Aerobic performance among healthy (non-asthmatic) adults using beta2-agonists: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective To examine the effect of beta2-agonists on aerobic performance in healthy, non-asthmatic study participants.

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. Studies examining the effect of beta2-agonists on maximal physical performance lasting longer than 1 min were included in the meta-analysis. Data are presented as standardised difference in mean (SDM) with 95% CI.

Results The present meta-analysis includes 47 studies. The studies comprise 607 participants in cross-over trials, including 99 participants in three-way cross-over trials and 27 participants in a four-way cross-over trial. Seventy-three participants were included in parallel trials. Beta2-agonists did not affect aerobic performance compared with placebo (SDM 0.051, 95% CI −0.020 to 0.122). The SDM for the included studies was not heterogeneous (I^2=0%, p=0.893), and the effect was not related to type of beta2-agonist, dose, administration route, duration of treatment or performance level of participants. Beta2-agonists had no effect on time trial performance, time to exhaustion or maximal oxygen consumption (p<0.218).

Conclusion/implication The present study shows that beta2-agonists do not affect aerobic performance in non-asthmatic subjects regardless of type, dose, administration route, duration of treatment or performance level of participants. The results of the present study should be of interest to WADA and to anyone who is interested in equal opportunities in competitive sports.

Systematic review registration PROSPERO CRD42018109223.

INTRODUCTION

Asthma is the most common chronic disease in elite athletes,[1] and endurance athletes regularly performing heavily increased ventilation are at increased risk of developing asthma.[2] Asthma is usually associated with airway hyper-responsiveness (AHR), and the recommended therapy for asthma is inhaled glucocorticoids with inhaled beta2-agonists pre-exercise and as a reliever of symptoms.[3] However, ever since inhaled beta2-agonists became available just before the Olympic Games in 1972, antidoping authorities have regulated the use of beta2-agonists in athletes due to possible performance-enhancing effects.[1] WADA annually updates the prohibited list, a list of substances and methods prohibited in elite sports. The prohibited list, effective from 1 January 2020, prohibits all use of beta2-agonists except inhaled salbutamol (maximum of 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 of 200 μg over 24 hours).[4]

Athletes with a medical history of asthma have consistently outperformed athletes without this condition during the Olympic Games.[2] There has been some suspicion that non-asthmatic athletes use beta2-agonists with intention to improve their performance.[5] Thus, the possible performance-enhancing effect of beta2-agonists has been examined in multiple studies. In 2007, Kindermann[5] reviewed the effect of beta2-agonists and concluded that inhaled beta2-agonists do not enhance endurance performance, while oral beta2-agonists enhance endurance performance. The year after, the IOC consensus statement claimed that inhaled beta2-agonists do not enhance endurance performance,[6] and a joint Task Force of European Respiratory Society and European Academy of Allergy and Clinical Immunology concluded that there was no evidence to suggest that asthma drugs can improve physical performance in healthy athletes.[7] In 2011, Pluim *et al*[8] published the first systematic review and meta-analysis on the effect of beta2-agonists on physical performance in healthy athletes. They did not identify any effect of inhaled beta2-agonists on endurance, strength 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 aerobic performance, and controversy with regard to the use of beta2-agonists in sports continuously exists, which has been highlighted in recent beta2-agonist antidoping investigations involving world-class athletes.[9 10] In a recent meta-analysis,[11] we assessed the effect of beta2-agonists on anaerobic performance in non-asthmatic subjects. Therefore, the aim of this systematic review and meta-analysis was to assess the effect of beta2-agonists on aerobic performance in healthy, non-asthmatic subjects.

METHODS

Search strategy and selection criteria

The study protocol for this systematic review and meta-analysis was registered at PROSPERO (International Prospective Register of Systematic Reviews) on 18 September 2018, with registration

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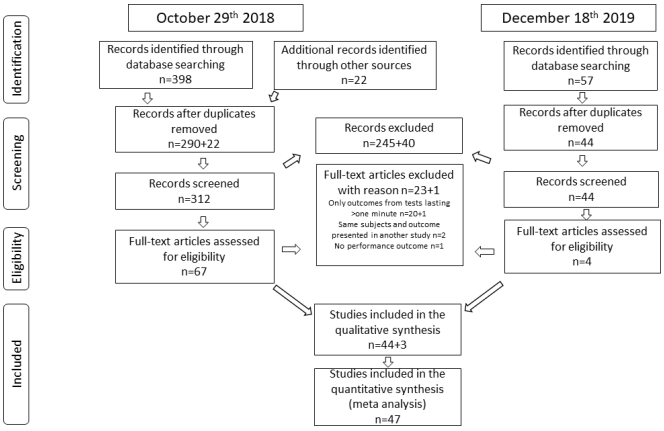


Figure 1 Flow chart of included studies, as proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 statement.[12]

number CRD42018109223, and complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines.[12]

Literature search

We systematically searched for published randomised controlled trials (RCT) that examined the effect of beta2-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 beta2-agonists listed in the WADA prohibited list[4] but were 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 Science 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 involving 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 60 s or less and non-performance variables such as neuromuscular function, oxygen kinetics and ventilation.

Included studies

From the first search 45 studies were selected for full-text eligibility assessment after screening of titles and abstracts, while 22 other studies were included based on previous knowledge of the studies or screening of the reference lists of the included studies. 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 lasting longer than 1 min, only 21 studies presenting data from performance outcomes with a duration of 1 min or less were excluded. Two studies presented results that were published in two other studies and were therefore excluded, and one study reported no performance outcome. Thus, 47 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 criteria. 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 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 AHR'. For a study to be classified as 'low risk for bias' on the seventh domain, an objective measure of AHR was required. Studies which screened participants using lung function measurement at rest, stethoscopy or a questionnaire on medical history or bronchial complaints were considered as 'high risk of bias'. An eighth domain was added to the risk of bias tool reporting the days between the treatments in cross-over studies. Carryover effect and period effect were also extracted from the study as part of bias assessment. Two authors (AR and JS) independently assessed the included studies that were not assessed in the meta-analysis by Pluim *et al*.[8] Any discrepancies in the assessments were resolved by discussion.

Analysis

AR and TS conducted data extraction of study results separately and settled discrepancy by mutual agreement. The main outcome was aerobic performance, defined as maximal physical performance lasting more than 1 min. Other outcomes were maximal/peak oxygen consumption ($VO_{2max/peak}$), measured by analysis of expiratory gas; and physical performance, measured as time to exhaustion, distance covered in a preset time, time to cover a distance/amount of work or contractions to task failure. If a study reported both $VO_{2max/peak}$ and physical performance, physical performance was included in the main analysis. If only $VO_{2max/peak}$ was reported, $VO_{2max/peak}$ was included as outcome in the main analysis. Performance tests were categorised into time to exhaustion/open-ended tests when the subjects performed running, walking, cycling or quadriceps contractions for as long as they could, and time trials/closed-ended tests when the subjects performed a given amount of work as fast as possible. The interventions were categorised in four different ways: (1) type of beta2-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 included as a category in the

meta-regression); (3) duration of treatment: acute treatment and multiple weeks of treatment; and (4) dose: approved and prohibited by WADA.[4] The four interventions were treated as categorical variables in the meta-regression analysis. The included studies were classified as 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'. If the subject in a study performed endurance training for more than 10 hours per week or had VO_{2max} >65 mL/kg/min (women >60 mL/kg/min), the subjects were classified as high-performance endurance athletes. Correlations between performance with active treatment and placebo were 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 SD when SEM and 95% CI were reported) in Excel (Microsoft) prior to transfer into Comprehensive Meta-Analysis (CMA) V.3 (Biostat, Englewood, New Jersey, 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 mean (SDM) with 95% CI. Heterogeneity is presented as I^2 and p values. Whether or not the effect size was related to type of beta2-agonist, administration route, duration of treatment, dose, publication bias or level of fitness was 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 and Begg and Mazumdar rank correlation test. 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.[14] Skewness of outcomes was assessed as baseline mean/SD. Variables with a mean to SD ratio >2 were considered skewed.[15] Significance level was set to $p<0.05$.

RESULTS

Study characteristics

The present meta-analysis consists of 47 RCTs, including 43 studies with a cross-over design,[16–58] of which 8 studies compared two interventions[33 35 39 44 46 53 55 58] and 1 study compared three different interventions[40] with placebo, and 4 studies with parallel design[59–62] (one with both acute and multiple-week intervention[62]). The meta-analysis of aerobic performance includes 60 different randomised and placebo-controlled comparisons with beta2-agonists, comprising 607 participants in cross-over trials that include 99 participants in three-way cross-over trials comparing two different treatments with placebo and 27 participants in a four-way cross-over trial comparing three different beta2-agonist treatments with placebo. Seventy-three participants were included in parallel trials. The included studies are presented in table 1.

Risk of bias

Twenty-five (53%) studies had high risk of bias in one domain or more, and the washout period varied from overnight to 4 weeks between the studies (online supplementary appendix table 1). The effect of beta2-agonists was not related to risk of bias (table 2). One study[52] reported period effect (p=0.12) and carryover effect (p=0.51) in addition to treatment effect (p=0.54). Examination of potential publication bias by assessing the funnel plot indicated no publication bias (online supplementary appendix figure 1). The Begg and Mazumdar rank correlation test found no publication bias, with a one-tailed p value of 0.466.

Effect of beta2-agonists

Beta2-agonists did not affect aerobic performance as compared with placebo (SDM 0.051, 95% CI −0.020 to 0.122). The SDM for the included studies was not heterogeneous (I^2=0%, p=0.893) (table 3). Neither type of beta2-agonist, administration route, duration of treatment nor dose of beta2-agonist did influence the SDM (p>0.340) (table 2). In a stratified analysis beta2-agonists prohibited by WADA (SDM 0.032, 95% CI −0.082 to 0.146) and beta2-agonists approved by WADA (SDM 0.063, 95% CI −0.02 to 0.153) had no effect on aerobic performance.

The effect of beta2-agonists on physical performance was assessed in 53 comparisons. Beta2-agonists did not improve aerobic physical performance (SDM 0.047, 95% CI −0.028 to 0.121). The SDM for the included studies was not heterogeneous (I^2=0%, p=0.778) (table 3, figure 2). Neither type of beta2-agonist, administration route, duration of treatment nor dose of beta2-agonist did influence the SDM (p>0.325) (table 2).

The SDM from 28 comparisons showed that beta2-agonists did not affect VO_{2max} (p=0.809) (table 3, figure 3), and type of beta2-agonist, administration route, duration of treatment or dose of beta2-agonist did not influence SDM (p>0.249) (table 2).

The effect on time trial performance was assessed in 17 comparisons and the effect on performance to exhaustion was assessed in 36 comparisons. Beta2-agonists did not improve time to exhaustion (p=0.411) or time trial performance (p=0.345) (table 3).

Sample size and skewness

Two of the 47 included studies included adequate numbers of participants to obtain an alpha <0.05 and a beta <0.2 (online supplementary table 1). Baseline performance values were skewed in four comparisons, and sensitivity analysis excluding these four comparisons found no effect of beta2-agonists on aerobic performance (SDM 0.046, p=0.213).

Sensitivity analysis

Eleven studies included high-performance endurance athletes (table 3), and there was no difference in response to beta2-agonists in the high-performance endurance athletes compared with the less fit subjects included in the other studies (table 2; p=0.808).

In a sensitivity analysis excluding the 16 comparisons with 10 or less pairwise comparisons between beta2-agonists and placebo, we did not find any effect of beta2-agonists on aerobic performance (SDM 0.059, p=0.171).

DISCUSSION

This meta-analysis of RCTs that examined the effect of beta2-agonists on aerobic performance provides the most comprehensive quantitative summary of the evidence to date, including 47 RCTs with 60 placebo-controlled comparisons comprising 680 participants. Twenty-five studies had high risk of bias due to side effects, single blinding or inadequate screening for AHR. Our study extends previous reviews by including 21 studies not

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

Study, year	Design	Subjects: n, sex, age, years±SD or range	Fitness	Intervention	Outcomes
Molphy *et al*, 2019[58]	Three-way cross-over	16, M/F 8/8, 23±3	Recreationally active >2 times/week	Inhaled terbutaline 2000 µg Inhaled terbutaline 4000 µg	3000 m treadmill time trial
Merlini *et al*, 2019[57]	Cross-over	13, M, 18±1	Amateur football	Inhaled salbutamol 1600 µg	Shuttle run test
Hafedh *et al*, 2019[56]	Cross-over	12, 6/6, 22±1	Recreationally active	Oral terbutaline 8000 µg	Shuttle run test
Laurent *et al*, 2018[55]	Three-way cross-over	14, M, 25±5	Endurance athletes 6±2 hours/week	Inhaled salbutamol 800 µg Oral salbutamol 4000 µg	Quadriceps contractions to task failure
Eckerström *et al*, 2018[54]	Cross-over	36, M/F 18/18, 26±5	Non-athletes	Inhaled salbutamol 900 µg	VO_{2max}
Molphy *et al*, 2017[53]	Three-way cross-over	7, M, 22±1	Recreational exercise ≥3 hours/week	Inhaled salbutamol 400 µg	3000 m treadmill time trial
Halabchi *et al*, 2017[52]	Cross-over	20, M, 17±1	Junior professional football players	Inhaled 200 µg salbutamol	20 m multistage shuttle run test
Hostrup *et al*, 2016[62]	Parallel	20, M, 26±4	National level endurance athletes*	Oral salbutamol 8000 µg acute and 8000 µg/day for 2 weeks	VO_{2max}, time to exhaustion
Koch *et al*, 2015[51]	Cross-over	35, M, 28±5	Experienced cyclists/triathletes, VO_{2max} ≥60 mL/kg/min or 5 L	Inhaled salbutamol 400 µg	10 km ergometer time trial
Koch *et al*, 2015[50]	Cross-over	15, F, 30±5	Cyclists and triathletes VO_{2max} 50 mL/kg/min or 4 L	Inhaled salbutamol 400 µg	10 km ergometer time trial
Koch *et al*, 2015[49]	Cross-over	12, M, 31±7	Competitive cyclists VO_{2max} ≥60 mL/kg/min or 5 L	Inhaled salbutamol 1600 µg	10 km ergometer time trial
Hostrup *et al*, 2015[61]	Parallel	18, M, 24±3	Recreationally active 4–8 hours/week	Oral terbutaline 5000 µg/30 kg body weight, two times per day for 28±1 days	VO_{2max}, cycling to exhaustion, incremental
Kalsen *et al*, 2014[48]	Cross-over	9, M, 24±3	Moderately trained	Inhaled terbutaline 15 000 µg	300 kcal cycling time trial
Hostrup *et al*, 2014[47]	Cross-over	9, M, 24±3	Recreationally active	Inhaled terbutaline 15 000 µg	100 kcal cycling time trial
Dickinson *et al*, 2014[60]	Parallel	16, M, 20±2	Amateur-level competition	Inhaled salbutamol 1600 µg/day for 6 weeks	VO_{2peak}, 3 km treadmill time trial
Dickinson *et al*, 2014[46]	Three-way cross-over	7, M, 22±4	Runners, >2 times/week	Inhaled salbutamol 800 µg and 1600 µg	5 km treadmill time trial in 18°C and 30°C
Sanchez *et al*, 2013[45]	Cross-over	7, M, 29±6	Competitive recreational athletes, 10 hours/week	Oral terbutaline 8000 µg	Cycling to exhaustion, VO_{2max}
Decorte *et al*, 2013[44]	Three-way cross-over	11, M, 33±6	Highly trained cyclists/triathletes/runners, 12±3 hours/week*	Inhaled salbutamol 200 µg and 800 µg	Quadriceps contractions to task failure
Elers *et al*, 2012[43]	Cross-over	9, M, 27±5	Endurance-trained 11 hours/week*	Inhaled 8000 µg salbutamol	Peak power output, incremental VO_{2max}
Beloka *et al*, 2011[42]	Cross-over	21, M, 23±2	Healthy non-athletes	Infused salbutamol 350 µg or 700 µg	VO_{2max}
Andersen and Kanstrup, 2009[41]	Cross-over	7, M, 25, 18–30	Highly endurance-trained*	Oral salbutamol 4000 µg	Running to exhaustion, VO_{2max}
Sporer *et al*, 2008[40]	Four-way cross-over	27, M, 29±6	Competitive cyclists and triathletes*	Inhaled salbutamol 200 µg, 400 µg and 800 µg	20 km cycling time trial
Decorte *et al*, 2008[39]	Three-way cross-over	10, M, 23±3	Healthy non-athletes	Inhaled salbutamol 200 µg and 800 µg	Cycling to exhaustion, incremental, VO_{2max}
Tjørhom *et al*, 2007[38]	Cross-over	23, M, 29±5	Endurance athletes, VO_{2max} 60.6 mL/kg/min	Inhaled formoterol 18 µg	Running to exhaustion at –20°C at 107% VO_{2max}, VO_{2max}
Riiser *et al*, 2006[37]	Cross-over	20, M, 29±4	Endurance athletes, VO_{2max} 61.1 mL/kg/min	Inhaled formoterol 18 µg	Running to exhaustion in hypobaric conditions at 107% VO_{2max}, VO_{2max}
van Baak *et al*, 2004[36]	Cross-over	16, M, 23±3	Cyclists and triathletes, training 11±3 hours/week*	Inhaled 800 µg salbutamol	Cycling time trial
Stewart *et al*, 2002[35]	Three-way cross-over	10, M, 26, 20–30	Highly trained athletes*	Inhaled formoterol 12 µg or inhaled salbutamol 400 µg	VO_{2max}
Collomp *et al*, 2002[34]	Cross-over	8, M, 26±2	Moderately trained	Oral salbutamol 6000 µg	10 min cycling time trial
Collomp *et al*, 2000[29]	Cross-over	9, M, 25±1	Moderately trained	Oral salbutamol 6000 µg	Cycling to exhaustion at 85% of VO_{2max}
Collomp *et al*, 2000[30]	Cross-over	8, M, 23±3	Recreational athletes, cycling/running 3–5 times/week	Oral salbutamol 12 000 µg/day for 3 weeks	Cycling to exhaustion at 85% of VO_{2max}
Goubault *et al*, 2001[33]	Three-way cross-over	13, M, 23±2	Competitive triathlete	Inhaled salbutamol 200 µg and 800 µg	Cycling to exhaustion at 85% of VO_{2max}

Continued

Table 1 Continued

Study, year	Design	Subjects: n, sex, age, years±SD or range	Fitness	Intervention	Outcomes
Carlsen *et al*, 2001[32]	Cross-over	24, M, 25±3	Competitive athletes*	Inhaled formoterol 9 µg	Running to exhaustion at 105% of VO_{2max} VO_{2max}
van Baak *et al*, 2000[31]	Cross-over	16, M, 23±2	Healthy non-athletes	Oral salbutamol 4000 µg	Cycling to exhaustion at 70% of VO_{2max}
Sue-Chu *et al*, 1999[28]	Cross-over	8, M, 19–28	Highly trained cross-country skiers*	Inhaled salmeterol 50 µg	Running to exhaustion at −15°C, incremental VO_{2max}
Sandsund *et al*, 1998[27]	Cross-over	8, M, 25±4	Highly trained cross-country skiers*	Aerosolised salbutamol 1200 µg	Running to exhaustion, incremental, VO_{2max}
Larsson *et al*, 1997[26]	Cross-over	20, M, 24, 18–31	Elite endurance athletes*	Inhaled terbutaline 3000 µg	Running to exhaustion, incremental, VO_{2max}
Carlsen *et al*, 1997[25]	Three-way cross-over	18, M, 23±6	Running >3 times/week	Inhaled salbutamol 800 µg Inhaled salmeterol 50 µg	Running until exhaustion, incremental, VO_{2max}
Norris *et al*, 1996[24]	Cross-over	15, M, 25±4	Highly trained cyclists	Inhaled 400 µg salbutamol	20 km cycling time trial VO_{2max}
Heir and Stemshaug, 1995[23]	Cross-over	17, M, 18–30	Highly conditioned endurance athletes*	Aerosolised salbutamol 50 µg/kg	Running to exhaustion at 110% VO_{2max}, VO_{2peak}
Unnithan *et al*, 1994[22]	Cross-over	10, M, 10±1	Healthy non-athletes	Inhaled terbutaline 500 µg	Total running time VO_{2peak}
Fleck *et al*, 1993[21]	Cross-over	21, M, 24±5	Elite cyclists	Inhaled salbutamol 360 µg	W-max VO_{2max}
Morton *et al*, 1992[20]	Cross-over	17, M/F 16/1, 22±4	High-performance runners*	Inhaled salbutamol 200 µg	Running to exhaustion, incremental VO_{2max}
Meeuwisse *et al*, 1992[19]	Cross-over	7, M, 24±4	Trained cyclists	Inhaled salbutamol 200 µ g	Endurance sprint time VO_{2max}
Violante *et al*, 1989[18]	Cross-over	7, M, 34±8	Sedentary non-athletes	Intravenous salbutamol 4 µg/kg followed by 3 µg/kg/hour	Walking to exhaustion, incremental
Bedi *et al*, 1988[16]	Cross-over	15, M/F 14/1, 23±5	Cyclists, triathletes	Inhaled salbutamol 180 µg	Cycling to exhaustion after 60 min submaximal exercise VO_{2max}
Booth, 1988[17]	Cross-over	10, F, 21±7	Trained cyclists	Inhaled salbutamol ×2, therapeutic dose	Cycling to exhaustion
McKenzie *et al*, 1983[59]	Parallel	4, M, 25±8 5, F, 27±10 5, M, 24±9 5, F, 26±13	Highly trained track and field athletes*	Inhaled salbutamol 800 µg	VO_{2max}

*Denotes high-performance endurance athletes.
F, female; M, male; VO_{2max}, Maximal oxygen consumption; W-max, maximal workload during incremental cycling.

previously meta-analysed and with an indepth analysis of aerobic performance. The results from our analysis demonstrated that beta2-agonists had no effect on aerobic performance. The result was consistent and not heterogeneous.

To our knowledge, no other studies have pooled data and meta-analysed the effects of beta2-agonists on aerobic performance to this extent. Pluim *et al*[8] presented a meta-analysis stratified by administration route (oral or inhaled) and analysed test-specific outcomes separately and did not find any effect of inhaled or oral beta2-agonists on any aerobic performance outcome. In our study, we included comparisons with inhaled and oral beta2-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 beta2-agonists.[63] 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 aerobic performance. We also investigated whether beta2-agonists prohibited by WADA had different effects from beta2-agonists (type and dose) approved by WADA and we found no difference. In addition, we meta-analysed different types of aerobic performance and stratified by VO_{2max}, performance, time trials (closed-ended tests) performance, and performance until exhaustion (open-ended tests). We combined 59 comparisons as compared with 2–18 comparisons (depending on the number of studies measuring aerobic performance in the same way) in the study by Pluim *et al*.[8] Thus, our results strengthen the findings from Pluim *et al*.[8] Type of beta2-agonist, administration route, duration of treatment, dose, fitness level of participants or study quality did not affect the result.

Analysis of performance categories

Maximal oxygen consumption was unaffected by the use of beta2-agonists. The effect size from the 27 comparisons included was not heterogeneous, and type of beta2-agonist, administration route, duration of treatment or dose did not affect the result. The finding builds on the evidence from Pluim *et al*,[8] who meta-analysed 18 studies with inhaled beta2-agonists.

Table 2 Regression of standardised difference in mean against type of beta2-agonist, administration route, duration of treatment, dose and risk of bias treated as categorical variables

	Aerobic performance	VO_{2max}	Physical performance	Time trial	To exhaustion
Type of beta2-agonist (reference: long-acting)				*	
Test of model, p value	0.552	0.687	0.693		0.724
Goodness of fit, p value	0.826	0.998	0.723		0.196
R^2 analogue	0	0	0		0
Administration route (reference: inhaled)					
Test of model, p value	0.340	0.464	0.325	0.99	0.300
Goodness of fit, p value	0.790	0.998	0.752	0.999	0.236
R^2 analogue	0	0	0	0	0
Duration of treatment (reference: acute)					
Test of model, p value	0.953	0.249	0.944	0.861	0.888
Goodness of fit, p value	0.816	0.999	0.718	0.998	0.193
R^2 analogue	0	0	0	0	0
Dose (reference: prohibited)					
Test of model, p value	0.659	0.913	0.467	0.338	0.869
Goodness of fit, p value	0.821	0.997	0.737	0.999	0.193
R^2 analogue	0	0	0	0	0
Type, route, duration, dose				*	
Test of model, p value	0.644	0.820	0.496		0.693
Goodness of fit, p value	0.809	0.997	0.738		0.180
R^2 analogue	0	0	0		0
Risk of bias (reference: high risk)					
Test of model, p value	0.928	0.845	0.744	0.130	0.485
Goodness of fit, p value	0.816	0.997	0.721	0.999	0.210
R^2 analogue	0	0	0	0	0.00
Performance level (reference: high-performance)					
Test of model, p value	0.808	0.538	0.639	0.557	0.865
Goodness of fit, p value	0.717	0.998	0.725	0.999	0.193
R^2 analogue	0	0	0	0	0

R^2 analogue: proportion of total between-study variance explained by the covariate.
Aerobic performance: maximal physical performance lasting more than 1 min.
Physical performance: time to exhaustion, distance covered in a preset time, time to cover a distance/amount of work or contractions to task failure. If a study reported both $VO_{2max/peak}$ and physical performance, physical performance was included in aerobic performance. If only $VO_{2max/peak}$ was reported, $VO_{2max/peak}$ was included in aerobic performance.
Time trial: closed-ended tests.
To exhaustion: open-ended tests.
*Could not be assessed due to a problem with collinearity.
$VO_{2max/peak}$, maximal oxygen consumption.

Beta2-agonists did not improve aerobic physical performance measured by closed-ended or open-ended tests. Closed-ended tests are usually recommended over open-ended tests due to better reliability[64] and possibly a better chance of detecting minor differences in performance. However, in the present study, neither type of protocol indicated an effect of beta2-agonists on aerobic performance.

Bias

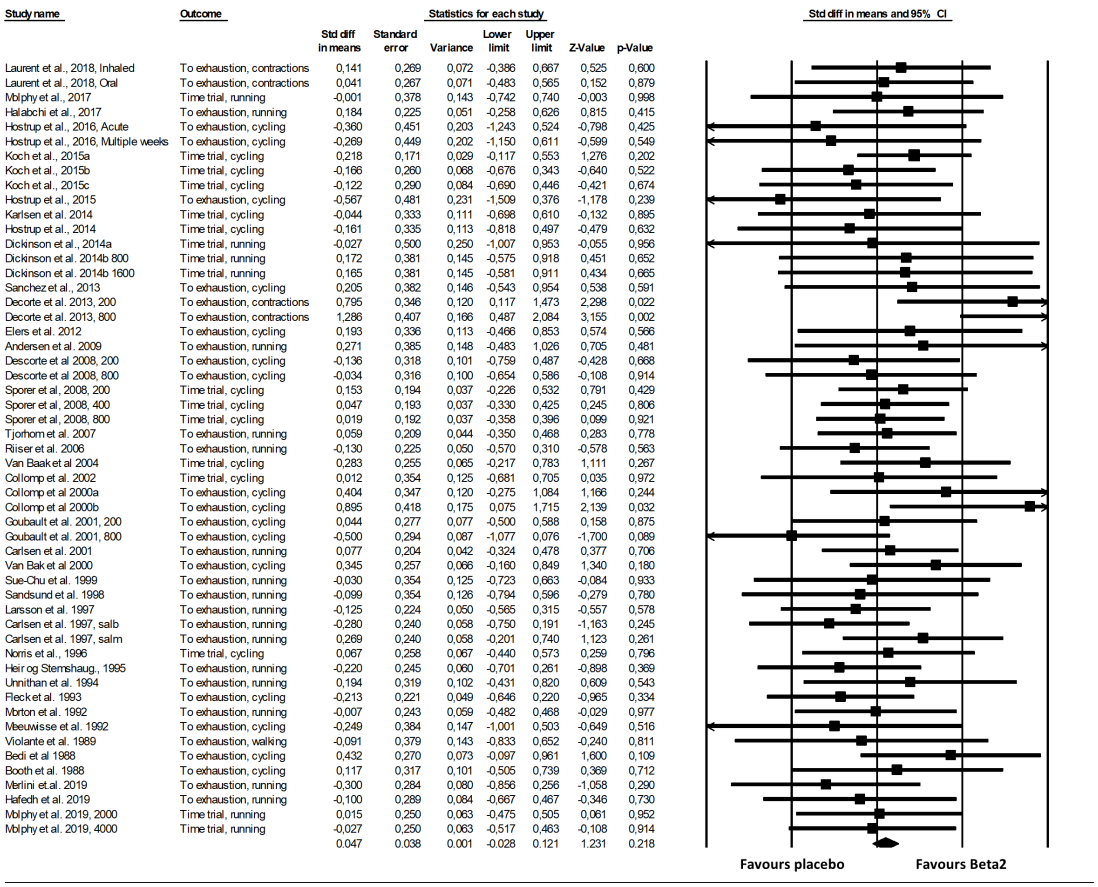
The funnel plot and the Begg and Mazumdar rank correlation test were negative for publication bias, indicating that the results do not influence whether the studies are published or not.

Tachycardia and tremor are characteristic adverse side effects of beta2-agonists.[65] These side effects may break the blinding if

Table 3 Meta-analysis for each outcome measure

		Meta-analysis of each outcome			Test of heterogeneity	
Outcome	Comparisons (n)	SDM	CI	P value	I^2 (%)	P value
Aerobic performance	60	0.051	−0.020 to 0.122	0.156	0	0.893
Physical performance	53	0.047	−0.028 to 0.121	0.218	0	0.778
VO_{2max}	28	−0.013	−0118 to 0.092	0.809	0	0.999
Time trial	17	0.059	−0.064 to 0.182	0.345	0	0.999
To exhaustion	36	0.043	−0.059 to 0.144	0.411	26	0.260

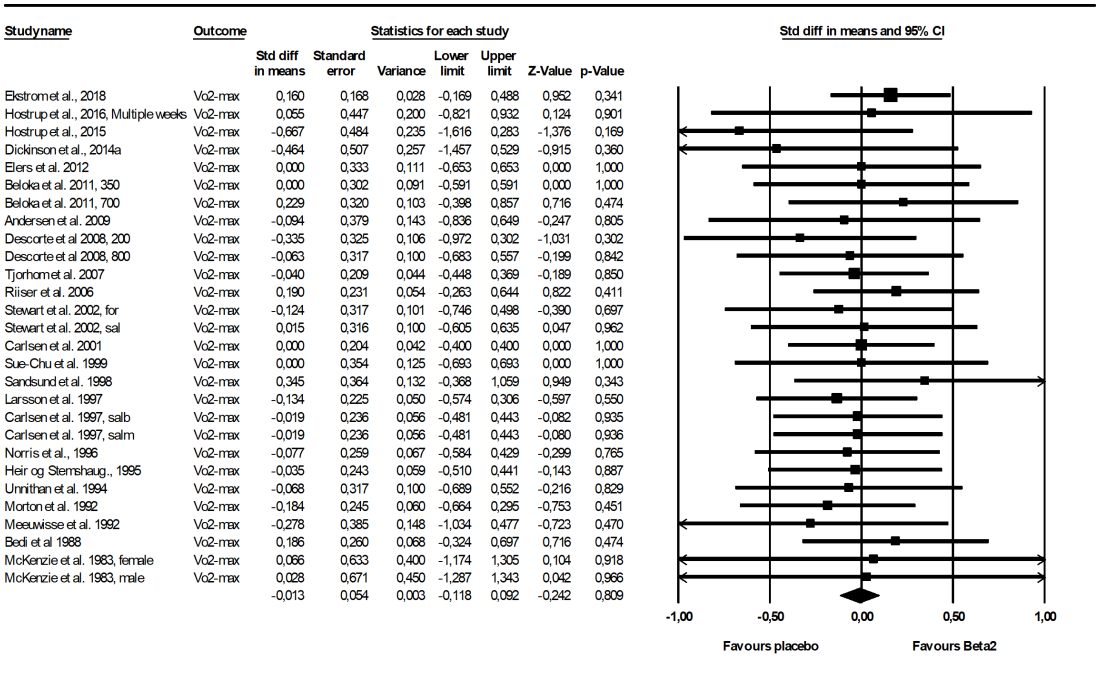
Aerobic performance: maximal physical performance lasting more than 1 min.
Physical performance: time to exhaustion, distance covered in a preset time, time to cover a distance/amount of work or contractions to task failure. If a study reported both $VO_{2max/peak}$ and physical performance, physical performance was included in aerobic performance. If only $VO_{2max/peak}$ was reported, $VO_{2max/peak}$ was included in aerobic performance.
Time trial: closed-ended tests.
To exhaustion: open-ended tests.
I^2: the proportion of variance that is due to real differences in effect size.
SDM, standardised difference in mean; $VO_{2max/peak}$, maximal oxygen consumption.



Study name	Outcome	Statistics for each study						
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Laurent et al., 2018, Inhaled	To exhaustion, contractions	0,141	0,269	0,072	-0,386	0,667	0,525	0,600
Laurent et al., 2018, Oral	To exhaustion, contractions	0,041	0,267	0,071	-0,483	0,565	0,152	0,879
Molphy et al., 2017	Time trial, running	-0,001	0,378	0,143	-0,742	0,740	-0,003	0,998
Halabchi et al., 2017	To exhaustion, running	0,184	0,225	0,051	-0,258	0,626	0,815	0,415
Hostrup et al., 2016, Acute	To exhaustion, cycling	-0,360	0,451	0,203	-1,243	0,524	-0,798	0,425
Hostrup et al., 2016, Multiple weeks	To exhaustion, cycling	-0,269	0,449	0,202	-1,150	0,611	-0,599	0,549
Koch et al., 2015a	Time trial, cycling	0,218	0,171	0,029	-0,117	0,553	1,276	0,202
Koch et al., 2015b	Time trial, cycling	-0,166	0,260	0,068	-0,676	0,343	-0,640	0,522
Koch et al., 2015c	Time trial, cycling	-0,122	0,290	0,084	-0,690	0,446	-0,421	0,674
Hostrup et al., 2015	To exhaustion, cycling	-0,567	0,481	0,231	-1,509	0,376	-1,178	0,239
Karlsen et al. 2014	Time trial, cycling	-0,044	0,333	0,111	-0,698	0,610	-0,132	0,895
Hostrup et al., 2014	Time trial, cycling	-0,161	0,335	0,113	-0,818	0,497	-0,479	0,632
Dickinson et al., 2014a	Time trial, running	-0,027	0,500	0,250	-1,007	0,953	-0,055	0,956
Dickinson et al. 2014b 800	Time trial, running	0,172	0,381	0,145	-0,575	0,918	0,451	0,652
Dickinson et al. 2014b 1600	Time trial, running	0,165	0,381	0,145	-0,581	0,911	0,434	0,665
Sanchez et al., 2013	To exhaustion, cycling	0,205	0,382	0,146	-0,543	0,954	0,538	0,591
Decorte et al. 2013, 200	To exhaustion, contractions	0,795	0,346	0,120	0,117	1,473	2,298	0,022
Decorte et al. 2013, 800	To exhaustion, contractions	1,286	0,407	0,166	0,487	2,084	3,155	0,002
Elers et al. 2012	To exhaustion, cycling	0,193	0,336	0,113	-0,466	0,853	0,574	0,566
Andersen et al. 2009	To exhaustion, running	0,271	0,385	0,148	-0,483	1,026	0,705	0,481
Descorte et al 2008, 200	To exhaustion, cycling	-0,136	0,318	0,101	-0,759	0,487	-0,428	0,668
Descorte et al 2008, 800	To exhaustion, cycling	-0,034	0,316	0,100	-0,654	0,586	-0,108	0,914
Sporer et al, 2008, 200	Time trial, cycling	0,153	0,194	0,037	-0,226	0,532	0,791	0,429
Sporer et al, 2008, 400	Time trial, cycling	0,047	0,193	0,037	-0,330	0,425	0,245	0,806
Sporer et al, 2008, 800	Time trial, cycling	0,019	0,192	0,037	-0,358	0,396	0,099	0,921
Tjorhom et al. 2007	To exhaustion, running	0,059	0,209	0,044	-0,350	0,468	0,283	0,778
Riiser et al. 2006	To exhaustion, running	-0,130	0,225	0,050	-0,570	0,310	-0,578	0,563
Van Baak et al 2004	Time trial, cycling	0,283	0,255	0,065	-0,217	0,783	1,111	0,267
Collomp et al. 2002	Time trial, cycling	0,012	0,354	0,125	-0,681	0,705	0,035	0,972
Collomp et al 2000a	To exhaustion, cycling	0,404	0,347	0,120	-0,275	1,084	1,166	0,244
Collomp et al 2000b	To exhaustion, cycling	0,895	0,418	0,175	0,075	1,715	2,139	0,032
Goubault et al. 2001, 200	To exhaustion, cycling	0,044	0,277	0,077	-0,500	0,588	0,158	0,875
Goubault et al. 2001, 800	To exhaustion, cycling	-0,500	0,294	0,087	-1,077	0,076	-1,700	0,089
Carlsen et al. 2001	To exhaustion, running	0,077	0,204	0,042	-0,324	0,478	0,377	0,706
Van Bak et al 2000	To exhaustion, cycling	0,345	0,257	0,066	-0,160	0,849	1,340	0,180
Sue-Chu et al. 1999	To exhaustion, running	-0,030	0,354	0,125	-0,723	0,663	-0,084	0,933
Sandsund et al. 1998	To exhaustion, running	-0,099	0,354	0,126	-0,794	0,596	-0,279	0,780
Larsson et al. 1997	To exhaustion, running	-0,125	0,224	0,050	-0,565	0,315	-0,557	0,578
Carlsen et al. 1997, salb	To exhaustion, running	-0,280	0,240	0,058	-0,750	0,191	-1,163	0,245
Carlsen et al. 1997, salm	To exhaustion, running	0,269	0,240	0,058	-0,201	0,740	1,123	0,261
Norris et al., 1996	Time trial, cycling	0,067	0,258	0,067	-0,440	0,573	0,259	0,796
Heir og Stemshaug., 1995	To exhaustion, running	-0,220	0,245	0,060	-0,701	0,261	-0,898	0,369
Unnithan et al. 1994	To exhaustion, running	0,194	0,319	0,102	-0,431	0,820	0,609	0,543
Fleck et al. 1993	To exhaustion, cycling	-0,213	0,221	0,049	-0,646	0,220	-0,965	0,334
Morton et al. 1992	To exhaustion, running	-0,007	0,243	0,059	-0,482	0,468	-0,029	0,977
Meeuwisse et al. 1992	To exhaustion, cycling	-0,249	0,384	0,147	-1,001	0,503	-0,649	0,516
Violante et al. 1989	To exhaustion, walking	-0,091	0,379	0,143	-0,833	0,652	-0,240	0,811
Bedi et al 1988	To exhaustion, cycling	0,432	0,270	0,073	-0,097	0,961	1,600	0,109
Booth et al. 1988	To exhaustion, cycling	0,117	0,317	0,101	-0,505	0,739	0,369	0,712
Marlini et al. 2019	To exhaustion, running	-0,300	0,284	0,080	-0,856	0,256	-1,058	0,290
Hafedh et al. 2019	To exhaustion, running	-0,100	0,289	0,084	-0,667	0,467	-0,346	0,730
Molphy et al. 2019, 2000	Time trial, running	0,015	0,250	0,063	-0,475	0,505	0,061	0,952
Molphy et al. 2019, 4000	Time trial, running	-0,027	0,250	0,063	-0,517	0,463	-0,108	0,914
		0,047	0,038	0,001	-0,028	0,121	1,231	0,218

Figure 2 Forest plot for the effect of beta2-agonists on aerobic physical performance.

the participants are aware of whether they receive beta2-agonists or placebo, and possibly motivate them to perform differently when receiving beta2-agonists. Fifteen studies were classified as high risk of bias due to lack of blinding (single-blinded design or reported side effects of the beta2-agonists), and 10 additional studies did not screen the participants sufficiently for AHR. However, high risk of bias did not influence the SDM in any analysis.



Study name	Outcome	Statistics for each study						
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ekstrom et al., 2018	Vo2-max	0,160	0,168	0,028	-0,169	0,488	0,952	0,341
Hostrup et al., 2016, Multiple weeks	Vo2-max	0,055	0,447	0,200	-0,821	0,932	0,124	0,901
Hostrup et al., 2015	Vo2-max	-0,667	0,484	0,235	-1,616	0,283	-1,376	0,169
Dickinson et al., 2014a	Vo2-max	-0,464	0,507	0,257	-1,457	0,529	-0,915	0,360
Elers et al. 2012	Vo2-max	0,000	0,333	0,111	-0,653	0,653	0,000	1,000
Beloka et al. 2011, 350	Vo2-max	0,000	0,302	0,091	-0,591	0,591	0,000	1,000
Beloka et al. 2011, 700	Vo2-max	0,229	0,320	0,103	-0,398	0,857	0,716	0,474
Andersen et al. 2009	Vo2-max	-0,094	0,379	0,143	-0,836	0,649	-0,247	0,805
Descorte et al 2008, 200	Vo2-max	-0,335	0,325	0,106	-0,972	0,302	-1,031	0,302
Descorte et al 2008, 800	Vo2-max	-0,063	0,317	0,100	-0,683	0,557	-0,199	0,842
Tjorhom et al. 2007	Vo2-max	-0,040	0,209	0,044	-0,448	0,369	-0,189	0,850
Riiser et al. 2006	Vo2-max	0,190	0,231	0,054	-0,263	0,644	0,822	0,411
Stewart et al. 2002, for	Vo2-max	-0,124	0,317	0,101	-0,746	0,498	-0,390	0,697
Stewart et al. 2002, sal	Vo2-max	0,015	0,316	0,100	-0,605	0,635	0,047	0,962
Carlsen et al. 2001	Vo2-max	0,000	0,204	0,042	-0,400	0,400	0,000	1,000
Sue-Chu et al. 1999	Vo2-max	0,000	0,354	0,125	-0,693	0,693	0,000	1,000
Sandsund et al. 1998	Vo2-max	0,345	0,364	0,132	-0,368	1,059	0,949	0,343
Larsson et al. 1997	Vo2-max	-0,134	0,225	0,050	-0,574	0,306	-0,597	0,550
Carlsen et al. 1997, salb	Vo2-max	-0,019	0,236	0,056	-0,481	0,443	-0,082	0,935
Carlsen et al. 1997, salm	Vo2-max	-0,019	0,236	0,056	-0,481	0,443	-0,080	0,936
Norris et al., 1996	Vo2-max	-0,077	0,259	0,067	-0,584	0,429	-0,299	0,765
Heir og Stemshaug., 1995	Vo2-max	-0,035	0,243	0,059	-0,510	0,441	-0,143	0,887
Unnithan et al. 1994	Vo2-max	-0,068	0,317	0,100	-0,689	0,552	-0,216	0,829
Morton et al. 1992	Vo2-max	-0,184	0,245	0,060	-0,664	0,295	-0,753	0,451
Meeuwisse et al. 1992	Vo2-max	-0,278	0,385	0,148	-1,034	0,477	-0,723	0,470
Bedi et al 1988	Vo2-max	0,186	0,260	0,068	-0,324	0,697	0,716	0,474
McKenzie et al. 1983, female	Vo2-max	0,066	0,633	0,400	-1,174	1,305	0,104	0,918
McKenzie et al. 1983, male	Vo2-max	0,028	0,671	0,450	-1,287	1,343	0,042	0,966
		-0,013	0,054	0,003	-0,118	0,092	-0,242	0,809

Figure 3 Forest plot for the effect of beta2-agonists on maximal oxygen consumption (VO_{2max}).

Our study included 16 comparisons between placebo and beta2-agonists that comprised less than 10 pairs (less than 20 subjects in parallel studies and 10 subjects in cross-over studies), and only two 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.[66 67] However, when we performed a sensitivity analysis excluding these 16 comparisons, the effect of beta2-agonists on aerobic performance was still not statistically significant. Normal distribution of data is an important assumption in the meta-analysis of continuous data and five comparisons had skewed baseline data; however, execution of these comparisons from the meta-analysis did not influence the result.

Strength and limitations

The present study is strengthened by the systematic search of the literature in multiple databases. It is therefore likely that all relevant studies were identified, and we included RCTs only. We consider all maximal performance tests lasting more than 1 min to be a measure of aerobic performance; thus, we used SDM as outcome in the meta-analysis.[68] This resulted in a large sample size and a high statistical power. We also investigated the effect of beta2-agonists separately on VO_{2max} and physical performance, which was further divided into open-ended and closed-ended tests to investigate any physiological (oxygen consumption) or performance test-specific effects. Further, we performed subgroup analyses on outcome categories and meta-regression to investigate the effect of the different types of intervention. For example, two recent studies[69 70] reported a potential negative effect of multiple weeks of beta2-agonist treatment, while one study[44] reported a positive effect of acute administration. If this was representative of the included studies, the opposite effects could even each other out in a meta-analysis but show difference in effects in a meta-regression categorised by duration of treatment.

Splitting up the interventions into subcategories can also be a limitation as the statistical power is reduced. Categories with few studies/participants (multiple weeks of treatment) usually have larger uncertainties in the effect estimates, and it is difficult to interpret if the lack of effect is due to no effect or to low statistical power to reveal the real effect. Another 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. Closed-ended tests are recommended over open-ended tests due to better reliability, and the coefficients of variation for open-ended tests are reported to decrease with increased intensity or decreased duration.[64] Thus, we performed separate meta-analyses on open-ended and closed-ended tests. However, both types of tests failed to demonstrate any effect of beta2-agonists. The fitness level of the participants included in our study varied from untrained to elite athletes, and fitness level has been suggested to confound the effect of beta2-agonists on physical performance.[71] However, in the present study beta2-agonists did not affect aerobic performance differently in high-performance endurance athletes compared with less endurance trained participants. The meta-analysis assumes independence between the subjects included. In the present study, the same subjects are included twice in the analysis if they participated in a three-way cross-over study with two different interventions with beta2-agonists, or if the same subjects are assessed after acute treatment and subsequently after multiple weeks of beta2-agonist treatment 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 pretest and post-test has been set to 0.5 for all studies. This is lower than the data made available from Dickinson *et al*[60] by request and similar to what Pluim *et al*[8] reported. RCTs are regarded as high-quality studies, but there is a possibility of bias especially related to the side effects from beta2-agonists breaking the blinding for the participants. In addition, the meta-analysis includes several single-blinded studies where the investigators knew when the subjects received beta2-agonists. This lack of blinding may allow the investigator to treat the subjects systematically different when knowing what the subjects have received. The possible difference in the way the investigator interacts with the subjects may lead to a systematic difference in performance. Many studies did not include objective tests for AHR and thus may have failed to exclude participants with AHR. However, risk of bias did not influence the effect size in the present meta-analysis, and Koch *et al*[51] found no difference in time trial performance between cyclists with and without AHR. In addition, a systematic review from 2014[72] concluded the current evidence is insufficient to prove a negative effect of AHR on physical performance.

Based on the previously mentioned limitations, the findings should be interpreted with caution, especially the results from subgroups with few studies/participants, but there is consistency in the results demonstrating that beta2-agonists do not affect aerobic performance in non-asthmatic subjects.

CONCLUSION

The present study, which summarises the best scientific evidence, shows that beta2-agonists do not affect aerobic performance in non-asthmatic subjects. Beta2-agonists had no effect on performance tests or VO_{2max}. The results from the present study should be of interest to WADA when revising the antidoping regulations and planning antidoping sample analysis, and to anyone who is interested in equal opportunities in competitive sports.

What is already known

- Asthma is the most common chronic disease in athletes.
- The gold standard for asthma therapy is inhaled glucocorticoids with inhaled beta2-agonists pre-exercise and as a reliever of symptoms.
- The use of beta2-agonists in sports is regulated by WADA due to possible performance-enhancing effects.

What are the new findings

- Beta2-agonists do not affect physical aerobic performance or maximal oxygen consumption in healthy subjects.
- Route of administration, type of beta2-agonist, duration of treatment or dose were not related to the effect of beta2-agonists in healthy subjects.
- Study bias or performance level of subjects had no impact on the effect of beta2-agonists on aerobic performance in healthy subjects.

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. 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 the studies for inclusion.

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Patient consent for publication Not required.

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