Can β2-agonists have an ergogenic effect on strength, sprint or power performance? Systematic review and meta-analysis of RCTs

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjsports-2019-100708).

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Accepted 12 June 2020

To cite: Riiser A, Stensrud T, Stang J, *et al*. *Br J Sports Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjsports-2019-100708

ABSTRACT

Objectives We aimed to examine the effect of β2-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 randomised controlled trials, published until December 2019, examining the effect of β2-agonists on maximal physical performance lasting 1 min or shorter. Data are presented as standardised difference in mean (SDM) with 95% confidence intervals (95% CI).

Results 34 studies were included in the present meta-analysis. The studies include 44 different randomised and placebo-controlled comparisons with β2-agonists comprising 323 participants in crossover trials, and 149 participants in parallel trials. In the overall analyses, β2-agonists improved anaerobic performance by 5% (SDM 0.29, 95% CI 0.16 to 0.42), but the effect was related to dose and administration route. In a stratified analysis, the SDM was 0.14 (95% CI 0.00 to 0.28) for approved β2-agonists and 0.46 (95% CI 0.24 to 0.68) for prohibited β2-agonists, respectively. Furthermore, SDM was 0.16 (95% CI 0.02 to 0.30) for inhaled administration and 0.51 (95% CI 0.25 to 0.77) for oral administration, respectively, and 0.20 (95% CI 0.07 to 0.33) for acute treatment and 0.50 (95% CI 0.20 to 0.80) for treatment for multiple weeks. Analyses stratified for the type of performance showed that strength (0.35, 95% CI 0.15 to 0.55) and sprint (0.17, 95% CI 0.06 to 0.29) performance were improved by β2-agonists.

Conclusion/implication Our study shows that non-asthmatic subjects can improve sprint and strength performance by using β2-agonists. It is uncertain, however, whether World Anti-Doping Agency (WADA)-approved doses of β2-agonists improve performance. Our results support that the use of β2-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 an 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 glucocorticoids with inhaled β2-agonists pre-exercise and as a reliever of symptoms.[1] However, the use of inhaled β2-agonists by athletes is surrounded by controversy. Inhaled β2-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. Since 1972, the regulations regarding the use of inhaled β2-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 1 January 2020 prohibits all use of β2-agonists except inhaled salbutamol (maximum 1600 μg over 24 hours in divided doses not to exceed 800 μg over 12 hours starting from any dose), inhaled formoterol (maximum delivered dose of 54 μg over 24 hours) and inhaled salmeterol (maximum 200 μg over 24 hours).[4]

It has been speculated that non-asthmatic athletes use β2-agonists, believing they 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 β2-agonists has been examined in multiple studies. In 2007, Kindermann reviewed the effect of β2-agonists and concluded that inhaled β2-agonists do not enhance endurance performance, anaerobic power or muscle strength, while oral β2-agonists seemed to improve both endurance and strength.[5] The year after, the IOC consensus statement considered that inhaled β2-agonists do not to enhance endurance performance, while oral ingestion of salbutamol was considered to increase strength.[6] However, the joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) concluded that there was no evidence to suggest that asthma drugs improved physical performance in healthy athletes.[7] In 2011, Pluim *et al* published the first systematic review and meta-analysis on the effect of β2-agonists on physical performance in healthy athletes, including studies published before August 2009.[8] They did not detect any effect of inhaled β2-agonists on aerobic, anaerobic or sprint performance, but did find some weak evidence indicating a performance enhancing effect of systemic β2-agonists on anaerobic performance. Since August 2009, multiple studies have investigated the effect of β2-agonists on anaerobic performance, and continuous controversy regarding the use of β2-agonists in sports exists, which has been highlighted in recent β2-agonist anti-doping investigations involving world-class athletes.[9 10]

Therefore, the aim of our systematic review and meta-analysis was to assess the effect of β2-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 18 September 2018, with registration number CRD42018109223, and complied with the guidelines.[11]

Literature search

We performed a systematic search of published randomised controlled trials (RCTs) that examined the effect of β2-agonists on physical performance in healthy humans on 29 October 2018. 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 Science 36, and SPORTDiscus 157). After elimination of duplicates, 290 records remained. On 18 December 2019 we performed an updated search in the four databases, adding the term "beta2-agonist" and all β2-agonists listed in the WADA prohibited list[4] but not included in the original search (beta2-agonist OR Fenoterol OR Higenamine OR Indacaterol OR Olodaterol OR Procaterol OR Reproterol OR Tretoquinol OR Tulobuterol OR Vilanterol). The updated search identified 57 records (PubMed 11, Embase 22, Web of Sience 5, and SPORTDiscus 19). After elimination of duplicates, 44 records remained (figure 1). The searches were performed by the first author and a librarian.

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 β2-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 s per trial and non-performance variables such as neuromuscular function, oxygen kinetics and ventilation.

Included studies

After screening of titles and abstracts from the first search, 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. From the updated search four studies were selected for full text eligibility assessment after screening of titles and abstracts. In total 71 studies met the primary inclusion criteria. As the present study includes only performance outcomes of 1 min or less, 37 studies only presenting data from performance outcomes with a duration of more than 1 min were excluded. One study reported "no significant difference" and the authors could not provide data on request.[12] Thus, 34 studies were included in the present meta-analysis (figure 1).

Study quality assessment

The included studies were assessed using the Cochrane Collaboration Risk of Bias Tool to evaluate seven bias domains[13] 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

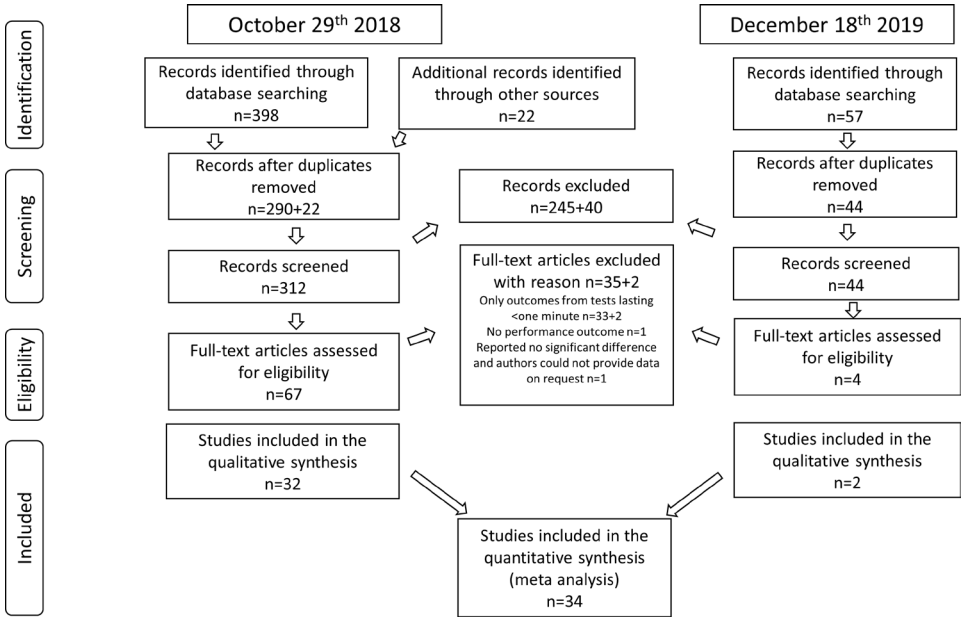


Figure 1 Flow chart of included studies as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[11]

β2-agonists even if the blinding procedure in the study was performed 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 seventh domain (other bias) was defined as "Participants screened for asthma". For a study to be classified as "Low risk for bias" on the seventh 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*,[8] while the studies already assessed by Pluim and colleagues were evaluated by one author (AR). Any discrepancy in the assessments were resolved by discussion. An 8th domain was added to the risk of bias tool reporting the washout 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 discrepancies by mutual agreement after reassessing the data in question. AR contacted the corresponding author of papers when an e-mail address was provided, and relevant outcomes were reported in figures[14–16] or as "no significant difference".[12] Beloka *et al*[12] was excluded as the authors could not provide data. When data were presented in figures only and no email address for the corresponding author was provided or the corresponding author had no access to the requested data, data were extracted manually[14 17–19] by AR. The main outcome was physical performance lasting 1 min or less and defined as anaerobic performance. Anaerobic performance was further categorised into sprint performance assessed by maximal running,[15 20–23] ergometer cycling[16 17 24–39] (mean power/total work) or swim ergometer sprint.[40] Strength performance (leg) was assessed by one repetition maximum (1 RM)[41] or maximal voluntary contraction (MVC)[14 16 18 19 21 27 35–37 42–45] and power performance was assessed by vertical jump[22] and force velocity sprint.[46] If several outcomes were presented after one intervention, only one outcome was included in each meta-analysis. This inclusion was prioritised in the following order: Sprint outcomes were prioritised over strength outcomes and long sprints were prioritised over short sprints and power outcomes. Maximal voluntary contraction was prioritised over 1 RM and vertical jump. When results from multiple trials were reported separately, the results from all trials were meta-analysed 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-analysed into one variable and this variable was used in further analysis. The interventions were categorised in four different ways. (1) Type of β2-agonist: short-acting (salbutamol and terbutaline) and long-acting (formoterol and salmeterol). (2) Administration route: inhaled, oral and infusion (infusion was only used in one comparison and was not a category in the meta-regression). (3) Duration of treatment: acute treatment and multiple weeks of treatment. (4) Dose: approved by WADA and not approved by WADA.[4] 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 deviation (SD) when standard error (SE) of the mean and 95% confidence intervals (95% CI) were reported) in Excel (Microsoft Corp) before 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 standardised difference in means (SDM) with 95% CI. Heterogeneity is presented as I^2, and p value. Whether or not the effect size was different between type of β2-agonist, administration route, duration of treatment and dose were analysed 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 analogue. Potential publication bias was assessed by funnel plot, Begg and Mazumdar rank correlation test and classic fail-safe N. Standardised difference in means was back transferred to original units by multiplying SDM 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 α of 0.05 and a β of 0.2.[47] 47 Skewness of outcomes was assessed as baseline mean/SD. Variables with a mean/SD ratio >2 were considered skewed.[48] Significance level was set at $p<0.05$. P values <0.1 >0.05 from the meta-regression were discussed as tendencies.

RESULTS

Study characteristics

The present meta-analysis consists of 34 RCTs, including 27 studies with crossover design[14 15 17 20 22–35 37–40 42–46] (seven comparing two different interventions with placebo[21 24 43–46]) and seven studies[16 18 19 21 36 41 49] with parallel design (one with both acute and multiple week intervention[16] and one comparing two different β2-agonists with placebo).[21] The meta-analysis includes 44 different randomised and placebo-controlled comparisons with β2-agonists comprising 323 participants in crossover trials, including 51 participants in three-way crossover trials. Eighty-three participants received β2-agonists and 66 participants received placebo in the parallel trials. The included studies are summarised in table 1.

Risk of bias

Twenty-one studies (62%) had high risk of bias in one domain or more and the washout period varied from 1 day to 4 weeks between the studies (online supplementary table 1). There was no difference in the effect of β2-agonists between high and low bias studies for any performance category (table 2). One study[22] 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 an effect of β2-agonists (online supplementary figure 3). The Begg and Mazumdar rank correlation test confirmed publication bias with a one-tailed p value=0.003, and the fail-safe N

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 (type, route, and dose of β2- agonist)	Outcomes
Merlini *et al* 2019a[21]	Parallel, three arms	23/15, m/f, 26±5	Recreationally active	Inhaled salmeterol 200 µg* Inhaled formoterol 24 µg*	30 m sprint MVC
Merlini *et al* 2019b[15]	Crossover	13, m, 18±1	Amateur football players	Inhaled salbutamol 1600 µg	30 m sprint
Halabchi *et al* 2017[22]	Crossover	20, m, 17±1	Junior professional football players	Inhaled salbutamol 200 µg*	Fastest 30 m sprint Vertical Jump
Kalsen *et al* 2016a[34]	Crossover	9, m, 24±3	Recreationally active	Inhaled terbutaline 15 000 µg	10 s cycle sprint
Kalsen *et al* 2016b[35]	Crossover	13, m, 32±8	Training 1.8±1 h/w	Inhaled formoterol 54 µg*	30 s cycle sprint
Hostrup *et al* 2016[16]	Parallel	20, m, 26±4	National level endurance athletes	Oral salbutamol 8000 µg acute and 8 mg/day for 2 weeks	3×30 s cycle sprint MVC
Altarawneh *et al* 2016[39]	Crossover	7, m, 23±6	Recreationally active 4 d/w	Inhaled salbutamol 1000 µg	3 set 5×4 s cycle sprint
Hostrup *et al* 2015[36]	Parallel	18, m, 24±3	Recreationally active 4–8 h/w	Oral terbutaline 5000 µg/30 twice daily for 28±1 days	30 s cycling sprint MVC
Dickinson *et al* 2015[23]	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[40]	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	Exp 1, 10, m, 24±3 Exp 2, 20, m, 24±4	Exp 1: Highly trained Exp 2: Trained	Exp 1: inhaled terbutaline 20 000 µg Exp 2: oral terbutaline 5000 µg/15 kg	MVC
Hostrup *et al* 2014b[37]	Crossover	9, m, 24±3	Recreationally active	Inhaled terbutaline 15 000 µg	30 s cycle sprint MVC
Dickinson *et al* 2014[41]	Parallel	16, m, 20±2	Amateur-level competition	Inhaled salbutamol 1600 µg / day for 6 weeks	1 RM
Sanchez *et al* 2013[20]	Crossover	7, m, 29±6	Competitive athletes, 10 h/week	Oral terbutaline 8000 µg	70 m running sprint
Decorte *et al* 2013[44]	Three-way Crossover	11, 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[46]	Three-way Crossover	8, m, 23±1	Recreational sports, 10 h/w	Oral salbutamol 6000 µg acute Oral salbutamol 12 000 µg/day for 3 weeks	Force–velocity sprint on cycle ergometer
Descorte *et al* 2008[43]	Three-way Crossover	9, m, 23±3	Healthy non-athletes	Inhaled salbutamol 200 µg* Inhaled salbutamol 800 µg*	MVC
Le Pance *et al* 2007[32]	Crossover	12, f, 22±3	Recreationally active 1–3 d/w	Oral salbutamol 4000 µg	30 s cycle sprint
Le Panse *et al* 2006[33]	Crossover	14, f, 22±1	Recreationally active,[7] sedentary[7]	Oral salbutamol 12 000 µg/day for 4 weeks	30 s cycle sprint
Le Panse *et al* 2005[31]	Crossover	15, m, 30±6	Strength-trained athletes,[8] sedentary[7]	Oral salbutamol 12 000 µg/day for 3 weeks	30 s cycle sprint
Collomp *et al* 2005[38]	Crossover	13, m, 31±6	Sedentary non-athletes and recreational weightlifters, 1–3 d/w	Oral salbutamol 4000 µg	30 s cycle sprint
Caruso *et al* 2005[19]	Parallel	22, m, 18–22	Healthy non-athletes (after 10 weeks of strength training)	Oral salbutamol 4–16 000 µg/ day for 3 weeks	MVC
Stewart *et al* 2002[24]	Three-way Crossover	10, m, 26 20–30	Highly trained athletes	Inhaled formoterol 12 µg* Inhaled salbutamol 400 µg*	30 s cycle sprint
van Baak *et al* 2000[14]	Crossover	16, m, 23±2	Healthy non-athletes	Oral salbutamol 4000 µg	MVC
Mc Dowell *et al* 1997[29]	Crossover	11, m, 25±4	Amateur cyclists	Inhaled salmeterol 42 µg*	30 s cycle sprint
Norris *et al* 1996[26]	Crossover	15, m, 25±4	Highly trained cyclists	Inhaled salbutamol 400 µg*	60 s cycle sprint
Morton *et al* 1996[42]	Crossover	16, m, 23±4	High performance cyclists and triathletes	Inhaled salmeterol 50 µg*	10 s cycle sprint MVC
Lemmer *et al* 1995[30]	Crossover	14, m, 23±1	Elite cyclists	Inhaled salbutamol 360 µg*	30 s cycle sprint
Caruso *et al* 1995[49]	Parallel	22, m, 21±3	Sedentary or recreationally active non-athletes	Oral salbutamol 16 000 µg/day for 6 weeks	MVC
Morton *et al* 1993[27]	Crossover	17, m, 22±4	Athletes (power events)	Inhaled salbutamol 200 µg*	10 s cycle sprint MVC
Signorile *et al* 1992[25]	Crossover	8/7, m/f, 18–33	Healthy non-athletes	Inhaled salbutamol 180 µg*	15 s cycle sprint
Morton *et al* 1992[17]	Crossover	16/1 m/f, 22±4	High performance runners	Inhaled salbutamol 200 µg*	30 s cycle sprint
Meeuwisse *et al* 1992[28]	Crossover	7, m, 24±4	Trained cyclists	Inhaled salbutamol 200 µg*	30 s cycle sprint

Continued

Table 1 Continued

Study, year	Design	Subjects: n, sex, age (years±SD)	Fitness level	Intervention (type, route, and dose of β2- agonist)	Outcomes
Martineau *et al*. 1992[18]	Parallel	12, m, 19–38	Healthy non-athletes	Oral salbutamol 16 000 µg/day for 3 weeks	30 s cycle sprint

*Dose approved by WADA.[4]

d/w, days per week; Exp, experiment; f, female; h/w, hours per week; iv, intravenous; m, male; MVC, maximal voluntary isometric contraction; RM, repetition maximum; s, seconds; WADA, World Anti-Doping Agency.

was 458 meaning that there would need to exist 458 unpublished comparisons finding no effect of β2-agonists to nullify the effect found in the 44 comparisons in our study.

Effect of β2-agonists

β2-agonists improved anaerobic performance compared with placebo with an SDM of 0.287 (95% CI 0.157 to 0.417) (figure 2). The SDMs for the included studies were heterogeneous (I^2=56%, p<0.001) and the difference was related to dose (p=0.047, R^2=0.00) and administration route (p=0.025, R^2=0.02). In stratified analysis, approved β2-agonists did not improve anaerobic performance (0.141, 95% CI −0.001 to 0.282) and prohibited β2-agonists improved anaerobic performance (0.457, 95% CI 0.239 to 0.675). Stratified by administration route, both inhalation (0.157, 95% CI 0.022 to 0.293) and oral administration (0.511, 95% CI 0.251 to 0.771) of β2-agonists improved anaerobic performance. In stratified analysis, the SDM for acute treatment was 0.200 (95% CI 0.067 to 0.333) and 0.501 (95% CI 0.203 to 0.798) for multiple weeks of treatment.

The SDM from 31 comparisons showed that β2-agonists improved sprint performance (0.17, 95% CI 0.06 to 0.29) (table 2, supplementary figure 1) and the effect was not related to the type of β2-agonist, administration route, duration of treatment, or dose in the multivariate meta regression (p>0.104) (table 2). In stratified analysis approved doses of β2-agonists had no effect on sprint performance (p=0.219) and prohibited doses of β2-agonists improved sprint performance (p=0.003)

The effect on strength performance was assessed in 21 comparisons and β2-agonists improved maximal muscular strength (0.35, 95% CI 0.15 to 0.55). The results were heterogeneous (I^2=68%, p<0.001) (table 3) and the effect was related to the duration of treatment and administration route in the simple models (p<0.031) and all variants of treatment combined in one model (p=0.026, R^2=0.31) (table 2). For strength performance the SDM was greater (p=0.030) after multiple weeks of

Table 2 Regression of standardised difference in means against type of β2-agonist, administration route, duration of treatment, dose and risk of bias treated as categorical variables

	Anaerobic performance	Sprint performance	Strength performance
Type of β2-agonist; reference, long-acting			
Test of model, p value	0.535	0.794	0.147
Goodness of fit, p value	<0.001	0.112	<0.001
R^2 analogue	0.00	0.00	0.00
Administration route; reference, inhaled			
Test of model, p value	0.025	0.376	0.008
Goodness of fit, p value	<0.001	0.138	<0.001
R^2 analogue	0.02	0.04	0.06
Duration of treatment; reference, acute			
Test of model, p value	0.077	0.303	0.030
Goodness of fit, p value	<0.001	0.126	0.008
R^2 analogue	0.15	0.06	0.38
Dose; reference, approved by WADA			
Test of model, p value	0.047	0.105	0.136
Goodness of fit, p value	<0.001	0.194	<0.001
R^2 analogue	0.00	0.26	0.00
Type, route, duration, dose			
Test of model, p value	0.253	0.348	0.026
Goodness of fit, p value	<0.001	0.148	0.015
R^2 analogue	0.00	0.06	0.31
Risk of bias; reference, high risk			
Test of model, p value	0.222	0.189	0.199
Goodness of fit, p value	<0.001	0.159	<0.001
R^2 analogue	0.00	0.12	0.00

R^2 analogue: proportion of total between-study variance explained by the covariate. Anaerobic performance: maximal physical performance lasting 1 min or less. Sprint performance: maximal running cycling or swimming for 1 min or less. Strength performance: maximal voluntary contraction or one repetition maximum.
WADA, World Anti-Doping Agency.

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

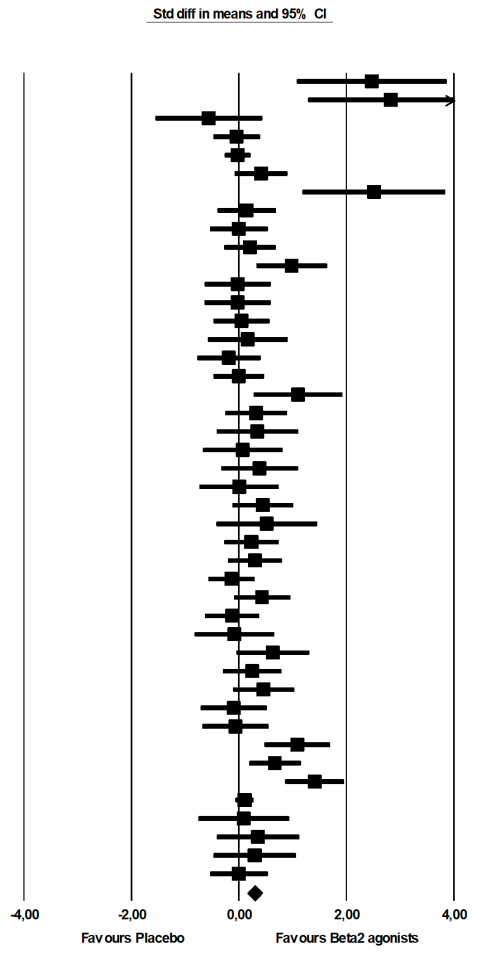


Figure 2 Forest plot of the effect of β2-agonists on anaerobic performance.

treatment (0.502, 95% CI 0.012 to 0.993) compared with acute treatment (0.235, 95% CI 0.046 to 0.423) (figure 3), and in oral ingestion (0.632, 95% CI 0.212 to 1.060) compared with inhalation (0.18, 95% CI −0.041 to 0.393). In stratified analysis approved doses of β2-agonists had no effect on sprint performance (p=0.187) and prohibited doses of β2-agonists improved sprint performance (p=0.003).

Power performance was assessed in four comparisons and no statistically significant effect of β2-agonists was found (table 2, supplementary figure 2).

Sample size and skewness

One of the 34 included studies included adequate numbers of participants to obtain an α <0.05 and a β <0.2 (online supplementary table 1).[22] None of the 34 comparisons reporting baseline mean and SD/SE was skewed.

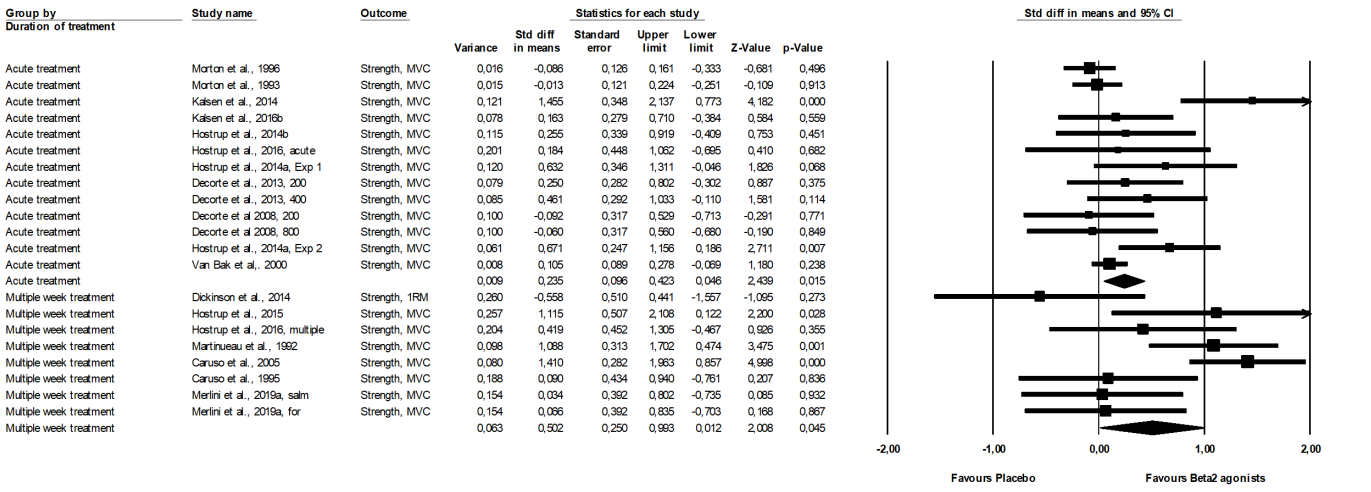
Sensitivity analysis

We performed a sensitivity analysis excluding the six comparisons with the highest SDM and the combined SDM for the remaining 38 interventions was 0.139 (95% CI 0.058 to 0.219; p=0.001). We also performed a sensitivity analysis excluding the 12 comparisons with less than 10 data pairs with β2-agonist and placebo (SDM 0.224, 95% CI 0.110 to 0.338). In addition, we meta-analysed the effects of β2-agonists on anaerobic performance including only comparisons with different subjects and the SDM of these 38 comparisons was 0.289 (95% CI 0.151 to

Table 3 Meta-analysis for each outcome measure

Outcome	Number of comparisons	Meta-analysis of each outcome			Test of heterogeneity	
		SDM	95% CI	P value	I^2*	P value
Anaerobic performance	44	0.287	0.157 to 0.417	<0.001	56%	<0.001
Sprint performance	31	0.173	0.057 to 0.288	0.003	21%	0.152
Strength performance	21	0.345	0.145 to 0.545	0.001	68%	<0.001
Power performance	4	1.107	−0.323 to 2.536	0.129	88%	<0.001

Anaerobic performance: maximal physical performance lasting 1 min or less. Sprint performance: maximal running, cycling or swimming for 1 min or less. Strength performance: maximal voluntary contraction or one repetition maximum. Power performance: force velocity sprint or vertical jump.
SDM, standardised difference in mean.



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

Figure 3 Forest plot of the effect of β2-agonists on strength performance stratified by duration of treatment.

0.428; p<0.001). This means that the results are consistent also when stricter criteria for including studies are used.

Percent change

An SDM of 0.287 corresponds to a mean improvement of 5% (SD 3) in the 34 included comparisons reporting baseline mean and SD or SE. Specifically, 70 m sprint time and MVC improved by 5% in populations of competitive athletes[20] and high performance cyclists and triathletes,[42] respectively. If we apply the SDM specific for sprint (0.173) and strength (0.345) performance, the estimated percent improvement from β2-agonist would be 3% and 6% in the respective populations.

DISCUSSION

This meta-analysis of RCTs, examining the effect of β2-agonists on anaerobic performance, provides the most comprehensive quantitative summary of the evidence to date, including 34 RCTs with 44 placebo-controlled comparisons comprising 472 participants. Twenty-one studies were classified as high risk of bias due to side effects, single blinding 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 β2-agonists improve anaerobic performance by 5%, an improvement that would change the outcome of most athletic competitions.

Oral administration had a larger effect than inhalation even if both administration routes improved performance, and prohibited doses of β2-agonists had a different effect than approved doses of β2-agonists. The difference in effect between approved and prohibited doses may be caused by larger (prohibited) doses taken orally or by inhalation increasing the serum values more,[45] thus having a larger potential effect on anaerobic performance. This means that prohibiting terbutaline and high doses of salbutamol, salmeterol and formoterol reduce risk of performance enhancement due to use of these drugs.

Approved doses of β2-agonists did not effect anaerobic performance as predefined by us (p<0.05). However, there was a tendency (p=0.05) towards enhanced performance by approved doses of β2-agonists. This means that it is still uncertain whether approved doses improve anaerobic performance. There was also a tendency towards greater effect of multiple weeks of treatment compared with acute treatment (p=0.08).

To our knowledge, no other studies have pooled data using meta-analysis on the effects of β2-agonists on anaerobic performance. Pluim *et al*[8] presented a meta-analysis stratified by administration route (oral or inhaled) and analysed test-specific outcomes separately. Pluim *et al*[8] did not find any effect of inhaled β2-agonists on any outcome while the pooled results from four studies revealed a positive effect of oral β2-agonists on peak power, but not mean power during a 30 s Wingate test.

Since the review by Pluim *et al*,[8] 16 studies meeting our inclusion criteria have been published. In our study, we included comparisons with inhaled and oral β2-agonists in the same analysis, as we hypothesised 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 β2-agonists.[45] However, in a clinical setting inhaled β2-agonists are prescribed in substantially lower doses compared with the doses prescribed for oral ingestion. This assumption was partly supported by the findings in the present study, as oral administration had a greater effect, but both administration routes improved performance. Multiple weeks of treatment with β2-agonists tended to have a greater effect than acute treatment.

Analysis of performance categories

Sprint performance was improved using β2-agonists. The effect size from the 31 comparisons included was not heterogeneous. The finding is in contrast to Pluim *et al*[8] who meta-analysed four studies with oral β2-agonists and five studies with inhaled β2-agonists separately and reported no statistically significant improvement in mean power during a 30 s Wingate test. The present study provides greater statistical power due to more than seven times as many comparisons in the meta-analysis, which may explain why we found an effect and Pluim *et al*[8] did not.

β2-agonists improved strength performance. The effect was heterogeneous and related to duration of treatment and administration route, where treatment with β2-agonists over multiple weeks and oral administration provided a greater improvement in strength compared with interventions consisting of acute treatment. Differences in duration of treatment and route of administration explained 38% and 6% of the total between

study variance. When all covariates were included in one model, the model explained 31% 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[50] and oral β2-agonists.[36 51] β2-agonists prescribed for oral ingestion are prescribed in higher doses than inhaled β2-agonists. This may partly explain why oral β2-agonists improve strength more than inhaled β2-agonists.

Only four interventions investigated the effect of β2-agonists on power performance and the effect was not statistically significant. However, the study investigating the effect of β2-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 β2-agonists (online supplementary figure 2).

Bias

The funnel plot indicated a tendency for published studies that found a significant effect of β2-agonists, and the Begg and Mazumdar rank correlation test indicated publication bias. However, the fail-safe N is 458, meaning that there would need to be 10 not published comparisons with no effect per published comparison to nullify the effect of the 44 comparisons included in the present study. We also performed sensitivity analysis by removing the six studies with the largest SDM in favour of β2-agonists and the 12 comparisons with less than 10 participants receiving β2-agonists. Without these studies, the effect of β2-agonists on anaerobic performance was still highly statistically significant. This strengthens the assumption that the effects of β2-agonists on anaerobic performance presented in the present study are real effects and not caused by bias.

Tachycardia and tremor are characteristic adverse side effects of β2-agonists[37 52] and 11 studies reported side effects of the β2-agonists. The side effects may make the participants aware of whether they received β2-agonists or placebo, thus breaking the blinding and possibly motivating the participants to perform better when receiving β2-agonists. In one study,[34] seven out of nine participants reported side effects after receiving β2-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. Fifteen studies did not screen the participants for asthma with objective tests, possibly including subjects with airway hyperresponsiveness (AHR). However, AHR probably does 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[35] or swimmers with and without [40]AHR and risk for bias did not influence the SDM in any analysis.

Our study included 12 comparisons between placebo and β2-agonists that comprised fewer than 10 pairs (fewer 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 SDM.[53 54] However, when we performed a sensitivity analysis excluding these 12 comparisons the effect of β2-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 dose and administration route on anaerobic performance indicated an effect and the analogue R^2s were 0.0 and 0.02, which should be interpreted as the proportion of between study variance explained by administration route is 0% and 2%. This may be counter-intuitive as variables explaining 0% and 2% of the variation is normally not statistically significant. In both primary studies and meta-analysis, R^2 is based on two estimates of variance. Unlike in primary studies, R^2 in meta-analysis is based on separate analysis where both estimates (T^2) can be over- or underestimated. Thus, a positive effect yet with no/low explained variation for any covariate is a possible outcome of the analysis if the effect is small.[55] We should therefore interpret the findings with caution.

An SDM may be difficult to interpret. We therefore back transferred the SDM to the units presented in the respective included studies and computed the effect of β2-agonists as percent change from baseline. The mean improvement on anaerobic performance was 5%. However, this must be interpreted with caution as the percent change is dependent on the population (mean and SD). Similarly, the SDMs in the present study are low to moderate according to Cohen's rule of thumb.[56] However, the difference between failure and success within elite sports is often marginal, and if β2-agonists have a small effect on anaerobic performance it may decide the outcome of the competition. A 5% difference may be small in many aspects, but when it comes to athletic performance, it will have a vast impact on the result in almost any competition. We would therefore recommend that WADA has criteria for the use of β2-agonists in sports where anaerobic performance is essential for the outcome. The criteria should be based on objective tests for asthma and a doctor's diagnosis. β2-agonists should not be prohibited in athletic competitions, because they are a necessary treatment for athletes with asthma, but they 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 1 min or shorter to be a measure of anaerobic performance; thus we used SDM as outcome in the meta-analysis.[57] 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 were assessed by laboratory tests, which are not identical to actual athletic competitions. Reliable, sensitive and valid test protocols are important. 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.[58] However, the quality of the test protocols was not accounted for in the present analysis. The fitness level of the participants varied from untrained to elite athletes, but the athletes did not necessarily exercise for, or compete in, events where the abilities tested in the included studies were the most relevant factors for performance in the respective sport disciplines. Thus, fitness level was not included in the analysis even if fitness level may confound the effect of β2-agonists on physical performance.[59 60] The meta-analysis assumes independence between the subjects included. In the present study, the same subjects were included twice in the same analysis if they participated in a three-way crossover study with placebo and two different interventions with β2-agonists, or if

the same subjects were assessed after acute and multiple weeks of β2-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 participants were 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*[41] by request and similar to what Pluim *et al*[8] reported. In the analysis of anaerobic performance only, 17% of the variation in effect sizes from the individual comparisons were explained by the differences in the interventions, thus the reason for most of the heterogeneity was not clear.

In the meta-regression the β2-agonist interventions were classified into different subcategories and the effect of the different interventions are compared. By splitting up the outcome and the interventions into categories, the statistical power and the probability of detecting statistically significant differences were reduced. Thus, categories with few studies/participants usually have larger uncertainties in the effect estimates. We have therefore chosen to discuss $p<0.1$ from the meta-regression as tendencies. Future studies will add to the evidence and perhaps reveal differences in the effect of β2-agonists between more subcategories. The effect of treatment in crossover studies is possibly influenced by period effect and carryover effect, and these effects were only examined in one of the 27 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 β2-agonists, deactivation of receptors and the dose administered. Thus, the minimum washout period is difficult to assess. The half-life of the β2-agonists assessed in the present study range from 3 to 6 hours (salbutamol) to 10 hours (formoterol).[61] The first search was limited to four types of β2-agonists. The additional search included the term "beta2-agonists" and all β2-agonists listed in WADAs prohibited list. The second search gave two additional relevant studies but these studies were published after the first search.

Based on these limitations the findings should be interpreted with caution, but the results demonstrate that anaerobic performance was enhanced in healthy individuals by use of β2-agonists.

CONCLUSION

Our systematic review and meta-analysis which summarises the current scientific evidence from 34 studies, of which 13 are low risk of bias, shows that people who do not suffer from asthma can improve their anaerobic performance by using β2-agonists. β2-agonists improve both sprint and strength performance, with oral administration being more effective compared with inhalation. There is a difference in effect between prohibited and approved β2-agonists and it is uncertain whether approved doses of β2-agonists improve anaerobic performance. The results of the present study should be of interest to WADA and anyone who is interested in equal opportunities in competitive sports. The use of β2-agonists in athletes should be regulated and limited to those with an asthma diagnosis documented with objective tests.

Correction notice This article has been corrected since it published Online First. The second affiliation has been corrected.

Contributors All authors reviewed the report. AR generated the hypotheses, did the literature search, analysed the data and wrote the first draft of the manuscript. AR, TS, JS and LBA revised the manuscript critically for important intellectual content.

What is already known?

- The gold standard for asthma therapy is inhaled glucocorticoids with inhaled β2-agonists pre-exercise and as a reliever for symptoms.
- The use of β2-agonists in sports is regulated by WADA due to possible performance enhancing effects.

What are the findings?

- β2-agonists can improve anaerobic performance in healthy subjects.
- β2-agonists can improve sprint and strength performance in healthy subjects.
- There is a difference in terms of effect between use of prohibited and approved β2-agonists.
  - Prohibited doses of β2-agonists improve anaerobic performance in healthy subjects.
  - It is uncertain whether β2-agonists, in doses approved by WADA, can improve anaerobic performance in healthy subjects.
- Oral treatment enhances performance more than inhalation.

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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019. Available: www.ginasthma.org [Accessed 26 Sep 2019].
2 Fitch KD. An overview of asthma and airway hyper-responsiveness in Olympic athletes. *Br J Sports Med* 2012;46:413–6.
3 McKenzie DC, Fitch KD. The asthmatic athlete: inhaled beta-2 agonists, sport performance, and doping. *Clin J Sport Med* 2011;21:46–50.
4 The World Anti-Doping Agency. Available: www.wada-ma.org/sites/default/files/wada_2019_english_prohibited_list.pdf [Accessed 08 Nov 2018].
5 Kindermann W. Do inhaled beta(2)-agonists have an ergogenic potential in non-asthmatic competitive athletes? *Sports Med* 2007;37:95–102.
6 Fitch KD, Sue-Chu M, Anderson SD, *et al*. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22-24, 2008. *J Allergy Clin Immunol* 2008;122:254–60.
7 Carlsen KH, Anderson SD, Bjermer L, *et al*. Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: Part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2)LEN. *Allergy* 2008;63:492–505.
8 Pluim BM, de Hon O, Staal JB, *et al*. β_2-agonists and physical performance: a systematic review and meta-analysis of randomized controlled trials. *Sports Med* 2011;41:39–57.
9 More details of Chris Froome's successful salbutamol defence. Available: http://www.cyclingnews.com/news/more-details-of-chris-froomes-successful-salbutamol-defence/ [Accessed 13 May 2019].
10 Norway's cross-country Olympic success clouded by asthma drug ethics. Available: https://www.reuters.com/article/us-olympics-2018-nors-norway/norways-cross-country-olympic-success-clouded-by-asthma-drug-ethics- [Accessed 14 May 2019].
11 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.

12 Beloka SP, Janssen C, Woff E, *et al*. Effects of β2-adrenergic stimulation on exercise capacity in normal subjects. *Eur J Appl Physiol* 2011;111:2239–47.
13 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
14 van Baak MA, Mayer LH, Kempinski RE, *et al*. Effect of salbutamol on muscle strength and endurance performance in nonasthmatic men. *Med Sci Sports Exerc* 2000;32:1300–6.
15 Merlini M, Beato M, Marcora S, *et al*. The effect of 1600 µg inhaled salbutamol administration on 30 M sprint performance pre and post a Yo-Yo intermittent running test in football players. *J Sport Sci Med* 2019;18:716–21.
16 Hostrup M, Kalsen A, Auchenberg M, *et al*. Effects of acute and 2-week administration of oral salbutamol on exercise performance and muscle strength in athletes. *Scand J Med Sci Sports* 2016;26:8–16.
17 Morton AR, Papalia SM, Fitch KD. Is salbutamol ergogenic?: The effect of salbutamol on physical performance in high performance nonasthmatic athletes. *Clin J Sport Med* 1992;2:93–7.
18 Martineau L, Horan MA, Rothwell NJ, *et al*. Salbutamol, a beta 2-adrenoceptor agonist, increases skeletal muscle strength in young men. *Clin Sci* 1992;83:615–21.
19 Caruso JF, Hamill JL, De Garmo N. Oral albuterol dosing during the latter stages of a resistance exercise program. *J Strength Cond Res* 2005;19:102–7.
20 Sanchez AMJ, Borrani F, Le Fur MA, *et al*. Acute supra-therapeutic oral terbutaline administration has no ergogenic effect in non-asthmatic athletes. *Eur J Appl Physiol* 2013;113:411–8.
21 Merlini M, Whyte G, Marcora S, *et al*. Improved sprint performance with inhaled long-acting β2-agonists combined with resistance exercise. *Int J Sports Physiol Perform* 2019:1344–9.
22 Halabchi F, Abarashi M, Mansournia MA, *et al*. Effects of inhaled salbutamol on sport-specific fitness of non-asthmatic football players. *Acta Med Iran* 2017;55:324–32.
23 Dickinson J, Hu J, Chester N, *et al*. The impact of inhaled salbutamol on repeated sprint ability in pre-fatigued soccer players. *J Sports Med Doping Stud* 2015;5.
24 Stewart IB, Labreche JM, McKenzie DC. Acute formoterol administration has no ergogenic effect in nonasthmatic athletes. *Med Sci Sports Exerc* 2002;34:213–7.
25 Signorile JF, Kaplan TA, Applegate B, *et al*. Effects of acute inhalation of the bronchodilator, albuterol, on power output. *Med Sci Sports Exerc* 1992;24:638–42.
26 Norris SR, Petersen SR, Jones RL. The effect of salbutamol on performance in endurance cyclists. *Eur J Appl Physiol Occup Physiol* 1996;73:364–8.
27 Morton AR, Joyce K, Papalia SM, *et al*. Is salmeterol ergogenic? *Clin J Sport Med* 1996;6:220–5.
28 Meeuwisse WH, McKenzie DC, Hopkins SR, *et al*. The effect of salbutamol on performance in elite nonasthmatic athletes. *Med Sci Sports Exerc* 1992;24:1161–6.
29 McDowell SL, Fleck SJ, Storms WW. The effects of salmeterol on power output in nonasthmatic athletes. *J Allergy Clin Immunol* 1997;99:443–9.
30 Lemmer JT, Fleck SJ, Wallach JM, *et al*. The effects of albuterol on power output in non-asthmatic athletes. *Int J Sports Med* 1995;16:243–9.
31 Le Panse B, Collomp K, Portier H, *et al*. Effects of short-term salbutamol ingestion during a Wingate test. *Int J Sports Med* 2005;26:518–23.
32 Le Panse B, Arlettaz A, Portier H, *et al*. Effects of acute salbutamol intake during supramaximal exercise in women. *Br J Sports Med* 2007;41:430–4.
33 Le Panse B, Arlettaz A, Portier H, *et al*. Short term salbutamol ingestion and supramaximal exercise in healthy women. *Br J Sports Med* 2006;40:627–31.
34 Kalsen A, Hostrup M, Söderlund K, *et al*. Inhaled beta2-agonist increases power output and glycolysis during sprinting in men. *Med Sci Sports Exerc* 2016;48:39–48.
35 Kalsen A, Hostrup M, Backer V, *et al*. Effect of formoterol, a long-acting β2-adrenergic agonist, on muscle strength and power output, metabolism, and fatigue during maximal sprinting in men. *Am J Physiol Regul Integr Comp Physiol* 2016;310:R1312–21.
36 Hostrup M, Kalsen A, Onslev J, *et al*. Mechanisms underlying enhancements in muscle force and power output during maximal cycle ergometer exercise induced by chronic β2-adrenergic stimulation in men. *J Appl Physiol* 2015;119:475–86.
37 Hostrup M, Kalsen A, Bangsbo J, *et al*. High-dose inhaled terbutaline increases muscle strength and enhances maximal sprint performance in trained men. *Eur J Appl Physiol* 2014;114:2499–508.
38 Collomp K, Le Panse B, Portier H, *et al*. Effects of acute salbutamol intake during a Wingate test. *Int J Sports Med* 2005;26:513–7.
39 Altarawneh MM, Petersen A, Smith R, *et al*. Salbutamol effects on systemic potassium dynamics during and following intense continuous and intermittent exercise. *Eur J Appl Physiol* 2016;116:2389–99.
40 Kalsen A, Hostrup M, Bangsbo J, *et al*. Combined inhalation of beta2 -agonists improves swim ergometer sprint performance but not high-intensity swim performance. *Scand J Med Sci Sports* 2014;24:814–22.
41 Dickinson J, Molphy J, Chester N, *et al*. The ergogenic effect of long-term use of high dose salbutamol. *Clin J Sport Med* 2014;24:474–81.
42 Morton AR, Papalia SM, Fitch KD. Changes in anaerobic power and strength performance after inhalation of salbutamol in nonasthmatic athletes. *Clin J Sport Med* 1993;3:14–19.
43 Decorte N, Verges S, Flore P, *et al*. Effects of acute salbutamol inhalation on quadriceps force and fatigability. *Med Sci Sports Exerc* 2008;40:1220–7.
44 Decorte N, Bachasson D, Guinot M, *et al*. Effect of salbutamol on neuromuscular function in endurance athletes. *Med Sci Sports Exerc* 2013;45:1925–32.
45 Hostrup M, Kalsen A, Ortenblad N, *et al*. β2-adrenergic stimulation enhances Ca2+ release and contractile properties of skeletal muscles, and counteracts exercise-induced reductions in Na+-K+-ATPase Vmax in trained men. *J Physiol* 2014;592:5445–59.
46 Sanchez AMJ, Collomp K, Carra J, *et al*. Effect of acute and short-term oral salbutamol treatments on maximal power output in non-asthmatic athletes. *Eur J Appl Physiol* 2012;112:3251–8.
47 Kane SP. Sample size calculator. ClinCalc, 2018. Available: https://clincalc.com/stats/SampleSize.aspx [Accessed 18 Dec 2019].
48 Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;313:1200.
49 Caruso JF, Signorile JF, Perry AC, *et al*. The effects of albuterol and isokinetic exercise on the quadriceps muscle group. *Med Sci Sports Exerc* 1995;27:1471???1476–6.
50 Jessen S, Onslev J, Lemminger A, *et al*. Hypertrophic effect of inhaled beta2-agonist with and without concurrent exercise training: a randomized controlled trial. *Scand J Med Sci Sports* 2018;28:2114–22.
51 Lee P, Birzniece V, Umpleby AM, *et al*. Formoterol, a highly β2-selective agonist, induces gender-dimorphic whole body leucine metabolism in humans. *Metabolism* 2015;64:506–12.
52 Cazzola M, Matera MG. Tremor and β(2)-adrenergic agents: is it a real clinical problem? *Pulm Pharmacol Ther* 2012;25:4–10 https://doi.org/
53 Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016;352:i1981.
54 Lin L. Bias caused by sampling error in meta-analysis with small sample sizes. *PLoS One* 2018;13:e0204056.
55 Regression in meta-analysis. Available: https://www.meta-analysis.com/downloads/MRManual.pdf [Accessed 01 Dec 2018].
56 Cohen J. *Statistical power analysis for the behavioral sciences*. Taylor & Francis Inc, 1988.
57 Gastin PB. Energy system interaction and relative contribution during maximal exercise. *Sports Med* 2001;31:725–41.
58 Currell K, Jeukendrup AE. Validity, reliability and sensitivity of measures of sporting performance. *Sports Med* 2008;38:297–316.
59 van Baak MA, de Hon OM, Hartgens F, *et al*. Inhaled salbutamol and endurance cycling performance in non-asthmatic athletes. *Int J Sports Med* 2004;25): :533–8.
60 Hostrup M, Reitelseder S, Jessen S, *et al*. Beta2-adrenoceptor agonist salbutamol increases protein turnover rates and alters signalling in skeletal muscle after resistance exercise in young men. *J Physiol* 2018;596:4121–39.
61 US National Library of Medicine. PubChem. Available: https://pubchem.ncbi.nlm.nih.gov/ [Accessed 13 May 2019].