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Global prevalence of exercise-induced bronchoconstriction in childhood: A meta-analysis

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Abstract

Aim: This systematic review and meta-analysis aimed to estimate the global prevalence of exercise-induced bronchoconstriction (EIB) in children and adolescents.

Method: We searched PubMed, Google Scholar, and the Virtual Health Library-BIREME from inception to December 23, 2017. We selected observational studies that reported the prevalence of EIB (diagnosed by exercise challenge test) in children and adolescents aged 5-18 years. We conducted random-effects meta-analyses to estimate the pooled prevalence of EIB and 95% CI.

Results: We included 66 studies (55 696 participants, 5670 cases of EIB) in the review, of which 33 in general population of children and adolescents, 10 in child and adolescent athletes and 23 in children and adolescents with asthma. The global mean prevalence of EIB in the general population of children and adolescents was 9% (IC95%: 8-10%), with a higher rate (12%) in Asia-Pacific and America. The mean prevalence of EIB was 15% (95% CI: 9-21%) in child and adolescent athletes, and 46% (95% CI: 39-53%) in children and adolescents with asthma. We estimated that, globally, around 16.5 million (95% CI: 15-18 million) children and adolescents up to 18 years of age may have EIB.

Conclusion: EIB in childhood should be considered as a global public health problem that needs more attention. The substantial heterogeneity between studies highlights the need for evidence-based guidelines for diagnosis of EIB in this age group.

KEYWORDS

childhood, exercise challenge test, exercise-induced bronchoconstriction, meta-analysis, prevalence, systematic review

1 | INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is defined as a transient narrowing of the lower airways in association with exercise.[1,2] EIB occurs most frequently in patients with clinically recognized asthma, but may also occur in individuals without underlying asthma. The mechanism for EIB relates to the thermal and osmotic effects of evaporative water loss from the airway surface during exercise.[3] People with EIB may present with wheeze, cough, chest tightness, chest pain, shortness of breath (dyspnea), and excessive mucus production that are related to vigorous exercise. However, these symptoms are neither sensitive nor specific for identifying individuals with EIB, and the diagnosis should be based on changes in lung function after exercise.[1,2]

Abbreviations: BIREME, Latin American and Caribbean Center on Health Sciences Information; EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in the first second; HR, heart rate; HRmax, maximum heart rate for age; NIH, National Institutes of Health; PEF, peak expiratory flow; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

EIB may negatively impact quality of life and practice of physical activities.[4–6] However, the early recognition and appropriate management of EIB can allow children and adolescents to participate fully in physical activities at school and outside of school.[7]

Numerous studies have reported the prevalence of EIB in children and adolescents,[8–13] but to our knowledge, no systematic review has yet addressed this topic which makes it difficult to draw an overall picture of burden of EIB in childhood. We conducted this systematic review and meta-analysis to estimate the global prevalence of EIB in children and adolescents, including general population, child and adolescent athletes and children and adolescents with asthma. These data would provide useful insights into the global burden of EIB in childhood.

2 | METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[14] to conduct and report this review. The review protocol was completed in 2015 and approved by a panel of experts consisting of one epidemiologist and two pulmonologists.

2.1 | Data sources and search strategy

We conducted a search on PubMed, Google Scholar, and the Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information (BIREME) which contains MEDLINE and more than 20 other databases (http://bvsalud.org). Given that MEDLINE is a subset of the PubMed database, we searched BIREME database excluding MEDLINE content to avoid excessive duplicate records. All databases were initially searched from inception to December 31, 2015, without language restriction. We updated the searches of PubMed and BIREME on December 23, 2017. We used the following search strategy: exercise-induced bronchoconstriction OR exercise-induced bronchospasm OR exercise-induced asthma. The full search strategy and the results of the searches of PubMed and BIREME can be found in the Supplementary Table S1. Given the excessive number of records (18 400 pages containing more than 368 000 records) on Google Scholar, we searched only the titles of articles using advanced search options. We checked the reference lists of retrieved papers to identify additional relevant studies.

2.2 | Study selection

The inclusion criteria were any observational studies reporting prevalence of EIB (diagnosed by exercise challenge test) in children and adolescents aged 5-18 years. Study participants included general population with and without asthma, athletes, and asthmatics. We excluded studies in children with possible co-morbidities such as chronic lung disease of prematurity and obesity, and studies that did not explicitly report diagnostic criteria for EIB.

Two review authors (KBA, MA) independently assessed the titles and abstracts of all citations identified by the searches. The definitive inclusion of studies was made after reviewing the full-text articles. Any disagreements about study selection were resolved by discussion and, if necessary, a third reviewer (LZ) was consulted.

2.3 | Data extraction

One review author (KBA) extracted the data from the included studies using a standardized data extraction form. These were checked by another review author (LZ). We extracted the following data: (i) Study characteristics: name of the first author, year of publication, location of study; (ii) Participants: age, gender, sample size calculation; (iii) Methods: study design, type of sampling, type of diagnostic test and criteria for EIB; (iv) Results: number of participants, number of individuals with EIB, prevalence/incidence of EIB and their confidence intervals (95% CI). When different cut-off values of the percent fall in forced expiratory volume in the first second (FEV_1) or peak expiratory flow (PEF) were used for diagnosis of EIB, we used only the cut-off value of ≥15%. Higher values for percent fall in FEV_1 have been recommended for diagnosing EIB in children.[2] If both FEV_1 and PEF were used as the pulmonary function measurements for exercise challenge test, we used only the prevalence of EIB based on the value of FEV_1.

2.4 | Study quality assessment

Two review authors (KBA, LZ) independently assessed the quality of each study according to the criteria of the National Institutes of Health (NIH).[15] The study quality was rated good, fair or poor, mainly based on the potential risk of selection bias, information bias, and measurement bias.

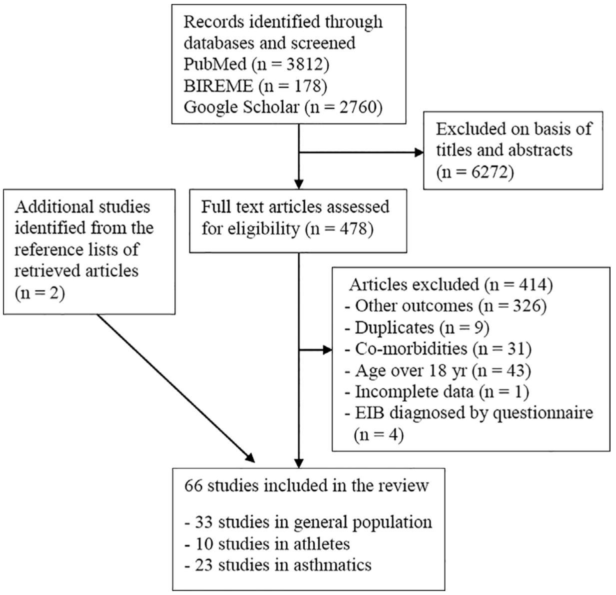

FIGURE 1 PRISMA flow diagram of study selection. A flow diagram describes the process of identification, screening, assessment for eligibility, and inclusion of studies

TABLE 1 Characteristics of included studies

Source/location	Study design	Participants	Cases of EIB/ sample size	Exercise challenge test	Cut-off value of % fall in FEV_1 or PEF	Study quality rating
Addo Yobo et al[17]/Ghana	Cross-sectional	All children and adolescents (9-16 yr) from three schools in Kumasi	34/1095	6-min free running outdoors (HR 170/min or 85% of HRmax)	PEF > 12.5%	Good
Addo-Yobo et al[8]/Ghana	Cross-sectional	All children and adolescents (9-16 yr) from three schools in Kumasi	96/1848	6-min free running outdoors (HR 170/min or 85% of HRmax)	PEF > 12.5%	Good
Anthracopoulos et al[18]/Greece	Cross-sectional	Children (10-12 yr) from 18 randomly selected public schools in Athens	63/607	6-min free running indoors (90% of HRmax)	$FEV_1 \geq 13\%$	Good
Austin et al[19] /UK	Cross-sectional	A random sample of children (12-13 yr) from 23 schools in the Highland region of Scotland	151/1702	6-min free running indoors	PEF > 15%	Good
Backer and Ulrik[20]/Denmark	Cross-sectional	A random sample of children and adolescents (7-16 yr) in Copenhagen	30/494	6-min running on a 10% sloping treadmill in a climate chamber (HR 160-180/min)	$FEV_1 \geq 15\%$	Good
Bardagi et al[21] /Spain	Cross-sectional	A random sample of school children (9-14 yr) in Mataró	136/2056	5-min free running outdoors (90% of HRmax)	PEF ≥ 15%	Good
Barry et al[22] /New Zealand*	Cross-sectional	All children aged 12 yr from 12 schools in Hastings	106/868	6-min free running indoors	PEF ≥ 15%	Good
Benarab-Boucherit et al[9]/Algérie	Cross-sectional	A cluster sample of school children (10-15 yr) in Annaba	46/286	6-min free running outdoors (85% of HRmax)	PEF > 15%	Good
Burr et al[23]/UK	Cross-sectional	All school children aged 12 yr in Cardiff and Glamorgan, South Wales	54/812	6-min free running indoors	PEF > 15%	Good
Burr et al[24]/UK	Cross-sectional	All school children aged 12 yr in Cardiff and Glamorgan, South Wales	74/960	6-min free running indoors	PEF > 15%	Good
Burr et al[25]/UK	Cross-sectional	All school children aged 12 yr in Cardiff and Glamorgan, South Wales	54/1148	6-min free running indoors	PEF > 15%	Good
Busquets et al[13]/Spain	Cross-sectional	All school children (13-14 yr) in Santn Marti and Ciutat Vella	324/2842	6-min free running outdoors (>85% of HRmax)	PEF ≥ 15%	Good
Calvert and Burney[26] /South Africa	Cross-sectional	A random sample of children (8-12 yr) from 18 rural schools in Eastern Cape and 6 urban schools in Western Cape	392/3322	6-min free running outdoors	$FEV_1 \geq 15\%$ or $FEF_{25\text{-}75\%} \geq 26\%$	Good
Chen et al[27] /China	Cross-sectional	A cluster sample of children (10-13 yr) from one urban and one suburban school in Beijing	89/773	Free running outdoors (1000 meters for male, 800 meters for female)	PEF > 15%	Good
De Baets et al[28] /Belgium	Cross-sectional	All children (7-12 yr) from 149 primary schools	1112/15 035	6-min free running (≥90% of HRmax for age)	PEF ≥ 15%	Good
Frischer et al[29] /Germany	Cross-sectional	All primary-school children (mean age of 7 yr) in southern Germany	98/1461	4- to 6-min free running indoors (HR >170/min)	PEF ≥ 15%	Good

(Continues)

TABLE 1 (Continued)

Source/location	Study design	Participants	Cases of EIB/ sample size	Exercise challenge test	Cut-off value of % fall in FEV_1 or PEF	Study quality rating
Guille and Clarck[30]/UK	Cross-sectional	A random sample of children (9-10 yr) from one school	6/90	6-min free running outdoors	$FEV_1 \geq 10\%$	Fair
Heaman and Estes[31]/USA	Cross-sectional	A convenience sample of children (10-13 yr) from three rural Alabama schools	25/437	4- to 8-min free running outdoors	PEF ≥ 15%	Fair
Henmelgarn and Ernst[32]/Canada	Cross-sectional	All Inuit primary-school children (6-13 yr) in far northern Quebec	30/509	6-min free running indoors (HRmax)	$FEV_1 \geq 15\%$	Good
Huber[33]/Brazil	Cross-sectional	A random sample of school children (13-14 yr) in Capivari de Baixo, southern Brazil	42/220	6- to 8-min running on a treadmill (80-90% of HRmax)	$FEV_1 \geq 10\%$	Good
Jones et al[34]/UK	Cross-sectional	A random sample of children (9 yr) from Scottish and inner city English schools	38/593	6-min continuous cycling on a cycle ergometer (85% of HRmax)	PEF > 15%	Good
Marshalane et al[36]/ South Africa	Cross-sectional	A random sample of children (9-10 yr) from 11 schools in Thokoza	34/468	6-min free running (80-85% of HRmax)	PEF > 15%	Good
Mtshali and Mokwena[35] /South Africa	Cross-sectional	A convenience sample of children and adolescents (8-16 yr) from one school in Ga-Rankuwa	26/112	6-min free running outdoors	PEF ≥ 10%	Poor
Ng'ang'a et al[37] /Kenya	Cross-sectional	All children and adolescents (8-17 yr) from five urban and five rural schools in Nairobi	85/1052	6-min free running outdoors	$FEV_1 \geq 15\%$	Good
Onazi et al[38] /Nigeria	Cross-sectional	A random sample of children (5-14 yr) from 18 primary schools in Gusau	64/1067	6-min free running outdoors (85% of HRmax)	PEF ≥ 15%	Good
Raherison et al[12] /France	Cross-sectional	Children (9-11 yr) selected in six cities of metropolitan France	610/7242	6-min free running outdoors	PEF ≥ 10%	Good
Randolph et al[11] /USA	Cross-sectional	Adolescents (15-17 yr) selected from one local high school	25/112	7-min free running outdoors (HR 160/min)	PEF ≥ 15%	Poor
Sudhir and Prasad[10] /India	Cross-sectional	School children (7-15 yr) from one urban and one rural area	46/394	6-min free running outdoors	$FEV_1 \geq 10\%$	Fair
Vacek[39]/Canada	Cross-sectional	A random sample of adolescents (14-17 yr) from three school districts in British Columbia	110/830	6-min free running (HR 170/min)	PEF ≥ 15%	Good
Vacek[40]/Canada	Cross-sectional	A random sample of adolescents (14-17 yr) from schools in Vancouver-Canada and Prague-Czech Republic	55/430 (Vancouver) 26/219 (Prague)	6-min free running (HR 170/min)	PEF ≥ 15%	Good
Vasar et al[41] /Estonia	Cross-sectional	Children (10-12 yr) from 16 schools in two Estonian cities	149/1156	6-min free running indoors (HR 160-180/min)	$FEV_1 > 15\%$	Good

(Continues)

TABLE 1 (Continued)

Source/location	Study design	Participants	Cases of EIB/ sample size	Exercise challenge test	Cut-off value of % fall in FEV_1 or PEF	Study quality rating
Kuti et al[42] /Nigeria	Cross-sectional	A random sample of children (8-16 yr) from two schools in rural Ilesa	23/250	6- to 8-min free running indoors (80% of HRmax)	PEF ≥ 15%	Good
Stelmach et al[43] /Poland	Cross-sectional	A random sample of adolescents (13-16 yr) from 11 schools in the greater Lodz area	94/1033	ATS/ERS exercise test on a motor-driven treadmill	FEV_1 ≥ 10%	Good
Aissa et al[44] /Tunisia	Cross-sectional	Male amateur football players (13-14 yr) in three different regions	59/196	7-min free running (80-90% of HRmax)	FEV_1 ≥ 10%	Fair
Bavarian et al[45] /Iran	Cross-sectional	All male soccer player (7-16 yr) of three schools of a town south of Tehran	19/371	15-min soccer playing in natural grass ground	FEV_1 > 15%	Fair
Feinsten et al[46] /USA	Cross-sectional	A convenience sample of male football players (14-18 yr)	9/48	6-min submaximal step test (HR 150/min)	FEV_1 ≥ 15%	Fair
Hallstrand et al[47] /USA	Cross-sectional	Student athletes (mean age of 14 yr) from three suburban Western Washington schools	24/256	7-min free running (HR >120/min)	FEV_1 ≥ 10%	Good
Kukajka et al[48] /USA	Cross-sectional	Male high school athletes (15-17 yr) from nine high schools in Philadelphia	19/214	6-min free running outdoors (80% of HRmax)	PEF ≥ 15%	Fair
Rika et al[49] /Indonesia	Cross-sectional	All students (11-18 yr) of the Ragunan Sport School, Jakarta	23/168	6-min running on a static cycle ergometer (90% of HRMax)	FEV_1 ≥ 10%	Good
Rupp et al[50] /USA	Cross-sectional	High school student athletes (12-18 yr)	22/166	6-min running on a treadmill (85% of HRMax)	FEV_1 ≥ 15%	Good
Sidiropoulou et al[51] /Greece	Cross-sectional	Male soccer players (8-13 yr) from an athletic team of Thessaloniki	12/30	6-min free running (80-90% of HRmax)	FEV_1>15%	Fair
Sidiropoulou et al[52] /Greece	Cross-sectional	Male adolescent athletes (14-18 yr) of football, basketball, and water polo	22/90	6-min free running (80-90% of HRmax)	FEV_1 ≥ 10%	Fair
Ziaee et al[53]/Iran	Cross-sectional	Male soccer players (7-16 yr) from all schools of Shahr Rey, Tehran	14/234	5-min warm up and 15-min soccer playing	FEV_1 ≥ 10%	Good
Bar-Or et al[54] /Israel	Cross-sectional	Children and adolescents (6-14 yr) with physician-diagnosed extrinsic perennial asthma	9/20	6- to 8-min running or walking on a treadmill (80-90% of HRmax)	FEV_1 > 10%	Poor
Brockmann et al[55] /Chile	Cross-sectional	Children and adolescents (6-15 yr) with mild asthma diagnosed by ATS criteria at a teaching hospital	30/75	Running on a treadmill (85% of HRmax)	FEV_1 ≥ 15%	Fair
Cabral et al[56] /Brazil	Cross-sectional	Children and adolescents (7-17 yr) with mild-to-severe asthma diagnosed by GINA criteria, recruited by local media advertisement	75/164	6-min cycling on a cycle ergometer (80% of HRmax)	FEV_1 ≥ 10%	Good

(Continues)

TABLE 1 (Continued)

Source/location	Study design	Participants	Cases of EIB/ sample size	Exercise challenge test	Cut-off value of % fall in FEV_1 or PEF	Study quality rating
Cassol et al[57] /Brazil	Cross-sectional	A convenience sample of children and adolescents (7-18 yr) with mild-to-severe asthma diagnosed by NHLBI criteria at a Pediatric Pulmonary Clinic	26/40	6- to 8-min running on a treadmill (85-90% of HRmax)	$FEV_1 \geq 10\%$	Poor
Fayezi et al[58] /Iran	Cross-sectional	Children and adolescents (6-18 yr) with physician-diagnosed asthma at a Pediatric Asthma Clinic	22/40	6-min running on a treadmill (80% of HRmax)	$FEV_1 \geq 10\%$	Poor
Fonseca-Guedes et al[59]/Brazil	Cross-sectional	Children and adolescents (7-17 yr) with physician-diagnosed intermittent-to-persistent severe asthma at a teaching hospital	68/164	6-min cycling on a cycle ergometer (80% of HRmax)	$FEF_{25-75\%}$ ≥26%	Fair
Henriksen et al[60] /Norway	Cross-sectional	A randomly selected group of adolescents (mean age of 17.9 yr) with current wheeze identified by questionnaire	21/63	6- to 8-min running on a treadmill (90% of HRmax)	$FEV_1 \geq 10\%$	Fair
Lee et al[61]/Korea	Cross-sectional	Children (mean age of 9 yr) with mild asthma diagnosed by ATS criteria at the Asthma and Allergy Clinics	195/268	8-min free running (80% of HRmax)	$FEV_1 \geq 15\%$	Fair
Madhuban et al[62] /Netherlands	Cross-sectional	Children and adolescents (10-15 yr) with pediatrician-diagnosed mild-to-moderate asthma at an outpatient clinic	86/200	6-min running on a treadmill (90% of HRmax)	$FEV_1 > 15\%$	Fair
Majak et al[63] /Poland	Cross-sectional	A consecutive group of children and adolescents (7-17 yr) with physician-diagnosed asthma at a pediatric allergology clinic	43/221	8-min running on a treadmill	$FEV_1 \geq 10\%$	Good
Martin-Muñoz et al[64] /Spain	Cross-sectional	All children and adolescents (6-14 yr) with asthma diagnosed by ATS criteria at an asthma clinic during 5 months	41/82	Running on a treadmill according to ATS criteria	$FEV_1 > 15\%$	Good
Panditi and Silverman[65]/UK	Cross-sectional	Children and adolescents (7-14 yr) with physician-diagnosed asthma taking inhaled corticosteroids at a Children's Asthma Center	26/43	6-min running on a treadmill (85% of HRmax)	$FEV_1 \geq 13\%$	Fair
Rapino et al[66] /Italy	Cross-sectional	Children and adolescents (6-17 yr) with asthma diagnosed by ATS criteria at a Pediatric Pulmonary Unit	23/81	ATS/ERS exercise test on a treadmill (80-90% of HRmax)	$FEV_1 > 10\%$	Fair
Garcia de la Rubia et al[67]/Spain	Cross-sectional	Children and adolescents (6-17 yr) with physician-diagnosed extrinsic asthma at a teaching hospital	16/30	6- to 8-min running on a treadmill (HR >170/min)	$FEV_1 \geq 20\%$	Fair

(Continues)

TABLE 1 (Continued)

Source/location	Study design	Participants	Cases of EIB/ sample size	Exercise challenge test	Cut-off value of % fall in FEV_1 or PEF	Study quality rating
Sano et al[68] /Brazil	Cross-sectional	Children and adolescents (6-16 yr) with physician-diagnosed mild-to-severe asthma at a Pediatric Allergy clinic	32/71	Cycling on a cycle ergometer (80-90% of HRmax)	$FEV_1 \geq 15\%$	Fair
Seear et al[69] /Canada	Cross-sectional	Children and adolescents (8-14 yr) with poor controlled exercise-induced asthma at an outpatient clinic over an 18-month period	8/52	Running on a treadmill (≥90% of HRmax)	$FEV_1 \geq 10\%$	Fair
Tancredi et al[70] /Italy	Cross-sectional	A consecutive group of children and adolescents (10-15 yr) with asthma diagnosed by ATS criteria at an outpatient clinic during a 2-year period	97/154	6- to 8-min running on a treadmill (>80% of HRmax)	$FEV_1 \geq 15\%$	Good
West et al[71] /Australia	Cross-sectional	Children (12-13 yr) with current wheeze identified by questionnaire at 3 schools	26/46	68-min cycling on a cycle ergometer	$FEV_1 > 10\%$	Poor
Zainudin et al[72] /Malysia	Cross-sectional	Children (7-12 yr) with current wheeze identified by ISAAC questionnaire at a primary school	16/31	6-min running on a treadmill (HR > 170/min)	$FEV_1 \geq 15\%$	Poor
Correia Junior et al[73]/Brazil	Cross-sectional	Adolescents (13-14 yr) with asthma identified by ISAAC questionnaire at schools	14/30	ATS exercise test on a motor-driven treadmill (80% of HRmax)	$FEV_1 \geq 10\%$	Fair
Inci et al[74] /Switzerland	Cross-sectional	A consectutive group of children and adolescents (7-15 yr) with physician-diagnosed asthma at an Asthma Clinic in Turkey over a period of 1 yr	60/179	ATS exercise test on a motor-driven treadmill (85% of HRmax)	$FEV_1 \geq 15\%$	Good
Lin et al[75]/Taiwan	Cross-sectional	Children (5-10 yr) with physician-diagnosed asthma at an outpatient setting	78/149	6-min running on a treadmill (90% of HRmax)	$FEV_1 \geq 10\%$	Fair
van Veen et al[76] /Netherlands	Cross-sectional	Children and adolescents (7-18 yr) with physician-diagnosed mild-to-moderate and clinical stable asthma at an outpatient clinic	103/212	ATS exercise test on a motor-driven treadmill (80-90% of HRmax)	$FEV_1 \geq 13\%$	Good

EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in the first second; HR, heart rate; HRmax, maximum heart rate for age; PEF, peak expiratory flow.
*For Barry et al[22] we used only the data of 873 New Zealand children because the data of 965 Welsh children have been reported by Burr et al.[24]

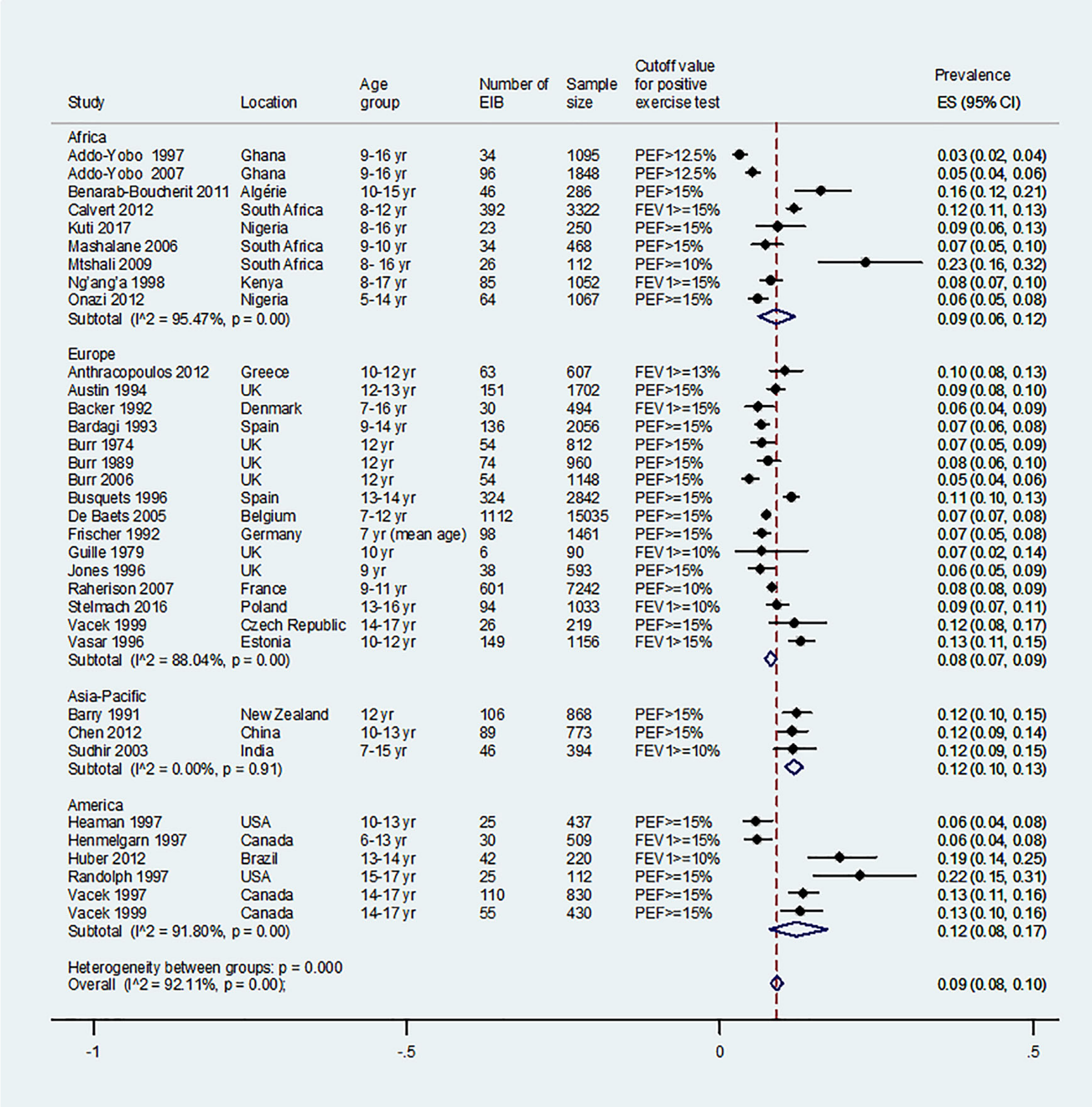

FIGURE 2 Global prevalence of EIB in children and adolescents. Solid squares represent point estimates and horizontal lines represent 95% CIs of the prevalence of EIB for each study. Open diamonds represent pooled estimates of prevalence and 95% CIs

2.5 | Statistical analysis

We conducted random-effects meta-analyses to estimate the pooled prevalence of EIB and 95% CI in general population of children and adolescents, in child and adolescent athletes and in children and adolescents with asthma.

Heterogeneity between studies was assessed through Cochran's Q test and quantified by I^2 statistic which measures the percentage of observed total variation across studies that is due to real heterogeneity rather than chance. The heterogeneity was considered statistically significant if $P < 0.1$ for Cochran's Q test and $I^2 > 50\%$.[16] To investigate possible sources of heterogeneity in the prevalence of general population, we conducted a prior subgroup analyses by geographic regions, type of exercise challenge test, type of pulmonary function parameter used for exercise test, cut-off value of the percent fall in FEV_1 or PEF from the baseline value for positive exercise test, study sample size and year of study publication. We classified study sample size as small (less than the first quartile—400), medium (between the first quartile—400, and the third quartile—1000) and large (more than the third quartile—1000). We conducted post hoc sensitivity analyses excluding studies with small sample size (<400) and those with "poor" study quality.

We assessed publication bias using a funnel plot and Egger's test. All meta-analyses were performed in Stata version 11.0 (Stata-Corp, College Station, TX), using the commands "metaprop" for pooling prevalence of EIB, "metafunnel" for producing funnel plot and "metabias" for assessing evidence for small-study effects.

3 | RESULTS

The search strategy identified 6750 records from PubMed, BIREME, and Google Scholar, of which 64 studies met the inclusion criteria. Two additional studies were found through reviewing the reference lists of

TABLE 2 Subgroup analyses on prevalence of EIB in the general population of children and adolescents

Subgroups	Number of studies	Prevalence of EIB (95% CI)	Heterogeneity between subgroups*
Type of exercise test used for diagnosis of EIB			$\chi^2 = 0.04$, $P = 0.8$
Standardized tests (treadmill or cycle ergometer)	4	9% (6-14%)	
Free running test	29	9% (8- 10%)	
Cut-off value of % fall in FEV_1 or PEF used for positive exercise test			$\chi^2 = 0.01$, $P = 0.9$
≥10% to <15%	10	9% (7-12%)	
≥15%	23	9% (8-10%)	
Pulmonary function measurement used for exercise test**			$\chi^2 = 0.51$, $P = 0.5$
FEV_1	3	10% (7-14%)	
PEF	19	9% (8-10%)	
Study sample size			$\chi^2 = 13.5$, $P < 0.001$
<400	7	15% (11-19%)	
400 to 1000	12	9% (7-10%)	
>1000	14	8% (7-9%)	
Year of publication			$\chi^2 = 3.6$, $P = 0.2$
Before 1990	3	7% (6-8%)	
1990 to 1999	15	9% (7-11%)	
2000 and thereafter	15	9% (8-11%)	

*$P < 0.1$ was considered statistically significant for subgroup comparison.
**Subgroup analysis included only 22 studies that had sample size >400 and used the cut-off value of ≥15% of the percent fall in FEV_1 or PEF for positive exercise test.

retrieved articles. Thus, a total of 66 studies were included in the review (Figure 1). Table 1 summarizes the characteristics of the 66 included studies. Thirty-three studies[8–13,17–43] investigated the prevalence of EIB in general population of children and adolescents. Ten studies[44–53] reported the prevalence of EIB in child and adolescent athletes, and 23 studies[54–76] in children and adolescents with asthma.

Thirty-three studies with a total of 51 523 participants (4338 cases of EIB) contributed data to the meta-analysis of prevalence in general population. The pooled global mean prevalence of EIB in children and adolescents was 9% (95% CI 8-10%) (Figure 2). The mean prevalence of EIB was 8% (95% CI: 7-9%) in Europe, 9% (CI 95%: 6-12%) in Africa, 12% (CI 95%: 10-13%) in Asia-Pacific and 12% (CI 95%: 8-17%) in America ($P < 0.001$ for heterogeneity between subgroups).

Table 2 shows the results of the subgroup analyses for the prevalence of EIB in general population of children and adolescents. Seven studies with sample size less than 400[9–11,31,34,36,42] showed a pooled mean prevalence of 15% (95% CI: 11-19%), compared with 9% (95% CI: 7-10%) in 12 studies with sample size between 400 and 1000,[18,20,22–24,27,31,32,34,36,39,40] and 8% (95% CI: 7-9%) in 14 studies with sample size greater than 1000[8,12,13,17,19,21,25,26,28,29,37,38,41,43] ($P < 0.001$ for heterogeneity between subgroups). The global mean prevalence of EIB was 8% (95% CI 7-9%) and 9% (95% CI 8-10%) in the post hoc sensitivity analyses, excluding seven studies with sample size less than 400 and two studies[11,35] with "poor" study quality, respectively. There were no significant differences in the prevalence of EIB between subgroups by type of exercise challenge test, type of pulmonary function parameter used for exercise test, cut-off value of the percent fall in FEV_1 or PEF for positive test and year of study publication.

Seven studies in general population reported the prevalence of EIB according to cut-off value of the percent fall in FEV_1 or PEF for positive exercise test.[20,23–25,36,37,41] The meta-analysis of these seven studies showed an inverse relationship between the cut-off value and the prevalence of EIB. The prevalence was 4% (95% CI: 2-7%), 8% (95% CI: 6-10%), and 17% (95% CI: 16-19%) for the cut-off value of ≥20%, ≥15%, and ≥10%, respectively ($P = 0.001$ for heterogeneity between subgroups).

Ten studies involving 1773 participants (223 cases of EIB) investigated the prevalence of EIB in child and adolescent athletes. Five studies[44–46,51,53] recruited male soccer players, and other five studies[47–50,52] included athletes of different modalities. The pooled prevalence of EIB was 15% (95% CI: 9-21%) (Figure 3).

Twenty-three studies[54–76] involving 2400 participants (1109 cases of EIB) reported the prevalence of EIB in children and adolescents with asthma. The diagnosis of asthma was made by physician in all but four studies,[60,71–73] in which the diagnosis was based on symptom questionnaire. The pooled prevalence of EIB was 46% (95% CI: 39-53%) (Figure 4). We conducted two unplanned post hoc sensitivity analyses excluding five studies[54,57,58,71,72] with "poor" study quality and 14 studies[54,57,58,71,72] with sample size less than 100. The pooled prevalence of EIB was 44% (95% CI: 36-52%) and 46% (95% CI: 35-58%), respectively. Three studies involving 275 patients reported the prevalence of EIB according to the severity of

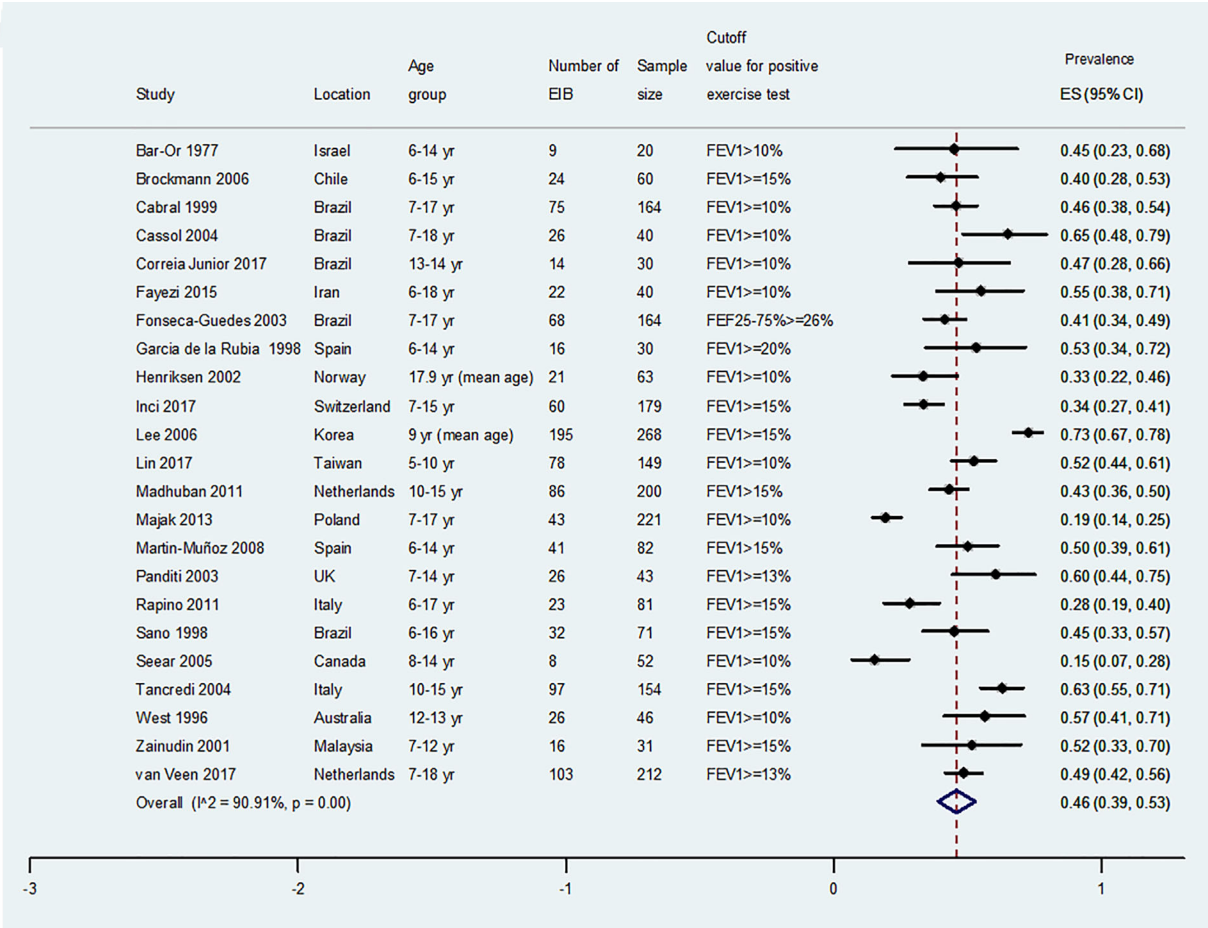

FIGURE 3 Prevalence of EIB in child and adolescent athletes. Solid squares represent point estimates and horizontal lines represent 95% CIs of the prevalence of EIB for each study. Open diamond represents pooled estimate of prevalence and 95% CI

asthma.[56,57,68] The meta-analysis of these three studies showed a mean prevalence of EIB of 29% (95% CI: 17-41%) in mild asthma, 74% (95% CI: 47-94%) in moderate asthma, and 81% (95% CI: 52-99%) in severe asthma ($P = 0.001$ for heterogeneity between subgroups).

Funnel plot and Egger's test did not reveal evidence of publication bias (Supplementary Figure S1).

4 | DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to estimate the global prevalence of EIB in childhood. The meta-analysis of 33 studies from 21 countries revealed a global mean prevalence of 9% (95% CI: 8-10%) of EIB in the general population of children and adolescents up to 18 years of age. The mean prevalence of EIB varied from 8% in Europe to 12% in America and Asia-Pacific. There was also remarkably variation in the prevalence of EIB between countries in the same continent, especially in Africa and America.

The subgroup analysis identified study sample size as the main factor associated with the prevalence rate of EIB. Studies with smaller sample size, especially those with less than 400 participants, were more likely to report higher prevalence of EIB with less precision. It is well known that the smaller the sample size, the larger the sampling error, and vice versa. Small studies often produce inflated results.[77]

Another factor associated with the prevalence rate of EIB was the cut-off value of the percent fall in FEV_1 or PEF from the baseline value for positive exercise test. Although the subgroup analysis failed to identify this factor, the meta-analysis of seven studies showed an inverse relationship between the cut-off value of the percent fall in FEV_1 or PEF and the prevalence rate of EIB, that is, the higher the cut-off value, the lower the prevalence of EIB. Generally, the percent fall in FEV_1 from the baseline value after exercise used to diagnose EIB is ≥10%.[1,2] However, the higher cut-off values (13-15%) have been used for diagnosis of EIB in children.[78–80] It is preferable to use FEV_1 as the pulmonary function parameter for exercise challenge test because this measurement has better repeatability and is more discriminating than PEF.[2] However, most of the studies in general population included in this review used PEF measured by a peak flow meter as the functional measurement for exercise test. It is much easier and cheaper to obtain FEF using a portable peak flow meter than to measure FEV_1 using a spirometry.

The diagnosis of EIB should be established by changes in lung function after exercise. The preferred modes of exercise are the

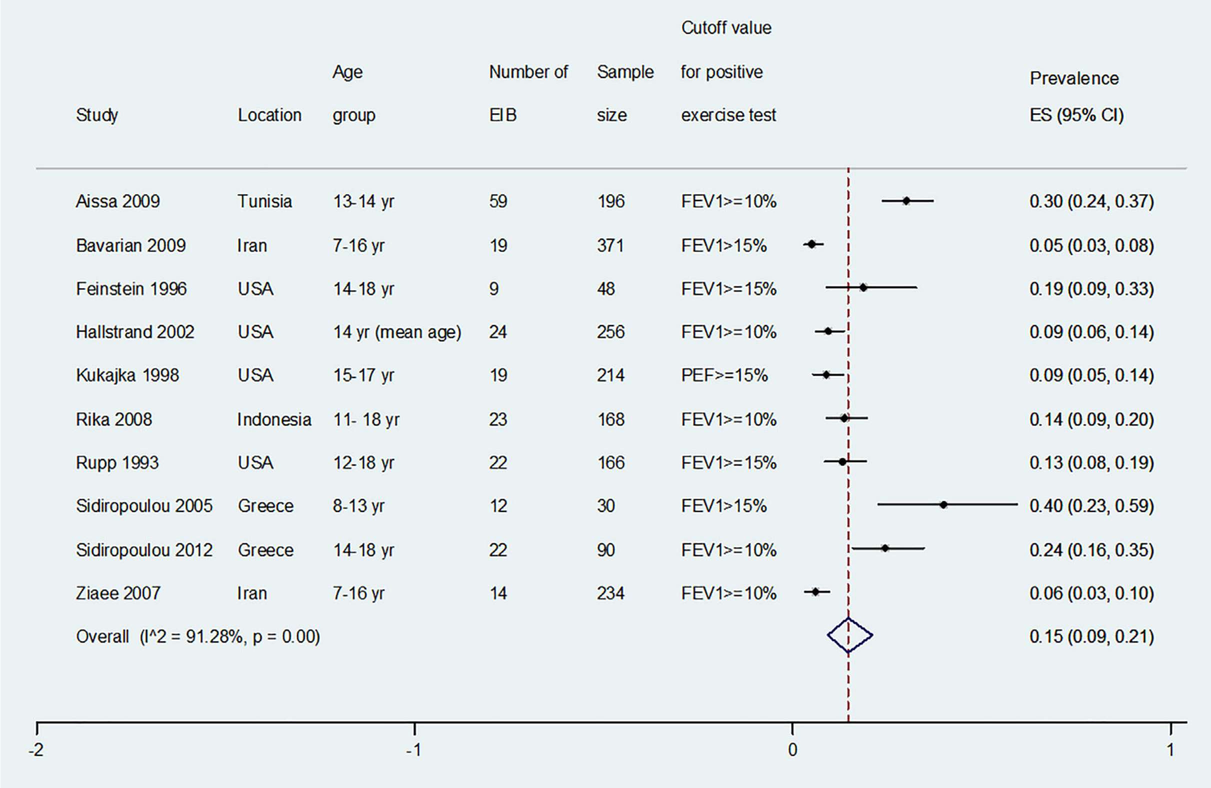

FIGURE 4 Prevalence of EIB in children and adolescents with asthma. Solid squares represent point estimates and horizontal lines represent 95% CIs of the prevalence of EIB for each study. Open diamond represent pooled estimate of prevalence and 95% CI

motor-driven treadmill with adjustable speed and grade or the electromagnetically braked cycle ergometer.[1,81] The American Thoracic Society (ATS) has established guidelines for exercise challenge test to diagnose EIB.[81] However, the requirement of equipment and trained personnel limits application of such standardized exercise test, especially in large-scale epidemiological studies. Of the 33 studies in general population, only four used a standardized exercise challenge test. The remaining 29 studies used a 6- to 8-min free running test to diagnose EIB. If environmental conditions (temperature and humidity), exercise intensity, and airway status are controlled, the free running test may have a similar diagnostic profile as a standardized exercise test to identify individuals with EIB.[67] However, the free running test was conducted outdoors in most of these 29 studies, and such a test might overestimate the prevalence rate of EIB.[27]

The meta-analysis of 10 studies revealed a higher mean prevalence (15%) of EIB among children and adolescent athletes than that in general population. The prevalence of EIB among athletes may vary substantially according to sport modality, intensity of effort, environmental conditions and diagnosis criteria.[2,82,83] The athletes who play sports with a >5- to 8-min effort, and/or in a dry/cold air environment, and/or in a noxious air environment (chlorine exposure, ultrafine particles, traffic air pollution), have a higher risk of EIB.[83] Unfortunately, the relatively small number of studies and wide variation in sport modalities across studies included in the review precluded the comparison of the prevalence of EIB between athletes of different sport modalities.

EIB has occurred in up to 90% of asthmatic patients.[82,84] The meta-analysis of 23 studies revealed a mean prevalence of EIB of 46% in children and adolescents with asthma, which was higher than that in general population and in athletes. EIB may be the result of an overall lack of asthma control.[84] This review also showed a significant association between the prevalence of EIB and asthma severity, that is, the more severe the disease, the higher the prevalence rate of EIB.

Based on the global mean prevalence of EIB of 9% (95% CI: 8-10%) and a population of approximately 183 million in the 5-19 years age group,[85] we estimated that, globally, around 16.5 million (95% CI: 15-18 million) children and adolescents up to 18 years of age may have EIB. It is very likely that most of individuals with EIB are not being diagnosed and treated, especially in developing countries. Screening for EIB has been proposed, however, there is still a lack of robust evidence on the cost-benefit ratio of screening program both in general population and in athletes.[2]

This systematic review included a large number of studies from four geographical regions, with a wide range of populations (general population, athletes and asthmatics), providing an evidence-based estimation of global burden of EIB in childhood. The quality of most included studies in general population was rated “good” due to low risk of bias. However, some limitations should be taken into account when interpreting the results of this review. There were substantial variations across studies regarding exercise test protocol, diagnosis criteria for EIB, and study sample size that may affect the prevalence rate of EIB. Most studies were conducted in Europe and Africa, and this may hamper the comparison of the prevalence of EIB between geographical regions. The number of studies and participants in child and adolescent athletes was limited, and the study samples were mainly composed of male soccer players. Most of studies (61%) in asthmatics had small sample size (less than 100 participants[86]) and one fourth of studies were classified as having "poor" study quality. However, the post hoc sensitivity analyses did not find significant impact of these limitations on the estimation of prevalence of EIB among asthmatics.

In conclusion, this systematic review and meta-analysis revealed a global mean prevalence of EIB of 9% (95% CI: 8-10%) in children and adolescents up to 18 years of age, 15% (95% CI: 9-21%) in child and adolescent athletes, and 46% (95% CI: 39-53%) in children and adolescents with asthma. The substantial heterogeneity between studies highlights the need for evidence-based guidelines for diagnosis of EIB in this age group. Given the high prevalence and its impact on quality of life and practice of physical activities, EIB in childhood should be considered as a global public health problem that deserves more attention from parents, teachers, and health-care providers. The development of an effective strategy in identifying and treating individuals with EIB is still a major challenge, and further population-based studies are needed.

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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SUPPORTING INFORMATION

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