Received: 15 January 2021 | Revised: 2 April 2021 | Accepted: 24 April 2021

DOI: 10.1111/pai.13530

ORIGINAL ARTICLE

WILEY

# Decision tree-based rules outperform risk scores for childhood asthma prognosis

Arthur H. Owora[1,2] | Robert S. Tepper[3] | Clare D. Ramsey[4] | Allan B. Becker[2]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Bloomington, IN, USA

[2]Children's Hospital Research Institute of Manitoba, Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, MB, Canada

[3]Indiana University School of Medicine, Indianapolis, IN, USA

[4]Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada

**Correspondence**
Arthur H. Owora, Department of Epidemiology and Biostatistics, School of Public Health, Bloomington, IN, USA.
Email: ahowora@iu.edu

**Funding information**
This study was supported by the Heart and Stroke Foundation and Canadian Lung Association Emerging Research Leaders Initiative, in partnership with the Canadian Respiratory Research Network and the Allergy, Genes and Environment Network of Centers of Excellence (AllerGen NCE). The study was funded by the Canadian Institutes of Health Research, the British Columbia Lung Association, and the Manitoba Medical Service Foundation.

**Editor:** Jon Genuneit

## Abstract

**Background:** There are no widely accepted prognostic tools for childhood asthma; this is in part due to the multifactorial and time-dependent nature of mechanisms and risk factors that contribute to asthma development. Our study objective was to develop and evaluate the prognostic performance of conditional inference decision tree–based rules using the Pediatric Asthma Risk Score (PARS) predictors as an alternative to the existing logistic regression-based risk score for childhood asthma prediction at 7 years in a high-risk population.

**Methods:** The Canadian Asthma Primary Prevention Study data were used to develop, compare, and contrast the prognostic performance (area under the curve [AUC], sensitivity, and specificity) of conditional inference tree-based decision rules to the pediatric asthma risk score for the prediction of childhood asthma at 7 years.

**Results:** Conditional inference decision tree–based rules have higher prognostic performance (AUC: 0.85; 95% CI: 0.81, 0.88; sensitivity = 47%; specificity = 93%) than the pediatric asthma risk score at an optimal cutoff of ≥6 (AUC: 0.71; 95% CI: 0.67, 0.76; sensitivity = 60%; specificity = 74%). Moreover, the pediatric asthma risk score is not linearly related to asthma risk, and at any given pediatric asthma risk score value, different combinations of its pediatric asthma risk score clinical variables differentially predict asthma risk.

**Conclusion:** Conditional inference tree–based decision rules could be a useful childhood asthma prognostic tool, providing an alternative way to identify unique subgroups of at-risk children, and insights into associations and effect mechanisms that are suggestive of appropriate tailored preventive interventions. However, the feasibility and effectiveness of such decision rules in clinical practice is warranted.

KEYWORDS
asthma prediction, childhood asthma, decision rules, prognosis

[Correction added on 21 December 2021, after original publication: The copyright statement was updated.]

**Abbreviations:** AUC, area under the curve; CAPPS, Canadian Asthma Primary Prevention Study; CCAAPS, Cincinnati Childhood Allergy and Air Pollution Study; GAM, generalized additive model; GINA, Global Initiative for Asthma; PARS, Pediatric Asthma Risk Score; ROC, receiver operating curve; SPT, skin prick test.

## 1 | INTRODUCTION

There are no widely accepted prognostic tools for childhood asthma[1,2]; this is in part due to the multifactorial nature of mechanisms and risk factors that contribute to asthma development, which also may vary over time.[3] Consequently, clinicians often rely on risk scores such as the Asthma Predictive Index (sensitivity = 28%; specificity = 96%)[4] and recently the Pediatric Asthma Risk Score (PARS: sensitivity = 68%, specificity = 77%),[5] which have modest prognostic accuracy (area under the curve ≤80%). Both the API and PARS are based on limiting logistic regression model assumptions; for example, the effect of risk factors on asthma risk is assumed to be linear and homogenous (ie, effects increase uniformly throughout the range of predictors). These regression models are limited to a small number of variables (for model parsimony) to aid asthma prognosis. Although such models are useful and often necessary in association analyses, this is not necessarily the case in prediction analyses, where the focus is on the outcome instead of the predictors.[2] Moreover, the predictor variables in both the API and PARS are conceptualized as single time point assessments that do not mimic the way a healthcare provider may approach prognosis of a patient with a series of questions guiding the clinician, with subsequent questions based on the answer to the prior. Risk and prognostic factors are assumed to have time-invariant effects on asthma risk over time ignoring the intricate interplay of biologic pathways that result in the changing risk of asthma incidence and recurrence.[2] Yet, for example, previous longitudinal studies have shown that not all children who suffer from early persistent wheezing in childhood go on to develop asthma at 2, 7, and 15 years of age.[6]

In this study, we use the data from the Canadian Asthma Primary Prevention Study (CAPPS) to develop and compare the prognostic performance of conditional inference tree-based decision rules with a revised PARS for the prediction of childhood asthma at 7 years. We hypothesize that conditional inference–based decision rules have higher prognostic performance than risk scores derived from PARS clinical variables using logistic regression models. Also, PARS values are not linearly related to asthma risk, and at any given PARS value, different combinations of PARS clinical variables differentially predict childhood asthma risk.

**Key Message**

Conditional inference decision rules can be operationalized to achieve higher prognostic performance for childhood asthma risk than risk score–based inference. Pediatric Asthma Risk Score (PARS) values are not linearly related to asthma risk (in the log scale). At any single PARS value, different combinations of PARS clinical variables differentially predict asthma risk. The risk of asthma can be predicted with modest accuracy using early childhood (≤2 years) clinical information.

## 2 | METHODS

### 2.1 | Data source and study population

Our secondary analysis used data from the CAPPS Study, which has been described previously.[7] Only children who had an assessment of current asthma at 7 years and PARS clinical variables before their 3rd birthday were included in our analytic sample ($N$ = 375).

### 2.2 | Wheezing outcomes

Wheezing outcomes were reported by parents at ages 2 weeks, 4, 8, 12, 18, and 24 months, and 7 years using a modified version of the International Study of Asthma and Allergy in Childhood questionnaire.[8] The operational definition of wheezing was a "whistling-like sound arising from the chest." Wheezing without a cold was defined as present if the total number of parent-reported episodes of wheezing minus the number of wheezing episodes that occurred after a cold was greater than 0 at ages 1 and 2 years.

### 2.3 | Asthma and atopy outcomes

Asthma and atopic disorder diagnoses were made by a pediatric allergist who did not provide healthcare services to the study family (ie, parents and child) without knowledge of intervention group allocation status using a standardized form to record symptoms and physical findings at the 1st-, 2nd-, and 7th-year follow-up.[7,9,10] The diagnoses of asthma and other atopic disorders were clinical decisions made by the pediatric allergists without knowledge of the results of the questionnaire, allergy skin tests, spirometry, or methacholine challenge tests.[10]

### 2.4 | Skin prick test outcomes

Skin prick test (SPT) outcomes were determined for 6 aeroallergens (Alternaria species, Cladosporium species, cat, dog, cockroach, and dust mite mix [Dermatophagoides farinae and Dermatophagoides pteronyssinus]) and 5 foods (wheat, soy, peanut, cow's milk, and hen's egg) at 12 and 24 months. A positive SPT response was defined as a wheal of 3 mm or more larger than that elicited by the saline control after 15 min.

### 2.5 | Revised PARS values and clinical variables

PARS values were generated for each child using the PARS scoring sheet derived from the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS);[5] if present before age 3 years, parental history of asthma (P1) was assigned a weight of - **2**, eczema (P2) - **2**, wheezing apart from colds (P3) - **3**, wheezing (P4) - **3**, cold climate

(P5 revised) - **2**, and ≥2 positive SPTs (P6) - **2** for a maximum total score of 14. The climate variable (P5 revised) was chosen to replace the African American race variable (P5) in the original PARS tool[5] since this was not available or applicable in the Canadian population. Winnipeg versus Vancouver residence was used to capture children who live in an area of cold versus warm climate, respectively; this is a more transferable construct compared to race outside of the United States (where the PARS tool was developed). Although, the cold climate construct does not capture genetic risk the way race/ethnicity does, it embodies an environmental basis—a demonstrated childhood asthma predictor, which may not be captured by race/ethnicity.[11] Moreover, the cold climate construct could be useful when examining asthma risk within or among populations for whom genetic risk as a function of race might be more homogenous. This is particularly true for other countries where the "race" construct may not connote or explain a substantial amount of variation in asthma risk as it does in the United States as a function of socioeconomic status and differences in healthcare access, quality, and equity. Additionally, because of multicollinearity between two of the original PARS variables (ie, wheezing with and without colds), as a replacement, we examined the prognostic utility of an early persistent wheezing (EP) variable (yes/no) defined as wheezing that occurred at least twice (8–12 months apart) during the first 24 months.[6,9]

## 2.6 | Sample size considerations

Informed by the work of Riley et al,[12] given the asthma prevalence in our study population is anticipated to be 19%,[9] if we assume conservatively that a six-risk factor model (similar to the original PARS) will explain at least 50% of the variability in asthma risk (because predictors such as wheezing and SPTs are part of the routine workup for a diagnosis of childhood asthma), the anticipated Cox-Snell $R^2$ statistic is 0.31, with a maximum value of 0.62 (based on a prevalence of 19%). For precise estimation of a child's future risk of asthma (within +/−0.05 of the average outcome risk), we needed at least 237 children corresponding to an event per predictor (EPP) ratio of 7.5. Sample size requirements for other criteria considered are summarized in Table S1.

## 2.7 | Statistical methods

Logistic regression and receiver operating curve (ROC) analyses were used to determine optimal cutoffs of our revised PARS. This was based on a minimized difference threshold framework to maximize sensitivity and specificity,[13] and evaluate the prognostic performance (sensitivity, specificity, predictive values, and likelihood ratios) of the revised PARS and its clinical variables for asthma predictions. Prognostic accuracy is defined as the overall probability that a child is correctly classified (ie, sensitivity ×prevalence + specificity × (1 −prevalence). Model diagnostics and goodness of fit were evaluated and compared against a generalized additive model (GAM) that capitalizes on the strengths of the logistic regression without requiring the problematic assumption that the model be linear in the logit (ie, log scale of asthma risk). The GAM was used to identify the appropriate form of dependence between asthma risk and revised PARS values to determine the appropriate functional form needed to model the relationship between the logit and PARS values in polynomial logistic models.

A conditional inference tree (CIT),[14] a family of classification and regression models, was used for partitioning our analytic sample into distinct subgroups of children who shared similar risk of developing asthma at 7 years based on their 1st- and 2nd-year PARS-related clinical variables. CIT candidate predictors included six variables: parental history of asthma—P1, eczema—P2, early persistent wheezing (EP)—P3/P4 revised, cold climate (ie, city of residence)—P5 revised, number of positive SPTs in the 1$^{st}$ year (*new*), and number of positive SPTs in the 2nd year—P6 revised. EP wheezing and SPTs were time-dependent (different from CCAAPS PARS where predictors are used as time-invariant factors that are present/absent before age 3 years). Significance tests at a type I error (α) of 0.05 were used to select and split recursively the most important predictor variable for an asthma diagnosis. At each splitting (in descending order of predictor importance), the algorithm stops if there is no dependence between predictor variables and asthma outcomes. Variable importance identifies the most important variables based on their contribution to the model predictive accuracy.

Compared with logistic models, CITs can be used to adequately model non-linear relationships, and time-dependent and joint effects, and accommodate many clinical variables in the same prediction model. Consequently, the CIT estimates more parameters than the logistic model, which increases the potential for overfitting; this problem is addressed in our analysis using a 10 cross-validation routine (with 50 repeats) to generate averaged estimates of our final model's prognostic accuracy. The 10-fold cross-validation with repeat routine generally results in a less biased (and less optimistic) estimate of a model's performance compared with routines such as fivefold to 10-fold cross-validation (without repeats), bootstrap validation, or a simple train/test split.[15]

As a sensitivity analysis, a random Forest model[16] was used to confirm the choice and variable importance of our final CIT predictor variables. The random forest algorithm consists of building multiple independent decision trees by repeatedly using multiple bootstrapped subsets of the data and averaging the models. At each splitting step of the tree algorithm, a random sample of predictors is chosen as split candidates from the full set of the predictors.

A pediatric allergist's diagnosis of asthma at 7 years was used as the reference standard for our prediction models. Our CIT and random forest analyses were implemented via the *partykit*[17] and

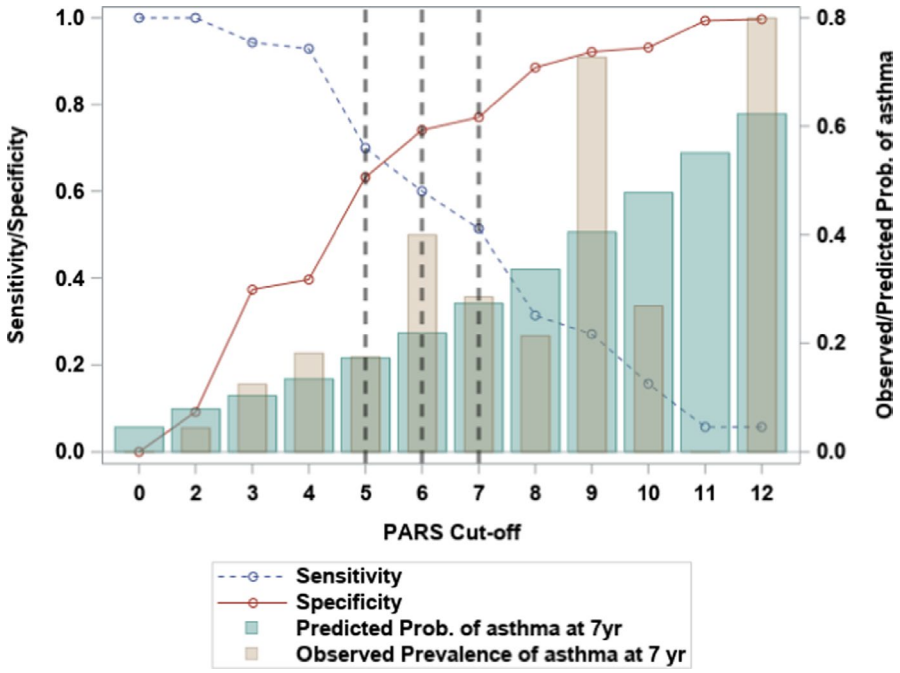


**FIGURE 1** Distribution of observed and predicted probability of asthma at 7 years at different PARS cutoff scores with their corresponding sensitivity (short dash line) and specificity (solid line) values ($N$ = 375). The predicted probability is derived from a logistic regression model with linear term: logit = ln (p/1-$p$) = −3.041 + 0.2952 × PARS cutoff. Original (≥7) and revised (≥6 and ≥5) PARS cutoff points/thresholds are represented y the gray dashed vertical lines. The revised PARS model scores are the sum of weights for parental asthma [P1], eczema [P2], wheezing apart from colds before 3 years [P3], wheezing before 3 years [P4], cold climate [P5 Revised], and SPTs positive to ≥2 allergens at year 2 [P6]

**TABLE 1** Multivariable logistic model of PARS clinical variables in the CCAAPS versus CAPPS study

| | Adjusted odds ratio (95%CI) | | | |
|---|---|---|---|---|
| **PARS clinical variables** | **CCAAPS[1] Original PARS** | **CAPPS Revised PARS** | **CAPPS Revised PARS + EP** | **CAPPS CIT** |
| Parental Asthma: P1 | 1.92 (1.17, 3.16)[c] | 1.95 (0.97, 3.93)[a] | 1.92 (0.94, 3.90)[a] | |
| Eczema before age 3 years: P2 | 1.97 (1.09, 3.06)[b] | 3.42 (1.66, 7.03)[c] | 3.42 (1.65, 7.06)[c] | 2.76 (1.32, 5.75)[c] |
| Wheezing before 3 years (≠cold): P3 | 2.64 (1.39, 5.13)[c] | 0.98 (0.43, 2.24) | | |
| Wheezing before 3 years: P4 | 2.88 (1.52, 5.37)[c] | 2.54 (1.32, 4.87)[c] | | |
| Race/ethnicity–CCAAPS: P5 | 2.04 (1.19, 3.47)[c] | | | |
| Cold climate (Winnipeg): P5 revised | | 3.00 (1.55, 5.82)[c] | 3.16 (1.63, 6.13)[c] | 3.35 (1.72, 6.52)[c] |
| SPT positive to ≥2 allergens at year 2: P6 | 2.44 (1.49, 4.05)[c] | 9.89 (3.69, 26.48)[c] | 8.85(3.33, 23.56)[c] | 4.68 (1.68, 12.99)[c] |
| SPT positive to ≥1 allergens at year 1 | | | | 2.87 (1.45, 5.67)[c] |
| EP—early persistent Wheezing | | | 3.43 (1.86, 6.36)[c] | 3.63 (1.95, 6.75)[c] |
| *ROC area under the curve* | | 0.77 | 0.79 | 0.79 |
| *Somers' D/C statistic* | | 0.55/0.77 | 0.58/0.79 | 0.59/0.79 |

*Note:* Each column (2–5) represents all variables included and adjusted for in each model (eg, in the CAPPS Revised PARS column [3], the model is adjusted for P1-P4, P5 revised and P6. CAPPS Revised PARS—includes original PARS variables but cold climate is used to replace race/ethnicity, CAPPS Revised PARS + EP—includes revised PARS variables but EP is used to replace wheezing (P4 and P3), respectively. CAPPS CIT—includes revised PARS + EP (excludes P1) variables selected in our final conditional inference tree (CIT) model. That is, the final model includes 5 predictors: eczema (P2), EP (P3/P4 revised), cold climate (P5 revised), number of positive SPTs at year 1 (*new*) and number of positive SPTs at year 2 (P6 revised).[5]

Abbreviations: CAPPS, Canadian Asthma Primary Prevention Study; CCAAPS, Cincinnati Childhood Allergy and Air Pollution Study.

[a]$p < 0.1$

[b]$p < 0.05$

[c]$p < 0.01$

*randomForest*[18] R software packages, respectively. Generalized U statistics,[19] a nonparametric approach, was used to compare prognostic performance between prediction models. Model discrimination was evaluated by using the area under the receiver operating characteristics curve (AUC). All statistical analyses were conducted using R and/or SAS 9.4 (SAS Institute Inc.,).

**TABLE 2** Prognostic performance of the Logistic Pediatric Asthma Risk Score (PARS) and conditional inference tree (CIT) models at age 7 years

| Study/Model | Asthma diagnoses | | Crude odds ratio (95%CI) | Observed/predicted prevalence (%) | Sensitivity (%) | Specificity (%) | AUC (95%CI) | PPV (%) | NPV (%) | LR+/LR- |
|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | | | | | | | | |
| CCAAPS/PARS (≥7) at 7 years[1] | | | | 16/30 | 68 | 77 | 0.80 (0.75, 0.84) | 37 | 93 | 3.02/0.41 |
| Yes | 65 | 114 | 7.22 (4.47, 11.68) | | | | | | | |
| No | 30 | 380 | Reference | | | | | | | |
| IOW/PARS (≥6) at 10 years[1] | | | | 15/28 | 67 | 79 | 0.79 (0.75, 0.83) | 36 | 93 | 3.25/0.41 |
| Yes | 110 | 196 | 7.52 (5.25, 10.78) | | | | | | | |
| No | 55 | 737 | Reference | | | | | | | |
| CAPPS/Revised PARS (≥6) at 7 years | | | | 19/32 | 60 (49, 71) | 74 (69,79) | 0.71 (0.67, 0.76) | 35 (26,43) | 89 (85,93) | 2.32/0.53 |
| Yes | 42 | 79 | 4.29 (2.49, 7.38) | | | | | | | |
| No | 28 | 226 | Reference | | | | | | | |
| CAPPS/CIT algorithm at 7 years | | | | 19/14 | 47(35, 59) | 93(90, 96) | 0.85 (0.81, 0.88) | 63 (51, 73) | 88 (86, 90) | 7.19/0.57 |
| Yes | 33 | 20 | 12.71 (6.62, 24.41) | | | | | | | |
| No | 37 | 285 | Reference | | | | | | | |

*Note:* CIT (conditional inference tree) variable importance: ≥2 positive SPTs at year 2, early persistent wheezing, eczema, cold climate, and ≥1 positive SPTs at 1 year. *Sensitivity*: probability that a predicted result will be positive when the disease is present (true-positive rate). *Specificity*: probability that a predicted result will be negative when the disease is not present (true-negative rate). *Positive likelihood ratio*: ratio between the probability of a positive predicted result given the *presence* of the disease and the probability of a positive predicted result given the *absence* of the disease, that is, true-positive rate/false-positive rate = sensitivity/(1-specificity). *Negative likelihood ratio*: ratio between the probability of a negative predicted result given the *presence* of the disease and the probability of a negative predicted result given the *absence* of the disease, that is, false-negative rate/true-negative rate = (1−sensitivity) / specificity. *Positive predictive value*: probability that the disease is present when the predicted result is positive. *Negative predictive value*: probability that the disease is not present when the predicted result is negative. *Accuracy*: overall probability that a patient is correctly classified = Sensitivity × Prevalence + Specificity × (1−Prevalence).[5]

Abbreviations: AUC, area under the curve; CAPPS, Canadian Asthma Primary Prevention Study; CCAAPS, Cincinnati Childhood Allergy and Air Pollution Study; IOW, Isle of Wight birth cohort; LR−, negative likelihood ratioLR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

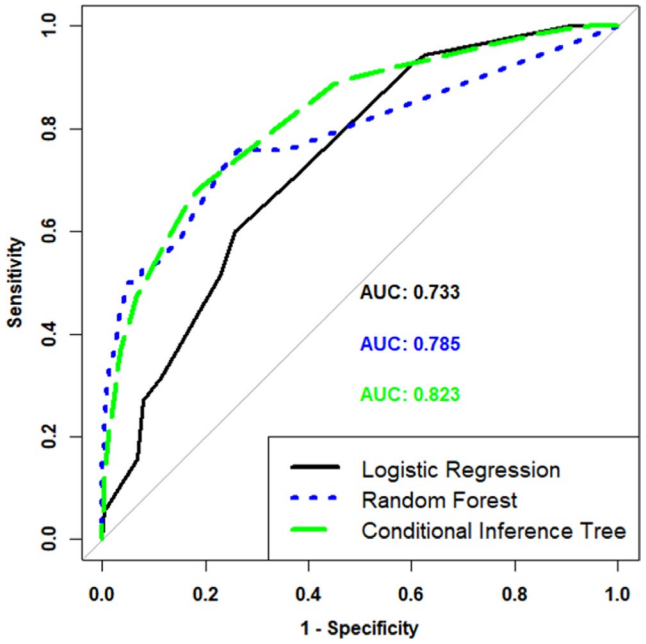


**FIGURE 2** ROC curves for conditional inference tree, random forest and logistic regression models based on 10-fold cross-validation (50 repeats) using the CAPPS study sample ($N$ = 375). Variable importance for CIT and random forest models is based on 6 candidate predictors: parental history of asthma—P1, eczema—P2, early persistent wheezing (EP)—P3/P4 revised, cold climate—P5 revised, number of positive SPTs in the 1st year (*new*), and number of positive SPTs in the 2nd year—P6. Conditional inference tree: P6, EP, P2, P5 revised, and SPTs at 1 year. P1 is excluded in the final model. Random Forest: EP, SPTs at year 1, P6, P2, P5 revised, and P1. Logistic regression results are generated from the revised PARS model (score = sum of weights for parental asthma [P1], eczema [P2], wheezing apart from colds before 3 years [P3], wheezing before 3 years [P4], cold climate [P5 Revised], and SPTs positive to ≥2 allergens at year 2 [P6]). Wilcoxon signed-rank test: $p$ values

## 3 | RESULTS

Overall, the observed prevalence of asthma at 7 years was 19% ($n$ = 375) and varied across PARS (Figure 1). The prevalence of having a history of parental asthma was 72%, followed by living in a city with cold climate (Winnipeg)—53%, any wheezing—42%, early persistent wheezing—22%, eczema—16%, wheezing apart from colds—13%, and ≥2 positive SPTs at 2nd year—7%. The odds of an asthma diagnosis at 7 years were 4.68 times greater among children with ≥2 positive SPTs at year 2 (CIT model Table 1: adjusted odds ratio [aOR]: 4.68; 95%CI: 1.86, 12.99). Having ≥2 positive SPTs at year 2 also had the highest predictor-specific prognostic accuracy (Table S2: AUC: 0.83; 95%CI: 0.79, 0.87). The observed and predicted prevalence of asthma differed across PARS values (Figure 1). The prognostic performance of our revised PARS at a positivity threshold (cutoff) of ≥6 was comparable to that observed in the CCAAPS study[5] (Table 2; sensitivity: 60% versus 68% and specificity: 74% versus 77%, respectively). At a lower cutoff (≥5), we observed higher sensitivity (70%), but lower specificity (63%) (Figure 1); however, there were no statistically significant differences for overall prognostic accuracy at the 5, 6, and 7 cutoffs (AUC differences, $p > 0.05$).

Our final CIT model included 5 predictors (parental asthma [P1] was excluded): eczema (P2), EP (P3/P4 revised), cold climate (P5 revised), positive SPTs at year 1 (≥1), and positive SPTs at year 2 (≥2 or P6). This CIT model had higher prognostic performance than the revised PARS logistic regression model (Table 2; Figure 2), with higher AUC in lower PARS risk strata (Table S2). PARS-related predictors showed varying prognostic importance based on the decision hierarchy used for the prediction of asthma at 7 years (Figure 3; Table S3). Having ≥2 positive SPTs in the 2nd year was associated with a 62% probability of asthma. If a child had less than two positive SPTs in the 2nd year but experienced early persistent wheezing and at least one positive SPT in the 1st year, their risk of asthma was 63%. A child who lived in an area with cold climate, and had less than two positive SPTs in the 2nd year and eczema but did not have early persistent wheezing had a 64% risk of asthma. Other predictor combinations were associated with less than a 25% risk of asthma. Although the order of variable importance was different between our CIT and random forest models, the final selected variables were consistent (Figure 2). The random forest model had comparable accuracy to our CIT model when examined against our 6 CIT candidate predictors using a 10-fold cross-validation with 50 repeats (Figure 2: Wilcoxon signed-rank test, $p$ = 0.08); however, here, we focus on CIT results for the interpretability of decision rules.

For illustration, at a revised PARS value of 6 (Table 3), the CIT model had a lower proportion of misclassified children than the logistic model at PARS cutoff of ≥6 when compared to physician diagnoses at 7 years (McNemar test: 4/15, $p$ = 0.625 versus 9/15, $p$ = 0.004). Table S4 summarizes the individual-level predictions across different logistic models (ie, linear, quartic PARS terms, and multivariable models). Table S4 and Table S5 show that at any given PARS value, different combinations of PARS predictors (Figure 3: terminal nodes) are associated with varying risk of asthma at 7 years. Overall, in the full study sample, the CIT model performed better than the logistic models at all revised PARS values except the tail values (0–3 and 11–12; Figure S1 [predicted probability] and Figure S2[ROC]).

Results from our GAM showed that the predictions corresponding to revised PARS values have a strong non-linear pattern (Figure S3 [logit]) and explained 12.4% of the deviance in predicted asthma ($\chi^2(8) = 32.14$, $p < 0.001$). Multivariable logistic models showed that the association between asthma and early persistent wheezing varied depending on city climate (ie, wheeze x climate interaction term; $p < 0.001$; Figure S4). In the warm climate city, the odds of a future asthma diagnosis were 8.45 times higher among children with early persistent wheezing than those without early persistent wheezing (aOR: 8.45, 95%CI: 2.74, 26.07). The strength of this association was lower among children in the cold climate city (aOR: 2.35, 95%CI: 1.13, 4.90).

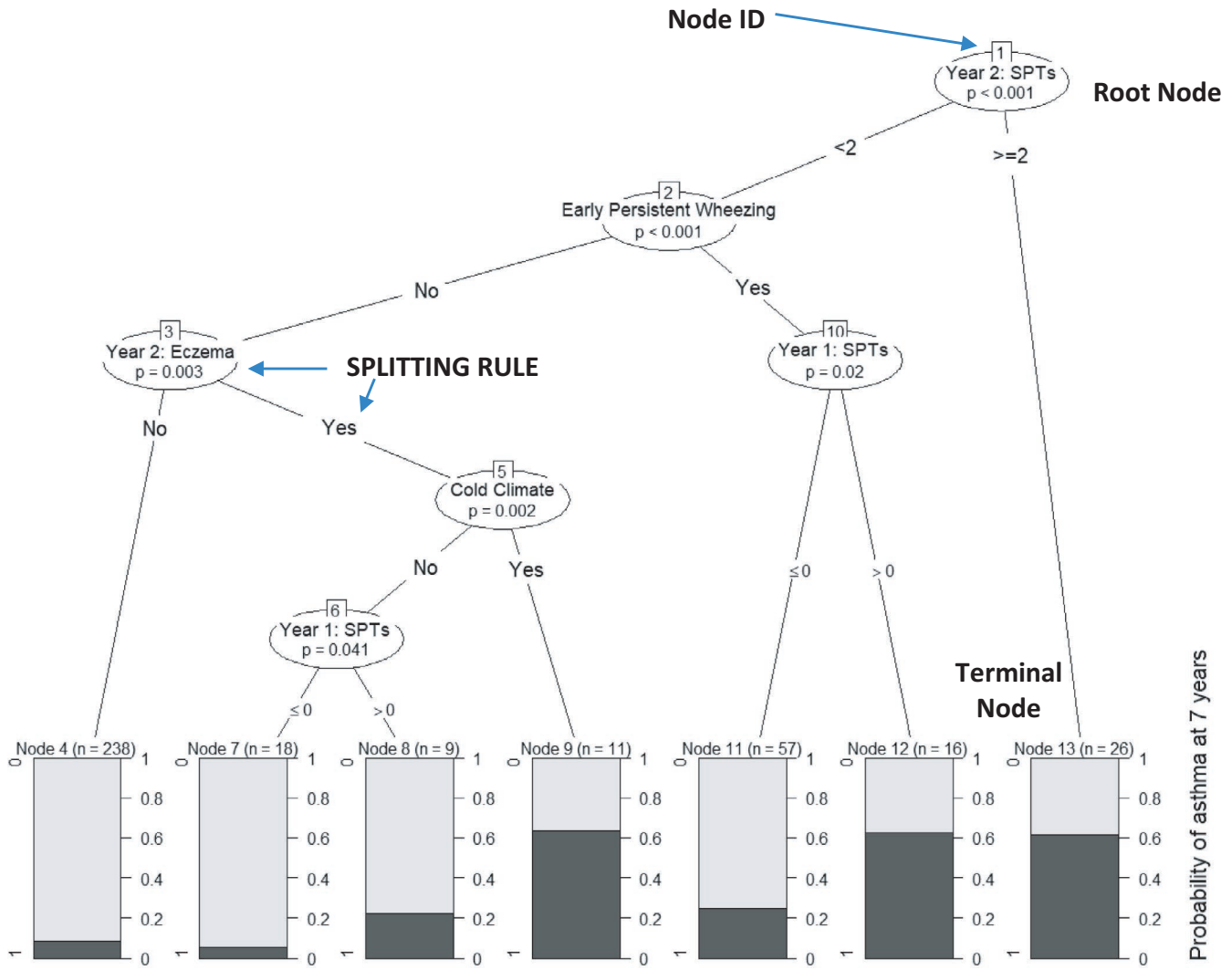


**FIGURE 3** Conditional inference decision tree showing the association between childhood asthma risk at 7 years and PARS-related clinical variables. The *p* values indicate the association between a given predictor and asthma risk. The 1st decision point (root node) shows that SPTs in the 2nd year is most strongly associated with asthma (*p* value <0.0001) and thus is selected as the first decision point. The black portion of the bars represents the probability of asthma at each terminal node (4, 7–13)

## 4 | DISCUSSION

Our findings show that CIT decision rules could be a useful childhood asthma prognostic tool with higher prognostic accuracy than logistic regression risk score–based approaches at the heart of existing tools (ie, API and PARS). CIT decision rules provide an alternative way to identify unique subgroups of at-risk children, and insights into associations and effect mechanisms that are suggestive of appropriate tailored preventive interventions. Although a modified version of the PARS can be generalizable outside the United States, its clinical utility is diminished by the non-linear relationship between PARS values and asthma risk in high-risk populations. In fact, at any given PARS value, different combinations of PARS-related clinical variables differentially predict asthma at 7 years.

This study builds on existing literature by identifying prognostic algorithms early in life that can be used to predict school-age asthma risk based on recommended methodologic standards for the development of prognostic tools.[20] Our study focused on PARS-related variables because they are noninvasive (ie, do not require invasive measures such as spirometry, blood draws), easily translatable to clinical practice (ie, use variables often assessed in routine allergy/asthma clinical workups), and have modest accuracy when used as a risk score to predict childhood asthma.[5] However, different from the CCAPPS study, we redefine wheezing as early persistent (ie, at least two reports of wheezing 8–12 months apart) and consider SPTs at the 1st and 2nd year to better capture time-varying risk constructs with potentially different implications for future risk of asthma. The utility of these considerations is highlighted in our decision rules that show time-dependent risk thresholds for developing asthma at

**TABLE 3** Predicted probability of asthma of children with a PARS of 6 but different combinations of PARS predictors derived from the logistic and CIT models using the CAPPS study data

| | PARS Predictors ≤2 years | | | | | | | Predicted probability | | Reference standard (physician diagnosis) |
|---|---|---|---|---|---|---|---|---|---|---|
| Child ID | P1 | P2 | P3 | P4 | P5 | P6 | EP | Logistic model Linear PARS | Conditional inference tree (CIT) | Asthma at 7 years |
| 1 | 0 | 0 | √ | √ | 0 | 0 | 0 | 0.21934 | *0.0840*[j] | Yes |
| 2 | 0 | 0 | √ | √ | 0 | 0 | √ | **0.21934**[f] | 0.2456 | No |
| 3 | 0 | 0 | √ | √ | 0 | 0 | √ | **0.21934**[f] | 0.2456 | No |
| 4 | √ | √ | 0 | 0 | 0 | √ | 0 | 0.21934 | 0.6153 | Yes |
| 5 | 0 | 0 | √ | √ | 0 | 0 | 0 | **0.21934**[f] | 0.0840 | No |
| 6 | 0 | 0 | √ | √ | 0 | 0 | 0 | **0.21934**[f] | 0.0840 | No |
| 7 | 0 | 0 | √ | √ | 0 | 0 | 0 | **0.21934**[f] | 0.0840 | No |
| 8 | 0 | 0 | √ | √ | 0 | 0 | 0 | **0.21934**[f] | 0.0840 | No |
| 9 | √ | √ | 0 | 0 | 0 | √ | 0 | 0.21934 | 0.6153 | Yes |
| 10 | √ | √ | 0 | 0 | 0 | √ | 0 | **0.21934**[f] | **0.6153**[f] | No |
| 11 | √ | √ | 0 | 0 | 0 | √ | 0 | **0.21934**[f] | **0.6153**[f] | No |
| 12 | √ | √ | 0 | 0 | 0 | √ | 0 | **0.21934**[f] | **0.6153**[f] | No |
| 13 | √ | √ | 0 | 0 | √ | 0 | 0 | 0.21934 | 0.6364 | Yes |
| 14 | √ | √ | 0 | 0 | √ | 0 | 0 | 0.21934 | 0.6364 | Yes |
| 15 | √ | √ | 0 | 0 | √ | 0 | 0 | 0.21934 | 0.6364 | Yes |

*Note:* √—yes; 0—no; **bold font probabilities**[f] represent false positives; *italicized font probabilities*[j] represent false negatives. Revised PARS logistic model: Logit($p_i$) = $\beta_0 + \beta_1$ (PARS). Based on revised PARS linear-term logistic model, all 15 children were predicted to develop asthma at 7 years based on the ≥6 cutoff but only 6 developed asthma at 7 years.

Abbreviations: EP, early persistent wheezing; P1, parental asthma; P2, eczema before age 3 years; P3, wheezing before 3 years (≠cold); P4, wheezing before 3 years; P5, cold climate (Winnipeg); P6, SPT positive to ≥2 allergens.

7 years that result in higher prognostic performance than the revised PARS logistic model. Also, the inclusion of an environmental marker such as cold climate addresses a key risk factor that was not examined in the CCAAPS PARS study.

Our decision rules reflect an analytical reasoning approach[21] that presents possible combinations of predictor variables along with quantified probabilities of asthma risk (at decision terminal nodes). Compared with PARS, our CIT decision rules provide a thorough heuristic to aid clinicians in predicting who is at risk of asthma in early childhood with good accuracy in a high-risk population. This is important because on the one hand, false-negative predictions could lead to delayed or non-intervention to prevent disease progression; and on the other hand, false-positive predictions could lead to initiation of inappropriate treatments. Decision trees have been used before to predict severity[22,23] and hospitalizations[24] associated with childhood asthma. Here, we present the first decision tree to predict asthma at 7 years using early childhood PARS-related clinical variables.

To date, there are no clinical trials that have demonstrated whether the use of API or PARS as a prognosis tool is better than considering the predictors or clinical variables that constitute these risk scores individually. Providing some insight to this gap in existing literature, our PARS predictor–specific analyses show that some predictors such as having ≥2 SPTs in the 2nd year of life and parental asthma have higher specificity and sensitivity, respectively, than the revised PARS at a ≥6 cutoff. Moreover, our variable importance results suggest that some predictors weight more than others; this is consistent with the rationale used in the development of scores for the PARS.[5] However, different from the original PARS, our CIT results suggest that repeated sampling of asthma predictors at discrete time points (eg, SPT results in 1st and 2nd years) and not just at one reference time point or period is critical to improving overall prognosis accuracy. Additionally, our decision rules provide statistically significant thresholds for number of SPTs (eg, in the 1st year>0) and highlight the potential for joint effects (eg, eczema and cold climate, early persistent wheezing, and positive SPTs in the 1st year of follow-up) with time-varying effects when discrete time points are sampled and used to inform prognosis. The fact that children defined by these two distinct combinations of predictors have relatively similar risk of asthma (ie, a probability of 62–64%) is consistent with the hypothesis of multiple pathways contributing to asthma development. It is also possible that these two distinct pathways may require different intervention strategies: For example, children with eczema who live in a city with cold climate might be effectively targeted by an approach that seeks to reduce risk associated with cold climate regions such as indoor air pollution, under the logic that due to their high propensity to develop asthma, indoor pollution–related triggers are more likely to increase asthma risk. Children who experience early persistent wheezing and are positive to at least one

SPT in the 1st year, on the other hand, might be more responsive to pharmacologic intervention aimed at managing wheeze symptoms. These findings support recent Global Initiative for Asthma (GINA) guidelines that recommend for personalized prognosis of childhood asthma that considers the entirety of a child's risk profile including the possibility of joint or time-varying risk effects.[25-27]

The generalizability of the logistic regression–based predictions by the revised PARS is demonstrated by comparable prognostic performance to the CCAPPS study[5]; however, this comes at a high cost reflected in the false-positive and false-negative proportions of 26% and 40%, respectively. Our results demonstrate that some of these errors in prognosis could be due to the non-linearity, and joint or time-varying effects of predictor variables on asthma risk that are not easily captured in the logistic regression models used to inform PARS predictions.

Some limitations of our study need to be considered though. These stem from the constraints on the generalizability of our results given the enrollment criteria for the CAPPS study, which only enrolled children with an immediate family history of asthma or two first-degree relatives with classical IgE-mediated allergy. Some important risk factors such as genetics, fraction of exhaled nitric oxide,[28] and other environmental exposures[11] that might improve prognostic accuracy were not examined. The replacement of African American race in the original PARS by a variable that captures geography/climate might limit the back-translation of our algorithms in US populations where race captures aspects of risk related to genetics and social-economic disadvantage. To address this limitation, future studies should examine the external validity of our algorithms and include cohorts with a more diverse spectrum of childhood asthma risk. We acknowledge that CIT modeling might require a larger sample size because a higher number of parameters are modeled compared with the multivariable logistic model (the basis of our sample size calculations); therefore, we evaluated the robustness of our findings using a 10-fold cross-validation (with 50 repeats) routine and a sensitivity analysis using a random forest predictive modeling approach. The next steps in evaluating our decision algorithms will require external validation, operationalization into a clinical decision support tool, and evaluation of such a tool's impact on actual clinical practice (ie, whether its application reduces unnecessary asthma-related treatment and/or risk of disease progression due to late or delayed intervention). It is important to note, however, that the infrequent assessment and documentation of asthma-related symptoms (eg, wheeze and SPTs history) in current clinical practice would represent a major barrier to the widespread use of such a decision support tool. However, as more pediatric clinics incorporate standardized clinical information capture using electronic medical records into their process flows, decision rule-based prognosis, such as the one described here, can be of great value.

In conclusion, conditional inference tree-based decision rules could be a useful childhood asthma prognostic tool, providing a way to identify unique subgroups of at-risk children, and insights into associations and effect mechanisms that are suggestive of appropriate target interventions. However, in its present form, our decision rule algorithm needs further development so that it can easily be integrated into existing electronic medical records as a clinical support decision tool. Additionally, the feasibility and effectiveness of such a tool in clinical practice is warranted.

## ACKNOWLEDGEMENTS

We thank the Canadian Asthma Primary Prevention Study families, Meghan B. Azad, study coordinators (Rishma Chooniedass, RN, BN, CAE, Department of Pediatrics and Child Health, University of Manitoba; Marilyn Lilley, RN, Department of Pediatrics and Child Health, University of Manitoba; and Roxanne Rousseau, BSc, CCRP, Department of Medicine, University of British Columbia), and the Canadian Asthma Primary Prevention Study research team, whose commitment and hard work have made this research possible.

## CONFLICT OF INTEREST

All authors declare they have no relevant conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Arthur H. Owora:** Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead). **Robert S. Tepper:** Conceptualization (supporting); Writing-review & editing (supporting). **Clare D. Ramsey:** Conceptualization (supporting); Writing-review & editing (supporting). **Allan B. Becker:** Conceptualization (equal); Writing-review & editing (supporting).

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13530.

## ORCID

*Arthur H. Owora* https://orcid.org/0000-0002-4580-7428

## REFERENCES

1. Kothalawala DM, Kadalayil L, Weiss VBN, et al. Prediction models for childhood asthma: a systematic review. *Pediatr Allergy Immunol*. 2020;31(6):616-627.
2. Owora AH, Zhang Y. Comments on Kothalawala et al. *Pediatr Allergy Immunol*. 2021;32(2):389-392.
3. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ*. 2009;181(9):E181-E190.
4. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000;162(4 Pt 1):1403-1406.
5. Biagini Myers JM, Schauberger E, He H, et al. A pediatric asthma risk score to better predict asthma development in young children. *J Allergy Clin Immunol*. 2019;143(5):1803-1810.e1802.
6. Owora AH, Zhang Y. Childhood wheeze trajectory-specific risk factors: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2021;32(1):34-50.
7. Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. *Arch Pediatr Adolesc Med*. 2000;154(7):657-663.

8. ISAAC. *ISAAC Coordinating Committee. Manual for the International Study of Asthma and Allergies in Childhood (ISAAC)*. Bochum and Aukland: ISAAC Coordinating Committee; 1992.
9. Owora AH, Becker AB, Chan-Yeung M, et al. Wheeze trajectories are modifiable through early-life intervention and predict asthma in adolescence. *Pediatr Allergy Immunol*. 2018;29(6):612-621.
10. Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol*. 2004;113(4):650-656.
11. Dick S, Friend A, Dynes K, et al. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. *BMJ open*. 2014;4(11):e006554.
12. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*. 2020;368:m441.
13. Jiménez-Valverde A, Lobo JM. Threshold criteria for conversion of probability of species presence to either–or presence–absence. *Acta Oecologica*. 2007;31(3):361-369.
14. Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. *J Comput Graph Stat*. 2006;15(3):651-674.
15. James G, Witten D, Hastie T, Tibshirani R. *An Introduction to Statistical Learning: With Applications in R*. New York, NY: Springer; 2013.
16. Tin KH. The random subspace method for constructing decision forests. *IEEE Trans Pattern Anal Mach Intell*. 1998;20(8):832-844.
17. Hothorn T, Zeileis A. Partykit: a modular toolkit for recursive partytioning in R. *J Mach Learn Res*. 2015;16(1):3905-3909.
18. Breiman L. Random Forests. *Mach Learn*. 2001;45(1):5-32.
19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.
20. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for Individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *J Clin Epidemiol*. 2015;68(2):134-143.
21. Pelaccia T, Tardif J, Triby E, Charlin B. An analysis of clinical reasoning through a recent and comprehensive approach: the dual-process theory. *Med Educ Online*. 2011;16(1):5890.
22. Farion KJ, Wilk S, Michalowski W, O'Sullivan D, Sayyad-Shirabad J. Comparing predictions made by a prediction model, clinical score, and physicians: pediatric asthma exacerbations in the emergency department. *Appl Clin Inform*. 2013;4(3):376-391.
23. Farion K, Michalowski W, Wilk S, O'Sullivan D, Matwin S. A tree-based decision model to support prediction of the severity of asthma exacerbations in children. *J Med Syst*. 2010;34(4):551-562.
24. Alnaji F, Zemek R, Barrowman N, Plint A. PRAM score as predictor of pediatric asthma hospitalization. *Acad Emerg Med*. 2014;21(8):872-878.
25. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1):143.
26. GINA Report. Global strategy of asthma management and prevention. 2020. https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf
27. Niespodziana K, Borochova K, Pazderova P, et al. Toward personalization of asthma treatment according to trigger factors. *J Allergy Clin Immunol*. 2020;145(6):1529-1534.
28. Balinotti JE, Colom A, Kofman C, Teper A. Association between the asthma predictive index and levels of exhaled nitric oxide in infants and toddlers with recurrent wheezing. *Arch Argent Pediatr*. 2013;111(3):191-195.

## SUPPORTING INFORMATION

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

**How to cite this article:** Owora AH, Tepper RS, Ramsey CD, Becker AB. Decision tree-based rules outperform risk scores for childhood asthma prognosis. *Pediatr Allergy Immunol*. 2021;32:1464–1473. https://doi.org/10.1111/pai.13530