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ORIGINAL ARTICLE

WILEY

Preschool wheezing and asthma in children: A systematic review of guidelines and quality appraisal with the AGREE II instrument

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Abstract

Background: Asthma-like symptoms in preschool children, such as wheezing and dyspnea, are common time- and resource-consuming diagnostic and management challenges. Quality of wheezing and asthma recommendations varies. The purpose of this study, carried out by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force for Preschool Wheeze, was to systematically review and assess the quality of guidelines for diagnosis and treatment of preschool wheezing and/or asthma.

Methods: The Cochrane Library, MEDLINE, and EMBASE were searched until June 2018. The methodological rigor, quality, and transparency of relevant guidelines were assessed with the use of the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool.

of this paper was accepted by the Executive Committee of the EAACI.

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Results: We identified 26 guidelines. The quality scores for each domain varied. Of all domains, clarity and presentation had the highest mean score, whereas applicability and stakeholder involvement had the lowest. The scores (median) for individual domains were as follows: score and purpose 86%; stakeholder involvement 49%; rigor of development 54%; clarity of presentation 85%; applicability 51%; and editorial independence 63%.

Conclusion: Although several guidelines on asthma management in children are available, however, their quality varies. Additionally, there is a considerable gap in reliable recommendations on the management and treatment of non-asthmatic preschool wheeze.

KEYWORDS

AGREE, asthma, children, guidelines, preschool wheezing, systematic review

1 | INTRODUCTION

Wheezing and shortness of breath in preschool children is one of the most commonly presented symptoms in everyday pediatric practice. A considerable minority of children will continue to experience wheezing in school years and beyond, diagnosed as “asthma”.¹ Preschool wheeze has been classified in several different ways, based on time of appearance, natural history, comorbidities, and triggers. Some of these children with different phenotypes of wheezing will develop asthma later in life. However, until the diagnosis is confirmed, decision making regarding the proper treatment is uncertain and challenging.^{2,3}

The term “preschool wheeze” has not been appropriately defined, and it varies considerably between countries (eg, a 2-5 years gap according to the Centers for Disease Control and Prevention, CDC, <4 years in the UK, and <7 in Scandinavian countries and Poland). Nonetheless, majority of birth cohorts show that significant changes in the epidemiology of recurrent wheeze take place around the age of 6 years,¹⁻³ so we assumed the age of 6, as the most commonly accepted.

The relative prevalence of these phenotypes varies with the age of the child and partially overlap. All the above-mentioned factors suggest that our understanding of wheezing needs revision.⁴

There is a tremendous demand to propose an effective diagnostic approach and management of preschool wheezing/early-life asthma for at least three reasons. Firstly, pre-schoolers have the highest rate of unscheduled medical visits for wheezing and asthma symptoms, compared with all other age groups.⁵ Secondly, episodes of wheezing, difficulty in breathing and cough usually lead to more limitations of everyday activities than in older children.¹ Thirdly, early life wheezing and repeated and cumulative lung injury due to viral respiratory infections (mainly rhinovirus or respiratory syncytial virus) may be causally associated with reduced lung function at 6 years of age, which might persist until adulthood.⁶ Furthermore, these children consume a disproportionately high number of medications (mostly bronchodilators, and steroids) since the diagnosis of

Key Message

Wheezing and shortness of breath in preschool children is a heterogeneous condition, and one of the most commonly presented symptoms in everyday pediatric practice. A systematic review mapping the currently available guidelines for the diagnosis and management of preschool wheeze and/or asthma was necessary to provide a baseline for further development of European Academy of Allergy and Clinical Immunology recommendations. There is an abundance of guidelines targeting asthma in children, and their quality is rather good. However, the number of guidelines for preschool wheezing is lacking. Future guidelines for Preschool Wheezing should and will aim to identify EARLY individuals who are at risk for subsequent asthma inception and to provide them appropriate management and treatment.

asthma in preschoolers is difficult and depend on many factors, including persistence of symptoms of wheezing at the age of 6 years.

Given the significant burden of disease and the magnitude of pediatric healthcare utilization, several national and international consortia have published guidelines to assist the clinical management of preschool wheezing/asthma and to improve resource use over the past 20 years. In 2017, the European Academy of Allergy and Clinical Immunology (EAACI) established a Task Force on Preschool Wheeze, to assess the quality of present guidelines and to propose new clinical practice recommendations. A joint working group was formed with the mandate to develop an EAACI position on the diagnosis and management of wheezing in pre-schoolers. The international multidisciplinary group included academic and non-academic clinicians, clinician-scientists, scientists, physicians trained in the evidence-based medicine, and medical students from 10 countries (D, DK, FIN, GR, NL, N, PL, S, TR, UK). This multidisciplinary team aimed

to evaluate (critically appraise) all existing guidelines on asthma or preschool wheeze published in English over the past 20 years and their use of evidence in making clinical recommendations.

2 | METHODS

2.1 | Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) statement (Appendix S1), according to a pre-defined protocol and search strategy (Appendices S2 and S3).

Our team searched through MEDLINE, EMBASE, and the Cochrane Library until June 2018. In July 2019, a cross-reference with subsequent manual search was repeated in order to identify recommendations and/or guidelines on the diagnosis and management of wheezing and asthma in children, published in English, over the past 20 years. The search strategy was prepared by a professional librarian. Main search terms included wheezing, bronchiolitis, bronchitis, obstructive lung disease, obstructive airway disease, and asthma, in children (aged 0-18 years). We excluded review papers, commentaries, guidelines summaries, old versions of included guidelines, conference abstracts, and letters.

The search and selection of the publications were conducted independently by five reviewers, and each time, the discrepancies between reviewers were solved by the discussion. We retained all the potentially relevant articles and critically reviewed their full texts.

Our aim was to assess the process of guideline development and reporting; thus, we used the Appraisal of Guidelines for Research and Evaluation II (AGREE II), which is an internationally accepted standard for evaluation of the methodological quality of clinical practice guidelines. We used an electronic, online version of the AGREE II tool (available at: <http://www.agreetrust.org/>). This 23-item questionnaire was prepared and disseminated by the AGREE Research Trust⁷. It addresses six domains, of guideline quality, preparation, and dissemination as follows:

1. *Scope and purpose*: In this domain, overall aim of the guideline, specific health questions, and target of the guideline is addressed.
2. *Stakeholder involvement*: The second domain focuses on questions connected with stakeholders and views of potential users.
3. *Rigor of development*: In the third domain number, the process of collecting, synthesizing the evidence, formulation of the recommendations, and updating are reviewed.
4. *Clarity of presentation*: Language, structure, format, and presentation are assessed in the fourth domain.
5. *Applicability*: Identification of possible barriers and facilitators in the guideline implementation process and presenting strategies of uptake improvement and guideline application are addressed in the fifth domain.
6. *Editorial independence*: The last domain deals with conflict of interest presentation.

Altogether, there are 23 questions rated on the 7-point Likert scale that ranges from "strongly agree" to "strongly disagree," in a six-domain tool. AGREE II tool incorporates two additional items. The first one, called the Overall Guidelines Assessment in which the reviewer again, using the 7-point Likert scale, judges the overall quality of the guideline. The second one addresses the question as to whether the assessed guideline should be used. The possible answers are "yes," "yes with modification," or "no."

The number of reviewers recommended by the AGREE II consortium consists of at least two and preferably four people. In this paper, each guideline was appraised by at least three and up to eight reviewers independently.

Scores, for each question, were summed up, and then calculated as the percentage of the maximum possible score, using the AGREE II formula: $[(\text{score obtained} - \text{minimum possible score}) / (\text{maximum possible score} - \text{minimum possible score})] \times 100$. Scores range from 0% to 100%; however, there is no range or threshold provided by the AGREE II consortium that enables differentiation between high or low-quality guidelines. We arbitrarily set quality cut off at 60% as other authors used it.⁸

Four to eight reviewers independently assessed the methodology of the guidelines using the AGREE II instrument. Two of the authors had previous experience with the AGREE II instrument, while the rest of the team underwent online AGREE II training that consists of a tutorial and practice exercise's available at www.agreetrust.org. Any disagreement, resulting in a difference in scoring by >2 points was resolved by discussion and second reassessment. All other disagreements between the reviewers were resolved via discussions until a consensus was reached. A change of the quality of guidelines over time was also assessed.

Additionally, all guidelines were reviewed for the grading method used.

2.2 | Statistical analysis

We (MR, WF) used descriptive statistics, for the basic features of the data in a study. Continuous non-parametric data were presented as a median followed by range, first and third interquartiles, and interquartiles range, whereas parametric data were presented as a mean \pm SD, and we calculated it with the use of Microsoft Excel (ver. 2019 16.0.6742.2048). The agreement among reviewers/appraisers was calculated using the alpha Cronbach score, and SPSS software (ver. 26).⁹

3 | RESULTS

3.1 | Guidelines identification and interobserver agreement

For a flow diagram documenting the identification process for the eligible documents, see Figure 1. Overall, 26 guidelines were

included.^{2,3,10-33} We identified 26 guidelines, ten of which were developed by international societies or international consortia.^{2,3,12,17,19,25,28-30,33} The rest of identified guidelines were developed either by expert groups or national health organizations.

Cronbach's alpha reliability coefficient varied from 0.68 to 0.93, with the mean value across all guidelines 0.834 (0.08 SD) and median 0.865. In one case, all reviewers agreed with 100% of the answers. Therefore, calculating the Cronbach's alpha was impossible due to lack of variance between answers.¹⁰

3.2 | The AGREE II quality scores

Scores for each domain, overall assessment, and Cronbach's alpha coefficient and grading method are presented in Tables 1 and 2, respectively. Median for various domains ranged from 49% up to 86%. Domain 1 (scope and purpose) and domain 4 (clarity and presentation) were scored the highest (medians: 86% and 85% respectively), while domain 2 (stakeholder involvement) and domain 5 (applicability) were scored the lowest (medians 49% and 51%).

3.2.1 | Scope and purpose

For the scope and purpose domain, the median was 86% (range: 28% to 100%). The highest scores in the first domain earned the

Australian book of asthma and NICE guidelines,^{10,13} while three guidelines scored below 60%.^{27,28,31} Lack of proper reporting—which means that authors did not address thoroughly issues connected with scope and purpose (such, for example, target users of the guideline, etc) of the assessed guideline was the reason for such low scoring.

3.2.2 | Stakeholder involvement

Patient and public involvement (stakeholders) had a median score of 49% (range: 10% to 100%). Two guidelines received the highest score for this domain (100%) (the Australian book of asthma, and NICE guidelines).^{10,13} Score for this domain was among the two lowest scored domains. The main reason for this was again due to lack of reporting.

3.2.3 | Rigor of development

In the third domain, the median was 54% (range: 8% to 100%). The highest score for this domain was 100% and was scored by Australian guidelines.¹⁰ Twelve guidelines received scores below 60%. The lowest score was 15% and was related to Japanese guidelines.³² Consistently, the lack of adequate information provided by authors justified such a low scoring.

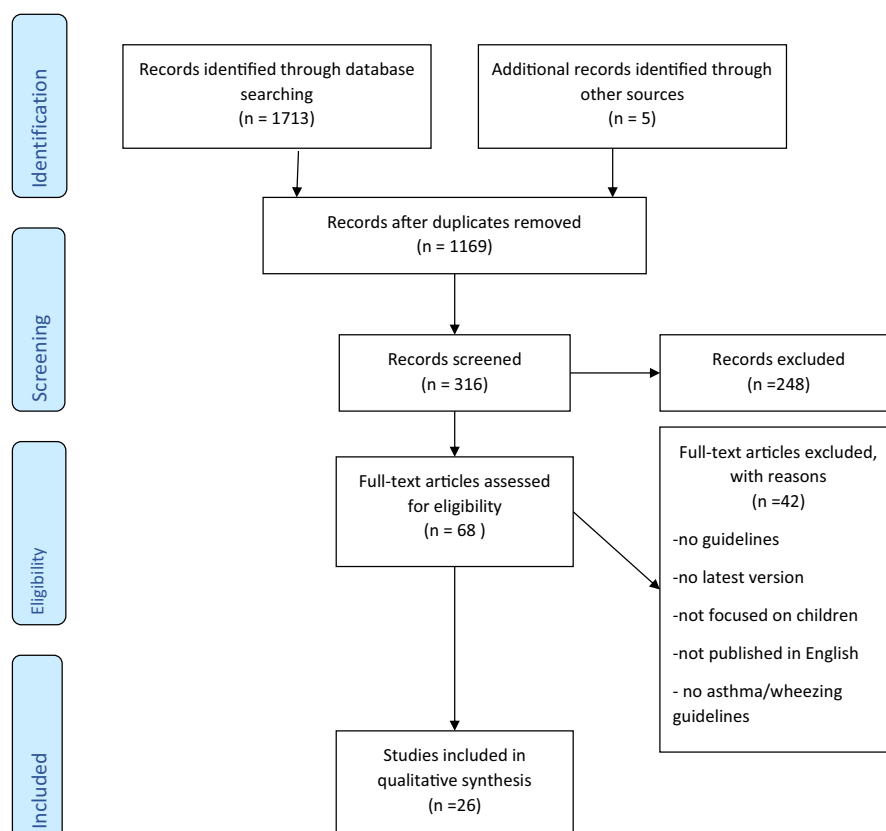


FIGURE 1 Flow chart (study selection) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Domain scores and overall assessment of guidelines using the AGREE II instrument

Country/organization	Year	Guideline title (reference number)	Grading	Method of grading	GIN	Domain numbers						Would you use it?	
						1	2	3	4	5	6	yes/ywm/	no
Australian	2019	Australian book of asthma ¹⁰	Yes	NHRMC grading method	Not reported	100%	100%	100%	100%	100%	100%	4/0/0	No variance
International	2017	Global Initiative for Asthma 2018. Global strategy for asthma management and prevention ¹²	Yes	GRADE	Not reported	99%	79%	94%	100%	97%	95%	5/0/0	0.79
UK/NICE	2016	National Institute for Health and Care Excellence (NICE). Quality standard for asthma. London: NICE ¹³	Yes	GRADE	Not reported	100%	100%	99%	90%	99%	42%	2/1/0	0.68
UK/BTS	2016	British Thoracic Society and Scottish Intercollegiate Guidelines Network (2016) British guideline on the management of asthma. SIGN clinical guideline ¹⁴	Yes	GRADE	Not reported	98%	86%	93%	96%	90%	87%	6/0/0	0.79
Spain	2016	GEMA 2016 (Spanish guideline on the management of asthma) ¹⁵	Yes	GEMA based on GRADE	Not reported	79%	97%	86%	100%	83%	60%	3/1/0	0.88
USA/NHLBI	2007	Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma-Summary Report ¹⁶	Yes	Based on Jadad	Not reported	90%	89%	83%	94%	98%	100%	3/0/0	0.87
International	2012	International consensus on (ICON) pediatric asthma ¹⁷	Yes	ICON	Not reported	92%	36%	57%	97%	57%	92%	3/2/0	0.73

(Continues)

TABLE 1 (Continued)

Country/organization	Year	Guideline title (reference number)	Grading	Method of grading	GIN	Domain numbers						Would you use it?	
						1	2	3	4	5	6	yes/ywm/	no
Canada/CTS	2012	Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults ²⁶	Yes	Based on ACCP grading	Not reported	97%	75%	77%	94%	88%	88%	3/1/0	0.93
USA/ATS	2012	Official American thoracic society clinical practice guidelines: Diagnostic evaluation of infants with recurrent or persistent wheezing ¹⁹	Yes	GRADE	Not reported	92%	53%	71%	80%	47%	67%	4/1/0	0.93
International	2007	Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report ¹⁹	Not reported	Not reported	Not reported	88%	52%	34%	96%	75%	67%	4/1/0	0.89
Finland	2015	Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children ²²	Yes	Own method	Not reported	90%	44%	80%	89%	20%	60%	1/3/0	0.72
USA/NASPGHAN	2002	Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: Recommendations of the North America Society for Pediatric Gastroenterology and Nutrition.	Yes	Own method/ unknown	Not reported	91%	60%	62%	91%	57%	5%	3/2/0	0.92
Netherlands	2012	Assessment of Controversial Pediatric Asthma Management Options Using GRADE ²¹	Yes	GRADE	Not reported	96%	53%	73%	72%	60%	92%	3/1/0	0.76

(Continues)

TABLE 1 (Continued)

Country/organization	Year	Guideline title (reference number)	Grading	Method of grading	GIN	Domain numbers						Would you use it?	
						1	2	3	4	5	6	yes/ywm/	Cronbach α
South Africa/SACAWG	2013	Guideline for the management of acute asthma in children: 2013 ²³	Yes	Own method based on GINA 2009	Not reported	66%	22%	50%	83%	48%	50%	2/3/0	0.9
USA	2009	VA/DoD clinical practice guideline for management of asthma in children and adults. Department of Defense ¹¹	Yes	US Preventative Services Task Force grading system	Not reported	100%	40%	51%	100%	68%	10%	2/2/0	0.8
Canada/CTS	2015	Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Pediatric Society position paper ²⁴	Not reported	Not reported	Not reported	92%	65%	34%	90%	74%	88%	1/6/0	0.927
International/ERS	2008	Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach ²⁵	Yes	Own, based on GRADE	Not reported	81%	29%	63%	73%	13%	38%	0/5/0	0.86
Saudi Arabia	2019	The Saudi initiative for asthma—2012 update: Guidelines for the diagnosis and management of asthma in adults and children ²⁷	Yes	Own method	Not reported	59%	48%	50%	87%	52%	70%	3/0/2	0.92
International/IPCRCG	2006	International Primary Care Respiratory Group (IPCRCG) Guidelines: diagnosis of respiratory diseases in primary care ²⁸	Not reported	Not reported	Not reported	58%	50%	32%	67%	53%	52%	0/0/4	0.9

(Continues)

TABLE 1 (Continued)

Country/organization	Year	Guideline title (reference number)	Grading	Method of grading	GIN	Domain numbers						Would you use it?	
						1	2	3	4	5	6	yes/yw/m/	no
International/IPCGRG	2006	IPCGRG guidelines: management of asthma ²⁹	Not reported	Not reported	Not reported	80%	57%	24%	77%	49%	65%	1/2/2	0.92
International/France/SPLF	2008	Asthma and allergy: short texts and recommendations of the expert conference of the French Speaking Pneumology Society (SPLF) ³⁰	Yes	Agence Nationale d'Accreditation et d'Evaluation en Sante	Not reported	83%	67%	57%	67%	31%	2%	1/3/1	0.93
Spain/SEPAR	2015	Guidelines for severe uncontrolled asthma ³¹	Yes	GRADE	Not reported	57%	38%	41%	78%	35%	42%	0/5/1	0.75
International	2014	Classification and pharmacological treatment of preschool wheezing: changes since 2008 ²	Not stated	Not stated	Not reported	88%	19%	80%	92%	24%	67%	0/4/0	0.78
Japan	2017	Japanese guidelines for childhood asthma 2017 ³²	Not reported	Not reported	Not reported	73%	44%	15%	78%	35%	56%	1/1/5	0.76
International	2008	Treatment of asthma in young children: evidence-based recommendations Asthma research and practice ³	Not reported	Not reported	Not reported	81%	10%	37%	34%	3%	94%	0/3/3	0.77
International/IPCGRG	2006	IPCGRG guidelines: integrating diagnostic guidelines for managing chronic respiratory diseases in primary care ³³	Not reported	Not reported	Not reported	28%	22%	8%	37%	24%	47%	0/0/4	0.73
Median						86%	49%	54%	85%	51%	63%		
q1, q3						0.79, 0.95	0.38, 0.73	0.38, 0.8	0.77, 0.94	0.35, 0.81	0.47, 0.88		
IQR						0.15	0.34	0.42	0.16	0.46	0.40		

Abbreviation: AGREE, Appraisal of Guidelines for Research and Evaluation.

TABLE 2 Assessment of guidelines using the AGREE II instrument—all questions (percentages)[Colour figure can be viewed at wileyonlinelibrary.com]

AGREE II question	Guideline number (from best to worst score)										
	1	2	3	4	5	6	7	8	9	10	11
1. The overall objective(s) of the guideline is (are) specifically described	100%	100%	100%	98%	87%	100%	97%	96%	87%	87%	100%
2. The health question(s) covered by the guideline is (are) specifically described	100%	97%	100%	98%	67%	100%	83%	100%	97%	87%	83%
3. The population (eg, patients, public) to whom the guideline is meant to apply is specifically described	100%	100%	100%	100%	83%	71%	97%	96%	93%	90%	88%
4. The guideline development group includes individuals from all relevant professional groups	100%	73%	100%	95%	100%	92%	80%	83%	40%	57%	100%
5. The views and preferences of the target population (eg, patients, public) have been sought	100%	80%	100%	64%	90%	100%	7%	46%	47%	7%	0%
6. The target users of the guideline are clearly defined	100%	83%	100%	98%	100%	75%	20%	96%	73%	93%	33%
7. Systematic methods were used to search for evidence	100%	93%	100%	98%	87%	79%	0%	75%	53%	17%	100%
8. The criteria for selecting evidence are clearly described	100%	97%	100%	83%	83%	79%	13%	71%	73%	23%	100%
9. The strengths and limitations of the body of evidence are clearly described	100%	93%	100%	98%	93%	79%	13%	71%	97%	33%	100%
10. The methods for formulating the recommendations are clearly described	100%	97%	100%	90%	90%	79%	87%	83%	90%	30%	100%
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	100%	97%	100%	95%	93%	92%	90%	88%	90%	97%	46%
12. There is an explicit link between the recommendations and supporting evidence	100%	97%	92%	95%	77%	100%	97%	75%	97%	60%	96%
13. The guideline has been externally reviewed by experts before its publication	100%	80%	100%	98%	93%	96%	90%	83%	63%	0%	96%
14. A procedure for updating the guideline is provided	100%	100%	100%	83%	70%	58%	67%	71%	3%	10%	0%
15. The recommendations are specific and unambiguous	100%	100%	100%	95%	100%	100%	100%	92%	87%	97%	100%
16. The different options for management of the condition or health issue are clearly presented	100%	100%	96%	95%	100%	100%	97%	92%	67%	100%	71%
17. Key recommendations are easily identifiable	83%	100%	75%	98%	100%	83%	93%	100%	87%	90%	96%
18. The guideline describes facilitators and barriers to its application	100%	100%	100%	88%	90%	92%	53%	88%	57%	53%	0%
19. The guideline provides advice and/or tools on how the recommendations can be put into practice	100%	100%	100%	98%	100%	100%	63%	92%	27%	90%	4%
20. The potential resource implications of applying the recommendations have been considered	100%	87%	96%	83%	43%	100%	23%	83%	57%	60%	0%
21. The guideline presents monitoring and/or auditing criteria	100%	100%	100%	90%	97%	100%	87%	88%	47%	97%	4%
22. The views of the funding body have not influenced the content of the guideline	100%	97%	13%	81%	47%	100%	87%	100%	43%	47%	13%
23. Competing interests of guideline development group members have been recorded and addressed	100%	93%	71%	93%	73%	100%	97%	75%	90%	87%	0%

															Results			
12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Median	q1	q3	IQR
93%	100%	80%	100%	93%	90%	67%	83%	87%	87%	67%	79%	81%	89%	17%	89%	84%	99%	15%
87%	100%	53%	100%	88%	63%	47%	33%	60%	97%	44%	100%	57%	89%	11%	87%	60%	99%	38%
93%	88%	63%	100%	95%	90%	63%	57%	93%	67%	61%	83%	81%	64%	56%	89%	67%	95%	27%
83%	88%	43%	13%	86%	70%	50%	53%	67%	90%	42%	38%	45%	22%	6%	72%	43%	89%	45%
0%	4%	0%	8%	17%	0%	7%	0%	7%	50%	11%	0%	2%	3%	0%	7%	0.5%	49%	48%
97%	67%	23%	100%	93%	17%	87%	97%	97%	60%	61%	21%	86%	6%	61%	85%	60%	96%	36%
73%	100%	67%	46%	19%	83%	23%	20%	0%	47%	44%	8%	0%	81%	0%	60%	19%	85%	66%
83%	92%	70%	8%	12%	80%	30%	30%	30%	33%	44%	0%	0%	61%	0%	66%	25%	83%	58%
83%	96%	53%	67%	12%	80%	37%	63%	33%	80%	72%	0%	2%	36%	11%	72%	34%	93%	59%
83%	92%	27%	100%	60%	83%	50%	13%	7%	90%	14%	0%	0%	6%	0%	83%	17%	90%	73%
90%	83%	87%	88%	52%	80%	83%	47%	77%	63%	69%	38%	48%	67%	33%	85%	64%	91%	25%
80%	100%	73%	38%	21%	83%	63%	57%	47%	80%	75%	17%	21%	47%	17%	76%	49%	95%	46%
0%	0%	10%	0%	81%	0%	70%	23%	0%	63%	0%	0%	38%	0%	0%	51%	0	88%	88%
0%	25%	17%	58%	12%	17%	40%	0%	0%	0%	6%	4%	10%	0%	0%	14%	0.8%	64%	63%
93%	88%	83%	100%	93%	83%	90%	70%	73%	90%	81%	92%	81%	31%	39%	92%	83%	100%	17%
93%	83%	83%	100%	86%	77%	93%	63%	97%	60%	86%	92%	79%	56%	17%	92%	77%	96%	19%
87%	46%	83%	100%	93%	60%	77%	67%	60%	50%	67%	92%	74%	17%	56%	83%	66%	93%	26%
43%	92%	43%	50%	64%	23%	40%	67%	40%	47%	6%	71%	17%	0%	61%	55%	40%	87%	47%
67%	54%	57%	71%	95%	13%	77%	57%	43%	3%	39%	17%	57%	0%	11%	60%	29%	94%	64%
43%	67%	30%	50%	50%	13%	37%	33%	37%	40%	25%	8%	2%	3%	11%	42%	23%	65%	41%
73%	29%	63%	100%	88%	3%	53%	57%	77%	33%	69%	0%	71%	8%	11%	72%	36%	95%	58%
7%	88%	10%	17%	95%	20%	73%	50%	67%	3%	6%	46%	24%	100%	0%	47%	13%	87%	73%
3%	96%	90%	4%	81%	57%	67%	53%	63%	0%	78%	88%	88%	89%	94%	84%	64%	92%	28%

■, 100%-81%; ■, 80%-61%; ■, 60%-40%; ■, 39%-20%; ■, <20%.

Abbreviation: AGREE, Appraisal of Guidelines for Research and Evaluation.

3.2.4 | Clarity of presentation

For the clarity of presentation domain, the median for the score was 85%, range 34% to 100%. The highest (100%) score was granted for GINA and GEMA guidelines.^{12,15} This domain proved to be one of the two most effectively addressed domains with only two guidelines scoring below 60% (ranging from 34% to 37%). Low scores were again due to limited reporting.^{3,33}

3.2.5 | Applicability

In the fifth domain, the median for the score was 51%, range: 3% to 100%, with the highest score of 100% being granted only for the Australian guidelines.¹⁰ The lowest score accounted for 3%.³ Again, the lack of proper reporting was the reason for low scores in this domain.

3.2.6 | Editorial independence

For this domain, the median was 63% (range: 2% to 100%). 100% was the highest score, and only two guidelines achieved it, again, the Australian book of asthma guidelines and Expert Panel Report 3 guidelines.^{10,16} The lowest score (2%) in this domain came for French guidelines.³⁰

3.2.7 | Change of overall quality score in time

Interestingly, the overall quality of the guidelines shows an improvement trend to improve over the last 20 years (in the 20 years), even though it was statistically not significant. Correlation coefficient (r) equals .3036, and r^2 equals .0921. $P = .13$. (Figure 2).

4 | DISCUSSION

We systematically reviewed the quality of guidelines concerning preschool wheezing and asthma as part of the EAACI Task Force preparation of new clinical practice recommendations for diagnosis and management of preschool wheeze by using one method—AGREE II. Our inclusion criteria fulfilled 26 guidelines published in English. Using the AGREE II, the National Council of Asthma Australia received top ratings, followed by an international expert consortium "GINA," and other guidelines, signed by the British national organizations—NICE and BTS.^{10,12-14}

The quality scores for each domain varied. Almost all guidelines have correctly introduced their scope and purpose, and clearly presented their recommendations, and therefore, gained the highest scores (domain 1 and 4 with medians of 86% and 85%, respectively). On the other hand, the broad involvement of stakeholders, including patients' groups (domain 2) as well as ease of guideline applicability with identification of possible costs and barriers (domain 5), was most troublesome and gained the lowest scores of 49% and 51%,

respectively. In our search, there several guidelines for asthma (23), while there were only four guidelines focused solely on wheezing. Those guidelines had considerably varied quality indicating a considerable gap in current recommendations in this clinical field.

"Overall quality score" reflects more reviewers opinion of the reviewers on quality of each guideline, than actual credibility. We are aware that the robustness of guidelines is more than just any AGREE II score, and it has been the common pitfall of putting undue emphasis on any aggregate "overall score." Therefore, we decided not to show this specific result. Moreover, it should be emphasized that no guideline was perfect. Therefore, we present all results in detail in Table 2, to show separate results for each of 23—AGREE II question for every identified guideline.

A critical assessment of asthma and wheezing guidelines has not been fully elucidated so far.

Acuña-Izcaray et al. have published a systematic review of available clinical guidelines for asthma management published between 2000 and 2010.³⁴ In this the review, authors identified 18 guidelines, and their scores were markedly lower in comparison to ours. Although the authors conclude that the quality of guidelines improves over time, a similar observation was made by Lytras et al in their systematic review.³⁵ Armstrong et al also observed improvement in the quality of guidelines marked over time, in their publication.³⁶ In our review, the majority of the guidelines (16 of 26) are published after 2010.

In 2017, Bakel et al published a systematic review of guidelines for asthma and bronchiolitis in children, focusing on quantification of agreement among the above-mentioned guidelines using weighted and unweighted K score.³⁷ In their report, the authors concluded that different guidelines for asthma show low consistency. The main discrepancy between this study and ours is the number of guidelines included (9 vs 26 in our study), which may be due to different scopes and different exclusion criteria in their review. Moreover, our study is more detailed in terms of results regarding the AGREE domains.

The AGREE II instrument was used in the appraisal of several guidelines, consistently showing differences in quality between different guidelines.³⁴⁻⁴⁰ Strikingly, a substantial portion of the published guidelines remains at least, average quality. Moreover, there is a visible scarcity in guidelines regarding preschool wheezing.

Recently, Sun et al have analyzed 50 different pediatric guidelines (not explicitly addressed to asthma), by using AGREE II method.³⁹ Their results are similar to ours and show deficiencies and strengths in corresponding domains. Similarly, domain 2 (involvement of stakeholders) and domain 5 (guideline applicability) were the lowest scored domains, while domains 1 and 4 scored the highest. There were negligible numerical differences between our results and those of Sun and colleagues.

4.1 | Limitations

Firstly, we limited our search to the past 20 years, even though most authors suggest that an update is generally required after 3 to 5 years.⁴¹

Our search was also significantly limited to English guidelines. Thus, high-quality guidelines but published in other than English languages might have been omitted in our search, resulting in language bias.

In our methodology, there was no blinding to neither authors nor organizations who developed these guidelines—which may be another potential source of bias. However, since we were already familiar with the majority of the identified guidelines, thus true blinding was not possible.

In this paper, we used AGREE II, as only one method of assessment. However, other assessment systems exist such as GRADE or GIN. The use of one of those systems considerably increases the quality of the guidelines. Therefore, the lack of full GRADE assessment in our study may be regarded as a potential limitation of our study.

Finally, some of the reviewers/appraisers had no previous experience with the AGREE II instrument. Therefore, all reviewers were asked to take part in the recommended AGREE II consortium online training, which was in accordance with other AGREE evaluation groups.^{34,40}

Another possible drawback is that, even though the AGREE II tool is considered both valid and reliable, this instrument has its limitations, such as lack of clear criteria for applying each point on the Likert scale. We could see tendency in our scoring to score either low or high, which is result of rather dichotomic answer to many AGREE questions. Moreover, it is focused mostly on the methodological side of guidelines, even though it also deals with the quality of evidence, and one may feel that this part of guidelines preparation is not covered enough.⁴¹ Moreover, it is worth mentioning that there is no range or threshold provided by the AGREE II consortium to enable differentiation between high or low-quality guidelines. Therefore, in our paper, we decided not to show overall quality results, but we showed scores not only for each domain but also for each of the 23 questions as well.⁸ Last but not least, an analysis of changes over time has shown a trend for guideline quality improvement. For that reason, adopting any objective values may inaccurate.

Last but not least among the limitations should be mentioned, that understanding of the term “preschool wheeze,” that has not been adequately defined yet. In our Task Force activities, we arbitrarily assumed “preschool” as children between the ages of 2 and 6, reflecting age differences in school systems and the epidemiology of recurrent wheezing.

5 | CONCLUSIONS AND IMPLICATIONS

Early wheezing episodes are heterogeneous conditions, and we believe that their management should be based on good recommendations, resulting from a more personalized approach. A thorough history and physical examination in wheezy preschoolers may help to identify children with a risk of asthma/atopy since it will guide the likelihood of symptoms persisting. In these patients, a treatment basing on the well-prepared guidelines can be applied, since many of

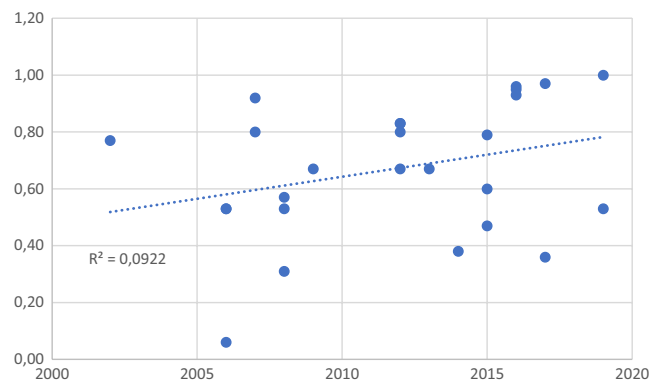


FIGURE 2 An overall quality of guidelines (Appraisal of Guidelines for Research and Evaluation score change) over time. 95% CI [−0.0049, 0.03604], $P = .13$; β : 5.71

them are good enough to instruct how to control clinical symptoms of wheezing.

Clinical practice guidelines play a tremendous role in health-care decision-making. This review uses current evidence to highlight the impact of standardization in guideline development on their quality. The AGREE II tool is not only helpful in assessing guidelines but also in improving quality if used during the planning and preparation of guidelines. Also, it should be emphasized that the recommendations rarely consider the views of the patient and the public.

We conclude that, even though there is an abundance of guidelines targeting asthma in children, the number of guidelines for preschool wheezing remains low. It seems essential that future guidelines for wheezy preschoolers would aim to identify individuals who may suffer from asthma in older age, in order to provide appropriate management and treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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