

Predicting who will have asthma at school age among preschool children

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It is difficult to distinguish at preschool age whether a wheezing child will or will not have asthma at school age. A prediction rule for asthma in preschool children might help to determine a prognosis and to study improvements in treatment and prevention. This review discusses (1) the development and use of clinical prediction rules, (2) the European Respiratory Society Task Force classification of wheeze at preschool age, (3) published prediction rules developed to identify preschool children who will have asthma at school age, and (4) recommendations to improve asthma prediction. Prediction rules are currently created more frequently, yet their clinical use remains low. The classification of episodic wheeze and multiple-trigger wheeze in preschool children shows conflicting results as to whether episodic wheeze and multiple-trigger wheeze differ in clinical features and has limited value in predicting asthma at school age. Clearly, more studies are needed to confirm this. Currently available prediction rules aiming to identify preschool children having asthma at school age are of modest clinical value. Prediction can be improved by more precise definitions and measures and, ultimately, by more knowledge of pathophysiologic mechanisms. In the future, biomarkers and genomic risk profiles to develop personalized medicine might further improve asthma prediction, treatment, and prevention. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Asthma, prediction, preschool, children, episodic wheeze, multiple-trigger wheeze

Abbreviations used

API: Asthma Predictive Index
ERS: European Respiratory Society
EW: Episodic wheeze
FENO: Fraction of exhaled nitric oxide
LR+: Likelihood ratio of a positive test result
MTW: Multiple-trigger wheeze
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
PPV: Positive predictive value

For more than 20 years, it has been recognized that wheeze in preschool children is a heterogeneous condition. Different wheezing phenotypes, such as early-onset and persistent wheeze, have been defined in epidemiologic studies.¹⁻³ Wheezing phenotypes used in epidemiologic studies are frequently defined retrospectively and are therefore not usable in clinical practice.

Several studies have shown that the preschool years are very important in asthma development, especially with respect to lung growth, maturation of the immune system, and exposures, such as tobacco smoke, allergens, and viral infections.⁴⁻⁶ Approximately 30% of preschool wheezing children will have asthma at school age. However, it is very difficult to distinguish at a young age which children with wheeze will have asthma at school age. Distinguishing children who will and will not develop asthma at an early age will help to provide parents a prognosis of respiratory symptoms and can help in the performance of research on the effects of more guided treatment or prevention strategies. This distinction might be generated by a classification or a prediction rule.

In 2008, a European Respiratory Society (ERS) Task Force proposed a clinical classification of preschool children with wheeze to identify 2 subgroups of preschool children who will and will not have asthma at school age.⁷ Moreover, several prediction rules have been proposed for clinical use to predict which preschool children will have asthma at school age.

The aim of this review is to (1) review prediction rules in clinical practice in general, (2) evaluate the classification of the ERS Task Force, (3) review published prediction rules developed to identify children with asthma at school age, and (4) make recommendations to improve asthma prediction in preschool children. We acknowledge that there are many symptom-based classifications of preschool wheezing children. This review is limited to a thorough evaluation of the ERS Task Force classification and a comparison of prediction rules that are developed for clinical use.

PREDICTION RULES IN CLINICAL PRACTICE

Prediction rules are decision-making tools that use variables of history, physical examination, or a simple test to provide the

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probability of an outcome, prognosis, or likely response to treatment in an individual patient.⁸⁻¹⁰ Development of a prediction rule includes the creation, validation, and impact analysis on clinician's behavior and clinical outcome (and implementation) phases.⁸⁻¹⁰ There are increasing numbers of scientific articles discussing prediction rules.^{10,11} In the field of pediatrics, the number of articles published about prediction rules has increased over the last decades; however, most of these prediction rules do not proceed further than the creation phase.¹¹ This lack of validation and impact analysis, together with a lack of user friendliness, might reflect the controversy concerning their usefulness by clinicians.¹² Nevertheless, there are well-known, clinically used prediction rules in children. The most famous example is probably the Apgar score, which predicts survival during the neonatal period in newborn infants.¹³ In a preschool child with respiratory symptoms, a prediction rule might help to determine prognosis and to study the effect of more guided treatment or prevention strategies in homogeneous subgroups.

MULTIPLE-TRIGGER WHEEZE VERSUS EPISODIC WHEEZE: EARLY PHENOTYPES OF ASTHMA?

In 2008, an ERS Task Force acknowledged that preschool children with wheeze form a heterogeneous population.⁷ Because the longitudinally derived wheezing phenotypes were defined by repeated measurements in childhood and therefore are not usable in a clinical situation, they proposed a classification of preschool children with wheeze based on literature review and expert opinion.⁷ The classification evolved as follows: (1) episodic (viral) wheeze (EW; ie, "wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes") and (2) multiple-trigger wheeze (MTW; ie, "wheezing that shows discrete exacerbations, but also symptoms between episodes").⁷ It was assumed that EW was associated with viral respiratory tract infections and that its prevalence decreased over time. MTW was assumed to be associated with chronic allergic airway inflammation and to occur in response to viral respiratory tract infections and other triggers, such as allergens, exercise, and emotions; thus MTW can precede asthma.⁷

At face value, EW and MTW appear to be clear-cut easy-to-use phenotypes. However, they are not simple diagnoses because the triggers of wheeze might not always be easy to identify in clinical practice. In addition, it is unknown whether this classification provides homogeneous subgroups in preschool children that have predictive value for having asthma at school age. We therefore analyzed EW and MTW and longitudinally derived wheezing phenotypes in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study (Fig 1).^{1,3,14} EW and MTW did not correspond to specific longitudinally derived wheezing phenotypes made by using either longitudinal latent class analysis³ or by using hypothesis-based definitions of transient early and persistent wheeze.¹ Thus we cannot relate available longitudinal data on wheezing phenotypes to MTW and EW. More data are needed to investigate whether MTW and EW represent a classification that distinguishes 2 homogeneous subgroups of preschool children.

A small number of studies analyzed whether children with MTW differ from children with EW in respect to clinical and pathologic features of asthma, such as lung function levels, skin prick test results, and airway inflammation. A case-control study

in 4- to 6-year-old children showed that children with MTW had more frequent atopy, higher fraction of exhaled nitric oxide (FENO) levels, and lower lung function levels than children with EW, as measured on the basis of multiple-breath washout.¹⁵ However, another study showed no differences between 0- to 3-year-old children with MTW and EW in terms of age, sex, parental history of asthma, atopic eczema, skin prick test response, exposure to environmental tobacco smoke, forced expiratory flow at functional residual capacity, and functional residual capacity and FENO levels.¹⁶ One study compared bronchial biopsy specimens obtained at 2 years of age between 14 children with MTW at 5 years and 8 children with EW at 5 years. Children with MTW had a thicker reticular basement membrane and more mucosal eosinophilic inflammation than children with EW.¹⁷ These findings are in concordance with a report showing that children with respiratory symptoms apart from colds had more eosinophils and a thicker basement membrane in their bronchial biopsy specimens than healthy control subjects.¹⁸ Overall, there is a small number of studies reporting on MTW and EW, providing conflicting results as to whether MTW and EW differ in clinical features at preschool age. This suggests that the classification of EW and MTW does not identify homogeneous subgroups of preschool children. Children with MTW can already have pathologic features of asthma from age 2 years; however, given the small number of studies available, more data are needed to support this.

Although the classification of EW and MTW does not provide homogeneous subgroups of preschool children that correspond with longitudinally derived wheezing phenotypes or that can be differentiated in terms of clinical features of asthma, this classification might predict who will and will not have asthma at school age. One study addressing this topic partly followed up preschool children with severe EW until school age.¹⁹ Severe EW was defined as being referred to a pediatrician because of EW. Sixty-seven percent of the children with severe EW had asthma symptoms at school age.¹⁹ This study shows that severe EW can also precede asthma. This suggests that the classification of EW and MTW is limited in its capability to distinguish among preschool children who will and will not have asthma at school age. Hence this is the only study available analyzing whether the ERS Task Force classification in preschool children predicts the presence of asthma at school age; more research is needed to confirm this.

Because the classification of EW and MTW has not been substantiated with much scientific evidence up to now, it is surprising that reviews about asthma medication in preschool children frequently use the classification of EW and MTW,²⁰⁻²³ even more so because the presence of EW and MTW can change over time.²⁴ Therefore we will review the ability of other prediction rules to distinguish preschool children who will and will not have asthma at school age below.

PREDICTING ASTHMA IN PRESCHOOL CHILDREN BY USING PREDICTION RULES

Several prediction rules have been developed to predict whether preschool children will have asthma at school age, such as the stringent and loose forms of the Asthma Predictive Index (API),²⁵ the modified API,²⁶ the cumulative risk score of the Isle of Wright birth cohort,²⁷ the severity score for obstructive airway disease,²⁸ an extension of the severity score,²⁹ the PIAMA

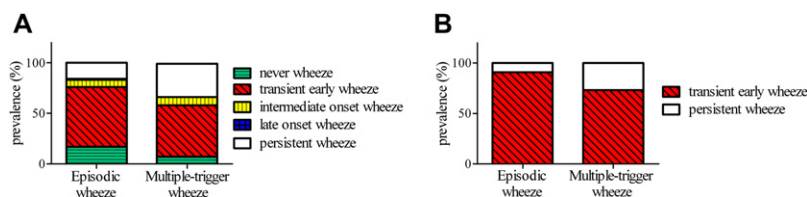


FIG 1. Disagreement between classification of EW and MTW and longitudinally derived wheezing phenotypes in the PIAMA birth cohort study.¹⁴ This figure shows in 3-year-old children that both EW (a positive answer to the parental question “Has your child wheezed with colds in the last 12 months?” and a negative answer to “Has your child wheezed without a cold in the last 12 months?”) and MTW (positive answers to both parental questions) comprise various different longitudinally derived phenotypes of wheeze, as defined by longitudinal latent class analysis (A)³ and as defined as wheezing phenotypes in the Tucson Children’s Respiratory Study (B).¹ EW and MTW do not equalize the longitudinally derived wheezing phenotypes of transient early wheeze and persistent wheeze, respectively.

risk score,³⁰ a probability matrix of wheeze at 5 years,⁶ the Persistent Asthma Predictive Score,³¹ and risk prediction based on the presence of 1 or more risk factors for asthma development.^{32–34} The stringent and loose forms of the API, the PIAMA risk score, and the cumulative risk score have been externally validated, with results comparable with those of the initial cohort, showing their generalizability.^{35–37}

The generalizability of prediction rules could imply that they are applicable in clinical practice. However, this seems not to be the case for several reasons. First, the aim of the prediction rule must be clear: will it be used as a screening tool (to rule out asthma in a general population) or as a diagnostic tool (to identify children at risk in a population with a high prevalence of asthma development)? The above mentioned rules all are diagnostic tools for to identify preschool children who will have asthma at school age. Such prediction rules need a high positive predictive value (PPV; ie, probability that a child with a positive prediction rule result will have asthma at school age) and a high sensitivity (ie, probability that a child with asthma at school age had a positive prediction rule result at preschool age). Table E1 in this article’s Online Repository at www.jacionline.org provides an overview of all published prediction rules, and Table I^{6,25,27–32,34–37} presents a selection of this overview. It is clear from Table I that PPVs are generally low (<80%; ie, a child with a positive test result will have a considerable risk of being falsely identified as a future asthmatic patient). Furthermore, when using these prediction rules, most children with asthma at a later stage will be missed (sensitivity <50%), which might partly be due to even later development of asthma. Thus the clinical value of these prediction rules is only modest.

More insight will be gained if we understand why the clinical value of these prediction rules is only modest and therefore why the sensitivity and PPV are far from optimal. As mentioned above, the sensitivity might be low because of later development of asthma than at preschool age. The PPV depends on a derivation of the prevalence of asthma in the study population on the one hand and a derivation of the sensitivity and specificity (the likelihood ratio of a positive test result [LR+]) on the other hand (see Table E2 in this article’s Online Repository at www.jacionline.org). An LR+ of greater than 5 is considered an informative prediction rule because it generates a large shift from pretest to posttest probability of asthma at school age (see Table E2).³⁸ Many prediction rules have an LR+ of less than 5 and can be considered not informative as a diagnostic tool to identify preschool children who will have asthma at school age. The prediction rule “persistence of early frequent wheeze” has an LR+ range of 6.0 to 12.0

depending on the studied population (Table I) and is an example of an informative prediction rule. Nevertheless, the persistence of early frequent wheeze has a low PPV in different studied populations because of the low prevalence of asthma at school age, ranging from 8% to 17% (Table I). Taken together, reasons why prediction rules have little clinical value are that asthma also develops later than the preschool years, some prediction rules are not informative, and the prevalence of asthma at school age is low in the studied population.

Second, the lack of a gold standard to diagnose asthma at school age is an important shortcoming of prediction rules. The definition of asthma differs between studies developing prediction rules (Table I).^{39,40} In addition to the fact that it is unknown which definition of asthma truly identifies the disease, this complicates the comparison of prediction rules. The asthma definition will influence the pretest probability of the outcome in the studied population and therefore affect the PPV of a prediction rule.

Third, addition of a prediction rule in clinical practice might affect clinical judgment. Analysis of the effect of a prediction rule on the clinician’s behavior and clinical outcome has not been done for one of the prediction rules.^{8–10} Consequently, it becomes unlikely that a prediction rule will be implemented in clinical practice. Finally, a prediction rule needs to be simple and noninvasive to be a profitable tool.

Recently, Leonardi et al³⁵ evaluated the predictive performance of the stringent and loose forms of the API, simpler prediction rules, and even random prediction rules. They validated the stringent and loose forms of the API in the Leicester 1998b Respiratory Cohort. The stringent and loose forms of the API had the highest overall performance to predict asthma; however, this was still quite poor and comparable with that of a simple prediction rule based on the persistence of wheeze. Simpler prediction rules based only on frequency of early wheezing could therefore effectively replace the API in terms of predictive performance (Table I).³⁵ Furthermore, prediction rules did not perform adequately in a selected population of preschool children with wheeze because the prevalence of asthma in the studied population was not substantially higher than the prevalence of asthma in the general population (Table I).³⁵

Despite the low-to-moderate performance of prediction rules to assess asthma in preschool children with reasonable certainty, the modified API is regularly used in clinical research to identify preschool children at risk for asthma later in childhood, especially in asthma medication trials.^{41–43} This makes it surprising that the modified API has not been studied for its predictive performance as a diagnostic tool, as with other prediction rules.

TABLE I. Performance characteristics of prediction rules in preschool children to predict asthma at school age*

Reference	Age at prediction (y)	Studied population	Prediction rule	Age at outcome (y)	Outcome	LR+	Prevalence	PPV	NPV	Sensitivity	Specificity	OR
Leonardi et al, 2011 ³⁵	3	General population	Stringent API LRC	7	DDA, active	5.2	17	51	88	31	94	7.3
Castro-Rodriguez, 2000 ²⁵	3	General population	Stringent API	6	Active asthma	7.4	11	48	92	28	96	9.8
Castro-Rodriguez, 2000 ²⁵	3	General population	Stringent API	8	Active asthma	4.9	14	44	88	16	97	5.8
Leonardi et al, 2011 ³⁵	3	Wheeze at 2 or 3 y	Stringent API LRC	7	Active asthma	2.6	21	40	86	49	81	3.9
Leonardi et al, 2011 ³⁵	3	General population	Stringent API LRC	7	Active asthma	5.3	11	40	93	37	93	8.2
Leonardi et al, 2011 ³⁵	3	General population	Stringent API LRC	10	Current wheeze	4.3	13	39	89	26	94	5.1
Rodriguez-Martinez et al, 2011 ³⁶	1-3	Wheeze ever	Stringent API	5-6	Active asthma	2.1	23	38	83	43	79	2.9†
Leonardi et al, 2011 ³⁵	3	General population	Stringent API LRC	10	Active asthma	5.3	9	35	92	32	94	6.7
Castro-Rodriguez, 2000 ²⁵	3	General population	Loose API	6	Active asthma	2.9	11	26	94	57	81	5.5
Leonardi et al, 2011 ³⁵	3	General population	Loose API LRC	7	Active asthma	2.9	11	26	94	57	80	5.2
Rodriguez-Martinez et al, 2011 ³⁶	1-3	Wheeze ever	Loose API	5-6	Active asthma	1.1	23	24	80	71	33	1.3†
Rodriguez-Martinez et al, 2011 ³⁶	1-3	Wheeze ever	PIAMA risk score ≥ 25	5-6	Active asthma	2.6	54	75	60	55	79	4.5†
Caudri et al, 2009 ³⁰	4	Wheeze/nighttime cough	PIAMA risk score ≥ 25	7 and 8	Active asthma	4.0	11	32	92	36	91	5.4†
Caudri et al, 2009 ³⁰	4	Wheeze/nighttime cough	PIAMA risk score ≥ 20	7 and 8	Active asthma	2.5	11	23	94	60	76	4.6†
Leonardi et al, 2011 ³⁵	3	General population	Persistent early frequent wheeze	7	DDA, active	9.0	16	64	84	9	99	9.5
Leonardi et al, 2011 ³⁵	3	Wheeze at 2 or 3 y	Persistent early frequent wheeze	10	Active asthma	6.0	17	55	84	18	97	6.2
Leonardi et al, 2011 ³⁵	3	General population	Persistent early frequent wheeze	7	Active asthma	12.0	8	51	90	12	99	9.5
Leonardi et al, 2011 ³⁵	3	General population	Persistent early frequent wheeze	7	Current wheeze	9.0	10	51	86	9	99	6.4
Kurukulaaratchy et al, 2003 ²⁷	4	Wheeze at 1, 2, or 4 y	Cumulative risk score > 2	10	Persistent wheeze	3.4	39	68	74	53	85	6.1†
Matricardi et al, 2010 ³⁷	4	Wheeze at 1, 2 or 4 y	Cumulative risk score > 2	8-10	Persistent wheeze	6.4	23	65	81	22	97	7.9†
Matricardi et al, 2008 ³²	3	Wheeze ever	Perennial sensitization	11-13	Wheezing	18.6	14	75	88	17	99	?
Matricardi et al, 2008 ³²	3	Wheeze ever	Any sensitization	11-13	Wheezing	6.0	13	48	89	28	95	?

(Continued)

ASTHMA PREDICTION THROUGH DIFFERENTIAL RESPONSE TO ASTHMA TREATMENT IN PRESCHOOL CHILDREN

Within randomized controlled trials that investigate the beneficial effects of inhaled corticosteroids and montelukast in

preschool children, there are differences in the magnitude of favorable response to asthma medication among preschool children. Children were more likely to respond favorably to medication when they had visited an emergency department or been hospitalized in the last year, were sensitized against aeroallergens,

TABLE I. (Continued)

Reference	Age at prediction (y)	Studied population	Prediction rule	Age at outcome (y)	Outcome	LR+	Prevalence	PPV	NPV	Sensitivity	Specificity	OR
Matricardi et al, 2008 ³²	3	Wheeze ever	Parental atopy [‡]	11-13	Wheezing	2.9	13	31	90	41	86	?
Devulapalli et al, 2008 ²⁸	2	Recurrent BO and controls	Severity score OAD >5	10	Active asthma	4.3	22	54	87	52	88	7.9
Vial Dupuy et al, 2011 ³¹	2	Recurrent wheeze	PAPS >1	6	Persistent asthma	4.1	33	67	76	42	90	6.3 [†]

The LR+ and prevalence were calculated from the published results of the studies.

BO, Bronchial obstruction; DDA, doctor-diagnosed asthma; LRC, Leicester Respiratory Cohort; NPV, negative predictive value; OAD, obstructive airway disease; OR, odds ratio; PAPS, Persistent Asthma Predictive Score.

*Prediction rules without data about performance characteristics of the prediction rule were not included in the table.^{6,29,34}

[†]Odds ratios were calculated from the published data.

[‡]Atopy was defined as asthma, hay fever, or atopic dermatitis.

were male, were white, had a positive API result, used oral corticosteroids in the last year, had atopic dermatitis or eczema, had a family history of asthma, or had increased serum eosinophil counts.⁴⁴⁻⁴⁶ Because these factors are associated with an improved response to asthma medication in preschool children with wheeze, it might be that these factors provide substantial predictive value for having asthma at school age. However, these associations are all found in selected populations and should therefore be further studied before they are used in asthma prediction.

RECOMMENDATIONS TO IMPROVE ASTHMA PREDICTION IN PRESCHOOL CHILDREN

Asthma prediction can be improved in several ways. First, more precise definitions of risk factors of asthma might improve a prediction rule. For example, sensitization is an important risk factor for asthma development in children. However, sensitization against multiple allergens is more strongly associated with asthma than monosensitization.^{31,47} Instead of a dichotomous variable for the presence of sensitization, use of quantitative levels of specific IgE might better predict asthma development.^{6,29,47} Further improvements might be obtained by using more objective measures instead of symptom assessment, such as lung function in early infancy and FENO measurements in 4-year-old children.⁴⁸⁻⁵⁰

Second, addition of environmental exposures might improve a prediction rule. Maternal smoking during pregnancy⁵¹⁻⁵³ and a rhinovirus or respiratory syncytial virus infection are environmental factors associated with an increased risk of asthma development in children.^{5,54,55} Addition of the interaction of risk factors and exposures might lead to further increased risk. For example, although sensitization and viral infections each separately increase the risk of asthma, the presence of both together leads to a higher risk than the sum of both independent risk factors.⁵ As another example, children with sensitization against house dust mite have more frequent asthma symptoms when they are also exposed to high levels of house dust mite.^{56,57}

Third, more precise phenotyping of asthma will lead to better agreement between clinical expression and pathologic mechanisms and might result in better prediction of asthma.⁵⁸ Addition of more objective measures that reflect the underlying pathophysiologic processes causing asthma can lead to more precise phenotypes. This concept has been reported in the term endotype, a

subtype of disease defined functionally and pathologically by a molecular mechanism or treatment response.⁵⁹

Fourth, combination of noninvasive objective measurements and developed prediction rules might improve asthma prediction. Many noninvasive techniques of airway inflammation, such as the composition of exhaled breath condensate, are not yet able to predict the persistence of asthma symptoms in preschool children.⁶⁰ Addition of the API to measurement of the exhaled breath condensate pH improved its performance substantially in discriminating atopic and nonatopic 5-year-olds with wheeze.⁶¹

Fifth, better characterization of the genetic risk might improve the prediction of asthma. Although common genetic variants performed poorly in the prediction of asthma in children,⁶² a personal genomic risk profile that also includes gene expression profiles, gene-gene and gene-environment interactions, and regulatory and epigenetic effects might together help to determine whether a child is at increased risk for asthma development.^{51,63-66} This genomic risk profile might also help to determine the most beneficial treatment for each patient.^{67,68}

Ultimately, these improvements all will help to identify the causative pathophysiologic mechanisms determining asthma development. Knowledge of the causative pathophysiologic mechanisms will allow us to disentangle these mechanisms in preschool children and help to research preventive, predictive, and therapeutic strategies in them.^{69,70} The understanding of the translation from genetic variances to functional changes in a disease process will enhance the development of personalized medicine,⁶⁷ in which prevention, prediction, and treatment might be adapted to a personal genetic predisposition. Therefore future research will have to focus on integration of genomics with systems biology.^{63,67} During this process, it could be that a reliable early biomarker will be identified that will increase our ability to identify preschool children at risk for asthma development or identify a subgroup that will have a favorable response in terms of prognosis, treatment, or prevention. Examples of a clinically useful biomarker are the combination of increased HbA_{1c} levels and impaired fasting plasma glucose levels that identify adults at risk for diabetes mellitus type 2⁷¹ or the presence of an epidermal growth factor receptor gene (*EGFR*) mutation that is a predictor of improved survival in subjects with pulmonary adenocarcinoma who use the chemotherapeutic agent gefitinib.⁷²

For now, the finding of such biomarkers is a wish for the future, and creation of a valid genomic risk profile with translation from genetic

variance to functional change in a disease process is a future goal for the implementation of personalized medicine and further investigation of options for asthma treatment, prediction, and prevention.

CONCLUSIONS

Wheeze in preschool children is a heterogeneous condition. A proposed classification of EW and MTW to identify preschool children who will develop asthma showed that patients with severe EW might have asthma at school age, suggesting that the classification is limited in distinguishing preschool children who will and will not have asthma at school age. Further research is needed to confirm this. Published prediction rules that identify preschool children having asthma at school age are only of modest clinical value, lack a gold standard for diagnosis of asthma at school age, and are not studied for their effect on clinical judgment. Prediction rules might be improved by (1) more precise definitions of risk factors, (2) addition of exposures and interactions of exposures with other risk factors, (3) more precise phenotyping with objective measures, (4) combination of noninvasive techniques with developed prediction rules, and (5) addition of a personal genomic risk profile, including gene expression profiles, genetic variance, gene-gene and gene-environment interactions, regulatory and epigenetic effects, and systems biology. These improvements will gain further insight into causative pathophysiologic mechanisms that determine asthma development in preschool children. In the future, personalized medicine might help to determine whether a child is at risk for asthma development and to perform novel research that might direct the most beneficial treatment for each asthmatic patient. This method of personalized medicine can be achieved by means of integration of genomics with systems biology to understand the translation from genetic variance to functional change in asthma development.

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1 **Table E1, All performance characteristics of prediction rules in preschool children to predict asthma at school age.***

Reference	AgeP (yrs)	Studied population	Prediction rule	AgeO (yrs)	Outcome	LR+	Prev	PPV	NPV	Sens	Spec	OR
Castro-R. '00	3	general population	stringent API	13	active asthma	4.9	18	52	84	15	97	5.7
Leonardi '10	3	general population	stringent API LRC	7	DDA, active	5.2	17	51	88	31	94	7.3
Leonardi '10	3	general population	stringent API LRC	10	DDA, active	4.5	17	48	87	27	94	6.2
Devulap. '08	2	recurr. BO & controls	stringent API	10	active asthma	3.3	22	48	87	57	83	6.4
Castro-R. '00	3	general population	stringent API	6	active asthma	7.4	11	48	92	28	96	9.8
Castro-R. '00	3	general population	stringent API	8	active asthma	4.9	14	44	88	16	97	5.8
Castro-R. '00	3	general population	stringent API	11	active asthma	3.8	16	42	86	15	96	4.3
Leonardi '10	3	general population	stringent API LRC	7	current wheeze	4.1	15	42	89	29	93	5.8
Leonardi '10	3	wheeze 2 or 3 yrs	stringent API LRC	7	active asthma	2.6	21	40	86	49	81	3.9
Leonardi '10	3	general population	stringent API LRC	7	active asthma	5.3	11	40	93	37	93	8.2
Leonardi '10	3	general population	stringent API LRC	10	current wheeze	4.3	13	39	89	26	94	5.1
Rodrig.-M. '11	1-3	wheeze ever	stringent API	5-6	active asthma	2.1	23	38	83	43	79	2.9†
Leonardi '10	3	wheeze 2 or 3 yrs	stringent API LRC	10	active asthma	2.4	19	35	87	47	80	3.5
Leonardi '10	3	general population	stringent API LRC	10	active asthma	5.3	9	35	92	32	94	6.7
Devulap. '08	2	recurr. BO & controls	loose API	10	active asthma	2.8	22	44	88	60	79	5.6
Leonardi '10	3	general population	loose API LRC	10	DDA, active	2.8	17	37	89	51	82	4.9
Leonardi '10	3	general population	loose API LRC	7	DDA, active	2.6	17	35	89	50	81	4.4
Castro-R. '00	3	general population	loose API	13	active asthma	2.2	17	32	87	39	82	3.0
Leonardi '10	3	general population	loose API LRC	10	current wheeze	2.7	14	31	91	51	81	4.5
Leonardi '10	3	general population	loose API LRC	7	current wheeze	2.5	15	30	90	50	80	4.0
Castro-R. '00	3	general population	loose API	8	active asthma	2.7	13	29	91	51	81	4.4
Castro-R. '00	3	general population	loose API	11	active asthma	2.0	16	27	88	40	80	2.6
Castro-R. '00	3	general population	loose API	6	active asthma	2.9	11	26	94	57	81	5.5
Leonardi '10	3	wheeze 2 or 3 yrs	loose API LRC	7	active asthma	1.3	21	26	86	74	43	2.2
Leonardi '10	3	general population	loose API LRC	7	active asthma	2.9	11	26	94	57	80	5.2
Leonardi '10	3	wheeze 2 or 3 yrs	loose API LRC	10	active asthma	1.5	18	25	92	82	45	3.8
Leonardi '10	3	general population	loose API LRC	10	active asthma	3.0	10	25	94	57	81	5.7
Rodrig.-M. '11	1-3	wheeze ever	loose API	5-6	active asthma	1.1	23	24	80	71	33	1.3†

Rodrig.-M. '11	1-3	wheeze ever	PIAMA risk score ≥ 25	5-6	active asthma	2.6	54	75	60	55	79	4.5†
Caudri '09	4	wheeze/night cough	PIAMA risk score ≥ 35	7&8	active asthma	7.0	13	50	90	7	99	8.6†
Caudri '09	4	wheeze/night cough	PIAMA risk score ≥ 30	7&8	active asthma	6.3	10	42	91	19	97	7.0†
Caudri '09	4	wheeze/night cough	PIAMA risk score ≥ 25	7&8	active asthma	4.0	11	32	92	36	91	5.4†
Caudri '09	4	wheeze/night cough	PIAMA risk score ≥ 20	7&8	active asthma	2.5	11	23	94	60	76	4.6†
Caudri '09	4	wheeze/night cough	PIAMA risk score ≥ 15	7&8	active asthma	1.7	11	17	96	82	51	4.7†
Caudri '09	4	wheeze/night cough	PIAMA risk score ≥ 10	7&8	active asthma	1.3	11	14	97	93	28	5.5†
Matricardi'10	4	wheeze 1, 2, or 4 yrs	cumul. risk score >3	8-10	persist. wheeze	-	-	100	78	5	100	-
Kurukul. '03	4	wheeze 1, 2, or 4 yrs	cumul. risk score >3	10	persist. wheeze	7.9	39	83	64	10	99	8.7†
Kurukul. '03	4	wheeze 1, 2, or 4 yrs	cumul. risk score >2	10	persist. wheeze	3.4	39	68	74	53	85	6.1†
Matricardi'10	4	wheeze 1, 2, or 4 yrs	cumul. risk score >2	8-10	persist. wheeze	6.4	23	65	81	22	97	7.9†
Kurukul. '03	4	wheeze 1, 2, or 4 yrs	cumul. risk score >1	10	persist. wheeze	1.4	39	48	81	85	40	3.8†
Kurukul. '03	4	wheeze 1, 2, or 4 yrs	cumul. risk score >0	10	persist. wheeze	1.0	39	40	80	98	5	2.6†
Matricardi'10	4	wheeze 1, 2, or 4 yrs	cumul. risk score >1	8-10	persist. wheeze	2.2	23	40	83	45	80	3.2†
Matricardi'10	4	wheeze 1, 2, or 4 yrs	cumul. risk score >0	8-10	persist. wheeze	1.3	23	28	89	84	38	3.1†
Devulap. '08	2	recurr. BO & controls	sev. score OAD >10	10	active asthma	5.2	22	60	79	3	99	5.6
Devulap. '08	2	recurr. BO & controls	sev. score OAD >8	10	active asthma	4.4	21	55	80	12	97	4.8
Devulap. '08	2	recurr. BO & controls	sev. score OAD >5	10	active asthma	4.3	22	54	87	52	88	7.9
Devulap. '08	2	recurr. BO & controls	sev. score OAD >4	10	active asthma	4.1	22	53	88	56	86	8.0
Devulap. '08	2	recurr. BO & controls	sev. score OAD >6	10	active asthma	3.8	22	51	82	27	93	4.8
Devulap. '08	2	recurr. BO & controls	sev. score OAD >11	10	active asthma	3.5	22	50	79	2	99	3.7
Devulap. '08	2	recurr. BO & controls	sev. score OAD >7	10	active asthma	3.6	22	50	82	26	93	4.5
Devulap. '08	2	recurr. BO & controls	sev. score OAD >9	10	active asthma	3.7	21	50	80	10	97	3.9
Devulap. '08	2	recurr. BO & controls	sev. score OAD >3	10	active asthma	2.9	22	44	88	62	79	6.0
Devulap. '08	2	recurr. BO & controls	sev. score OAD >2	10	active asthma	2.6	22	42	86	63	76	5.2
Devulap. '08	2	recurr. BO & controls	sev. score OAD >1	10	active asthma	2.3	22	39	93	81	65	8.0
Devulap. '08	2	recurr. BO & controls	sev. score OAD >0	10	active asthma	2.1	22	37	94	88	58	9.8
Vial Dupuy '11	<2	recurr. wheeze	PAPS >3	6	persist. asthma	-	-	100	69	11	100	-
Vial Dupuy '11	<2	recurr. wheeze	PAPS >2	6	persist. asthma	17.3	32	89	70	12	99	18.3†
Vial Dupuy '11	<2	recurr. wheeze	PAPS >1	6	persist. asthma	4.1	33	67	76	42	90	6.3†
Vial Dupuy '11	<2	recurr. wheeze	PAPS >0	6	persist. asthma	1.3	33	40	78	74	44	2.3†

Vial Dupuy '11	2	recurr. wheeze	PAPS >1	13	persist. asthma	1.9	19	31	89	63	67	3.5†
Matricardi'08	3	wheeze ever	parental atopic dermatitis	11-13	wheezing	4.6	13	41	88	12	97	?
Matricardi'08	3	wheeze ever	parental hay fever	11-13	wheezing	3.1	13	33	90	34	89	?
Matricardi'08	3	wheeze ever	parental atopy ‡	11-13	wheezing	2.9	13	31	90	41	86	?
Matricardi'08	3	wheeze ever	parental asthma	11-13	wheezing	2.9	13	31	88	20	93	?
Matricardi'08	3	no wheeze	parental asthma	11-13	wheezing	1.9	13	22	89	36	81	?
Matricardi'08	3	no wheeze	parental hay fever	11-13	wheezing	1.7	13	21	93	70	60	?
Matricardi'08	3	no wheeze	parental atopic dermatitis	11-13	wheezing	1.6	14	20	87	15	91	?
Matricardi'08	3	no wheeze	parental atopy ‡	11-13	wheezing	1.6	13	20	94	80	49	?
Matricardi'08	3	wheeze ever	perennial sensitiz.	11-13	wheezing	18.6	14	75	88	17	99	?
Matricardi'08	3	no wheeze	perennial sensitiz.	11-13	wheezing	8.5	13	57	89	22	97	?
Matricardi'08	3	wheeze ever	any inh. sensitiz. §	11-13	wheezing	6.9	14	52	89	22	97	?
Matricardi'08	3	wheeze ever	any sensitiz.	11-13	wheezing	6.0	13	48	89	28	95	?
Matricardi'08	3	wheeze ever	food sensitiz.	11-13	wheezing	5.7	14	47	88	16	97	?
Matricardi'08	3	wheeze ever	seasonal sensitiz.	11-13	wheezing	4.9	14	44	88	13	97	?
Matricardi'08	3	no wheeze	any inh. sensitiz. §	11-13	wheezing	4.2	14	40	90	33	92	?
Matricardi'08	3	no wheeze	seasonal sensitiz.	11-13	wheezing	3.3	14	34	88	20	94	?
Matricardi'08	3	no wheeze	any sensitiz.	11-13	wheezing	2.9	14	31	91	43	85	?
Matricardi'08	3	no wheeze	food sensitiz.	11-13	wheezing	2.3	14	27	88	24	90	?
Matricardi'08	3	wheeze ever	high exposure + sensitiz. ll	11-13	wheezing	31.0	14	83	88	9	100	?
Matricardi'08	3	no wheeze	high exposure + sensitiz. ll	11-13	wheezing	7.2	14	54	88	13	98	?
Matricardi'08	3	wheeze ever	high exposure cat/mite **	11-13	wheezing	2.5	14	29	89	35	86	?
Matricardi'08	3	no wheeze	high exposure cat/mite **	11-13	wheezing	1.0	14	13	86	59	40	?
Matricardi'08	3	wheeze ever	elevated total IgE	11-13	wheezing	2.6	13	29	89	27	90	?
Matricardi'08	3	no wheeze	elevated total IgE	11-13	wheezing	1.1	13	15	88	46	60	?
Matricardi'08	3	wheeze ever	atopic dermatitis ≤ 2 yrs	11-13	wheezing	4.5	14	41	89	20	96	?
Matricardi'08	3	no wheeze	atopic dermatitis ≤ 2 yrs	11-13	wheezing	2.7	13	30	90	36	87	?
Matricardi'08	3	wheeze ever	repeated LRIs	11-13	wheezing	1.4	13	18	87	17	88	?
Matricardi'08	3	no wheeze	repeated LRIs	11-13	wheezing	1.0	13	14	87	34	67	?
Leonardi '10	3	general population	early wheeze	7	DDA, active	2.1	17	30	91	70	66	4.5
Leonardi '10	3	general population	early wheeze	10	DDA, active	1.9	17	28	90	64	67	3.6

Leonardi '10	3	general population	early wheeze	7	current wheeze	2.0	16	27	92	70	65	4.3
Leonardi '10	3	general population	early wheeze	10	current wheeze	1.9	14	24	91	64	66	3.4
Leonardi '10	3	general population	early wheeze	7	active asthma	2.1	11	21	95	75	64	5.4
Leonardi '10	3	general population	early wheeze	10	active asthma	2.0	10	19	95	70	65	4.4
Leonardi '10	3	general population	early freq. wheeze	7	DDA, active	3.8	18	46	87	34	91	5.6
Leonardi '10	3	general population	early freq. wheeze	10	DDA, active	3.8	17	43	86	30	92	4.9
Leonardi '10	3	general population	early freq. wheeze	7	current wheeze	3.8	14	39	88	34	91	4.9
Leonardi '10	3	wheeze 2 or 3 yrs	early freq. wheeze	7	active asthma	2.1	21	36	86	55	74	3.4
Leonardi '10	3	general population	early freq. wheeze	7	active asthma	4.6	11	36	92	41	91	6.7
Leonardi '10	3	general population	early freq. wheeze	10	current wheeze	3.0	15	34	88	27	91	3.7
Leonardi '10	3	wheeze 2 or 3 yrs	early freq. wheeze	10	active asthma	1.8	19	30	86	48	73	2.5
Leonardi '10	3	general population	early freq. wheeze	10	active asthma	3.8	10	30	92	34	91	4.9
Leonardi '10	3	general population	persist. early wheeze	7	DDA, active	3.8	17	44	88	34	91	5.5
Leonardi '10	3	general population	persist. early wheeze	10	DDA, active	3.2	17	40	87	29	91	4.4
Leonardi '10	3	general population	persist. early wheeze	7	current wheeze	4.0	14	40	90	36	91	5.8
Leonardi '10	3	general population	persist. early wheeze	10	current wheeze	3.4	14	36	89	31	91	4.4
Leonardi '10	3	wheeze 2 or 3 yrs	persist. early wheeze	7	active asthma	2.0	20	34	87	58	71	3.4
Leonardi '10	3	general population	persist. early wheeze	7	active asthma	4.6	10	34	93	41	91	6.7
Leonardi '10	3	wheeze 2 or 3 yrs	persist. early wheeze	10	active asthma	1.7	19	29	86	53	69	2.6
Leonardi '10	3	general population	persist. early wheeze	10	active asthma	3.6	10	29	93	36	90	5.2
Leonardi '10	3	general population	persist. early freq. wheeze	10	DDA, active	9.0	17	65	84	9	99	9.8
Leonardi '10	3	general population	persist. early freq. wheeze	7	DDA, active	9.0	16	64	84	9	99	9.5
Leonardi '10	3	general population	persist. early freq. wheeze	10	current wheeze	9.0	13	57	86	9	99	8.4
Leonardi '10	3	wheeze 2 or 3 yrs	persist. early freq. wheeze	10	active asthma	6.0	17	55	84	18	97	6.2
Leonardi '10	3	general population	persist. early freq. wheeze	10	active asthma	12.0	9	55	91	12	99	12.0
Leonardi '10	3	wheeze 2 or 3 yrs	persist. early freq. wheeze	7	active asthma	4.0	21	51	82	16	96	4.6
Leonardi '10	3	general population	persist. early freq. wheeze	7	current wheeze	9.0	10	51	86	9	99	6.4
Leonardi '10	3	general population	persist. early freq. wheeze	7	active asthma	12.0	8	51	90	12	99	9.5
Frank '08	<5	wheeze last year	ex.-ind. wheeze + atopy††	6-16	persist. wheeze	3.1	0	53	85	61	80	6.4†
Frank '08	<5	wheeze last year	ex.-ind. wheeze & atopy††	6-16	persist. wheeze	0.3	0	17	35	19	33	0.1†
Matricardi'08	3	wheeze ever	male sex	11-13	wheezing	2.2	13	26	89	32	86	?

Matricardi'08	3	no wheeze	male sex	11-13	wheezing	1.1	13	14	87	56	47	?
Matricardi'08	3	no wheeze	wheeze 0-3 yrs	11-13	wheezing	1.8	13	22	90	48	74	?
Leonardi '10	3	wheeze 2 or 3 yrs	high risk random	7	active asthma	1.0	21	22	79	25	76	1.1
Leonardi '10	3	wheeze 2 or 3 yrs	high risk random	10	active asthma	1.0	19	20	81	26	75	1.1
Leonardi '10	3	general population	high risk random	7	current wheeze	1.2	15	18	85	12	90	1.2
Leonardi '10	3	general population	high risk random	7	DDA, active	1.0	17	17	83	11	89	1.0
Leonardi '10	3	general population	high risk random	10	current wheeze	1.0	15	15	85	11	89	1.0
Leonardi '10	3	general population	high risk random	10	DDA, active	0.8	17	13	82	9	88	0.7
Leonardi '10	3	general population	high risk random	10	active asthma	1.3	11	13	90	14	89	1.3
Leonardi '10	3	general population	high risk random	7	active asthma	1.1	11	12	89	12	89	1.1
Leonardi '10	3	wheeze 2 or 3 yrs	medium risk random	7	active asthma	1.0	22	22	79	62	38	1.0
Leonardi '10	3	wheeze 2 or 3 yrs	medium risk random	10	active asthma	1.0	19	19	80	62	36	0.9
Leonardi '10	3	general population	medium risk random	7	DDA, active	1.0	18	17	82	24	75	0.9
Leonardi '10	3	general population	medium risk random	10	DDA, active	0.9	17	16	82	23	75	0.9
Leonardi '10	3	general population	medium risk random	7	current wheeze	1.0	16	15	84	24	75	0.9
Leonardi '10	3	general population	medium risk random	10	current wheeze	1.0	14	14	85	25	75	1.0
Leonardi '10	3	general population	medium risk random	7	active asthma	1.1	12	13	89	27	75	1.1
Leonardi '10	3	general population	medium risk random	10	active asthma	1.1	11	12	90	27	76	1.1

The likelihood ratio of a positive prediction rule (LR+) and the prevalence in the studied population (Prev) were calculated from the published results of the studies.

*) Prediction rules without data about performance characteristics of the prediction rule were not included from the table.^{6,29,34}

†) Odds ratios were calculated from the published data.

‡) Atopy was defined as asthma, hay fever or atopic dermatitis.

§) Inhalation sensitization was defined as perennial sensitization or seasonal sensitization.

||) Sensitization to cat or mite and concurrent exposure to the respective allergen in the upper quartile of the respective distribution in the total Multicentre Allergy Study (MAS) population.

**) Exposure in the upper quartile of the respective distribution in the total Multicentre Allergy Study (MAS) population.

††) Parental report of hay fever or eczema by questionnaire.

Abbreviations: AgeP: Age at prediction; AgeO: age at outcome; API: asthma predictive index; BO: bronchial obstruction; cumul.: cumulative; DDA: doctor diagnosed asthma; ex.-ind.: exercise-induced; freq.: frequent; inh.: inhalation; LR+: likelihood ratio of positive test; LRC: Leicester Respiratory Cohort; LRIs: lower respiratory tract infections; NPV: negative predictive value; OAD: obstructive airway disease; OR: Odds ratio; PAPS: persistent asthma predictive score; persist.: persistent; PIAMA: Prevention and Incidence of Asthma and Mite Allergy; persist.: persistent; Prev: prevalence of asthma in the studied population; PPV: positive predicted value; recurr.: recurrent; sensitiz.: sensitization; Sens: sensitivity; Spec: specificity; sev.: severity.

Table E2, Overview of the mutual relationship of performance characteristics of prediction rules in a population.**Mutual relation of features of prediction rules in the studied population**

derivation of the PPV =	derivation of the prevalence x derivation based on sensitivity and specificity
post-test odds =	pre-test odds x positive likelihood ratio
positive likelihood ratio =	sensitivity/ (1 - specificity)
post-test odds =	post-test probability/ (1 - post-test probability)
post-test probability =	PPV
pre-test odds =	pre-test probability/ (1-pre-test probability)
pre-test probability =	prevalence

Abbreviations: PPV: positive predictive value.