen, A; 2016 [27]	C	13; M; 32±2	NS	45±0.2	Formoterol; 54µg; I	Muscle strength, power, metabolism and fatigue during a sprint
Koch, S; 2015a [28]	C	20; M; 20±6	Cycling; Triathlon	64.2±5.3 *	Salbutamol; 1600µg; I	10-km time trial
Koch, S; 2015b [29]	C	15; F; 30±5	Cycling; Triathlon	>50	Salbutamol; 400µg; I	FEV_1; Performance during a time trial
Koch, S; 2016 [30]	P	49(M); 20(F); 19-40	Cycling; Triathlon	62.3±7.2 *	Salbutamol; 400µg; I	FEV_1; Power during a time trial
Le Panse, B; 2005a [31]	C	15; M; 29.1±2.2	Strength athletics	#	Salbutamol;12mg/day for 3 weeks; O	30s-Wingate Test
Le Panse, B; 2006a [32]	C	14; F; 20.9±1.1	NS	#	Salbutamol;12mg/day for 4 weeks; O	30s-Wingate Test
Le Panse, B; 2006b [33]	C	14; F; 22±1.7	NS	#	Salbutamol; 12mg/day for 4 weeks; O	VO_{2max}
Le Panse, B; 2007 [34]	C	12; F; 22.3±0.9	Athletics; Weightlifting; Basketball	#	Salbutamol; 4mg; O	30s-Wingate Test
Lemmer, J T; 1995 [35]	C	14; M; 22.6±1	Cycling	#	Salbutamol; 360µg; I	30s-Wingate Test
Martineau, L; 1992 [36]	P	6(M); 29±2; 6(F); 25±2	NS	#	Salbutamol; 16mg/day for 3 weeks; O	Isometric strength of knee flexors and extensors
McDowell, S L; 1997 [37]	C	11; M; 24.64±1.1	Cycling	#	Salmeterol; 42µg; I	30s-Wingate Test

Mckenzie, D C; 1983 [38]	P	9(M); 10(F)	Running	Salbutamol (M): 66.7 Salbutamol (F): 59.1 Placebo (M): 64.8 Placebo (F): 61.9	Salbutamol; 200μg; I	VO_{2max}
Meeuwisse, H W; 1992 [39]	C	7; M; 23.6	Cycling	>60 *	Salbutamol; 200μg; I	VO_{2max}; 30s-Wingate Test; Running TTE at 70% VO_{2max} – after 15 min exercise
Morton, A R; 1992 [40]	C	16(M); 1(F); 18-29	Running	#	Salbutamol; 200μg; I	VO_{2max}; Running TTE during maximal exercise test; 10s 30s – Wingate Test
Morton, A R; 1993 [41]	C	17; M; 22±4	Running; Sprint; Weightlifting; Rugby; Volleyball; Weight release; Discus throw	#	Salbutamol; 200μg; I	10s-Wingate Test; Isokinetic force of knee flexors and extensors
Morton, A R; 1996 [42]	C	16; M; 23.2±3.5	Cycling; Triathlon	#	Salmeterol; 50μg; I	10s, 30s-Wingate Test; Isokinetic force in knee flexors and extensors
Norris, S R; 1996 [43]	C	15; M; 25±4	Cycling	63.4±6.7 *	Salbutamol; 400μg; I	VO_{2max}; 60-s Wingate test; 20-km time trial duration
Riiser, A; 2006 [44]	C	20; M; 29.2±4.4	NS	61.1±5.2 *	Formoterol; 18μg; I	VO_{2max}; Running TTE a 107% VO_{2max} at high altitudes
Sanchez, A M J; 2012 [45]	C	8; M; 23.3±0.6	NS	57.6±1.8	Salbutamol; 6mg; O	Force-Velocity Ratio; Maximum resistance cycling test
Sanchez, A M J; 2013 [46]	C	7; M; 29±6	NS	57±3	Terbutaline; 8mg; O	VO_{2max}; TTE
Sandsund, M; 1998 [47]	C	8; M; 25.1±3.6	Sky Cross Country	>70 *	Salbutamol; 400μg; I	VO_{2max}; Running TTE at 50-95% VO_{2max} [-15°C-23°C]

Signorile, J F; 1992 [48]	C	8(M); 7(F); 18-33	NS	#	Salbutamol; 180μg; I	15s-Wingate Test
Sporer,B C; 2008 [49]	4-way C	30; M; 29±6	Cycling; Triathlon	67.1±4.3 *	Salbutamol; 200μg; 400μg;800μg; I	Power (W); 20km time trial
Stewart, I B; 2002 [50]	C	10; M; 26.2±0.9	NS	65.6±2.4 *	Salbutamol (400μg); Formoterol (12μg); I	VO_{2max}; 30s-Wingate Test
Sue-Chu, M; 1999 [51]	C	8; M; 23	Ski Cross Country	#	Salmeterol; 50μg; I	VO_{2max}; Running at 90% and 80% VO_{2max} followed by a period of exhaustion at -15°C
Tjørhom, A; 2007 [52]	C	20; M; 29.2±4.5	NS	#	Formoterol; 18μg; I	Running TTE a 107% VO_{2max} at -20ºC
Van Baak, M A; 2000 [53]	C	16; M; 23.3±2.1	Athletics; Fitness; Hockey; Soccer; Cycling	55.9±7.2	Salbutamol; 4mg; O	TTE at 70% VO_{2max} in cycling; Isokinetic force of the leg
Van Baak, M A; 2004 [54]	C	16; M; 23±3	Cycling; Triathlon	#	Salbutamol; 800μg; I	TTE at 75% maximum aerobic power
Violante, B.; 1989 [55]	C	7; M; 33.7±7.8	NS	#	Salbutamol; 4μg/kg during 20min; 3μg/kg/min; IV	VO_{2max}; Walking for 12min

C – Crossover; F – Female; FEV_1 - Forced Expiratory Volume in the 1second; I – Inhaled, IV – Intravenous; M – Male; Max – Maximal; MIC – Muscle Isometric Contraction; MVIC – Maximum Voluntary Isometric Contraction; MVQC – Maximum Voluntary Quadriceps Contraction; NS – Not Specified; O – Oral; P – Parallel; TTE – Time to exhaustion; * - High-performance athletes; # - Relative VO_{2max} was not reported

RESULTS

Figure S1 represents the selection of the studies to be included in the systematic review and meta-analysis. Applying this search strategy, 62 studies were eligible for a full evaluation. Of these, 53 were included in the systematic review and 30 in the meta-analysis.

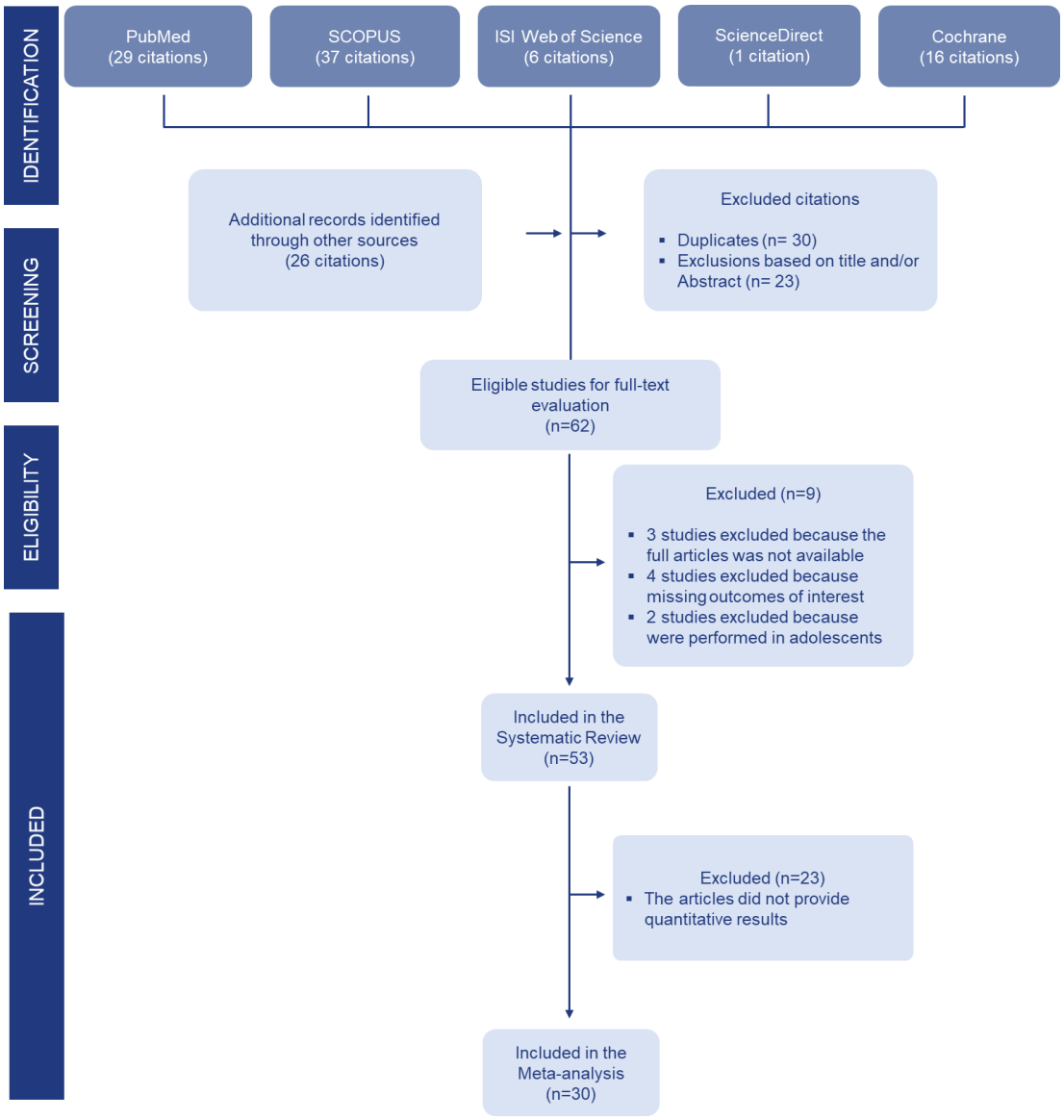

Figure S1. Selection of the studies included in the systematic review and meta-analysis.

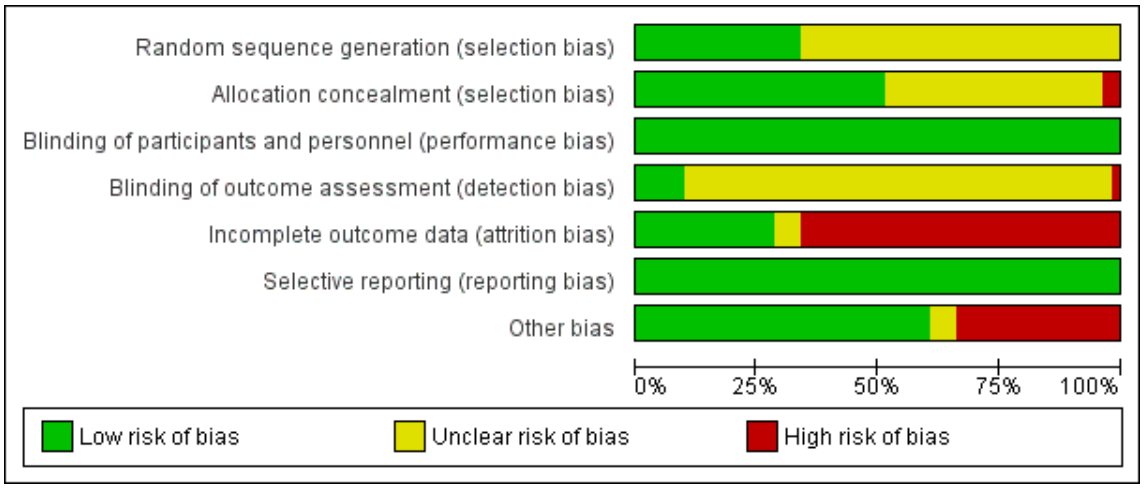

Figure S2 - Risk of bias graph of the included studies.

1. Meta-Analysis – Effect of ß2-agonists on VO_{2max}

The summary of the fixed-effects meta-analysis for comparison of MD of VO_{2max} between ß2-agonists and placebo is presented in Table S2.

Table S2. Summary of fixed-effects meta-analysis and complementary tests for comparison of MD of VO_{2max} between ß2-agonists and placebo.

VO_{2max} **ß2-agonists *vs.* Placebo (Fixed-Effects)**	
Salbutamol	
MD (mL/min/kg) (95% CI) Observed Adjusted	 0,284 (-0,457; 1,025) 0,284 (-0,457; 1,025)
P value	0,453
Cochran's Q Test Q Statistics df P value	 8,196 20 0,893
I^2 %	0,000
Formoterol	
MD (mL/min/kg) (95% CI) Observed Adjusted	 0,372 (-1,609; 2,353) 0,504 (-1,396; 2,403)
P value	0.713
Cochran's Q Test Q Statistics df P value	 0,745 3 0,863
I^2 %	0,000
Total	
MD (mL/min/kg) (95% CI) Observed Adjusted	 0,295 (-0,399; 0,988) 0,369 (-0,313; 1,051) [a]
P value	0,405
Cochran's Q Test Q Statistics df	 8,948 24

P value	0,998
I^2 %	0,000

[a] Duval and Tweedie's trim and fill

No publication bias was found for the meta-analysis including studies with Salbutamol (Figure S3). The meta-analysis that included the studies with Formoterol revealed the need for imputing one publication to obtain a slight adjustment in the MD on VO_{2max} (Table S2). The publication bias assessment for this meta-analysis is shown in Figure S4. When the total studies for Salbutamol and Formoterol were considered, it was necessary to impute two studies, which slightly adjusted the MD in VO_{2max} (adjusted MD=0.369; 95% CI: -0.313; 1.051) (Figure S5).

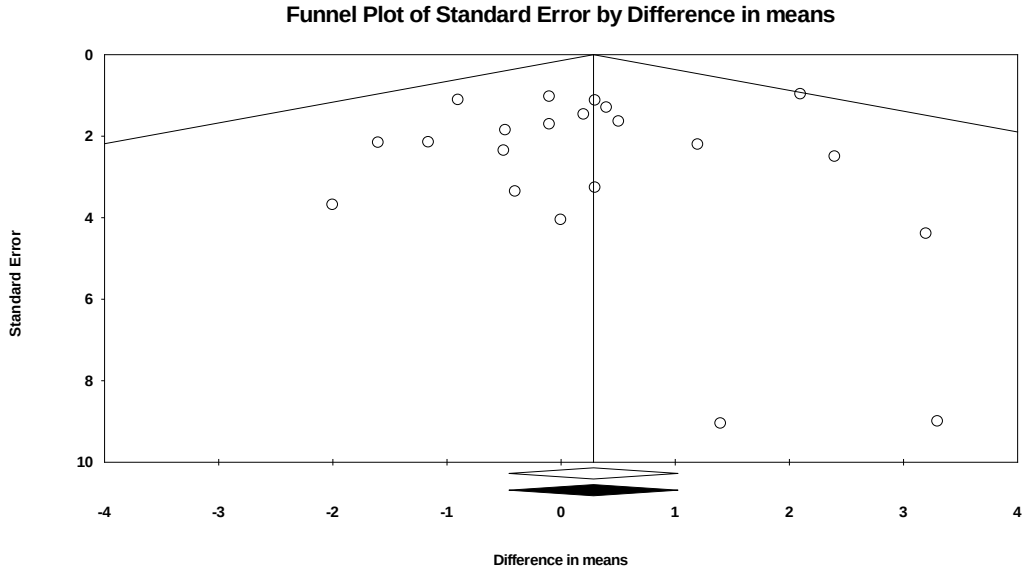

Figure S3. Funnel plot representing the analysis of publication bias for the meta-analysis including studies with salbutamol. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

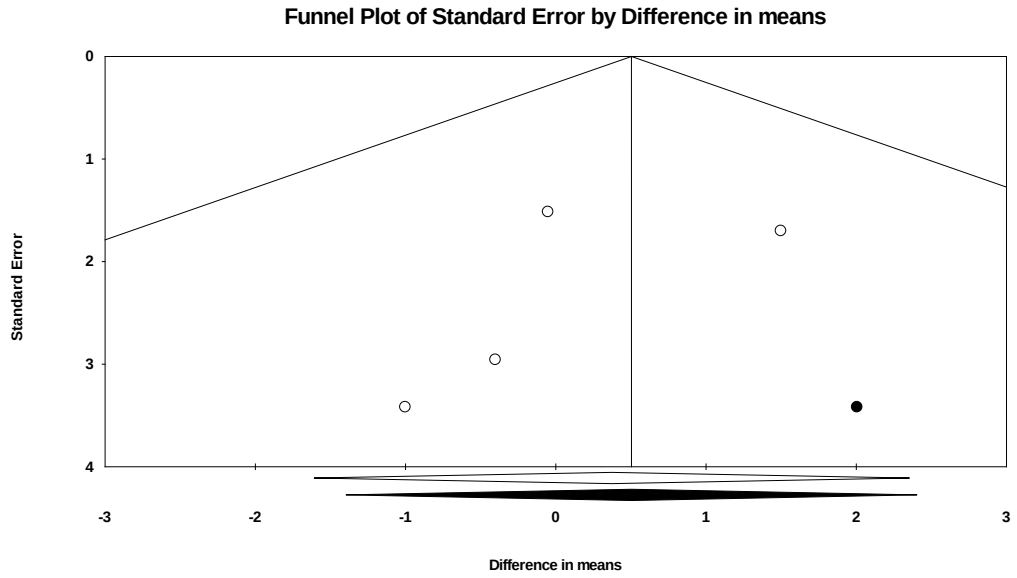

Figure S4. Funnel plot representing the analysis of publication bias for the meta-analysis including studies with formoterol. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

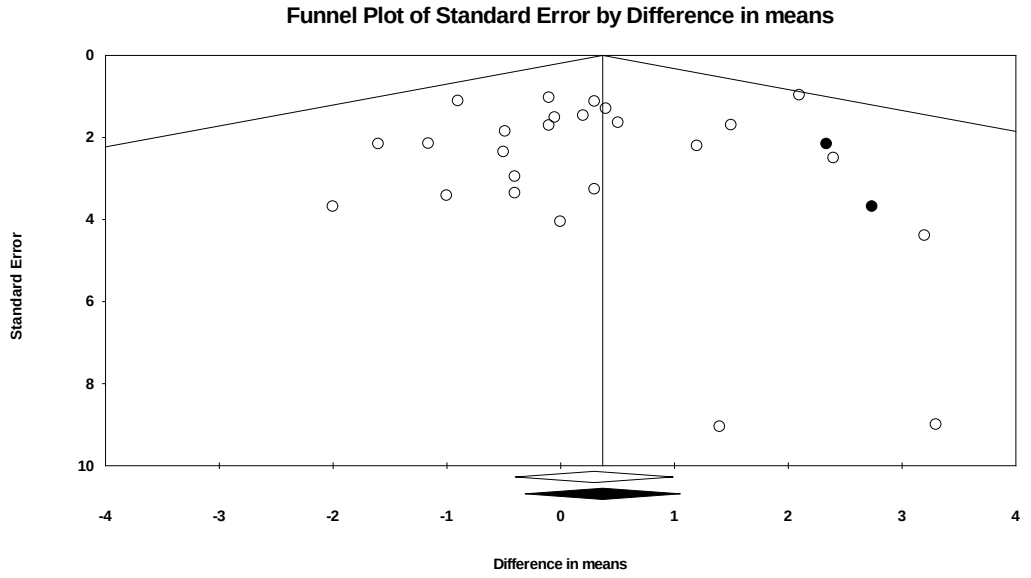

Figure S5. Funnel plot representing the analysis of publication bias for the meta-analysis considering studies with both ß2-agonists: salbutamol and formoterol. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

2. Meta-analysis - Effect of ß2-agonists on VO_{2max}: route of administration

The summary of the fixed-effects meta-analysis for comparison of MD of VO_{2max} between salbutamol and placebo, considering different routes of administration is presented in Table S3.

Table S3. Summary of fixed-effects meta-analysis and complementary tests for comparison of MD of VO_{2max} between salbutamol and placebo, considering different routes of administration.

VO_{2max} **Salbutamol *vs*. Placebo (Fixed-Effects)**	
Inhaled	
MD (mL/min/kg) (95% CI)	
Observed	0,323 (-0,478; 1,123)
Adjusted	0,316 (-0,484; 1,116)
P value	0,430
Cochran's Q Test	
Q Statistics	7,757
df	16
P value	0,956
I^2 %	0,000
Oral or IV	
MD (mL/min/kg) (95% CI)	
Observed	0,053 (-1,898; 2,003)
Adjusted	0,278 (-1,532; 2,089)[a]
P value	0.957
Cochran's Q Test	
Q Statistics	0,376
df	3
P value	0,945
I^2 %	0,000

IV: intravenous
[a] Duval and Tweedie's trim and fill

In the meta-analysis considering the effect of inhaled β2-agonists on endurance TTE no statistically significant difference was found between the mean endurance TTE of inhaled β2 agonists and placebo (Figure S6).

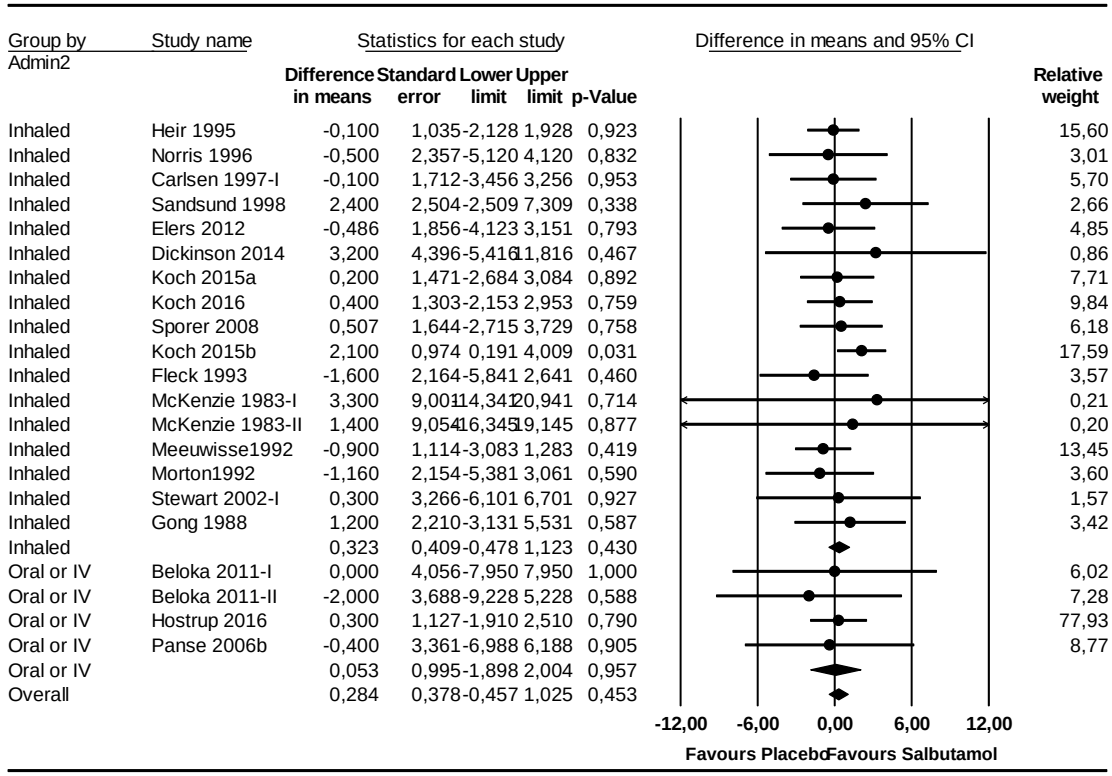

Figure S6. Forest plot representing the comparison of MD of VO_{2max} between salbutamol and placebo, considering different routes of administration.

Publication bias evaluation revealed the need for imputing one study in the placebo side, obtaining an adjusted VO_{2max} MD equal to 0.316 mL.kg-1.min; 95% CI: (-0.484; 1.116) (Figure S7).

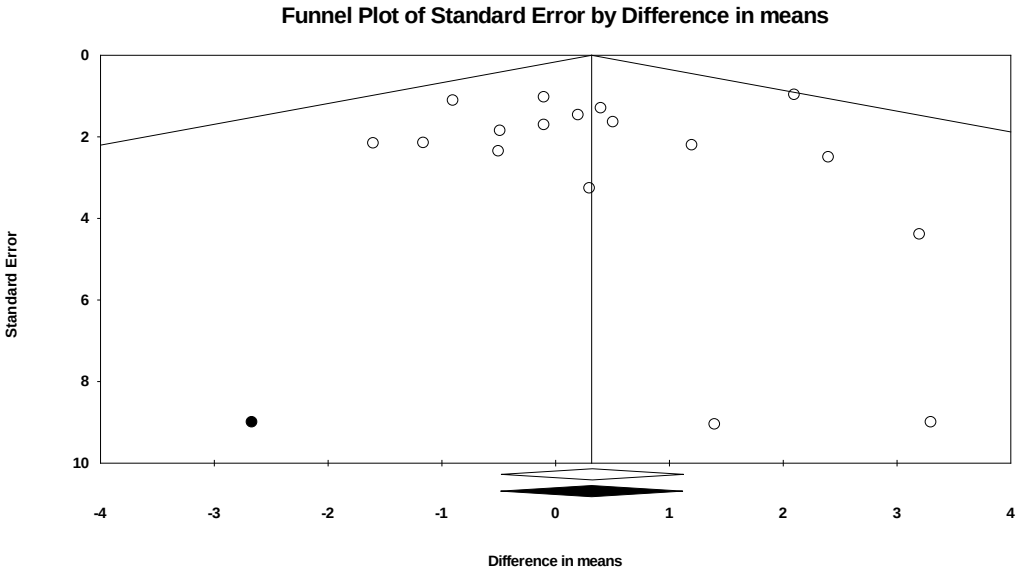

Figure S7. Funnel plot representing the analysis of publication bias for the meta-analysis considering studies with inhaled salbutamol. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the

imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

Publication bias evaluation revealed the need for imputing two studies in the salbutamol side (adjusted MD=0.278; 95% CI: (-1.532; 2.089) (Figure S8). Heterogeneity was null for both meta-analyses (I^2=0%).

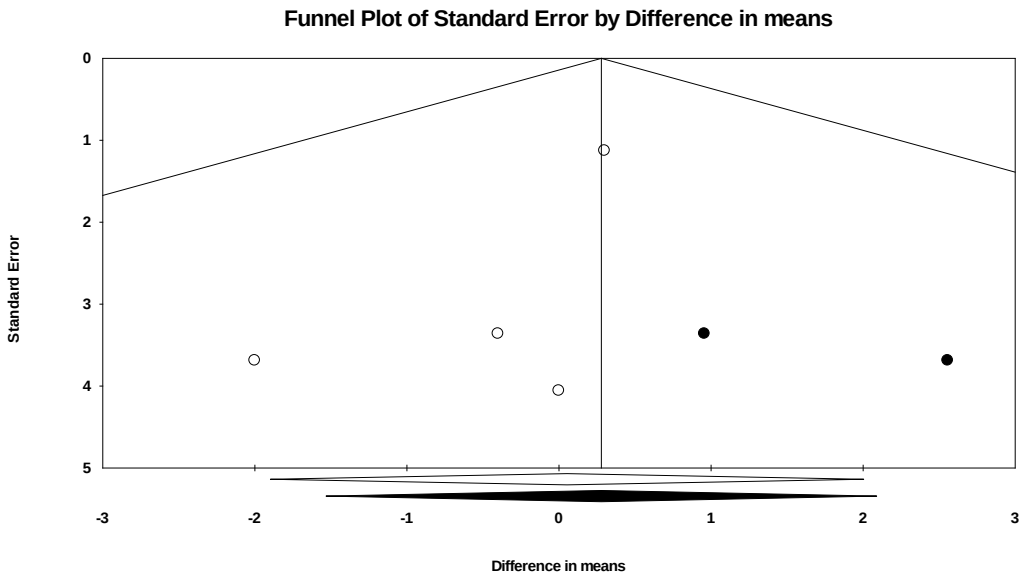

Figure S8. Funnel plot representing the analysis of publication bias for the meta-analysis considering studies with systemic salbutamol (oral or intravenous routes of administration). Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

3. Meta-analysis - Effect of ß2-agonists on endurance time to exhaustion (TTE)

The summary of the fixed-effects, random-effects and mixed-effects meta-analyses for comparison of MD of endurance time to exhaustion between ß2-agonists and placebo, considering different percentages of VO2max is presented in Table S4.

Table S4. Summary of fixed-effects, random-effects and mixed-effects meta-analysis and complementary tests for comparison of MD of endurance time to exhaustion between ß2-agonists and placebo, considering different percentages of VO_{2max}.

Endurance Time to Exhaustion ß2-agonists *vs*. Placebo (Fixed-, Random- and Mixed-Effects)	
≥100% VO_{2max}	
MD (min.) (95% CI) Observed Adjusted	 -0,054 (-0,163; 0,054) -0,055 (-0,163; 0,053)[a]
P value	0,324
Cochran's Q Test Q Statistics df P value	 4,073 8 0,851
I^2 %	0,000
<100% VO_{2max}	

MD (min.) (95% CI) Observed Adjusted	 1,712 (-1,013; 4,437) 0,676 (-1,900; 3,251)[a]
P value	0,218
Cochran's Q Test Q Statistics df P value	 14,213 5 0,014
I^2 %	64,820
Mixed-Effects	
MD (min.) (95% CI)	-0,052 (-0,160; 0,056)
P value	0,349
Cochran's Q Test Q Statistics df P value	 1,611 1 0,204

[a] Duval and Tweedie's trim and fill

Publication bias assessment revealed the need of imputing one study in the placebo side, obtaining an adjusted MD virtually identical to the unadjusted version (adjusted MD=-0.055; 95% CI: (-0.163; 0.053)) (Figure S9).

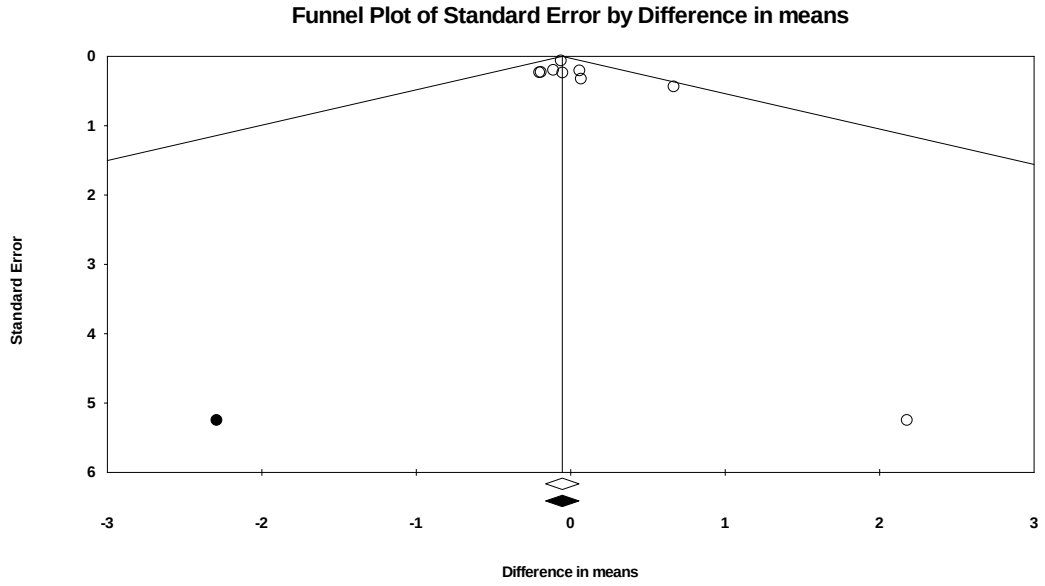

Figure S9. Funnel plot representing the analysis of publication bias for the meta-analysis considering endurance TTE ≥100% of VO_{2max}. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

The adjusted MD, considering the publication bias with the imputation of 2 studies in the placebo side, was closer to zero (adjusted MD=0.676; 95% CI: (-1.900; 3.251)) (Figure S10).

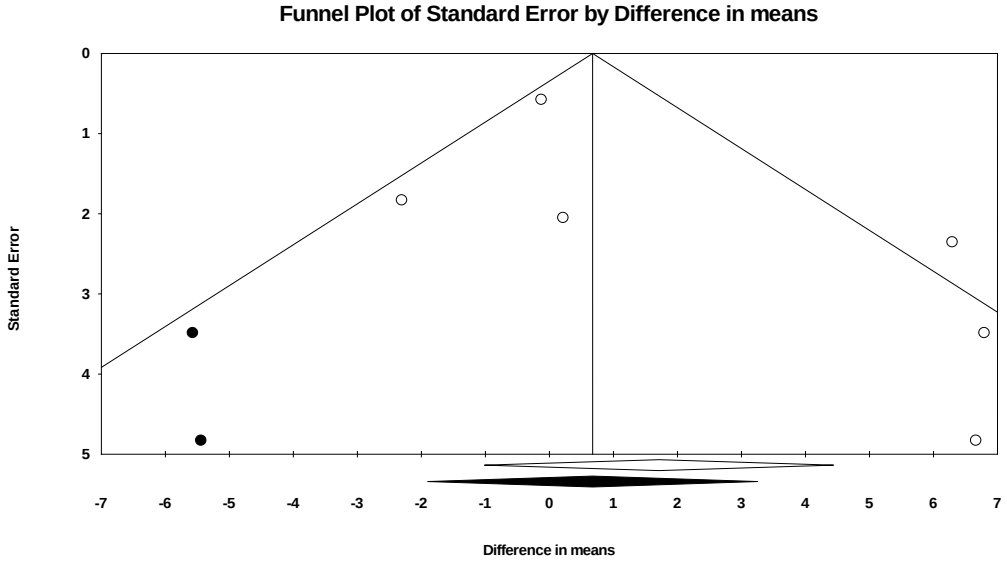

Figure S10. Funnel plot representing the analysis of publication bias for the meta-analysis considering endurance TTE <100% of VO_{2max}. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

The summary of the fixed-effects meta-analysis for comparison of MD of endurance TTE between ß2-agonists and placebo, considering the route of administration is presented in Table S5.

Table S5. Summary of fixed-effects meta-analysis and complementary tests for comparison of MD of endurance TTE between ß2-agonists and placebo, considering the route of administration.

Endurance Time to Exhaustion ß2-agonists *vs*. Placebo (Fixed-Effects)	
Inhaled	
MD (min.) (95% CI) Observed Adjusted	 -0,057 (-0,165; 0,051) -0,057 (-0,165; 0,051)[a]
P value	0,298
Cochran's Q Test Q Statistics df P value	 5,418 10 0,862
I^2 %	0,000
Oral	
MD (min.) (95% CI) Observed Adjusted	 6,029 (2,673; 9,385) 5,785 (2,772; 8,798)[a]
P value	<0,001
Cochran's Q Test Q Statistics df P value	 0,616 3 0,893
I^2 %	0,000
Total	
MD (min.) (95% CI) Observed Adjusted	 -0,051 (-0,158; 0,057) -2,544 (-17,490; 12,403)[a]
P value	0,354
Cochran's Q Test Q Statistics	 18,657

df	14
P value	0,178
I^2 %	24,961

[a] Duval and Tweedie's trim and fill

The fixed-effects meta-analysis considering the effect of oral ß2-agonists on endurance TTE (in minutes) showed a statistically significant mean increase in endurance TTE, after the administration of oral ß2-agonists when compared with placebo (Figure S11).

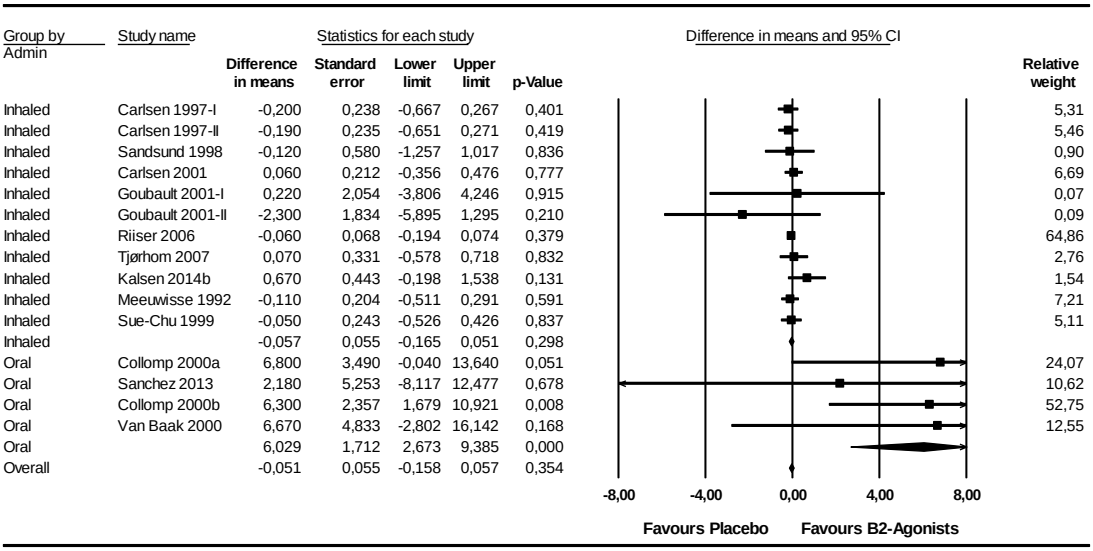

Figure S11: Forest plot representing the comparison of MD of endurance TTE between ß2 agonists and placebo, considering the route of administration.

Figures S12 and S13 represent publication bias assessment for the meta-analysis considering inhaled and oral ß2-agonists, respectively. The latter revealed the need of imputing one study in the placebo side, obtaining a slightly lower increase in means (MD=5.785; 95% CI: (2.772; 8.798)) (Figure S13).

A sensitivity analysis consisting of excluding one study at a time revealed a slightly greater effect of oral ß2-agonists on endurance TTE when excluded one study [46] (Figure S14). Of these 4 studies, all considered Salbutamol as the intervention, except the study Sanchez et al. (2013) [46], which considered Terbutaline.

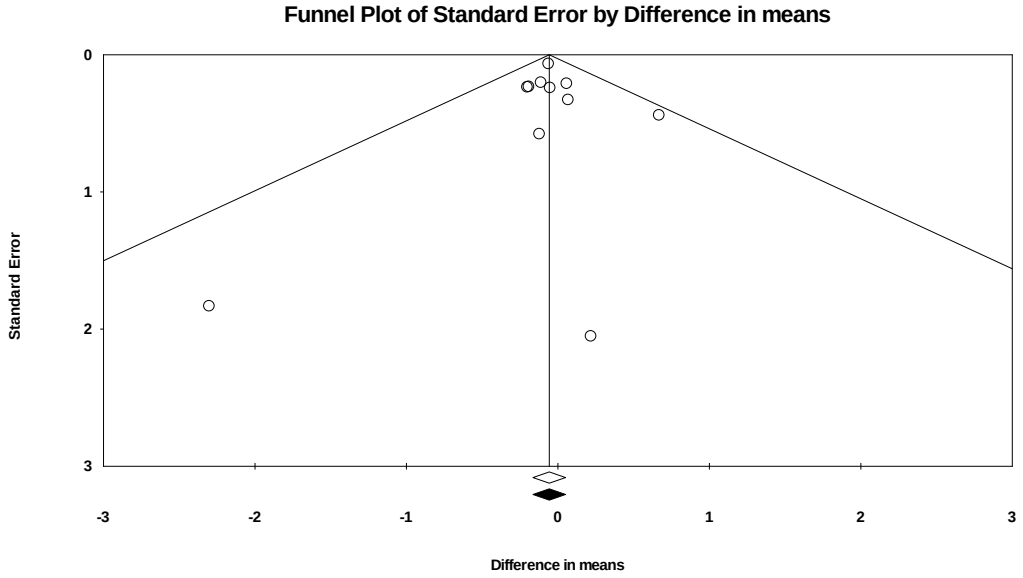

Figure S12. Funnel plot representing the analysis of publication bias for the meta-analysis considering endurance TTE between inhaled ß2-agonists and placebo. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

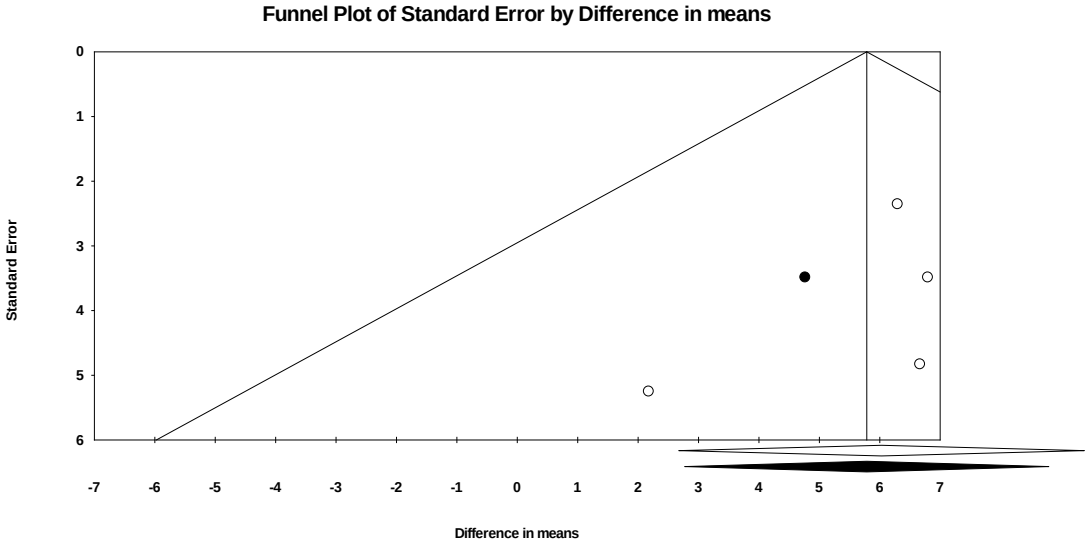

Figure S13. Funnel plot representing the analysis of publication bias for the meta-analysis considering endurance TTE between oral ß2-agonists and placebo. Open dots represent the studies included in the meta-analysis, and the observed OR is represented by the open diamond. Large studies are closer to the top and cluster around mean effect size. Smaller studies appear toward the bottom of the graph. Closed dots represent the imputed studies according to the trim and fill method, and the adjusted OR is represented by the closed diamond.

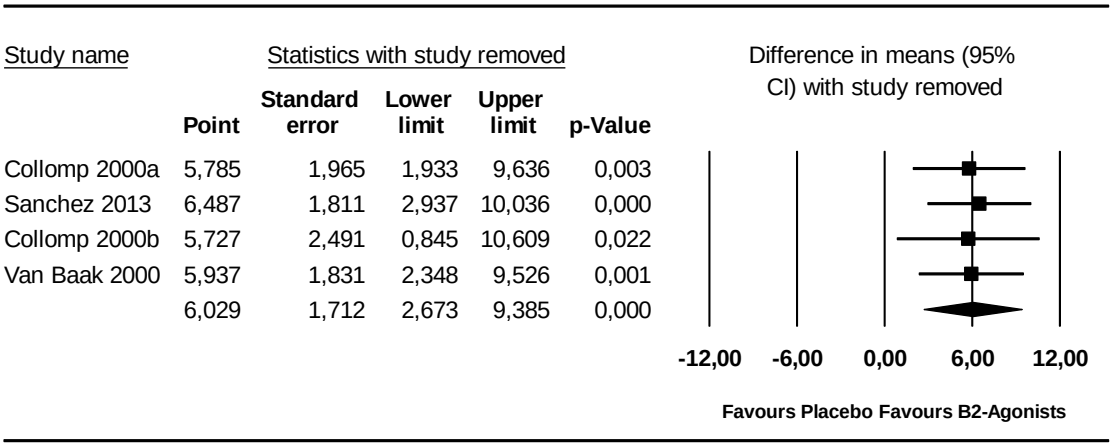

Figure S14. Sensitivity analysis of the fixed-effects meta-analysis comparing the MD of endurance time to exhaustion (in minutes) between oral β2-agonists and placebo.

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