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The effect of beta2-agonists on anaerobic performance – A systematic review and meta-analysis of randomized controlled trials

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What is already known?

- Asthma is the most common chronic disease in athletes.
- The gold standard for asthma therapy is inhaled beta2-agonists in combination with inhaled corticosteroids.
- The use of beta2-agonists in sports is regulated by WADA due to possible performance enhancing effects.

What are the new findings?

- Beta2-agonists improve anaerobic performance in healthy subjects.
- Beta2-agonists improve sprint and strength performance in healthy subjects.
- Long-term treatment enhances performance more than short-term treatment.
- Route of administration, type of beta2-agonist or dose was not related to the performance enhancing effect of beta2-agonists.

ABSTRACT

Objectives. We aimed to examine the effect of beta2-agonists on anaerobic performance in healthy non-asthmatic subjects.

Design. Systematic review and meta-analysis.

Eligibility criteria. We searched four databases (PubMed, Embase, SPORTDiscus and Web of Science) for randomized controlled trials, published until October 2018, examining the effect of beta2-agonists on maximal physical performance lasting one minute or shorter. Data are presented as standardized difference in mean (SDM) with 95% confidence intervals.

Results. Thirty-two studies were included in the present meta-analysis. The studies include 41 different randomized and placebo controlled comparisons with beta2-agonists comprising 317 participants in crossover trials, and 110 participants in parallel trials. Beta2-agonists improved anaerobic performance by 5 % (SMD 0.27, 0.14-0.41) and the effect was related to treatment duration. In a stratified analysis the SDM was 0.18 (0.05-0.30) for acute treatment and 0.53 (0.19-0.88) for treatment for multiple weeks. Analyses stratified for the type of performance showed that strength 0.33 (0.12-0.53) and sprint 0.18 (0.05- 0.30) performance was improved by beta2-agonists.

Conclusion/implication. Our study shows that non-asthmatic subjects can improve sprint and strength performance by using beta2-agonists. Multiple weeks of treatment is more effective for

improving performance than acute treatment. Our results supports that the usage of beta2-agonists should be controlled and restricted to athletes with documented asthma.

Systematic review registration. PROSPERO CRD42018109223

INTRODUCTION

Asthma is one of the World's most common chronic diseases and affects people of all ages [1]. Elite athletes, especially endurance athletes regularly performing heavily increased ventilation, have increased risk of asthma [2]. Asthma is the most common chronic disease in athletes participating in the Olympic Games [3]. The gold standard for asthma therapy is inhaled beta2-agonists in combination with inhaled corticosteroids [1]. However, the use of beta2-agonists by athletes is surrounded by controversy. Inhaled beta2-agonists became available just before the Olympic Games in 1972 where the International Olympic Committee's (IOC) Medical Commission, prohibited their use due to a possible performance enhancing effect. After 1972, the regulations regarding the use of inhaled beta2-agonists in elite athletes have been revised on numerous occasions [3]. The World Anti-Doping Agency (WADA) annually updates the prohibited list, a list of substances and methods prohibited in elite sports. The prohibited list from January the 1st 2019 prohibits all use of beta2-agonists except inhaled salbutamol (maximum 1600 micrograms over 24 hours in divided doses not to exceed 800 micrograms over 12 hours starting from any dose), inhaled formoterol (maximum delivered dose of 54 micrograms over 24 hours) and inhaled salmeterol (maximum 200 micrograms over 24 hours) [4].

It has been speculated that non-asthmatic athletes use beta2-agonists believing it will improve their performance [5] and asthmatic athletes have consistently outperformed non-asthmatic athletes during the Olympic Games [2]. Thus, the possible performance enhancing effect of beta2-agonists have been examined in multiple studies. In 2007, Kindermann reviewed the effect of beta2-agonists and concluded that inhaled beta2-agonists do not enhance endurance performance, anaerobic power or muscle strength while oral beta2-agonists seemed to improve both endurance and strength [5]. The year after, the IOC consensus statement considered inhaled beta2-agonists not to enhance endurance performance, while oral ingestion of salbutamol was considered to increase strength [6]. However, the joint Task Force of European Respiratory Society (ERS) and European Academy of

Allergy and Clinical Immunology (EAACI) concluded that there were no evidence to suggest that asthma drugs improve physical performance in healthy athletes [7]. In 2011, Pluim et al. published the first systematic review and meta-analysis on the effect of beta2-agonists on physical performance in healthy athletes including studies published before august 2009. They did not detect any effect of inhaled beta2-agonists on aerobic, anaerobic or sprint performance, but some weak evidence indicating a performance enhancing effect of systemic beta2-agonists on anaerobic performance. Since august 2009, multiple studies have investigated the effect of beta2-agonists on anaerobic performance, and continuous controversy regarding the use of beta2-agonists in sports exists, which have been highlighted in recent beta2-agonist anti-doping investigations involving world-class athletes [8, 9]. Therefore, the aim of our systematic review and meta-analysis was to assess the effect of beta2-agonists on anaerobic performance in healthy non-asthmatic subjects.

METHODS

Search strategy and selection criteria

The present study is a systematic review and a meta-analysis. The study protocol was registered at Prospero on September 18th , 2018, with registration number CRD42018109223 and complied with the PRISMA 2009 Guidelines.[10]

Literature search

We performed a systematic search of published randomised controlled trials (RCT) that examined the effect of beta2-agonists on physical performance in healthy humans on October 29th 2018. The first author (AR) performed the search in cooperation with a librarian. Peer-reviewed articles published in English were identified from four electronic databases: PubMed (All fields), Embase (All fields), SPORTDiscus (Text) and Web of Science (Topic). The search strategy consisted of four blocks of terms: (healthy OR non-asthmatic OR athletes) AND (salbutamol OR formoterol OR salmeterol OR terbutaline OR albuterol) AND (exhaustion OR power OR endurance OR strength OR aerobe OR anaerobe OR exercise OR performance) AND (rct OR randomized controlled trial* OR randomized control trial* OR controlled trial*). The search identified 398 records (PubMed 100, Embase 105, Web of Sience, 36 and SPORTDiscus 157). After elimination of duplicates, 290 record remained (Figure 1).

Inclusion criteria and selection process

Two authors (AR and LBA) independently assessed the studies for eligibility with subsequent consensus by discussion. We included RCTs including healthy, non-asthmatic subjects examining the effect of beta2-agonists on maximal physical performance.

Studies investigating the effect of salbutamol/albuterol, salmeterol, formoterol, and terbutaline alone or in various combinations, administered by inhalation, orally or by infusion were included. There were no restrictions related to dose or duration of treatment.

We excluded studies examining physical performance with a duration of more than 60 seconds per trial and non-performance variables like neuromuscular function, oxygen kinetics and ventilation.

Included studies

After screening of titles and abstracts, 45 studies were selected for full text eligibility assessment. Of these, 44 fulfilled the inclusion criteria, while 22 other studies were included based on previous knowledge of the studies or screening of the reference lists of the studies included. In total 67 studies met the primary inclusion criteria. As the present study includes only performance outcomes of one minute or less, 34 studies presenting data from performance outcomes with a duration of more than one minute were excluded. Thus, 33 studies were included in the present meta-analysis (figure 1).

----Insert **Figure 1.** Flow chart of included studies as proposed by PRISMA statement 2009[10] here ---

Study quality assessment

The included studies was assessed using the Cochrane Collaboration Risk of Bias Tool to evaluate seven bias domains [11] The domains were scored as low risk of bias, high risk of bias or unknown risk of bias according to the tool. For the domain "blinding of participants and personnel" the studies were scored as high risk of bias if the subject experienced side effects of the beta2-agonists even if the blinding procedure in the study was preformed according to the criteria for low risk of bias. The domains "incomplete data" and "selective reporting" were set to "low risk of bias" due to the nature of the studies. The 7th domain (other bias) was defined as "Participants screened for asthma". For a study to be classified as "Low risk for bias" on the 7th domain, a physical examination or an objective measure of bronchial hyperresponsiveness was required. Lung function measurement at rest, stethoscopy or a questionnaire on medical history or bronchial complaints were considered as a "high risk of bias". The studies were classified as studies with high risk of bias if they scored "high risk of bias" in one domain or more, and low risk of bias if all domains in the risk of bias assessment tool

were scored as “low risk of bias” or “unclear risk of bias”. Two authors (AR and JS) independently assessed the studies not included in the meta-analysis by Pluim et al. [12], while the studies already assessed by Pluim and coworkers were evaluated by one author (AR). Any discrepancy in the assessments were resolved by discussion. An eight domain was added to the risk of bias toll reporting the days between wash out period between the treatments in crossover studies. Carryover effect and period effect were also extracted from the study as a part of the bias assessment.

Analysis

AR and TS conducted data extraction of study results separately and settled discrepancy by mutual agreement. AR contacted the corresponding author of papers when an e-mail address was provided and relevant outcomes were reported in figures [13, 14] or as “no significant difference” [15]. Beloka et al. [15] was excluded as the authors could not provide data. When data was presented in figures only and no e-mail address for the corresponding author was provided or the corresponding author had no access to the requested data, data were extracted manually [13, 16-18] by AR. The main outcome was physical performance lasting one minute or less and defined as anaerobic performance. Anaerobic performance was further categorized into sprint performance assessed by maximal running [19-21], ergometer cycling [14, 16, 22-37] (mean power/total work) or swim ergometer sprint [37]. Strength performance (leg) was assessed by one repetition maximum [38] or maximal voluntary contraction (MVC) [13, 14, 17, 18, 25, 33-35, 39-41] and power performance was assess by vertical jump [20] and force velocity sprint [42]. If several outcomes were presented after one intervention, only one outcome was included in each meta-analysis. Sprint outcomes were prioritized over strength outcomes and long sprints were prioritized over short sprints and power outcomes. When results from multiple trials were reported separately, the results from all trials were meta-analyzed into one variable and this variable was used in further analysis. When trials were performed pre and post exercise only the pre-exercise trial was included in the meta-analysis. When MVC was measured at different velocities, angles or muscle groups, all trials were meta-analyzed into

one variable and this variable was used in further analysis. The interventions were categorized in four different ways; 1) Type of beta2- agonist: Salbutamol, formoterol, terbutaline and salmeterol. 2) Administration route: Inhaled, oral and infusion (infusion was only used in one comparison and not a category in the meta-regression). 3) Duration of treatment: Acute treatment and multiple weeks of treatment 4) Dose: Low dose, high dose and supra therapeutic/above the dose approved by the World Anti-Doping Agency [43, 4] (Supplementary table 1). The different interventions were treated as categorical variables in the meta-regression analysis. Correlation between performance with active treatment and placebo was seldom reported in the included studies thus a correlation coefficient of 0.5 was imputed for all comparisons.

Statistics

Extracted data from individual studies were collated and prepared for meta-analysis (computing standard deviations (SD) when standard error of the mean and 95% confidence intervals were reported) in Excel (Microsoft Corp) prior to transfer into Comprehensive Meta-Analysis version 3, (CMA.V3) (Biostat, Inc., Englewood, NJ, USA). Further analyses were performed in CMA. The meta-analyses were performed with random effects models and effect estimates are presented as standardized difference in means (SDM) with 95 % confidence intervals (CI). Heterogeneity is presented as I^2, and p-value. Whether or not the effect size was related to type of beta2-agonist, administration route, duration of treatment and dose was analyzed by meta-regression (test of model). In addition, meta-regression was used to perform the Goodness of fit to assess the presence of unexplained variance in the model. The proportion of total between study variance explained by the covariate is expressed as R^2 analog. Potential publication bias was assessed by funnel plot, Begg and Mazumdar rank correlation test and classic fail-safe N. Standardized difference in means was back transferred to original units by multiplying SMD with baseline SD from original studies and expressed as percent change from baseline value. Adequacy of sample size in each included study was assessed by calculation of the sample size required for the effect found in the respective study to

obtain an alpha of 0.05 and a beta of 0.2 [43]. Skewness of outcomes was assessed as baseline mean/SD. Variables with a mean/SD ratio > 2 was considered skewed [44]. Significance level was set to $p<0.05$.

RESULTS

Study characteristics

The present meta-analysis consists of 32 RCTs including 26 studies with crossover design [13, 16, 19-33, 35-37, 39-42, 45, 46] (six comparing two different interventions with placebo [21, 22, 40-42, 45] and 6 studies [14, 17, 18, 34, 38, 47] with parallel design (one with both acute and multiple week intervention [14]). The meta-analysis include 41 different randomized and placebo controlled comparisons with beta2-agonists comprising 317 participants in crossover trials including 53 participants in three-way crossover trials. Fifty-seven participants received beta2-agonists and 53 participants received placebo in the parallel trials. The included studies are summarized in table 1.

Table 1: Characteristics of the studies included in the systematic review and meta-analysis.

Study, year	Design	Subjects: n, sex, age (years ± SD)	Fitness level	Intervention	Outcomes
Halabchi et al., 2017 [20]	Crossover	20, m, 17 ± 1	Junior professional football players	Inhaled salbutamol 200 µg	Fastest 30 meter sprint Vertical Jump
Kalsen et al., 2016a [32]	Crossover	9, m, 24 ± 3	Recreational active	Inhaled terbutaline 15 mg	10 s cycle sprint
Kalsen et al., 2016b [33]	Crossover	13, m, 32 ± 8	Training 1.8 ± 1 h/w	Inhaled formoterol 54 µg	30 s cycle sprint
Hostrup et al., 2016 [14]	Parallel	20, m, 26 ± 4	National level endurance athletes	Oral salbutamol 8mg acute and 8 mg/day for two weeks	3 x 30 s cycle sprint MVC
Altarawneh et al., 2016 [37]	Crossover	7, m, 23 ± 6	Recreationally active 4 d/w	Inhaled salbutamol 1000 µg	3 set 5 x 4 s cycle sprint
Hostrup et al., 2015 [34]	Parallel	18, m, 24 ± 3	Recreationally active 4-8 h/w	Oral terbutaline 5 mg/30 twice daily for 28 ± 1 days	30s cycling sprint MVC
Dickinson et al., 2015 [21]	Three-way Crossover	7/6, m/f, 23 ± 4/21 ± 1	Competitive soccer ≥ 3 d/w	Inhaled salbutamol 800 µg Inhaled salbutamol 1600 µg	Repeated sprint ability
Kalsen et al., 2014 [46]	Crossover	13/4, m/f, 18 ± 4	Elite swimmers	Inhaled 1600 µg, salbutamol 200 µg salmeterol, and 36 µg formoterol	Swim ergometer sprint MVC
Hostrup et al., 2014a [45]	Crossover	Exp1 10, m 24 ± 3 Exp 2, 20, m, 24 ± 4	Exp 1: Highly trained Exp 2: Trained	Exp 1: Inhaled terbutaline 20mg Exp 2: Oral terbutaline 5mg/15 kg	MVC
Hostrup et al., 2014b [35]	Crossover	9, m, 24 ± 3	Recreationally active	Inhaled terbutaline 15 mg	30 s cycle sprint MVC
Dickinson et al., 2014 [38]	Parallel	16, m, 20 ± 2	Amateur-level competition	Inhaled salbutamol 1600 µg /day for 6 weeks	1 RM
Sanchez et al., 2013 [19]	Crossover	7, m, 29 ± 6	Competitive athletes, 10 h/week	Oral terbutaline 8 mg	70-m running sprint

Decorte et al., 2013 [41]	Three-way Crossover	13, m, 33 ± 6	Highly trained cyclists, triathletes and runners, 12 ± 3 h/w	Inhaled salbutamol 200 µg Inhaled salbutamol 800 µg	MVC
Sanchez et al., 2012 [42]	Three-way Crossover	8, m, 23 ± 1	Recreational sports, 10 h/w	Oral salbutamol 6 mg acute Oral salbutamol 12 mg/day for 3 weeks	Force–velocity sprint on cycle ergometer
Descorte et al 2008 [40]	Three-way Crossover	9, m, 23 ± 3	Healthy non-athletes	Inhaled salbutamol 200 µg Inhaled salbutamol 800 µg	MVC
Le Pance et al., 2007 [30]	Crossover	12, f, 22 ± 3	Recreationally active 1–3 d/w	Oral salbutamol 4mg	30 s cycle sprint
Le Panse et al., 2006 [31]	Crossover	14, f, 22 ± 1	Recreationally active (7), sedentary (7)	Oral salbutamol 12mg/day for 4 wk	30 s cycle sprint
Le Panse et al. 2005 [29]	Crossover	15, m, 30 ± 6	Strength-trained athletes (8), sedentary (7)	Oral salbutamol 12mg/day for 3 wk	30 s cycle sprint
Collomp et al., 2005 [36]	Crossover	13, m, 31 ± 6	Sedentary non-athletes and recreational weight-lifters, 1–3 d/w	Oral salbutamol 4mg	30 s cycle sprint
Caruso et al., 2005 [18]	Parallel	22, m, 18-22	Healthy non-athletes (after 10 weeks of strength training)	Oral salbutamol 4-16mg/day for 3 weeks	MVC
Stewart et al., 2002 [22]	Three-way Crossover	10, m, 26 20-30	Highly trained athletes	Inhaled formoterole 12 µg Inhaled salbutamol 400 µg	30 s cycle sprint
Van Bak et al 2000 [13]	Crossover	16, m, 23 ± 2	Healthy non-athletes	Oral salbutamol 4mg	MVC
Mc Dowell et al., 1997 [27]	Crossover	11, m, 25 ± 4	Amateur cyclists	Inhaled salmeterol 42 µg	30 s cycle sprint
Norris et al., 1996 [24]	Crossover	15, m, 25 ± 4	Highly trained cyclists	Inhaled salbutamol 400 µg	60 s cycle sprint
Morton et al. 1996 [25]	Crossover	16, m, 23 ± 4	High performance cyclists and triathletes	Inhaled salmeterol 50 µg	10 s cycle sprint MVC
Lemmer et al. 1995 [28]	Crossover	14, m, 23 ± 1	Elite cyclists	Inhaled salbutamol 360 µg	30 s cycle sprint
Caruso et al., 1995 [47]	Parallel	22, m, 21 ± 3	Sedentary or recreationally active non-athletes	Oral salbutamol 16 mg for 6 weeks	MVC
Morton et al. 1993 [39]	Crossover	22, m, 22 ± 4	Athletes (power events)	Inhaled salbutamol 200 µg	10 s cycle sprint MVC
Signorile et al. 1992 [23]	Crossover	8/7, m/f, 18–33	Healthy non-athletes	Inhaled salbutamol 360 µg	4 x 15 s cycle sprint
Morton et al. 1992 [16]	Crossover	16/1 m/f, 22 ± 4	High performance runners	Inhaled salmeterol 50 µg	30 s cycle sprint
Meeuwisse et al. 1992 [26]	Crossover	7, m, 24 ± 4	Trained cyclists	Inhaled salbutamol 200 mg	30 s cycle sprint
Martineau et al. 1992[17]	Parallel	12, m, 25 ± 5	Highly trained cyclists	Inhaled salbutamol 200 mg	30 s cycle sprint

MVC: Maximal voluntary isometric contraction, RM: repetition maximum, m: male, f: female, s: seconds h/w: hours per week, d/w: days per week, RM: repetition maximum, Exp: experiment, iv: intra venous

Risk of bias

Twenty studies (63%) had high risk of bias in one domain or more and the washout period varied from one day to four weeks between the studies (supplementary table 2). The effect of beta2-agonists was not related to risk of bias for any performance category (table 3). One study [19] reported period effect (p=0.45) and carryover effect (p=0.91) in addition to treatment effect (p= 0.83).

Examination of potential publication bias by assessing the funnel plot indicated a tendency for publishing studies that found a significant effect of beta2-agonists (supplementary figure 3). The Begg and Mazumdar rank correlation test confirmed publication bias with a 1-tailed p-value =0.009 and the fail-safe N was 369 meaning that there would need to exist 369 unpublished comparisons finding no effect of beta2-agonists to nullify the effect found in the 41 comparisons in our study.

The effect of beta2-agonists

Beta2-agonists improved anaerobic performance compared to placebo with a SDM of 0.273 (0.140-0.407) (figure 2). The SDMs for the included studies were heterogeneous (I^2= 56%, p<0.001) and the difference was related to duration of treatment (p=0.043, R^2=0.18) (table 3). In stratified analysis the SDM for acute treatment was 0.176 (0.047 - 0.304) and 0.545 (0.206 - 0.883) for multiple weeks of treatment.

Table 2: Meta-analysis for each outcome measure

Outcome	Number of comparisons	Meta-analysis of each outcome			Test of heterogeneity	
		SDM	CI	p-value	I^2*	p-value
Anaerobic performance	41	0.273	0.140-0.407	p<0.001	56%	p<0.001
Sprint performance	28	0.179	0.053 – 0.304	0.005	27%	0.091
Strength performance	19	0.325	0.121 – 0.529	0.002	68%	<0.001
Power performance	4	0.161	-0.259 – 0.725	0.109	88%	<0.001

SDM; Standardized difference in mean, CI; Confidence interval, Anaerobic performance; maximal physical performance lasting one minute or less, Sprint performance; maximal running, cycling or swimming for one minute or less, Strength performance; maximal voluntary contraction or one repetition maximum, Power performance; force velocity sprint or vertical jump.

Table 3. Regression of standardized difference in means against type of beta2-agonist, administration route, duration of treatment, dose and risk of bias treated as categorical variables.

R^2 analog: Proportion of total between-study variance explained by the covariate. Anaerobic performance; maximal physical performance lasting one minute or less, Sprint performance; maximal running cycling or swimming for one minute or less, Strength performance; maximal voluntary contraction or one repetition maximum

	Anaerobic performance	Sprint performance	Strength performance
Type of beta2-agonist; Reference salbutamol			
Test of model, p-value	0.275	0.059	0.060
Goodness of fit, p-value	<0.001	0.228	<0.001
R^2 analog	0.00	0.48	0.25
Administration route; Reference inhaled			
Test of model, p-value	0.039	0.410	0.101
Goodness of fit, p-value	<0.001	0.100	<0.001
R^2 analog	0.00	0.02	0.00
Duration of treatment; Reference acute			
Test of model, p-value	0.043	0.434	0.010
Goodness of fit, p-value	<0.001	0.093	0.002
R^2 analog	0.18	0.00	0.43
Dose ; Reference low dose			
Test of model, p-value	0.686	0.188	0.730
Goodness of fit, p-value	<0.001	0.149	<0.001
R^2 analog	0.00	0.19	0.00
Type, route, duration, dose			
Test of model, p-value	0.249	0.228	0.008
Goodness of fit, p-value	<0.001	0.184	0.051
R^2 analog	0.00	0.25	0.49
Risk of bias; Referance High risk			
Test of model, p-value	0.251	0.118	0.331
Goodness of fit, p-value	<0.001	0.142	<0.001
R^2 analog	0.00	0.19	0.00

--- Insert Figure 2. : Forest plot for the effect of beta2-agonists on anaerobic performance. here ---

The SDM from 28 comparisons showed that beta2-agonists improved sprint performance (table 2, supplementary figure 1) and the effect of the beta2-agonists was not related to type of beta2-agonist, administration route, duration of treatment, or dose (table 3).

The effect on strength performance was assessed in 19 comparisons and beta2-agonists improved maximal muscular strength and the results were heterogeneous (I^2=68%, p=0.010) (table 2). The effect was related to the duration for treatment in a simple model (p<0.001, R^2=0.43) and all variants of treatment combined in one model (p<0.001, R^2=0.49) (table 3). For strength performance the SDM

was greater (p=0.010) after multiple weeks of treatment 0.66 (0.08-1.24) compared to acute treatment 0.17 (0.00-0.33) (figure 3).

--- Insert Figure 3: Forest plot for the effect of beta2-agonists on strength performance stratified by route of administration here ---

Power performance was assessed in four comparisons and no statistically significant effect of beta2-agonists was found (table 2, supplementary figure 2).

Sample size and skewness

One of the 32 included studies [32] included adequate numbers of participants to obtain an alpha < 0.05 and a beta < 0.2 (supplementary table 2). None of the 40 comparisons reporting baseline mean and SD/SE were skewed.

Sensitivity analysis

We performed sensitivity analysis excluding the six comparisons with the highest SDM and the combined SDM for the remaining 36 interventions was 0.168 (0.066-0.270, p=0.001). We also performed a sensitivity analysis excluding the 12 comparisons with less than 10 data pairs with beta2-agonist and placebo (SMD 0.201, (0.087-0.315). In addition we meta-analyzed the effects of beta2-agonists on anaerobic performance including only comparisons with different subjects and the SDM of these 35 comparisons was 0.279 (0.142-416, p<0.001). This means that the results are consistent also when stricter criteria for including studies are used.

Percent change

A SMD of 0.273 corresponds to a mean improvement of 4.7 % (SD 2.8) in the 32 included comparisons reporting baseline mean and SD or SE. Specifically, 70 m sprint time and MVC improved by five percent in populations of competitive athletes [19] and high performance cyclists and triathletes [25], respectively. If we apply the SMD specific for sprint (0.179) and strength (0.325)

performance, the estimated percent improvement from beta2-agonist would be three and six present in the respective populations.

DISCUSSION

This meta-analysis of RCTs that examined the effect of beta2-agonists on anaerobic performance provides the most comprehensive quantitative summary of the evidence to date including 32 RCTs with 41 placebo-controlled comparisons comprising 427 participants. Twenty studies were classified as high risk of bias due to side effects or inadequate screening for asthma. However, these studies showed the same effect on performance as the other included studies.

Our study extends previous reviews by including studies not previously meta-analysed and with an in depth analysis of anaerobic performance. Our meta-analysis shows that beta2-agonists improve anaerobic performance by five percent, an improvement that would change the outcome of most athletic competitions. Multiple weeks of treatment had a larger effect than acute treatment and the treatment explained 18% of the total between study (comparison) variance.

To our knowledge, no other studies have pooled data using meta-analysis on the effects of beta2-agonists on anaerobic performance. Pluim et al. [12] presented a meta-analysis stratified by administration route (oral or inhaled) and analysed test specific outcomes separately. Pluim et al. [12] did not find any effect of inhaled beta2-agonists on any outcome while the pooled results from four studies revealed a significant positive effect of oral beta2-agonists on peak power, but not mean power during a 30 seconds Wingate test. Since the review by Pluim et al. [12], 14 studies meeting our inclusion criteria have been published. In our study, we included comparisons with inhaled and oral beta2-agonists in the same analysis, as we hypothesized that inhalation and oral ingestion may provide the same physiological stimuli, which depends on the dose and systemic bioavailability, because the two administration routes may induce similar serum concentrations of beta2-agonists [45]. This assumption was supported by the findings in the present study, as route of administration was not related to the effect of beta2-agonists on anaerobic performance. Multiple weeks of treatment with beta2-agonists had superior effect over acute treatment. This may be related to a

hypertrophic effect after multiple weeks of use, demonstrated after both inhaled [48] and oral beta2-agonists [34, 49].

Analysis of performance categories

Sprint performance was improved by the use of beta2-agonists. The effect size from the 28 comparisons included was not heterogeneous. The finding is in contrast to Pluim et al. [12] who meta-analysed four studies with oral beta2-agonists and five studies with inhaled beta2-agonists separately, and reported a not statistically significant improvement in mean power during a 30 s cycling tests. The present study provides greater statistical power due to more than five times as many comparisons in the meta-analysis, which may explain why we found a significant effect and Pluim et al. [12] did not.

Beta2-agonists improved strength performance. The effect was heterogeneous and related to duration of treatment where treatment with beta2-agonists over multiple weeks provided a greater improvement in strength compared to interventions consisting of acute treatment. Difference in duration of treatment explained 43% of the total between study variance. When all covariates were included in one model, the model explained 49 % of the total between study variance. The superior effect with multiple weeks of treatment may be related to a hypertrophic effect demonstrated after multiple weeks of both inhaled [48] and oral beta2-agonists [34, 49].

Only four interventions investigated the effect of beta2-agonists on power performance and the effect was not statistically significant. However, the study investigating the effect of beta2-agonists on force-velocity cycling after acute and multiple weeks of treatment was among the comparisons with the largest effect sizes while the two studies with vertical jump as outcome found no effect of beta2-agonists (figure 5).

Bias

The funnel plot indicated a tendency for published studies that found a significant effect of beta2-agonists and the Begg and Mazumdar rank correlation test indicated publication bias. However, the fail-safe N is 369, meaning that there would need to be nine not published comparisons with no effect per published comparison to nullify the effect of the 41 comparisons included in the present study. We also performed a sensitivity analysis by removing the six studies with the largest SDM in favour of beta2-agonists and even without these studies, the effect of beta2-agonists on anaerobic performance was still highly statistically significant. This strengthen the assumption that the effects of beta2-agonists on anaerobic performance presented in the present study are real effects and not caused by publication bias.

Tachycardia and tremor are characteristic adverse side effects of beta2-agonists [35, 50] and ten studies reported side effects of the beta2-agonists. The side effects may make the participants aware of whether they receive beta2-agonists or placebo, thus brake the blinding and possibly motivate the participants to perform better when receiving beta2-agonists. In one study [32], seven out of nine participants reported side effects after receiving beta2-agonists. However, the subjects who did not experience side effects had comparable performance to participants with side effects in the latter study, indicating that possible failure to blind the participants of treatment did not influence the results. Fourteen studies did not screen the participants for asthma with objective tests, possibly including subjects with exercise induced bronchial constrictions (EIB). However, EIB probably do not influence sprint and strength performance. Individual studies included in our-meta analysis found no difference in anaerobic performance between cyclists with and without side effects [33] or swimmers with and without airway hyper responsiveness [46] and risk for bias did not influence the SDM in any analysis.

Our study included 12 comparisons between placebo and beta2-agonists that comprised less than 10 pairs (less than 20 subjects in parallel studies and 10 subjects in crossover studies) and only one of the included studies had a sample size providing an alpha < 0.05 and a beta < 0.2 for the measured

effect. This low sample size in the individual studies may have introduced sparse data bias in the SMD [51, 52]. However, when we performed a sensitivity analysis excluding these 12 comparisons the effect of beta2-agonists on anaerobic performance was practically the same. Normal distribution of data is an important assumption in meta-analysis of continuous data and all included studies appeared to have normally distributed baseline data.

The meta-regression model testing the effect of administration route indicated a significant effect ($p=0.039$) and the analog R^2 was 0.00, which should be interpreted as the proportion of between study variance explained by administration route is 0%. This is contra intuitive, but possible. In both primary studies and meta-analysis, R^2 is based on two estimates of variance, but unlike in primary studies R^2 in meta-analysis is based on separate analysis where both estimates (T^2) can be over or under estimated. Thus, a positive effect but no explained variation for route (or any other covariate) is a possible outcome of the analysis if the effect is small [53]. In the particular case of interoperating the effect of administration route on anaerobic performance, we err on the side of caution. Therefore, we conclude that the apparently significant effect of administration route is unreliable, not clinically significant, and should interpreted it as no effect.

A SMD may be difficult to interoperate. We therefore back transferred the SMD to the units presented in the respective included studies and computed the effect of beta2-agonists as percent change from baseline. The mean improvement on anaerobic performance was five percent. However, this must be interpreted with caution as the percent change is dependent on the population (mean and SD). Similarly, the SMDs in the present study are low to moderate according to Cohen's rule of thumb [54]. However, within elite sports the difference between failure and success is often marginal, and if beta2-agonists have a small effect on anaerobic performance it may decide the outcome of the competition. A five percent difference may be small in many aspects, but when it comes to athletic performance, it will have vast impact on the result in almost any competition. We would therefore recommend that WADA has criteria for the use of beta2-agonists in sports where

anaerobic performance essential for the outcome. The criteria should be based on objective tests for asthma and a doctor's diagnosis. Beta2-agonists should not be prohibited in athletic completions, because at is a necessary treatment for athletes with asthma, but it should be regulated and controlled.

Strength and limitations

The study is strengthened by the systematic search of the literature in multiple databases and it is likely that all relevant studies were identified. We included RCTs only. We consider all maximal performance tests lasting one minute or shorter to be a measure of anaerobic performance thus we used SMD as outcome in the meta-analysis [55]. This resulted in a large sample size and a high statistical power. Further, we performed subgroup analysis on outcome categories and meta-regression to investigate the effect of the different types of intervention.

A weakness in the present study is that all outcomes are assessed by laboratory tests, not identical to actual athletic competitions. Therefore, reliable, sensitive and valid test protocols are of importance. The sprint tests are closed-end tests which are recommended over open-end tests and the coefficients of variation for open-end tests are reported to decrease with increased intensity or decreased duration [56]. However, the quality of the test protocols are not accounted for in the present analysis. The fitness level of the participants vary from untrained to elite athletes, but the athletes do not necessarily exercise for, or compete in events where the abilities tested in the included studies are the most relevant factors for performance in the respective sport disciplines. Thus, fitness level is not included in the analysis even if fitness level may confound the effect of beta2-agonists on physical performance [57, 58]. The meta-analysis assumes independence between the subjects included. In the present study, the same subjects are included twice in the same analysis if they participated in a three-way crossover study with placebo and two different interventions beta2-agonists or if the same subjects are assessed after acute and multiple weeks of beta2-agonists or placebo. To investigate the effect of this potential bias we performed a meta-analysis including

comparisons with different people only, and the effect size was practically the same as when all relevant comparisons were included. There is also a possibility that the same subjects are included in different studies. Few studies reported correlation between trial results thus the correlation coefficient for pre and post-test has been set to 0.5 for all studies. This is lower than data made available from Dickinson et al. [38] by request and similar to what Pluim et al. [12] reported. In the analysis of anaerobic performance only, 18% of the variation in effect sizes from the individual comparisons were explained by duration of treatment thus the reason for most of the heterogeneity was not clear. The effect of treatment in crossover studies are possibly influenced by period effect and carryover effect, and these effects were only examined in one of the 26 crossover studies included in the meta analysis. The carryover effect can be caused by a too short washout period. The duration of effect is probably related to the half-life of the different beta2-agonists, deactivation of receptors and the dose administered. Thus, the minimum washout period is difficult to assess. The half-life of the beta2-agonists assessed in the present study range from 3-6 hours (salbutamol) to 10 hours (formoterol) [59].

Based on the previously mentioned limitations the findings should be interpreted with caution, but there is consistency in the results demonstrating that anaerobic performance is enhanced in healthy individuals by use of beta2-agonists.

Conclusion

Our systematic review and meta-analysis which summarizes the current scientific evidence from 32 studies of which 12 are low risk of bias. It shows that non-asthmatics can improve their anaerobic performance by using beta2-agonists. Beta2-agonists improve both sprint and strength performance, with multiple weeks of use being more effective compared to acute use. The results from the present study should be of interest to the World Anti-Doping Agency and anyone who is interested in equal opportunities in competitive sports. The use of beta2-agonists in athletes should

therefore be controlled/regulated and limited to those with an asthma diagnosis documented with objective tests.

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Author contributions: All authors reviewed the report. AR generated the hypotheses did the literature search analyzed the data and wrote the first draft of the manuscript. AR, TS, JS and LBA revised the manuscript critically for important intellectual content. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. AR and TS extracted the data. JS and AR assessed bias. AR and LBA evaluated studies for inclusion.

LEGENDS

Figure 1. Flow chart of included studies as proposed by Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement 2009 [8]

Figure 2: Forest plot for the effect of beta2-agonists on anaerobic performance

Figure 3: Forest plot for the effect of beta2-agonists on strength performance stratified by route of administration

Supplementary figure 1: Forest plot for the effect of beta-2 agonists on sprint performance

Supplementary figure 2: Forest plot for the effect of beta2-agonists on power performance

Supplementary figure 3: Funnel plot for the effect of beta2-agonists on anaerobe performance including observed studies (white dots) and imputed studies (Black dots). The plot indicate a proclivity for publishing studies that found a significant effect of beta2 -agonists. When this is

balanced by imputing studies the standardized difference in means is still in favour of beta2-agonists compared to placebo.

Supplementary table 1: Classification of all doses administrated in the included studies according to category.

Supplementary table 2: The quality of the included studies assessed using the Cochrane Collaboration Risk of Bias Tool.[1]

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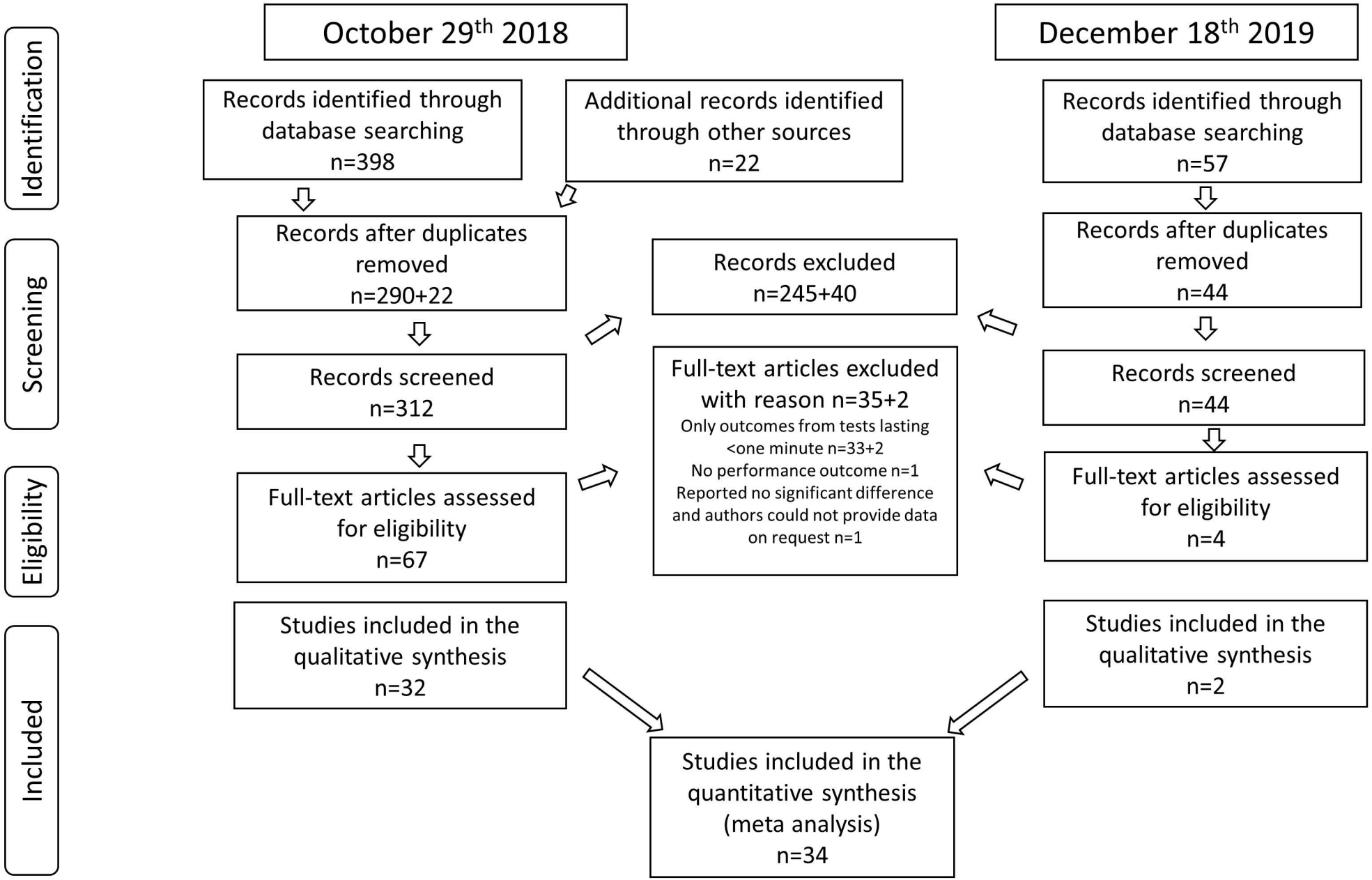
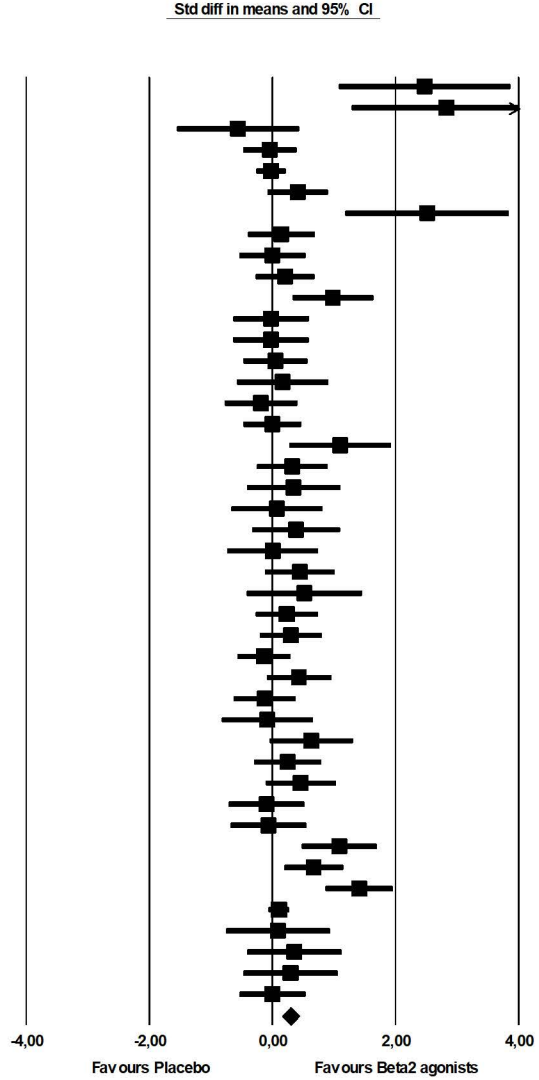
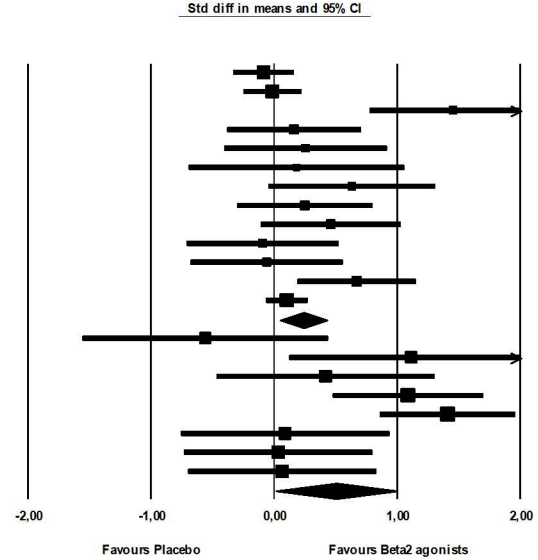


Figure 1. Flow chart of included studies as proposed by Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement 2009. [11]

Study name	Outcome	Statistics for each study						
		Variance	Std diff in means	Standard error	Upper limit	Lower limit	Z-Value	p-Value
Sanchez et al., 2012, acute	Power, Force-Velocity cycling	0,508	2,475	0,713	3,872	1,078	3,473	0,001
Sanchez et al., 2012, multiple	Power, Force-Velocity cycling	0,625	2,828	0,791	4,378	1,279	3,578	0,000
Dickinson et al., 2014	Strength, 1RM	0,260	-0,558	0,510	0,441	-1,557	-1,095	0,273
Halabchi et al. 2017	Sprint, 30 m run	0,050	-0,042	0,224	0,396	-0,481	-0,190	0,850
Morton et al., 1996	Sprint, 10 s cycling	0,016	-0,023	0,125	0,222	-0,268	-0,187	0,852
Morton et al., 1993	Sprint, 10 s cycling	0,064	0,412	0,253	0,907	-0,083	1,631	0,103
Kalsen et al., 2016a	Sprint, 10 s cycling	0,463	2,515	0,680	3,848	1,182	3,698	0,000
Dickinson et al., 2015, 800	Sprint, 12x17,5 m running	0,078	0,148	0,279	0,695	-0,398	0,532	0,594
Dickinson et al., 2015, 1600	Sprint, 12x17,5 m running	0,077	0,000	0,277	0,544	-0,544	0,000	1,000
Kalsen et al., 2014	Sprint, 200 m swim	0,060	0,207	0,245	0,688	-0,273	0,845	0,398
Kalsen et al., 2016b	Sprint, 30 s cycling	0,114	0,983	0,338	1,645	0,321	2,911	0,004
Stewart et al., 2002, for	Sprint, 30 s cycling	0,100	-0,021	0,316	0,599	-0,641	-0,066	0,948
Stewart et al., 2002, sal	Sprint, 30 s cycling	0,100	-0,024	0,316	0,595	-0,644	-0,077	0,939
Lemmer et al.,1995	Sprint, 30 s cycling	0,072	0,048	0,267	0,572	-0,476	0,181	0,857
Meeuwisse et al., 1992	Sprint, 30 s cycling	0,145	0,165	0,381	0,911	-0,580	0,435	0,664
Mc Dowell et al., 1997	Sprint, 30 s cycling	0,092	-0,183	0,304	0,413	-0,779	-0,603	0,547
Morton et al., 1992	Sprint, 30 s cycling	0,059	0,000	0,243	0,475	-0,475	0,000	1,000
Hostrup et al., 2014b	Sprint, 30 s cycling	0,178	1,100	0,422	1,928	0,272	2,605	0,009
Le Pance et al., 2007	Sprint, 30 s cycling	0,088	0,324	0,296	0,905	-0,256	1,094	0,274
Le Panse et al., 2006, trained	Sprint, 30 s cycling	0,151	0,344	0,389	1,106	-0,419	0,884	0,377
Le Panse et al., 2006, untrained	Sprint, 30 s cycling	0,143	0,073	0,378	0,815	-0,668	0,194	0,846
Le Panse et al. 2005, trained	Sprint, 30 s cycling	0,134	0,384	0,366	1,103	-0,334	1,049	0,294
Le Panse et al. 2005, untrained	Sprint, 30 s cycling	0,143	0,006	0,378	0,747	-0,735	0,017	0,987
Collomp et al., 2005	Sprint, 30 s cycling	0,085	0,445	0,291	1,015	-0,125	1,531	0,126
Hostrup et al., 2015	Sprint, 30 s cycling	0,230	0,520	0,479	1,459	-0,420	1,085	0,278
Hostrup et al., 2016, multiple	Sprint, 3x30 s cycling	0,067	0,234	0,259	0,742	-0,274	0,904	0,366
Hostrup et al., 2016, acute	Sprint, 3x30 s cycling	0,067	0,301	0,260	0,810	-0,208	1,160	0,246
Altarawneh et al., 2016	Sprint, 3x5x4 s cycling	0,048	-0,137	0,219	0,292	-0,567	-0,626	0,531
Signorile et al., 1992	Sprint, 5x15 s cycling	0,073	0,431	0,270	0,960	-0,098	1,597	0,110
Norris et al., 1996	Sprint, 60 s cycling	0,067	-0,123	0,259	0,385	-0,631	-0,476	0,634
Sanchez et al., 2013	Sprint, 70 m run	0,143	-0,082	0,379	0,660	-0,825	-0,218	0,828
Hostrup et al., 2014a, Exp 1	Strength, MVC	0,120	0,632	0,346	1,311	-0,046	1,826	0,068
Decorte et al., 2013, 200	Strength, MVC	0,079	0,250	0,282	0,802	-0,302	0,887	0,375
Decorte et al., 2013, 400	Strength, MVC	0,085	0,461	0,292	1,033	-0,110	1,581	0,114
Decorte et al 2008, 200	Strength, MVC	0,100	-0,092	0,317	0,529	-0,713	-0,291	0,771
Decorte et al 2008, 800	Strength, MVC	0,100	-0,060	0,317	0,560	-0,680	-0,190	0,849
Martineau et al., 1992	Strength, MVC	0,098	1,088	0,313	1,702	0,474	3,475	0,001
Hostrup et al., 2014a, Exp 2	Strength, MVC	0,061	0,671	0,247	1,156	0,186	2,711	0,007
Caruso et al., 2005	Strength, MVC	0,080	1,410	0,282	1,963	0,857	4,998	0,000
Van Bak et al,. 2000	Strength, MVC	0,008	0,105	0,089	0,278	-0,069	1,180	0,238
Caruso et al., 1995	Strength, MVC	0,188	0,090	0,434	0,940	-0,761	0,207	0,836
Merlini et al., 2019a, sal	Sprint, 30 m run	0,156	0,357	0,395	1,132	-0,418	0,904	0,366
Merlini et al., 2019a, for	Sprint, 30 m run	0,156	0,296	0,394	1,069	-0,477	0,749	0,454
Merlini et al., 2019b	Sprint, 30 m run	0,077	0,000	0,277	0,544	-0,544	0,000	1,000
		0,004	0,287	0,066	0,417	0,157	4,335	0,000



Group by Duration of treatment	Study name	Outcome	Statistics for each study						
			Variance	Std diff in means	Standard error	Upper limit	Lower limit	Z-Value	p-Value
Acute treatment	Morton et al., 1996	Strength, MVC	0,016	-0,086	0,126	0,161	-0,333	-0,681	0,496
Acute treatment	Morton et al., 1993	Strength, MVC	0,015	-0,013	0,121	0,224	-0,251	-0,109	0,913
Acute treatment	Kalsen et al., 2014	Strength, MVC	0,121	1,455	0,348	2,137	0,773	4,182	0,000
Acute treatment	Kalsen et al., 2016b	Strength, MVC	0,078	0,163	0,279	0,710	-0,384	0,584	0,559
Acute treatment	Hostrup et al., 2014b	Strength, MVC	0,115	0,255	0,339	0,919	-0,409	0,753	0,451
Acute treatment	Hostrup et al., 2016, acute	Strength, MVC	0,201	0,184	0,448	1,062	-0,695	0,410	0,682
Acute treatment	Hostrup et al., 2014a, Exp 1	Strength, MVC	0,120	0,632	0,346	1,311	-0,046	1,826	0,068
Acute treatment	Decorte et al., 2013, 200	Strength, MVC	0,079	0,250	0,282	0,802	-0,302	0,887	0,375
Acute treatment	Decorte et al., 2013, 400	Strength, MVC	0,085	0,461	0,292	1,033	-0,110	1,581	0,114
Acute treatment	Decorte et al 2008, 200	Strength, MVC	0,100	-0,092	0,317	0,529	-0,713	-0,291	0,771
Acute treatment	Decorte et al 2008, 800	Strength, MVC	0,100	-0,060	0,317	0,560	-0,680	-0,190	0,849
Acute treatment	Hostrup et al., 2014a, Exp 2	Strength, MVC	0,061	0,671	0,247	1,156	0,186	2,711	0,007
Acute treatment	Van Bak et al,. 2000	Strength, MVC	0,008	0,105	0,089	0,278	-0,069	1,180	0,238
Acute treatment			0,009	0,235	0,096	0,423	0,046	2,439	0,015
Multiple week treatment	Dickinson et al., 2014	Strength, 1RM	0,260	-0,558	0,510	0,441	-1,557	-1,095	0,273
Multiple week treatment	Hostrup et al., 2015	Strength, MVC	0,257	1,115	0,507	2,108	0,122	2,200	0,028
Multiple week treatment	Hostrup et al., 2016, multiple	Strength, MVC	0,204	0,419	0,452	1,305	-0,467	0,926	0,355
Multiple week treatment	Martineau et al., 1992	Strength, MVC	0,098	1,088	0,313	1,702	0,474	3,475	0,001
Multiple week treatment	Caruso et al., 2005	Strength, MVC	0,080	1,410	0,282	1,963	0,857	4,998	0,000
Multiple week treatment	Caruso et al., 1995	Strength, MVC	0,188	0,090	0,434	0,940	-0,761	0,207	0,836
Multiple week treatment	Merlini et al., 2019a, salm	Strength, MVC	0,154	0,034	0,392	0,802	-0,735	0,085	0,932
Multiple week treatment	Merlini et al., 2019a, for	Strength, MVC	0,154	0,066	0,392	0,835	-0,703	0,168	0,867
Multiple week treatment			0,063	0,502	0,250	0,993	0,012	2,008	0,045



Study name	Outcome	Statistics for each study						
		Variance	Std diff in means	Standard error	Upper limit	Lower limit	Z-Value	p-Value
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Morton et al., 1993	Strength, MVC	0,015	-0,013	0,121	0,224	-0,251	-0,109	0,913
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Hostrup et al., 2016, multiple	Strength, MVC	0,204	0,419	0,452	1,305	-0,467	0,926	0,355
Hostrup et al., 2016, acute	Strength, MVC	0,201	0,184	0,448	1,062	-0,695	0,410	0,682
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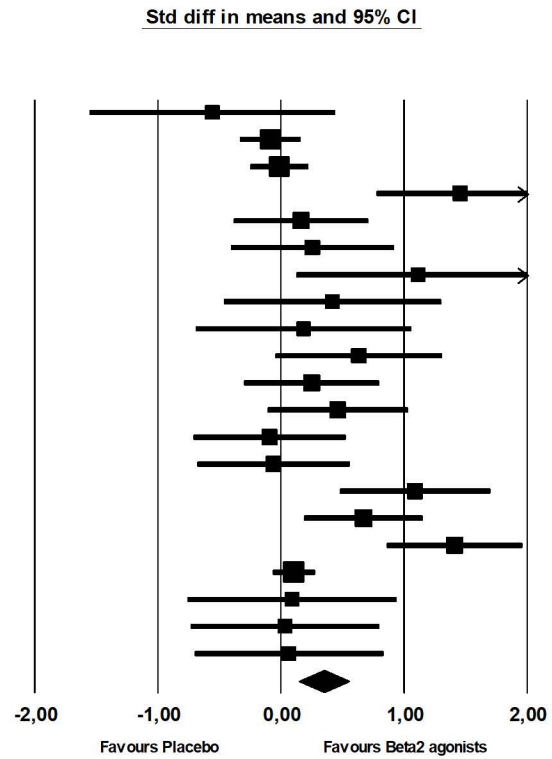
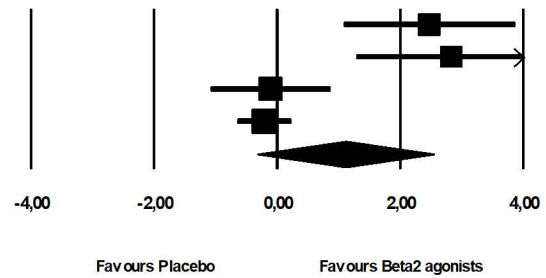
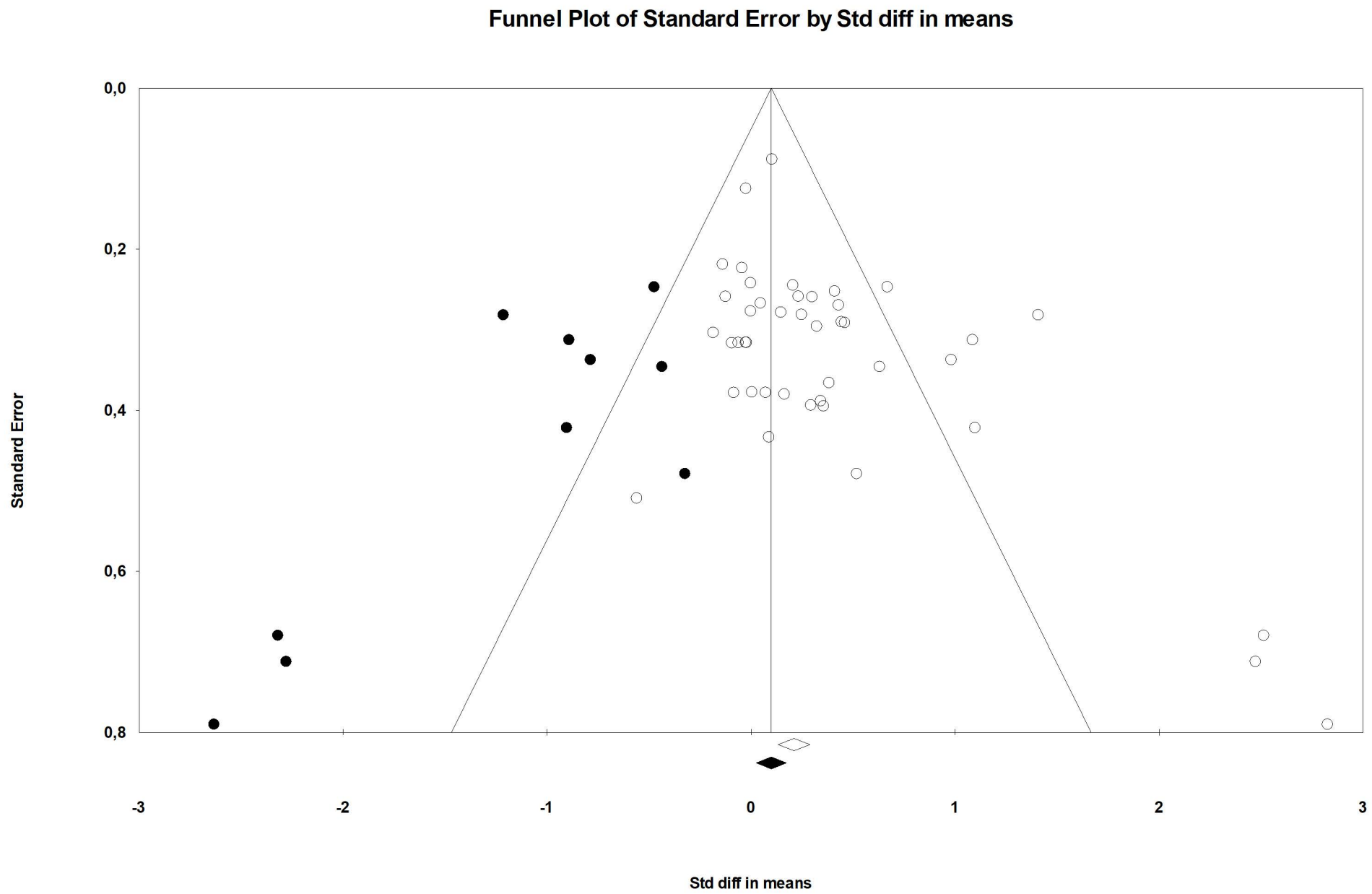
Merlini et al., 2019a, salm	Strength, MVC	0,154	0,034	0,392	0,802	-0,735	0,085	0,932
Merlini et al., 2019a, for	Strength, MVC	0,154	0,086	0,392	0,835	-0,703	0,168	0,867
		0,010	0,345	0,102	0,545	0,145	3,382	0,001



Studyname	Outcome	Statistics for each study						
		Variance	Std diff in means	Standard error	Upper limit	Lower limit	Z-Value	p-Value
Sanchez et al., 2012, acute	Power, Force-Velocity cycling	0,508	2,475	0,713	3,872	1,078	3,473	0,001
Sanchez et al., 2012, multiple	Power, Force-Velocity cycling	0,625	2,828	0,791	4,378	1,279	3,578	0,000
Dickinson et al., 2014	Power, Vertical jump	0,250	-0,107	0,500	0,873	-1,088	-0,215	0,830
Halabchi et al. 2017	Power, Vertical jump	0,051	-0,207	0,226	0,235	-0,650	-0,918	0,359
		0,532	1,107	0,729	2,536	-0,323	1,517	0,129




Funnel Plot of Standard Error by Std diff in means
0,0
0,2
0,4
0,6
0,8
Standard Error
-3
-2
-1
0
1
2
3
Std diff in means