Journal of *Personalized Medicine*

MDPI

Review

Prediction of Asthma Exacerbations in Children

Evangelia Sarikloglou [1], Sotirios Fouzas [2] and Emmanouil Paraskakis [3,*]

[1] Medical School, Democritus University of Thrace, 68100 Alexandroupolis, Greece; evsarikloglou@gmail.com
[2] Department of Pediatrics, University of Patras Medical School, 26504 Patras, Greece; sfouzas@upatras.gr
[3] Paediatric Respiratory Unit, Paediatric Department, University of Crete, 71500 Heraklion, Greece
* Correspondence: eparaska@uoc.gr

Abstract: Asthma exacerbations are common in asthmatic children, even among those with good disease control. Asthma attacks result in the children and their parents missing school and work days; limit the patient's social and physical activities; and lead to emergency department visits, hospital admissions, or even fatal events. Thus, the prompt identification of asthmatic children at risk for exacerbation is crucial, as it may allow for proactive measures that could prevent these episodes. Children prone to asthma exacerbation are a heterogeneous group; various demographic factors such as younger age, ethnic group, low family income, clinical parameters (history of an exacerbation in the past 12 months, poor asthma control, poor adherence to treatment, comorbidities), Th2 inflammation, and environmental exposures (pollutants, stress, viral and bacterial pathogens) determine the risk of a future exacerbation and should be carefully considered. This paper aims to review the existing evidence regarding the predictors of asthma exacerbations in children and offer practical monitoring guidance for promptly recognizing patients at risk.

Keywords: asthma attack; asthma exacerbation; children; biomarkers

Citation: Sarikloglou, E.; Fouzas, S.; Paraskakis, E. Prediction of Asthma Exacerbations in Children. *J. Pers. Med.* **2024**, *14*, 20. https://doi.org/10.3390/jpm14010020

Academic Editors: Giovanni Paoletti and Enrico Marco Heffler

Received: 26 November 2023
Revised: 17 December 2023
Accepted: 20 December 2023
Published: 22 December 2023

1. Introduction

Asthma is the most common chronic disorder of childhood and represents a significant health burden. The disease is characterized by chronic airway inflammation and acute episodes (exacerbations) of reversible airway obstruction with respiratory symptoms, such as wheezing, dyspnea, chest tightness, and coughing. Currently, asthma monitoring relies solely on the regular assessment of respiratory symptoms and lung function. However, the lack of a direct measurement of inflammation may result in the inappropriate recognition of children at risk for a future asthma attack [1–4].

Asthma exacerbations are not rare in asthmatic children, even among those with apparently reasonable disease control. Asthma attacks result in the children and their parents missing school and work days; limit the patient's social and physical activities; and lead to emergency department visits, hospital admissions, or even fatal events [5–12]. Thus, the prompt identification of asthmatic children at risk for exacerbation is crucial, as it may allow for proactive measures that could prevent these episodes [13]. Current asthma treatment strategies have generally succeeded in controlling daily symptoms and provide to asthmatic children a good quality of life [8]. Nevertheless, it is estimated that in the United States, half of the children with asthma will experience at least one exacerbation per year, while in Europe, more than one in three will have an unplanned hospital visit due to an asthma attack [14].

Of note, children prone to asthma exacerbation are a heterogeneous group [15]; various demographic factors such as younger age, ethnic group, low family income, clinical parameters (history of an exacerbation in the past 12 months, poor asthma control, poor adherence to treatment, comorbidities), Th2-type of inflammation, and environmental exposures (pollutants, stress, viral and bacterial pathogens) determine the risk of a future exacerbation and should be carefully considered [7,16–19].

This paper aims to review the existing evidence regarding the predictors of asthma exacerbations in children and offer practical monitoring guidance for promptly recognizing patients at risk.

2. Level of Asthma Control

Poor asthma control is a standard risk indicator for asthma exacerbation [12,20–23]. For example, children with partially controlled asthma have a 2-fold increase in the exacerbation rates, as compared to those with controlled disease [23]. However, symptom-based tools used to assess asthma control, such as the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ), cannot offer precise predictions on the time of exacerbation. In the study by Schatz et al., a lower ACT score was associated with an increased risk of emergency department visits and oral corticosteroid and beta-agonist use in the following 12 months [22,24]. Conversely, in another study by Meltzer et al., each 1-point increase in the ACQ score was associated with a 50% increase in exacerbation risk for the following two weeks [25]. On the other hand, other studies have demonstrated that asthma exacerbations can also occur in the context of reasonable asthma control [10,11,26]. These reports have questioned the predictive utility of ACT and ACQ scores, demonstrating that they are not superior to the frequency of rescue inhaler use alone [10,11,26]. In a 4-year study by Wu et al., 14% of the participants never reported troublesome asthma symptoms, although they had presented at least one severe exacerbation [12]. In another study of 612 asthmatic children, 54% of those who reported good asthma control had abnormal spirometry and or raised fractional exhaled nitric oxide (FeNO) [27]. Clearly, the factors that are associated with poor asthma control are not the same as those associated with asthma exacerbations. Moreover, the loss of disease control may be hard to identify by the patients and their parents [28,29]. Socioeconomic status also plays a crucial role in the way patients perceive and report their symptoms; in a cross-sectional study (N = 307) by Ganti et al., there was a significant positive correlation ($p < 0.001$) between the ACT score and the education and socioeconomic status of the family [30]. Nevertheless, it is generally accepted that ACT and ACQ scores can be used as part of the routine evaluation of asthmatic children and for assessing the risk of future exacerbations [31]. The combination of asthma symptom scores and medication scores could improve our ability to identify children at risk of an asthma attack in the future.

Several studies have shown that an asthma attack is by itself a strong predictor of an exacerbation of the disease in the future. The use of oral corticosteroids and emergency department visits or hospitalizations for symptoms related to asthma in the previous 12 months are strong and independent predictors of a future attack [9,12,18,23,32–38]. A study by Engelkes et al. demonstrated that patients with an asthma exacerbation have a 25% possibility of repeating the episode within the following year [32]. In a recent systematic review, Lowden et al. confirmed that a past exacerbation is the best predictor of a future exacerbation, regardless of the severity of the disease and the level of control [38]. The number of previous exacerbations is also important [17,37]; in the metropolitan area of St. Louis, the probability of hospital readmission for an asthma exacerbation over ten years increased by 30% after the first admission, 46% after a second admission, and 59% after a third admission [17]. On the other hand, Lowden et al. concluded that the severity of an asthma exacerbation does not necessarily relate to the severity of the previous exacerbations [38]. In any case, the asthma management plan for a given patient should be carefully reviewed when an exacerbation occurs. Various factors, such as female sex, higher FeNO levels, and escalating treatment, are associated with a higher exacerbation risk and, thus, may highlight the need for a more frequent follow-up [39].

3. Lung Function Testing

Spirometry is widely used for assessing the lung function of asthmatic patients. However, the test is notoriously unable to detect abnormalities at the level of small airways, as in the case of asthmatic children, where small airways are affected early in the course of

the disease [40]. Thus, the existing evidence on the usefulness of spirometry in detecting children at increased risk for asthma exacerbations is conflicting [11,33,41,42]. In a retrospective study of 13,842 children (100,292 observations) seen annually over 15 years, a strong association was noted between FEV1% predicted and risk of asthma exacerbation in the subsequent year [41]. Repeated measurements of FEV1, even if they are within the normal range, could add to the clinical risk assessment; a 10% reduction in FEV1% predicted within three months is associated with 28% increased odds for an asthma exacerbation [43]. Reversibility to bronchodilators may reveal specific obstruction phenotypes, also related to the risk of an asthma attack [44]. In other studies, mid-expiratory flows presented a good predictive value for a future exacerbation, even when the baseline FEV1 was normal [45,46].

Specific peak expiratory flow (PEF) patterns may also be related to loss of asthma control and risk of exacerbation [47]. Wide diurnal PEF variations signify loss of disease control, while a steep PEF decline without changes in variability is observed during exacerbations. Studies using complex statistical methods have suggested that PEF variability could help predict future asthma attacks in adults [48], but similar data in children are lacking. In a study by Kim et al., PEF was lower in asthmatic children in autumn than in winter, suggesting that seasonal variations should also be considered [49].

4. Adherence to Treatment

Poor adherence to treatment, including improper inhaled medication and/or breathing chamber use techniques, is associated with an increased risk of exacerbations, hospital admissions, and asthma-related deaths [50–52]. Children with asthma who have regular follow-up visits present a reduced risk of asthma attacks, while inadequate follow-up adherence relates to increased morbidity and more frequent exacerbations [53]. Additionally, incorporating patient preferences into treatment decisions (e.g., type of inhaler device, medication dosage) seems to result in longer exacerbation-free periods, especially for children with poor asthma control [54,55]. Interestingly, a recent study showed that during the COVID-19 pandemic, asthma exacerbations were reduced due to decreased exposure to environmental triggers and increased patient adherence [56]. It should be mentioned, however, that other studies failed to confirm a significant impact of adherence to treatment on impending asthma exacerbation in children [57,58].

5. Other Patient-Related Factors

A study conducted in the United States showed that race and ethnicity play an important role in adverse asthma outcomes since non-Hispanic black children had a greater risk for emergency department visits and deaths due to asthma compared to their non-Hispanic white counterparts [59,60]. Others have shown that Asian ethnicity is associated with a lower likelihood of future asthma attacks [61], while African American race and low socioeconomic status may increase the risk of asthma exacerbations [62,63]. However, further studies are required to explore the exact role of the genetic background in such populations [64]. Various socioeconomic factors determining the ease of accessing healthcare resources may contribute equally to an increased risk of asthma exacerbations [8,65,66]. Moreover, all these factors may vary and, thus, play different roles according to the child's age [13].

Overweight or obesity reduces the response to inhaled corticosteroids and predisposes one to asthma attacks. The role of chronic stress and anxiety is more complex and poorly understood, although an increased Th2 cytokine response has been reported [67,68]. In addition, chronic stress may lead asthmatic patients to poor adherence [69–74]. Interestingly, maternal depression is also associated with an increased risk of asthma exacerbation in children [75].

6. Salbutamol Overuse

A higher number of days of salbutamol use (>two days in two weeks) and a higher number of salbutamol doses per day are strong and independent predictors of severe

asthma exacerbation in the future [76]. Short-acting beta-agonist (SABA) overuse has also been associated with an increased risk of death due to asthma [77]. Patients who have learned to "control" their disease only by SABAs need special attention because SABA overuse seems to increase bronchial hyperreactivity and induce pro-inflammatory pathways [76,78,79]. In this regard, the monitoring of SABA use could offer better disease control and prevent future exacerbations. In a study from Sweden, one-third of asthmatic patients (12–45 years old) used three or more SABA canisters per year, while the risk of asthma exacerbation was directly related to the amount of SABA used [80]. In another study, Frey et al. have suggested that the frequent administration of SABAs (>4 times per day) may increase the risk of asthma attacks due to the loss of beta-agonist effectiveness. The prescription of more than three SABA canisters per year should alert healthcare professionals to the risk of an imminent asthma exacerbation [48,77].

Long-acting beta-agonists (LABAs) are more effective in stabilizing airway tone in the long term [48]. However, LABA monotherapy may also be associated with severe asthma exacerbations and asthma-related death, especially in younger children [81]. Nevertheless, the concurrent administration of LABAs with inhaled corticosteroids (ICSs), usually as a fixed LABA-ICS combination, has been associated with the reduced rate and severity of exacerbations and better clinical outcomes than using ICSs alone [81].

7. Biomarkers

Airway inflammation biomarkers are constantly evaluated concerning their ability to identify Th2 inflammation. The essential role of the Th2 type of inflammation in asthma exacerbation emerges from clinical trials of "biological" agents, such as IgE, IL-4, IL-5, and IL-13 inhibitors [82]. The administration of these novel drugs has consistently been associated with a significant reduction in asthma exacerbations, thus highlighting the pivotal role of Th2 inflammation in the susceptibility to asthma attacks [82]. Novel technologies that can be applied to multiple biological samples, such as metabolomics, proteomics, transcriptomics, and genomics, hold particular promise for identifying patients with poor disease control and are at risk for asthma exacerbations [82,83]. Among these techniques, "breathomics" is of particular interest due to its non-invasive nature that offers the possibility of frequent and repeated sampling.

Evidence on the utility of FeNO as a predictor of asthma exacerbations in children and adolescents remains conflicting. FeNO, alone or in combination with other biomarkers, is an essential tool for monitoring adherence and response to treatment [84–86]. In a recent observational study, Lo et al. correlated FeNO measurements with future asthma exacerbations and showed that higher FeNO levels could predict future asthma attacks [61]. A FeNO of $\geq$80 ppb has been proven useful in identifying poorly controlled asthma in children [87]. In a small study of adults, those who experienced an asthma exacerbation had significantly higher FeNO levels within two weeks before the event [88]. Moreover, the investigators showed that FeNO was the only significant and independent predictor of exacerbations compared to spirometric indices, quality of life scores, and medication usage [88]. On the other hand, similar studies in asthmatic children found that a single FeNO measurement is not useful in assessing the risk of an upcoming exacerbation [89,90]. In the Reducing Asthma Attacks in Children using Exhaled Nitric Oxide trial, a combined approach based on symptom-guided asthma treatment and FeNO levels did not reduce the asthma attacks [91,92]. Even FeNO measurements two weeks before an exacerbation in children with severe asthma may have poor positive predictive value [93]. In another cohort study from Ecuador, 283 children with asthma were followed for six months or until their next asthma attack; a previous severe exacerbation was the most reliable predictor of a future asthma attack, while the predictive ability of FeNO measurements was limited [94]. FeNO levels in children aged 0–4 years correlate well with the Asthma Predictive Index but cannot reliably predict a future asthma diagnosis or disease exacerbations [95]. A recent study confirmed the low predictive value of FeNO measurements even when combined with clinical characteristics [96], while Fielding et al. demonstrated that a significant

increase in FeNO levels between subsequent visits was associated with poor asthma outcomes but not a higher exacerbation risk [43]. On the other hand, two recent meta-analyses concluded that when FeNO is used to guide asthma management strategies, the frequency of asthma exacerbations can be reduced [97,98]. The significant intrasubject variability in FeNO values in children may have accounted for the above controversial findings [99].

FeNO partitioning, i.e., the measurement of FeNO at multiple exhalation flow rates, offers valuable information on the NO concentration in the most distal airways, the so-called alveolar NO (CalvNO) [100]. A recent study from our group explored the role of CalvNO as a predictor for asthma exacerbations in 68 asthmatic children [101]. We found that CalvNO levels > 7 ppb could predict asthma exacerbations in the subsequent four months with 90.9% specificity, while a CalvNO of <4 ppb could exclude a future exacerbation with 71.4% sensitivity. Moreover, an increase in CalvNO by 0.5 ppb between subsequent visits could predict future exacerbations with 92% sensitivity and 92% specificity, while the performance of ACT scores and spirometric indices (including reversibility testing) was significantly lower [101]. Therefore, distal inflammation plays a pivotal role in asthma exacerbations in children and should be further considered in future studies [101].

Sputum eosinophils is a cost-effective biomarker for assessing disease control in asthmatic patients [102]. However, sputum collection may be challenging in young and uncooperative children, while sputum eosinophils do not seem reliable in predicting future asthma attacks [90,93,103]. Novel saliva biomarkers, such as eotaxin, IL-5, and IL-8, are easier to collect and have shown a strong correlation with the level of asthma control [104], but their role is still to be determined.

Measurements of volatile organic compounds (VOCs) in the exhaled breath seems also promising, as specific VOC patterns are closely related to disease exacerbations in asthmatic children [105–107].

Generally, blood eosinophil counts (EOSs) of >300 cells/μL have been related to troublesome asthma in adults. In the Severe Asthma Research Program, EOSs > 400 cells/mL were associated with an increased risk of exacerbation [108,109]. However, in asthmatic children, the evidence is conflicting [110–112]. EOSs, combined with FeNO, have been used as markers of the Th2 inflammation pathway to predict the response to treatment in asthmatic children, with reasonable results [113–115].

Serum IL-6 was also associated with the risk of asthma exacerbation in children, but further studies are required [116]. Plasma eosinophilic cationic protein (ECP) concentration is a useful marker of Th2 inflammation and may help identify children at risk for recurrent asthma attacks who could benefit from corticosteroid treatment [117]. Other biomarkers of atopy, such as skin prick or specific IgE testing for sensitization to aeroallergens and total serum IgE, have been utilized to assess the risk of seasonal exacerbations [118]. Mucosa-associated lymphoid tissue translocation protein 1 (MALT1) is another novel biomarker [119].

Urinary leukotriene E4 (ULTE4) levels reflect systemic cysteinyl leukotriene production [120,121], and, when elevated, may predict asthma exacerbations in children exposed to tobacco smoke [122]. Also, urinary phthalate metabolites and urinary organic acids seem to be significantly associated with imminent asthma attacks [123,124]. More inflammatory mediators, including cytokines, chemokines, IL-5, and acidity levels, can be measured in the exhaled breath condensate and serve as metabolomic biomarkers of asthma exacerbation in the future [36,96].

Studies based on genome-wide association have revealed the existence of susceptibility variants that are specifically related to exacerbations and differ from those generally related to asthma. A cadherin-related family member gene variant (CDHR-3) has been linked to recurrent severe asthma exacerbations in preschool children of European descent [125], while the 17q21 locus and the ADRB2 gene (especially its Glu27 variant) are consistently associated with asthma attacks in asthmatic children and adults [5,126]. A recent meta-analysis demonstrated a significant association between a single-nucleotide polymorphism

in FLJ22447 (rs2253681) and severe asthma exacerbations [127]. Furthermore, three microRNA models (miR-146b, miR-206, and miR-720) that could predict exacerbations in asthmatic patients receiving inhaled corticosteroids have been detected [128]. Reduced responsiveness to SABAs, especially in those using long-acting beta-agonists (LABAs), has been associated with polymorphisms in the beta-2 adrenoceptor gene [129]. Finally, nasal airway transcriptomic analysis demonstrated that higher baseline Th2/Th1-interferon ratios can predict asthma attacks [130]. Future studies should explore the full spectrum of such genetic variabilities, with larger sample sizes, better representation of racial/ethnic diversity, and a more precise definition of asthma exacerbation.

8. Environmental Exposures

Environmental exposures, including aeroallergens, viral and bacterial pathogens, environmental pollutants, and stress, largely drive asthma exacerbations [131]. Atopic individuals, in particular, have the most significant risk when they are exposed to the aeroallergen to which they are sensitized [132]. The association between viral respiratory tract infection and asthma exacerbations is well established in childhood [133]. For example, in a study by Murray et al., this association tremendously increased the likelihood of an asthma exacerbation [134–136]. Such patients remain vulnerable to asthma attacks during respiratory infections even if the level of disease control is good [47]. Human rhinovirus (HRV) infection seems to be the most significant trigger of asthma exacerbations in children, and as such, it might be used as a "biomarker" for imminent asthma attacks. A study from Germany before the COVID-19 pandemic demonstrated that 41% of the children who experienced an exacerbation had a positive test result for HRV, while 14% were positive for the respiratory syncytial virus (RSV) [137,138]. Interestingly, HRV was particularly prevalent among asthmatic and atopic patients (56% and 66%, respectively) [137,138]. Respiratory microbiota and specific bacteria–host interactions may also determine the risk of asthma exacerbations. Several Moraxella and Haemophilus members may enrich viral respiratory illnesses during the fall season, leading to subsequent exacerbations [139]. These episodes seem to have a regular peak after returning to school from their summer holidays, i.e., in September for the Northern hemisphere and in January for the Southern [135,140–142].

Asthma exacerbations also present a second peak around the end of the hay fever season [143]. A 10-year-long study from Italy demonstrated that asthma exacerbations had seasonal peaks during autumn and spring. Pollens; wind speed; rainfall; and SO_2, NO, O_3, and NO_2 levels were strongly associated with asthma exacerbations in those children [144–146]. Meteorological factors are important modulators in asthmatic children and adults [147,148]. During the COVID-19 pandemic, the most important factors that reduced asthma attacks were the decreased exposure to environmental triggers (e.g., the time spent at home) and the increased adherence to treatment [56,149]. Thus, identifying environmental factors associated with asthma exacerbations could lead to prompt pharmacological interventions [143,150] and offer the possibility of reducing exposure to specific triggers [151,152].

Air pollution is another crucial risk factor for children living in urban areas [153–159]. In the study by Zhang et al., who examined 17,227 pediatric asthma admissions during the 2015–2016 period in Chinese urban areas, a strong relationship emerged between hospital visits and nitrogen dioxide (NO_2) ozone (O_3), and particulate matter of at least 2.5 mm ($PM_{2.5}$) levels [160]. A similar study, also from China, confirmed that $PM_{2.5}$, sulfur dioxide (SO_2), and NO_2 atmospheric concentrations were significantly associated with asthma attacks [161]. The effects of SO_2 were more potent in the cold season and those of NO_2 during the warm months, while preschool children were more susceptible to increased SO_2 levels [161]. In the same line, a relevant meta-analysis concluded that NO_2, SO_2, and $PM_{2.5}$ levels predispose to future asthma attacks in both children and adults [162]. Interestingly, even short-term exposure to high concentrations of air pollutants may significantly increase the risk of asthma exacerbations [163]. Short-term exposure is associated with reduced interferon beta (IFN-b) expression in the airway epithelium, facilitating viral

replication [164–166]. Tobacco smoke exposure, either first- or second-hand, has similar effects and may also trigger severe exacerbations [167]. In a prospective study of asthmatic Thai children, daily $PM_{2.5}$ exposure to levels above 12 mcg/m^3 was associated with asthma exacerbation within the next three days [168]. Accumulating evidence suggests that long-term exposure to air pollution, especially traffic-related air pollution (TRAP), can contribute to new-onset asthma in children and adults [169–171]. Four main mechanisms have been described: oxidative stress damage, airway remodeling, the activation of inflammatory pathways and immunological responses, and the enhancement of respiratory sensitization to aeroallergens [171].

Improving the air quality to prevent future asthma exacerbations and new cases of asthma in children would require solid governmental efforts. Until then, the continuous monitoring and online availability of air pollutant concentration and relevant meteorological data should be considered [172–174]. Informatics and wearable sensor technologies may further assist in collecting biometric data to understand pediatric asthma triggers and design appropriate and personalized monitoring and prevention strategies [163,175].

9. Risk Scores

Admittedly, a single marker for assessing the risk of asthma exacerbations is challenging to identify. Thus, current research focuses on combining risk factors into composite scores using advanced analytic methods, such as machine learning, to improve the risk stratification and recognition of the most vulnerable children [176,177]. These approaches are based on the systematic monitoring of known clinical and lung function exacerbation predictors, also offering the possibility of including widely available biomarkers (e.g., EOS, FeNO) or even air pollutant concentrations and relevant meteorological data [177].

A multidisciplinary, multi-factorial, and personalized approach is mandatory when managing pediatric asthma [13,178,179]. Current guidelines focus on the stepwise escalation/de-escalation of drug therapy to achieve improved control and reduce the risk of exacerbations. Therefore, the prompt identification of symptoms and the longitudinal monitoring of physiologic parameters (including lung function) are important. Huffaker et al. applied the passive nocturnal monitoring of heart rate, respiratory rate, and body movements by using a contactless bed sensor in a small cohort of asthmatic children (n = 16). Asthma symptoms and ACT scores were reported every two weeks. The investigators reported that nocturnal physiologic changes correlated well with asthma symptoms, suggesting that nocturnal physiologic monitoring could represent an objective tool for assessing disease control and predicting asthma exacerbations [180]. In a big cohort of 28,196 patients, Hatoun et al. recognized ten potential predictors that were subsequently included in an asthma exacerbation risk (AER) score [181]. The AER score is calculated monthly by healthcare professionals to identify children at risk for asthma exacerbation within the following year [181]. Another score, the test for respiratory and asthma control in kids (TRACK), has been designed to apply in preschoolers with acute wheezing episodes within the first five days of the event [182]. It has been reported that TRACK predicts a subsequent severe exacerbation (emergency department visit and/or need of systemic corticosteroids) within the next three months; for each 10-unit decrease in TRACK, the probability of a future exacerbation increases by 38% [182].

An advanced monitoring tool, the myAirCoach system, which includes an inhaler adapter, an indoor air-quality monitor, a physical activity tracker, a portable spirometer, a personal FeNO device, and a dedicated smartphone app, has been shown to improve asthma control and the quality of life of asthmatic patients [183,184]. The Biomedical Real-Time Health Evaluation (BREATH) platform is a similar tool that focuses on pediatric patients [185]. Although much work remains to be carried out about measurement collection and standardization, analyzing these data series using machine learning algorithms holds promise for developing reliable personalized predictive tools [186–189].

10. Conclusions

Pediatric asthma is a multifactorial, complex, and dynamic disease, and as such, it cannot be monitored using classical clinical tools or simple biomarkers. The ideal method for predicting the loss of disease control and imminent asthma exacerbations should be based on the combination of patient data (e.g., demographics, symptom-based scores, etc.), lung function measurements, various Th2 inflammation biomarkers (e.g., EOS, FeNO, "omics", etc.), and environmental exposures (e.g., aeroallergen and air pollutant concentrations, meteorological data, etc.). Machine or deep learning techniques should be used to analyze these big-data series further and ensure reliable and personalized predictions in the context of different disease subtypes. The above approach is summarized in Figure 1. Standardizing the criteria to diagnose asthma exacerbation is equally critical; both loose and stringent definitions of asthma attacks may lead to false associations, thus impeding the generalizability of the prediction models. Finally, an important future aim should be establishing an international pediatric exacerbation network that would significantly facilitate data collection and comparison, as well as assessing innovative technologies and applying relevant predictive strategies in clinical practice.

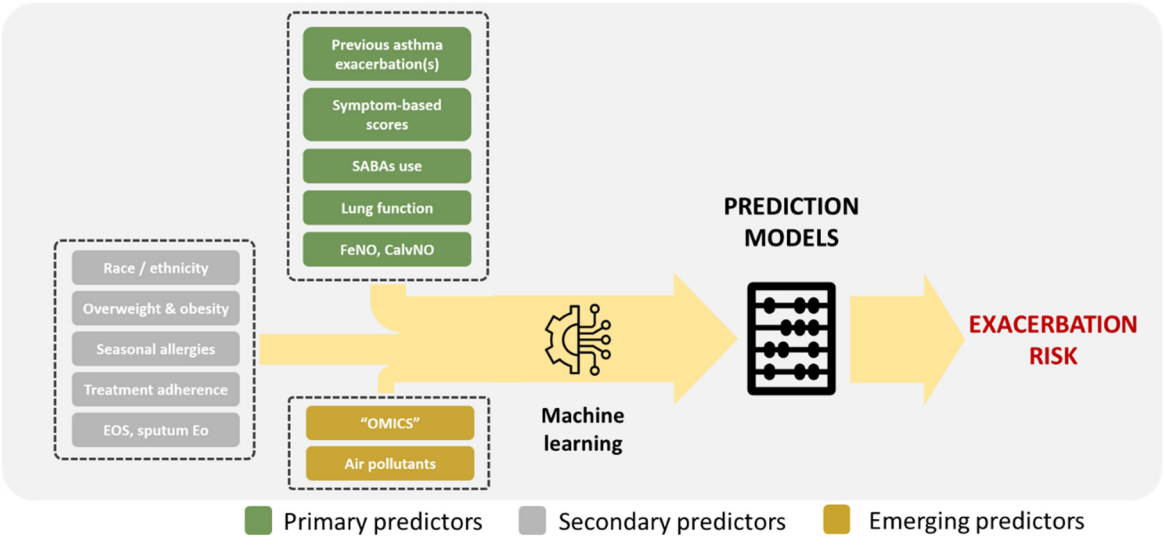

Figure 1. General approach for the prediction of asthma exacerbations in children.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Simoneau, T.; Cloutier, M.M. Controversies in Pediatric Asthma. *Pediatr. Ann.* **2019**, *48*, e128–e134. [CrossRef] [PubMed]
2. Masoli, M.; Fabian, D.; Holt, S.; Beasley, R.; Global Initiative for Asthma, P. The global burden of asthma: Executive summary of the GINA Dissemination Committee report. *Allergy* **2004**, *59*, 469–478. [CrossRef] [PubMed]
3. Plaza, V.; Serrano, J.; Picado, C.; Sanchis, J. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. *Eur. Respir. J.* **2002**, *19*, 846–852. [CrossRef] [PubMed]
4. Zhang, J.; Yu, C.; Holgate, S.T.; Reiss, T.F. Variability and lack of predictive ability of asthma end-points in clinical trials. *Eur. Respir. J.* **2002**, *20*, 1102–1109. [CrossRef] [PubMed]
5. Herrera-Luis, E.; Hernandez-Pacheco, N.; Vijverberg, S.J.; Flores, C.; Pino-Yanes, M. Role of genomics in asthma exacerbations. *Curr. Opin. Pulm. Med.* **2019**, *25*, 101–112. [CrossRef]
6. Pardue Jones, B.; Fleming, G.M.; Otillio, J.K.; Asokan, I.; Arnold, D.H. Pediatric acute asthma exacerbations: Evaluation and management from emergency department to intensive care unit. *J. Asthma* **2016**, *53*, 607–617. [CrossRef]

7. Denlinger, L.C.; Heymann, P.; Lutter, R.; Gern, J.E. Exacerbation-Prone Asthma. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 474–482. [CrossRef]
8. Moral, L.; Asensi Monzo, M.; Julia Benito, J.C.; Ortega Casanueva, C.; Paniagua Calzon, N.M.; Perez Garcia, M.I.; Rodriguez Fernandez-Oliva, C.R.; Sanz Ortega, J.; Valdesoiro Navarrete, L.; Valverde-Molina, J. Pediatric asthma: The REGAP consensus. *An. Pediatr. (Engl. Ed.)* **2021**, *95*, 125.e1–125.e11. [CrossRef]
9. Lieu, T.A.; Quesenberry, C.P.; Sorel, M.E.; Mendoza, G.R.; Leong, A.B. Computer-based models to identify high-risk children with asthma. *Am. J. Respir. Crit. Care Med.* **1998**, *157*, 1173–1180. [CrossRef]
10. Reddel, H.K.; Busse, W.W.; Pedersen, S.; Tan, W.C.; Chen, Y.Z.; Jorup, C.; Lythgoe, D.; O'Byrne, P.M. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: A post-hoc efficacy analysis of the START study. *Lancet* **2017**, *389*, 157–166. [CrossRef]
11. Romagnoli, M.; Caramori, G.; Braccioni, F.; Ravenna, F.; Barreiro, E.; Siafakas, N.M.; Vignola, A.M.; Chanez, P.; Fabbri, L.M.; Papi, A.; et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. *Clin. Exp. Allergy* **2007**, *37*, 552–557. [CrossRef] [PubMed]
12. Wu, A.C.; Tantisira, K.; Li, L.; Schuemann, B.; Weiss, S.T.; Fuhlbrigge, A.L. Predictors of symptoms are different from predictors of severe exacerbations from asthma in children. *Chest* **2011**, *140*, 100–107. [CrossRef] [PubMed]
13. Niu, C.; Xu, Y.; Schuler, C.L.; Gu, L.; Arora, K.; Huang, Y.; Naren, A.P.; Durrani, S.R.; Hossain, M.M.; Guilbert, T.W. Evaluation of Risk Scores to Predict Pediatric Severe Asthma Exacerbations. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 4393–4401.e8. [CrossRef] [PubMed]
14. Fleming, L. Asthma exacerbation prediction: Recent insights. *Curr. Opin. Allergy Clin. Immunol.* **2018**, *18*, 117–123. [CrossRef] [PubMed]
15. Grunwell, J.R.; Gillespie, S.; Morris, C.R.; Fitzpatrick, A.M. Latent Class Analysis of School-Age Children at Risk for Asthma Exacerbation. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 2275–2284.e2. [CrossRef] [PubMed]
16. Bacharier, L.B.; Phillips, B.R.; Bloomberg, G.R.; Zeiger, R.S.; Paul, I.M.; Krawiec, M.; Guilbert, T.; Chinchilli, V.M.; Strunk, R.C.; Childhood Asthma, R.; et al. Severe intermittent wheezing in preschool children: A distinct phenotype. *J. Allergy Clin. Immunol.* **2007**, *119*, 604–610. [CrossRef] [PubMed]
17. Bloomberg, G.R.; Trinkaus, K.M.; Fisher, E.B., Jr.; Musick, J.R.; Strunk, R.C. Hospital readmissions for childhood asthma: A 10-year metropolitan study. *Am. J. Respir. Crit. Care Med.* **2003**, *167*, 1068–1076. [CrossRef] [PubMed]
18. Haselkorn, T.; Zeiger, R.S.; Chipps, B.E.; Mink, D.R.; Szefler, S.J.; Simons, F.E.; Massanari, M.; Fish, J.E. Recent asthma exacerbations predict future exacerbations in children with severe or difficult-to-treat asthma. *J. Allergy Clin. Immunol.* **2009**, *124*, 921–927. [CrossRef]
19. Akinbami, L.J.; Simon, A.E.; Rossen, L.M. Changing Trends in Asthma Prevalence Among Children. *Pediatrics* **2016**, *137*, 1–7. [CrossRef]
20. Chipps, B.E.; Szefler, S.J.; Simons, F.E.; Haselkorn, T.; Mink, D.R.; Deniz, Y.; Lee, J.H.; Group, T.S. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. *J. Allergy Clin. Immunol.* **2007**, *119*, 1156–1163. [CrossRef]
21. Bateman, E.D.; Buhl, R.; O'Byrne, P.M.; Humbert, M.; Reddel, H.K.; Sears, M.R.; Jenkins, C.; Harrison, T.W.; Quirce, S.; Peterson, S.; et al. Development and validation of a novel risk score for asthma exacerbations: The risk score for exacerbations. *J. Allergy Clin. Immunol.* **2015**, *135*, 1457–1464.e4. [CrossRef] [PubMed]
22. Schatz, M.; Zeiger, R.S.; Vollmer, W.M.; Mosen, D.; Apter, A.J.; Stibolt, T.B.; Leong, A.; Johnson, M.S.; Mendoza, G.; Cook, E.F. Validation of a beta-agonist long-term asthma control scale derived from computerized pharmacy data. *J. Allergy Clin. Immunol.* **2006**, *117*, 995–1000. [CrossRef] [PubMed]
23. Zeiger, R.S.; Yegin, A.; Simons, F.E.; Haselkorn, T.; Rasouliyan, L.; Szefler, S.J.; Chipps, B.E.; Group, T.S. Evaluation of the National Heart, Lung, and Blood Institute guidelines impairment domain for classifying asthma control and predicting asthma exacerbations. *Ann. Allergy Asthma Immunol.* **2012**, *108*, 81–87. [CrossRef] [PubMed]
24. Forno, E.; Fuhlbrigge, A.; Soto-Quiros, M.E.; Avila, L.; Raby, B.A.; Brehm, J.; Sylvia, J.M.; Weiss, S.T.; Celedon, J.C. Risk factors and predictive clinical scores for asthma exacerbations in childhood. *Chest* **2010**, *138*, 1156–1165. [CrossRef] [PubMed]
25. Meltzer, E.O.; Busse, W.W.; Wenzel, S.E.; Belozeroff, V.; Weng, H.H.; Feng, J.; Chon, Y.; Chiou, C.F.; Globe, D.; Lin, S.L. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *J. Allergy Clin. Immunol.* **2011**, *127*, 167–172. [CrossRef] [PubMed]
26. Cajigal, S.; Wells, K.E.; Peterson, E.L.; Ahmedani, B.K.; Yang, J.J.; Kumar, R.; Burchard, E.G.; Williams, L.K. Predictive Properties of the Asthma Control Test and Its Component Questions for Severe Asthma Exacerbations. *J. Allergy Clin. Immunol. Pract.* **2017**, *5*, 121–127.e2. [CrossRef] [PubMed]
27. Lo, D.K.; Beardsmore, C.S.; Roland, D.; Richardson, M.; Yang, Y.; Danvers, L.; Wilson, A.; Gaillard, E.A. Lung function and asthma control in school-age children managed in UK primary care: A cohort study. *Thorax* **2020**, *75*, 101–107. [CrossRef] [PubMed]
28. Partridge, M.R.; van der Molen, T.; Myrseth, S.E.; Busse, W.W. Attitudes and actions of asthma patients on regular maintenance therapy: The INSPIRE study. *BMC Pulm. Med.* **2006**, *6*, 13. [CrossRef]
29. Davis, K.J.; Disantostefano, R.; Peden, D.B. Is Johnny wheezing? Parent-child agreement in the Childhood Asthma in America survey. *Pediatr. Allergy Immunol.* **2011**, *22*, 31–35. [CrossRef]
30. Ganti, P.; Suman, A.; Chaudhary, S.; Sangha, B.; David, L.; Sekhsaria, S. The effect of the socioeconomic status on the measurement of asthma control. *Allergy Asthma Proc.* **2022**, *43*, e11–e16. [CrossRef]

31. Lee, W.Y.; Suh, D.I.; Song, D.J.; Baek, H.S.; Shin, M.; Yoo, Y.; Kwon, J.W.; Jang, G.C.; Yang, H.J.; Lee, E.; et al. Asthma control test reflects not only lung function but also airway inflammation in children with stable asthma. *J. Asthma* **2020**, *57*, 648–653. [CrossRef] [PubMed]
32. Engelkes, M.; Janssens, H.M.; de Ridder, M.A.; Sturkenboom, M.C.; de Jongste, J.C.; Verhamme, K.M. Real life data on incidence and risk factors of severe asthma exacerbations in children in primary care. *Respir. Med.* **2016**, *119*, 48–54. [CrossRef] [PubMed]
33. Covar, R.A.; Szefler, S.J.; Zeiger, R.S.; Sorkness, C.A.; Moss, M.; Mauger, D.T.; Boehmer, S.J.; Strunk, R.C.; Martinez, F.D.; Taussig, L.M.; et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J. Allergy Clin. Immunol.* **2008**, *122*, 741–747.e4. [CrossRef] [PubMed]
34. Miller, M.K.; Lee, J.H.; Miller, D.P.; Wenzel, S.E.; Group, T.S. Recent asthma exacerbations: A key predictor of future exacerbations. *Respir. Med.* **2007**, *101*, 481–489. [CrossRef] [PubMed]
35. Price, D.B.; Rigazio, A.; Campbell, J.D.; Bleecker, E.R.; Corrigan, C.J.; Thomas, M.; Wenzel, S.E.; Wilson, A.M.; Small, M.B.; Gopalan, G.; et al. Blood eosinophil count and prospective annual asthma disease burden: A UK cohort study. *Lancet Respir. Med.* **2015**, *3*, 849–858. [CrossRef] [PubMed]
36. Robroeks, C.M.H.H.T.; van Vliet, D.; Jöbsis, Q.; Braekers, R.; Rijkers, G.T.; Wodzig, W.K.W.H.; Bast, A.; Zimmermann, L.J.I.; Dompeling, E. Prediction of asthma exacerbations in children: Results of a one-year prospective study. *Clin. Exp. Allergy* **2012**, *42*, 792–798. [CrossRef] [PubMed]
37. Peters, M.C.; Mauger, D.; Ross, K.R.; Phillips, B.; Gaston, B.; Cardet, J.C.; Israel, E.; Levy, B.D.; Phipatanakul, W.; Jarjour, N.N.; et al. Evidence for Exacerbation-Prone Asthma and Predictive Biomarkers of Exacerbation Frequency. *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 973–982. [CrossRef] [PubMed]
38. Lowden, R.; Turner, S. Past asthma exacerbation in children predicting future exacerbation: A systematic review. *ERJ Open Res.* **2022**, *8*, 00174-2022. [CrossRef]
39. Hauerslev, M.; Garpvall, K.; Marckmann, M.; Hermansen, M.N.; Hansen, K.S.; Chawes, B.L. Long-term predictors of loss of asthma control in school-aged well-controlled children with mild to moderate asthma: A 5-year follow-up. *Pediatr. Pulmonol.* **2022**, *57*, 81–89. [CrossRef]
40. Cottini, M.; Lombardi, C.; Berti, A.; Comberiati, P. Small-airway dysfunction in paediatric asthma. *Curr. Opin. Allergy Clin. Immunol.* **2021**, *21*, 128–134. [CrossRef]
41. Fuhlbrigge, A.L.; Kitch, B.T.; Paltiel, A.D.; Kuntz, K.M.; Neumann, P.J.; Dockery, D.W.; Weiss, S.T. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J. Allergy Clin. Immunol.* **2001**, *107*, 61–67. [CrossRef] [PubMed]
42. Kitch, B.T.; Paltiel, A.D.; Kuntz, K.M.; Dockery, D.W.; Schouten, J.P.; Weiss, S.T.; Fuhlbrigge, A.L. A Single Measure of FEV 1 Is Associated With Risk of Asthma Attacks in Long-term Follow-up. *Chest* **2004**, *126*, 1875–1882. [CrossRef] [PubMed]
43. Fielding, S.; Pijnenburg, M.; de Jongste, J.C.; Pike, K.C.; Roberts, G.; Petsky, H.; Chang, A.B.; Fritsch, M.; Frischer, T.; Szefler, S.; et al. Change in FEV(1) and Feno Measurements as Predictors of Future Asthma Outcomes in Children. *Chest* **2019**, *155*, 331–341. [CrossRef] [PubMed]
44. Sorkness, R.L.; Zoratti, E.M.; Kattan, M.; Gergen, P.J.; Evans, M.D.; Visness, C.M.; Gill, M.; Khurana Hershey, G.K.; Kercsmar, C.M.; Liu, A.H.; et al. Obstruction phenotype as a predictor of asthma severity and instability in children. *J. Allergy Clin. Immunol.* **2018**, *142*, 1090–1099.e4. [CrossRef] [PubMed]
45. Kang, M.G.; Yoon, S.A.; Sim, J.H.; Woo, S.I. Fractional exhaled nitric oxide and forced expiratory volume in 1 second/forced vital capacity have predictive value of asthma exacerbation in Korean school children. *Asia Pac. Allergy* **2020**, *10*, e7. [CrossRef] [PubMed]
46. Lazova, S.; Priftis, S.; Petrova, G.; Naseva, E.; Velikova, T. MMEF(25-75) may predict significant BDR and future risk of exacerbations in asthmatic children with normal baseline FEV(1). *Int. J. Physiol. Pathophysiol. Pharmacol.* **2022**, *14*, 33–47. [PubMed]
47. Reddel, H.; Ware, S.; Marks, G.; Salome, C.; Jenkins, C.; Woolcock, A. Differences between asthma exacerbations and poor asthma control. *Lancet* **1999**, *353*, 364–369. [CrossRef] [PubMed]
48. Frey, U.; Brodbeck, T.; Majumdar, A.; Taylor, D.R.; Town, G.I.; Silverman, M.; Suki, B. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. *Nature* **2005**, *438*, 667–670. [CrossRef]
49. Kim, M.; Kim, Y.M.; Lee, J.Y.; Yang, H.K.; Kim, H.; Ahn, S.; Baek, S.Y.; Kim, J.; Ahn, K. Seasonal and monthly variation in peak expiratory flow rate in children with asthma. *Asia Pac. Allergy* **2021**, *11*, e19. [CrossRef]
50. Klok, T.; Kaptein, A.A.; Duiverman, E.J.; Brand, P.L. Long-term adherence to inhaled corticosteroids in children with asthma: Observational study. *Respir. Med.* **2015**, *109*, 1114–1119. [CrossRef]
51. Vasbinder, E.C.; Belitser, S.V.; Souverein, P.C.; van Dijk, L.; Vulto, A.G.; van den Bemt, P.M. Non-adherence to inhaled corticosteroids and the risk of asthma exacerbations in children. *Patient Prefer. Adherence* **2016**, *10*, 531–538. [CrossRef] [PubMed]
52. Engelkes, M.; Janssens, H.M.; de Jongste, J.C.; Sturkenboom, M.C.; Verhamme, K.M. Medication adherence and the risk of severe asthma exacerbations: A systematic review. *Eur. Respir. J.* **2014**, *45*, 396–407. [CrossRef] [PubMed]
53. Lang, J.E.; Tang, M.; Zhao, C.; Hurst, J.; Wu, A.; Goldstein, B.A. Well-Child Care Attendance and Risk of Asthma Exacerbations. *Pediatrics* **2020**, *146*. [CrossRef] [PubMed]
54. Liu, T.L.; Taylor, Y.J.; Mahabaleshwarkar, R.; Blanchette, C.M.; Tapp, H.; Dulin, M.F. Shared decision making and time to exacerbation in children with asthma. *J. Asthma* **2018**, *55*, 949–955. [CrossRef] [PubMed]

55. Duncan, C.L.; Hogan, M.B.; Tien, K.J.; Graves, M.M.; Chorney, J.M.; Zettler, M.D.; Koven, L.; Wilson, N.W.; Dinakar, C.; Portnoy, J. Efficacy of a parent-youth teamwork intervention to promote adherence in pediatric asthma. *J. Pediatr. Psychol.* **2013**, *38*, 617–628. [CrossRef] [PubMed]
56. Papadopoulos, N.G.; Mathioudakis, A.G.; Custovic, A.; Deschildre, A.; Phipatanakul, W.; Wong, G.; Xepapadaki, P.; Abou-Taam, R.; Agache, I.; Castro-Rodriguez, J.A.; et al. Childhood asthma outcomes during the COVID-19 pandemic: Findings from the PeARL multi-national cohort. *Allergy* **2021**, *76*, 1765–1775. [CrossRef] [PubMed]
57. Normansell, R.; Kew, K.M.; Stovold, E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst. Rev.* **2017**, *4*, CD012226. [CrossRef]
58. Jochmann, A.; Artusio, L.; Jamalzadeh, A.; Nagakumar, P.; Delgado-Eckert, E.; Saglani, S.; Bush, A.; Frey, U.; Fleming, L.J. Electronic monitoring of adherence to inhaled corticosteroids: An essential tool in identifying severe asthma in children. *Eur. Respir. J.* **2017**, *50*, 1700910. [CrossRef]
59. Akinbami, L.J.; Moorman, J.E.; Garbe, P.L.; Sondik, E.J. Status of childhood asthma in the United States, 1980-2007. *Pediatrics* **2009**, *123* (Suppl. S3), S131–S145. [CrossRef]
60. Leong, A.B.; Ramsey, C.D.; Celedon, J.C. The challenge of asthma in minority populations. *Clin. Rev. Allergy Immunol.* **2012**, *43*, 156–183. [CrossRef]
61. Lo, D.; Beardsmore, C.; Roland, D.; Richardson, M.; Yang, Y.; Danvers, L.; Wilson, A.; Gaillard, E.A. Risk factors for asthma attacks and poor control in children: A prospective observational study in UK primary care. *Arch. Dis. Child.* **2022**, *107*, 26–31. [CrossRef] [PubMed]
62. Kopel, L.S.; Phipatanakul, W.; Gaffin, J.M. Social Disadvantage and Asthma Control in Children. *Paediatr. Respir. Rev.* **2014**, *15*, 256–263. [CrossRef] [PubMed]
63. Ardura-Garcia, C.; Stolbrink, M.; Zaidi, S.; Cooper, P.J.; Blakey, J.D. Predictors of repeated acute hospital attendance for asthma in children: A systematic review and meta-analysis. *Pediatr. Pulmonol.* **2018**, *53*, 1179–1192. [CrossRef] [PubMed]
64. Forno, E.; Celedon, J.C. Asthma and ethnic minorities: Socioeconomic status and beyond. *Curr. Opin. Allergy Clin. Immunol.* **2009**, *9*, 154–160. [CrossRef] [PubMed]
65. Ungar, W.J.; Paterson, J.M.; Gomes, T.; Bikangaga, P.; Gold, M.; To, T.; Kozyrskyj, A.L. Relationship of asthma management, socioeconomic status, and medication insurance characteristics to exacerbation frequency in children with asthma. *Ann. Allergy Asthma Immunol.* **2011**, *106*, 17–23. [CrossRef] [PubMed]
66. Lieu, T.A.; Lozano, P.; Finkelstein, J.A.; Chi, F.W.; Jensvold, N.G.; Capra, A.M.; Quesenberry, C.P.; Selby, J.V.; Farber, H.J. Racial/ethnic variation in asthma status and management practices among children in managed medicaid. *Pediatrics* **2002**, *109*, 857–865. [CrossRef] [PubMed]
67. Bender, B.G. Risk taking, depression, adherence, and symptom control in adolescents and young adults with asthma. *Am. J. Respir. Crit. Care Med.* **2006**, *173*, 953–957. [CrossRef] [PubMed]
68. Chen, E.; Hanson, M.D.; Paterson, L.Q.; Griffin, M.J.; Walker, H.A.; Miller, G.E. Socioeconomic status and inflammatory processes in childhood asthma: The role of psychological stress. *J. Allergy Clin. Immunol.* **2006**, *117*, 1014–1020. [CrossRef]
69. Brehm, J.M.; Ramratnam, S.K.; Tse, S.M.; Croteau-Chonka, D.C.; Pino-Yanes, M.; Rosas-Salazar, C.; Litonjua, A.A.; Raby, B.A.; Boutaoui, N.; Han, Y.Y.; et al. Stress and Bronchodilator Response in Children with Asthma. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 47–56. [CrossRef]
70. Forno, E.; Lescher, R.; Strunk, R.; Weiss, S.; Fuhlbrigge, A.; Celedon, J.C. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J. Allergy Clin. Immunol.* **2011**, *127*, 741–749. [CrossRef]
71. Katon, W.J.; Richardson, L.; Lozano, P.; McCauley, E. The relationship of asthma and anxiety disorders. *Psychosom. Med.* **2004**, *66*, 349–355. [CrossRef] [PubMed]
72. Vila, G.; Nollet-Clemencon, C.; de Blic, J.; Mouren-Simeoni, M.C.; Scheinmann, P. Prevalence of DSM IV anxiety and affective disorders in a pediatric population of asthmatic children and adolescents. *J. Affect. Disord.* **2000**, *58*, 223–231. [CrossRef] [PubMed]
73. Sandberg, S.; Jarvenpaa, S.; Penttinen, A.; Paton, J.Y.; McCann, D.C. Asthma exacerbations in children immediately following stressful life events: A Cox's hierarchical regression. *Thorax* **2004**, *59*, 1046–1051. [CrossRef] [PubMed]
74. Sandberg, S.; Paton, J.Y.; Ahola, S.; McCann, D.C.; McGuinness, D.; Hillary, C.R.; Oja, H. The role of acute and chronic stress in asthma attacks in children. *Lancet* **2000**, *356*, 982–987. [CrossRef] [PubMed]
75. Stevens, E.L.; Han, Y.Y.; Rosser, F.; Forno, E.; Acosta-Perez, E.; Miller, G.E.; Canino, G.; Celedon, J.C. Maternal Depressive Symptoms, Lung Function, and Severe Asthma Exacerbations in Puerto Rican Children. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 1319–1326.e3. [CrossRef] [PubMed]
76. Patel, M.; Pilcher, J.; Reddel, H.K.; Pritchard, A.; Corin, A.; Helm, C.; Tofield, C.; Shaw, D.; Black, P.; Weatherall, M.; et al. Metrics of salbutamol use as predictors of future adverse outcomes in asthma. *Clin. Exp. Allergy* **2013**, *43*, 1144–1151. [CrossRef] [PubMed]
77. Fy, O.K.R. Why Asthma Still Kills. *Ulster Med. J.* **2017**, *86*, 44.
78. Johnston, S.L.; Edwards, M.R. Mechanisms of adverse effects of beta-agonists in asthma. *Thorax* **2009**, *64*, 739–741. [CrossRef]
79. Edwards, M.R.; Haas, J.; Panettieri, R.A., Jr.; Johnson, M.; Johnston, S.L. Corticosteroids and beta2 agonists differentially regulate rhinovirus-induced interleukin-6 via distinct Cis-acting elements. *J. Biol. Chem.* **2007**, *282*, 15366–15375. [CrossRef]
80. Nwaru, B.I.; Ekstrom, M.; Hasvold, P.; Wiklund, F.; Telg, G.; Janson, C. Overuse of short-acting beta(2)-agonists in asthma is associated with increased risk of exacerbation and mortality: A nationwide cohort study of the global SABINA programme. *Eur. Respir. J.* **2020**, *55*, 1901872. [CrossRef]

81. Xia, Y.; Kelton, C.M.L.; Xue, L.; Guo, J.J.; Bian, B.; Wigle, P.R. Safety of long-acting beta agonists and inhaled corticosteroids in children and adolescents with asthma. *Ther. Adv. Drug Saf.* **2013**, *4*, 254–263. [CrossRef] [PubMed]
82. Dunican, E.M.; Fahy, J.V. The Role of Type 2 Inflammation in the Pathogenesis of Asthma Exacerbations. *Ann. Am. Thorac. Soc.* **2015**, *12*, S144–S149. [CrossRef] [PubMed]
83. Bush, A. Translating Asthma: Dissecting the Role of Metabolomics, Genomics and Personalized Medicine. *Indian J. Pediatr.* **2018**, *85*, 643–650. [CrossRef] [PubMed]
84. Bush, A. Pathophysiological Mechanisms of Asthma. *Front. Pediatr.* **2019**, *7*, 68. [CrossRef] [PubMed]
85. Wojsyk-Banaszak, I.; Mikoś, M.; Szczepankiewicz, A.; Wielebska, A.; Sobkowiak, P.; Kamińska, A.; Bręborowicz, A. Evaluation of exhaled breath temperature (EBT) as a marker and predictor of asthma exacerbation in children and adolescents. *J. Asthma* **2017**, *54*, 699–705. [CrossRef] [PubMed]
86. Ulrik, C.S.; Lange, P.; Hilberg, O. Fractional exhaled nitric oxide as a determinant for the clinical course of asthma: A systematic review. *Eur. Clin. Respir. J.* **2021**, *8*, 1891725. [CrossRef] [PubMed]
87. Li, R.; Dong, X.Y.; Jiang, K.; Wang, C.; Sun, C.; Yuan, L.; Dong, N. Application of fractional exhaled nitric oxide and nasal nitric oxide in control evaluation of bronchial asthma and diagnosis of allergic rhinitis in children. *Zhongguo Dang Dai Er Ke Za Zhi* **2022**, *24*, 90–95. [CrossRef] [PubMed]
88. Kharitonov, S.A.; Barnes, P.J. Exhaled biomarkers. *Chest* **2006**, *130*, 1541–1546. [CrossRef]
89. Diamant, N.; Amirav, I.; Armoni-Domany, K.; Sadot, E.; Shapira, U.; Cahal, M.; Be'er, M.; Rochman, M.; Lavie, M. High fractional exhaled nitric oxide levels in asthma patients: Does size matter? *Pediatr. Pulmonol.* **2021**, *56*, 1449–1454. [CrossRef]
90. Harkins, M.S.; Fiato, K.L.; Iwamoto, G.K. Exhaled nitric oxide predicts asthma exacerbation. *J. Asthma* **2004**, *41*, 471–476. [CrossRef]
91. Visser, C.A.; Brand, P.L. Does a single measurement of exhaled nitric oxide predict asthma exacerbations? *Arch. Dis. Child.* **2011**, *96*, 781–782. [CrossRef] [PubMed]
92. Zacharasiewicz, A.; Erin, E.M.; Bush, A. Noninvasive monitoring of airway inflammation and steroid reduction in children with asthma. *Curr. Opin. Allergy Clin. Immunol.* **2006**, *6*, 155–160. [CrossRef] [PubMed]
93. Turner, S.; Cotton, S.; Wood, J.; Bell, V.; Raja, E.A.; Scott, N.W.; Morgan, H.; Lawrie, L.; Emele, D.; Kennedy, C.; et al. Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: A multicentre, parallel, randomised, controlled, phase 3 trial. *Lancet Respir. Med.* **2022**, *10*, 584–592. [CrossRef] [PubMed]
94. Turner, S.; Cotton, S.; Wood, J.; Bell, V.; Raja, E.A.; Scott, N.W.; Morgan, H.; Lawrie, L.; Emele, D.; Kennedy, C.; et al. *Treatment Guided by Fractional Exhaled Nitric Oxide in Addition to Standard Care in 6- to 15-Year-Olds with Asthma: The RAACENO RCT*; Efficacy and Mechanism Evaluation: Southampton, UK, 2022. [CrossRef]
95. Fleming, L.; Tsartsali, L.; Wilson, N.; Regamey, N.; Bush, A. Non-invasive markers of inflammation as predictors of a severe exacerbation in children with problematic asthma. *Thorax* **2008**, *63*, A35–A37.
96. Ardura-Garcia, C.; Arias, E.; Hurtado, P.; Bonnett, L.J.; Sandoval, C.; Maldonado, A.; Workman, L.J.; Platts-Mills, T.A.E.; Cooper, P.J.; Blakey, J.D. Predictors of severe asthma attack re-attendance in Ecuadorian children: A cohort study. *Eur. Respir. J.* **2019**, *54*, 1802419. [CrossRef] [PubMed]
97. Wang, Z.; Pianosi, P.; Keogh, K.; Zaiem, F.; Alsawas, M.; Alahdab, F.; Almasri, J.; Mohammed, K.; Larrea-Mantilla, L.; Farah, W.; et al. *The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management*; US Agency for Healthcare Research and Quality: Rockville, MD, USA, 2017.
98. van Vliet, D.; Alonso, A.; Rijkers, G.; Heynens, J.; Rosias, P.; Muris, J.; Jobsis, Q.; Dompeling, E. Prediction of asthma exacerbations in children by innovative exhaled inflammatory markers: Results of a longitudinal study. *PLoS ONE* **2015**, *10*, e0119434. [CrossRef] [PubMed]
99. Wang, X.; Tan, X.; Li, Q. Effectiveness of fractional exhaled nitric oxide for asthma management in children: A systematic review and meta-analysis. *Pediatr. Pulmonol.* **2020**, *55*, 1936–1945. [CrossRef] [PubMed]
100. Petsky, H.L.; Cates, C.J.; Kew, K.M.; Chang, A.B. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): A systematic review and meta-analysis. *Thorax* **2018**, *73*, 1110–1119. [CrossRef]
101. Turner, S. Exhaled nitric oxide and the management of childhood asthma--yet another promising biomarker "has been" or a misunderstood gem. *Paediatr. Respir. Rev.* **2015**, *16*, 88–96. [CrossRef]
102. Paraskakis, E.; Zihlif, N.; Bush, A. Nitric oxide production in PCD: Possible evidence for differential nitric oxide synthase function. *Pediatr. Pulmonol.* **2007**, *42*, 876–880. [CrossRef]
103. Paraskakis, E.; Sarikloglou, E.; Fouzas, S.; Steiropoulos, P.; Tsalkidis, A.; Bush, A. Improved prediction of asthma exacerbations by measuring distal airway inflammation. *Eur. Respir. J.* **2022**, *60*, 2101684. [CrossRef] [PubMed]
104. Buendia, J.A.; Talamoni, H.L. Cost-utility of use of sputum eosinophil counts to guide management in children with asthma. *J. Asthma* **2022**, *59*, 31–37. [CrossRef] [PubMed]
105. Green, R.H.; Brightling, C.E.; McKenna, S.; Hargadon, B.; Parker, D.; Bradding, P.; Wardlaw, A.J.; Pavord, I.D. Asthma exacerbations and sputum eosinophil counts: A randomised controlled trial. *Lancet* **2002**, *360*, 1715–1721. [CrossRef] [PubMed]
106. Little, F.F.; Delgado, D.M.; Wexler, P.J.; Oppenheim, F.G.; Mitchell, P.; Feldman, J.A.; Walt, D.R.; Peng, R.D.; Matsui, E.C. Salivary inflammatory mediator profiling and correlation to clinical disease markers in asthma. *PLoS ONE* **2014**, *9*, e84449. [CrossRef] [PubMed]

107. van Vliet, D.; Smolinska, A.; Jobsis, Q.; Rosias, P.; Muris, J.; Dallinga, J.; Dompeling, E.; van Schooten, F.J. Can exhaled volatile organic compounds predict asthma exacerbations in children? *J. Breath. Res.* **2017**, *11*, 016016. [CrossRef] [PubMed]
108. Robroeks, C.M.; van Berkel, J.J.; Jobsis, Q.; van Schooten, F.J.; Dallinga, J.W.; Wouters, E.F.; Dompeling, E. Exhaled volatile organic compounds predict exacerbations of childhood asthma in a 1-year prospective study. *Eur. Respir. J.* **2013**, *42*, 98–106. [CrossRef] [PubMed]
109. Neerincx, A.H.; Vijverberg, S.J.H.; Bos, L.D.J.; Brinkman, P.; Van Der Schee, M.P.; De Vries, R.; Sterk, P.J.; Maitland-van Der Zee, A.-H. Breathomics from exhaled volatile organic compounds in pediatric asthma. *Pediatr. Pulmonol.* **2017**, *52*, 1616–1627. [CrossRef]
110. Mogensen, I.; Alving, K.; Jacinto, T.; Fonseca, J.; Janson, C.; Malinovschi, A. Simultaneously elevated FeNO and blood eosinophils relate to asthma morbidity in asthmatics from NHANES 2007-12. *Clin. Exp. Allergy* **2018**, *48*, 935–943. [CrossRef]
111. Denlinger, L.C.; Phillips, B.R.; Ramratnam, S.; Ross, K.; Bhakta, N.R.; Cardet, J.C.; Castro, M.; Peters, S.P.; Phipatanakul, W.; Aujla, S.; et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 302–313. [CrossRef]
112. Malinovschi, A.; Fonseca, J.A.; Jacinto, T.; Alving, K.; Janson, C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J. Allergy Clin. Immunol.* **2013**, *132*, 821–827.e5. [CrossRef]
113. Malinovschi, A.; Janson, C.; Borres, M.; Alving, K. Simultaneously increased fraction of exhaled nitric oxide levels and blood eosinophil counts relate to increased asthma morbidity. *J. Allergy Clin. Immunol.* **2016**, *138*, 1301–1308.e2. [CrossRef] [PubMed]
114. Buhl, R.; Korn, S.; Menzies-Gow, A.; Aubier, M.; Chapman, K.R.; Canonica, G.W.; Picado, C.; Martin, N.; Escobar, R.A.; Korom, S.; et al. Assessing biomarkers in a real-world severe asthma study (ARIETTA). *Respir. Med.* **2016**, *115*, 7–12. [CrossRef] [PubMed]
115. Poole, A.; Urbanek, C.; Eng, C.; Schageman, J.; Jacobson, S.; O'Connor, B.P.; Galanter, J.M.; Gignoux, C.R.; Roth, L.A.; Kumar, R.; et al. Dissecting childhood asthma with nasal transcriptomics distinguishes subphenotypes of disease. *J. Allergy Clin. Immunol.* **2014**, *133*, 670–678.e2. [CrossRef] [PubMed]
116. Woodruff, P.G.; Boushey, H.A.; Dolganov, G.M.; Barker, C.S.; Yang, Y.H.; Donnelly, S.; Ellwanger, A.; Sidhu, S.S.; Dao-Pick, T.P.; Pantoja, C.; et al. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 15858–15863. [CrossRef] [PubMed]
117. Woodruff, P.G.; Modrek, B.; Choy, D.F.; Jia, G.; Abbas, A.R.; Ellwanger, A.; Koth, L.L.; Arron, J.R.; Fahy, J.V. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am. J. Respir. Crit. Care Med.* **2009**, *180*, 388–395. [CrossRef] [PubMed]
118. Jackson, D.J.; Bacharier, L.B.; Calatroni, A.; Gill, M.A.; Hu, J.; Liu, A.H.; Wheatley, L.M.; Gern, J.E.; Gruchalla, R.S.; Khurana Hershey, G.K.; et al. Serum IL-6: A biomarker in childhood asthma? *J. Allergy Clin. Immunol.* **2020**, *145*, 1701–1704.e3. [CrossRef] [PubMed]
119. Shah, S.N.; Grunwell, J.R.; Mohammad, A.F.; Stephenson, S.T.; Lee, G.B.; Vickery, B.P.; Fitzpatrick, A.M. Performance of Eosinophil Cationic Protein as a Biomarker in Asthmatic Children. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 2761–2769.e2. [CrossRef] [PubMed]
120. Anderson, W.C., 3rd; Szefler, S.J. Controlling the Risk Domain in Pediatric Asthma through Personalized Care. *Semin. Respir. Crit. Care Med.* **2018**, *39*, 36–44. [CrossRef]
121. Liu, L.; Gao, Y.; Si, Y.; Liu, B.; Liu, X.; Li, G.; Wang, R. MALT1 in asthma children: A potential biomarker for monitoring exacerbation risk and Th1/Th2 imbalance-mediated inflammation. *J. Clin. Lab. Anal.* **2022**, *36*, e24379. [CrossRef]
122. Abd El-Motaleb, G.S.; Abou Amer, A.A.; Elawa, G.M.; Abo Alsood Abd Elfattah, M. Study of urinary leukotriene E4 levels in children with acute asthma. *Int. J. Gen. Med.* **2014**, *7*, 131–135. [CrossRef]
123. Busse, W.; Kraft, M. Cysteinyl leukotrienes in allergic inflammation: Strategic target for therapy. *Chest* **2005**, *127*, 1312–1326. [CrossRef] [PubMed]
124. Rabinovitch, N.; Reisdorph, N.; Silveira, L.; Gelfand, E.W. Urinary leukotriene E(4) levels identify children with tobacco smoke exposure at risk for asthma exacerbation. *J. Allergy Clin. Immunol.* **2011**, *128*, 323–327. [CrossRef] [PubMed]
125. Babadi, R.S.; Riederer, A.M.; Sampson, P.D.; Sathyanarayana, S.; Kavanagh, T.J.; Krenz, J.E.; Andra, S.S.; Kim-Schulze, S.; Jansen, K.L.; Torres, E.; et al. Longitudinal measures of phthalate exposure and asthma exacerbation in a rural agricultural cohort of Latino children in Yakima Valley, Washington. *Int. J. Hyg. Environ. Health* **2022**, *243*, 113954. [CrossRef] [PubMed]
126. Papamichael, M.M.; Katsardis, C.; Erbas, B.; Itsiopoulos, C.; Tsoukalas, D. Urinary organic acids as biomarkers in the assessment of pulmonary function in children with asthma. *Nutr. Res.* **2019**, *61*, 31–40. [CrossRef] [PubMed]
127. Bonnelykke, K.; Sleiman, P.; Nielsen, K.; Kreiner-Moller, E.; Mercader, J.M.; Belgrave, D.; den Dekker, H.T.; Husby, A.; Sevelsted, A.; Faura-Tellez, G.; et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. *Nat. Genet.* **2014**, *46*, 51–55. [CrossRef] [PubMed]
128. Sood, N.; Connolly, J.J.; Mentch, F.D.; Vazquez, L.; Sleiman, P.M.A.; Hysinger, E.B.; Hakonarson, H. Leveraging electronic health records to assess the role of ADRB2 single nucleotide polymorphisms in predicting exacerbation frequency in asthma patients. *Pharmacogenet. Genom.* **2018**, *28*, 256–259. [CrossRef] [PubMed]
129. Yan, Q.; Forno, E.; Herrera-Luis, E.; Pino-Yanes, M.; Yang, G.; Oh, S.; Acosta-Perez, E.; Hu, D.; Eng, C.; Huntsman, S.; et al. A genome-wide association study of asthma hospitalizations in adults. *J. Allergy Clin. Immunol.* **2021**, *147*, 933–940. [CrossRef] [PubMed]
130. Kho, A.T.; McGeachie, M.J.; Moore, K.G.; Sylvia, J.M.; Weiss, S.T.; Tantisira, K.G. Circulating microRNAs and prediction of asthma exacerbation in childhood asthma. *Respir. Res.* **2018**, *19*, 128. [CrossRef]

131. Turner, S.; Francis, B.; Vijverberg, S.; Pino-Yanes, M.; Maitland-van der Zee, A.H.; Basu, K.; Bignell, L.; Mukhopadhyay, S.; Tavendale, R.; Palmer, C.; et al. Childhood asthma exacerbations and the Arg16 beta2-receptor polymorphism: A meta-analysis stratified by treatment. *J. Allergy Clin. Immunol.* **2016**, *138*, 107–113.e5. [CrossRef]
132. Altman, M.C.; Gill, M.A.; Whalen, E.; Babineau, D.C.; Shao, B.; Liu, A.H.; Jepson, B.; Gruchalla, R.S.; O'Connor, G.T.; Pongracic, J.A.; et al. Transcriptome networks identify mechanisms of viral and nonviral asthma exacerbations in children. *Nat. Immunol.* **2019**, *20*, 637–651. [CrossRef]
133. Hurst, J.H.; Zhao, C.; Hostetler, H.P.; Ghiasi Gorveh, M.; Lang, J.E.; Goldstein, B.A. Environmental and clinical data utility in pediatric asthma exacerbation risk prediction models. *BMC Med. Inform. Decis. Mak.* **2022**, *22*, 108. [CrossRef] [PubMed]
134. Murray, C.S.; Poletti, G.; Kebadze, T.; Morris, J.; Woodcock, A.; Johnston, S.L.; Custovic, A. Study of modifiable risk factors for asthma exacerbations: Virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* **2006**, *61*, 376–382. [CrossRef] [PubMed]
135. Message, S.D.; Johnston, S.L. Viruses in asthma. *Br. Med. Bull.* **2002**, *61*, 29–43. [CrossRef] [PubMed]
136. Jackson, D.J.; Gangnon, R.E.; Evans, M.D.; Roberg, K.A.; Anderson, E.L.; Pappas, T.E.; Printz, M.C.; Lee, W.M.; Shult, P.A.; Reisdorf, E.; et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am. J. Respir. Crit. Care Med.* **2008**, *178*, 667–672. [CrossRef] [PubMed]
137. Johnston, N.W.; Johnston, S.L.; Duncan, J.M.; Greene, J.M.; Kebadze, T.; Keith, P.K.; Roy, M.; Waserman, S.; Sears, M.R. The September epidemic of asthma exacerbations in children: A search for etiology. *J. Allergy Clin. Immunol.* **2005**, *115*, 132–138. [CrossRef] [PubMed]
138. Zheng, S.Y.; Wang, L.L.; Ren, L.; Luo, J.; Liao, W.; Liu, E.M. Epidemiological analysis and follow-up of human rhinovirus infection in children with asthma exacerbation. *J. Med. Virol.* **2018**, *90*, 219–228. [CrossRef] [PubMed]
139. Sallard, E.; Schult, F.; Baehren, C.; Buedding, E.; Mboma, O.; Ahmad-Nejad, P.; Ghebremedhin, B.; Ehrhardt, A.; Wirth, S.; Aydin, M. Viral Infection and Respiratory Exacerbation in Children: Results from a Local German Pediatric Exacerbation Cohort. *Viruses* **2022**, *14*, 491. [CrossRef] [PubMed]
140. Sayed, S.; Diwadkar, A.R.; Dudley, J.W.; O'Brien, J.; Dvorin, D.; Kenyon, C.C.; Himes, B.E.; Hill, D.A.; Henrickson, S.E. COVID-19 Pandemic-Related Reductions in Pediatric Asthma Exacerbations Corresponded with an Overall Decrease in Respiratory Viral Infections. *J. Allergy Clin. Immunol. Pract.* **2022**, *10*, 91–99.e12. [CrossRef]
141. McCauley, K.E.; Flynn, K.; Calatroni, A.; DiMassa, V.; LaMere, B.; Fadrosh, D.W.; Lynch, K.V.; Gill, M.A.; Pongracic, J.A.; Khurana Hershey, G.K.; et al. Seasonal airway microbiome and transcriptome interactions promote childhood asthma exacerbations. *J. Allergy Clin. Immunol.* **2022**, *150*, 204–213. [CrossRef]
142. Johnston, N.W.; Sears, M.R. Asthma exacerbations 1: Epidemiology. *Thorax* **2006**, *61*, 722–728. [CrossRef]
143. Lincoln, D.; Morgan, G.; Sheppeard, V.; Jalaludin, B.; Corbett, S.; Beard, J. Childhood asthma and return to school in Sydney, Australia. *Public Health* **2006**, *120*, 854–862. [CrossRef] [PubMed]
144. Larsen, K.; Zhu, J.; Feldman, L.Y.; Simatovic, J.; Dell, S.; Gershon, A.S.; To, T. The Annual September Peak in Asthma Exacerbation Rates. Still a Reality? *Ann. Am. Thorac. Soc.* **2016**, *13*, 231–239. [CrossRef] [PubMed]
145. Teach, S.J.; Gill, M.A.; Togias, A.; Sorkness, C.A.; Arbes, S.J., Jr.; Calatroni, A.; Wildfire, J.J.; Gergen, P.J.; Cohen, R.T.; Pongracic, J.A.; et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J. Allergy Clin. Immunol.* **2015**, *136*, 1476–1485. [CrossRef] [PubMed]
146. Tosca, M.A.; Ruffoni, S.; Canonica, G.W.; Ciprandi, G. Asthma exacerbation in children: Relationship among pollens, weather, and air pollution. *Allergol. Immunopathol. (Madr.)* **2014**, *42*, 362–368. [CrossRef] [PubMed]
147. Teach, S.J.; Gergen, P.J.; Szefler, S.J.; Mitchell, H.E.; Calatroni, A.; Wildfire, J.; Bloomberg, G.R.; Kercsmar, C.M.; Liu, A.H.; Makhija, M.M.; et al. Seasonal risk factors for asthma exacerbations among inner-city children. *J. Allergy Clin. Immunol.* **2015**, *135*, 1465–1473.e5. [CrossRef] [PubMed]
148. Chane-Si-Ken, N.; Allou, N.; Beneteau, S.; Verduyn, M.; Gazaille, V.; Raherison, C.; Andre, M. Asthma exacerbations in Reunion Island: Environmental factors. *Respir. Med. Res.* **2022**, *81*, 100779. [CrossRef] [PubMed]
149. Yu, H.R.; Lin, C.R.; Tsai, J.H.; Hsieh, Y.T.; Tsai, T.A.; Tsai, C.K.; Lee, Y.C.; Liu, T.Y.; Tsai, C.M.; Chen, C.C.; et al. A Multifactorial Evaluation of the Effects of Air Pollution and Meteorological Factors on Asthma Exacerbation. *Int. J. Environ. Res. Public Health* **2020**, *17*, 4010. [CrossRef] [PubMed]
150. D'Amato, G.; Vitale, C.; D'Amato, M.; Cecchi, L.; Liccardi, G.; Molino, A.; Vatrella, A.; Sanduzzi, A.; Maesano, C.; Annesi-Maesano, I. Thunderstorm-related asthma: What happens and why. *Clin. Exp. Allergy* **2016**, *46*, 390–396. [CrossRef]
151. Kouis, P.; Michaelidou, E.; Kinni, P.; Michanikou, A.; Anagnostopoulou, P.; Dimitriou, H.; Karanicolas, K.; Matthaiou, A.M.; Achilleos, S.; Papatheodorou, S.I.; et al. Pediatric asthma symptom control during lockdown for the COVID-19 pandemic in Spring 2020: A prospective community-based study in Cyprus and Greece. *Pediatr. Pulmonol.* **2022**, *57*, 386–394. [CrossRef]
152. Soto-Quiros, M.; Avila, L.; Platts-Mills, T.A.; Hunt, J.F.; Erdman, D.D.; Carper, H.; Murphy, D.D.; Odio, S.; James, H.R.; Patrie, J.T.; et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J. Allergy Clin. Immunol.* **2012**, *129*, 1499–1505.e5. [CrossRef]
153. Murray, C.S.; Foden, P.; Sumner, H.; Shepley, E.; Custovic, A.; Simpson, A. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. *Am. J. Respir. Crit. Care Med.* **2017**, *196*, 150–158. [CrossRef] [PubMed]

154. Kanchongkittiphon, W.; Mendell, M.J.; Gaffin, J.M.; Wang, G.; Phipatanakul, W. Indoor environmental exposures and exacerbation of asthma: An update to the 2000 review by the Institute of Medicine. *Environ. Health Perspect.* **2015**, *123*, 6–20. [CrossRef] [PubMed]
155. Romieu, I.; Meneses, F.; Sienra-Monge, J.J.; Huerta, J.; Ruiz Velasco, S.; White, M.C.; Etzel, R.A.; Hernandez-Avila, M. Effects of urban air pollutants on emergency visits for childhood asthma in Mexico City. *Am. J. Epidemiol.* **1995**, *141*, 546–553. [CrossRef] [PubMed]
156. Schildcrout, J.S.; Sheppard, L.; Lumley, T.; Slaughter, J.C.; Koenig, J.Q.; Shapiro, G.G. Ambient air pollution and asthma exacerbations in children: An eight-city analysis. *Am. J. Epidemiol.* **2006**, *164*, 505–517. [CrossRef] [PubMed]
157. Anderson, H.R.; Bremner, S.A.; Atkinson, R.W.; Harrison, R.M.; Walters, S. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: Associations with fine and coarse particles, black smoke and sulphate. *Occup. Environ. Med.* **2001**, *58*, 504–510. [CrossRef] [PubMed]
158. Altman, M.C.; Kattan, M.; O'Connor, G.T.; Murphy, R.C.; Whalen, E.; LeBeau, P.; Calatroni, A.; Gill, M.A.; Gruchalla, R.S.; Liu, A.H.; et al. Associations between outdoor air pollutants and non-viral asthma exacerbations and airway inflammatory responses in children and adolescents living in urban areas in the USA: A retrospective secondary analysis. *Lancet Planet. Health* **2023**, *7*, e33–e44. [CrossRef] [PubMed]
159. Huang, J.; Yang, X.; Fan, F.; Hu, Y.; Wang, X.; Zhu, S.; Ren, G.; Wang, G. Outdoor air pollution and the risk of asthma exacerbations in single lag0 and lag1 exposure patterns: A systematic review and meta-analysis. *J. Asthma* **2022**, *59*, 2322–2339. [CrossRef]
160. Solanki, N.; Bruckman, D.; Wang, X.; Tang, A.; Attaway, A.; Khatri, S. Nitrogen dioxide, an EPA parameter, may forecast the incidence of asthma exacerbations across urban areas: An observational study. *Pediatr. Pulmonol.* **2023**, *58*, 262–270. [CrossRef]
161. Dosanjh, A. Complex pathways leading to future paediatric asthma exacerbations. *ERJ Open Res.* **2022**, *8*. [CrossRef]
162. Zhang, Y.; Ni, H.; Bai, L.; Cheng, Q.; Zhang, H.; Wang, S.; Xie, M.; Zhao, D.; Su, H. The short-term association between air pollution and childhood asthma hospital admissions in urban areas of Hefei City in China: A time-series study. *Environ. Res.* **2019**, *169*, 510–516. [CrossRef]
163. Zhao, Y.; Kong, D.; Fu, J.; Zhang, Y.; Chen, Y.; Liu, Y.; Chang, Z.; Liu, Y.; Liu, X.; Xu, K.; et al. Increased Risk of Hospital Admission for Asthma in Children From Short-Term Exposure to Air Pollution: Case-Crossover Evidence From Northern China. *Front. Public Health* **2021**, *9*, 798746. [CrossRef]
164. Orellano, P.; Quaranta, N.; Reynoso, J.; Balbi, B.; Vasquez, J. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. *PLoS ONE* **2017**, *12*, e0174050. [CrossRef] [PubMed]
165. Liu, L.; Liu, C.; Chen, R.; Zhou, Y.; Meng, X.; Hong, J.; Cao, L.; Lu, Y.; Dong, X.; Xia, M.; et al. Associations of short-term exposure to air pollution and emergency department visits for pediatric asthma in Shanghai, China. *Chemosphere* **2021**, *263*, 127856. [CrossRef] [PubMed]
166. Bonato, M.; Gallo, E.; Turrin, M.; Bazzan, E.; Baraldi, F.; Saetta, M.; Gregori, D.; Papi, A.; Contoli, M.; Baraldo, S. Air Pollution Exposure Impairs Airway Epithelium IFN-beta Expression in Pre-School Children. *Front. Immunol.* **2021**, *12*, 731968. [CrossRef] [PubMed]
167. Zheng, P.; Zhang, B.; Zhang, K.; Lv, X.; Wang, Q.; Bai, X. The Impact of Air Pollution on Intestinal Microbiome of Asthmatic Children: A Panel Study. *Biomed. Res. Int.* **2020**, *2020*, 5753427. [CrossRef] [PubMed]
168. He, L.; Norris, C.; Cui, X.; Li, Z.; Barkjohn, K.K.; Teng, Y.; Fang, L.; Lin, L.; Wang, Q.; Zhou, X.; et al. Oral cavity response to air pollutant exposure and association with pulmonary inflammation and symptoms in asthmatic children. *Environ. Res.* **2022**, *206*, 112275. [CrossRef] [PubMed]
169. Vargas, P.A.; Brenner, B.; Clark, S.; Boudreaux, E.D.; Camargo, C.A., Jr. Exposure to environmental tobacco smoke among children presenting to the emergency department with acute asthma: A multicenter study. *Pediatr. Pulmonol.* **2007**, *42*, 646–655. [CrossRef] [PubMed]
170. Chankaew, K.; Sinitkul, R.; Manuyakorn, W.; Roekworachai, K.; Kamalaporn, H. Spatial Estimation of PM(2.5) Exposure and its Association with Asthma Exacerbation: A Prospective Study in Thai Children. *Ann. Glob. Health* **2022**, *88*, 15. [CrossRef] [PubMed]
171. Brandt, S.J.; Perez, L.; Kunzli, N.; Lurmann, F.; McConnell, R. Costs of childhood asthma due to traffic-related pollution in two California communities. *Eur. Respir. J.* **2012**, *40*, 363–370. [CrossRef]
172. Stevens, E.L.; Rosser, F.; Han, Y.Y.; Forno, E.; Acosta-Perez, E.; Canino, G.; Celedon, J.C. Traffic-related Air Pollution, Dust Mite Allergen, and Childhood Asthma in Puerto Ricans. *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 144–146. [CrossRef]
173. Guarnieri, M.; Balmes, J.R. Outdoor air pollution and asthma. *Lancet* **2014**, *383*, 1581–1592. [CrossRef] [PubMed]
174. Jayawardene, W.P.; Youssefagha, A.H.; Lohrmann, D.K.; El Afandi, G.S. Prediction of asthma exacerbations among children through integrating air pollution, upper atmosphere, and school health surveillances. *Allergy Asthma Proc.* **2013**, *34*, e1–e8. [CrossRef] [PubMed]
175. Bousquet, J.; O'Hehir, R.E.; Anto, J.M.; D'Amato, G.; Mosges, R.; Hellings, P.W.; Van Eerd, M.; Sheikh, A. Assessment of thunderstorm-induced asthma using Google Trends. *J. Allergy Clin. Immunol.* **2017**, *140*, 891–893.e7. [CrossRef] [PubMed]
176. Ram, S.; Zhang, W.; Williams, M.; Pengetnze, Y. Predicting asthma-related emergency department visits using big data. *IEEE J. Biomed. Health Inform.* **2015**, *19*, 1216–1223. [CrossRef] [PubMed]

177. Hao, H.; Eckel, S.P.; Hosseini, A.; Van Vliet, E.D.S.; Dzubur, E.; Dunton, G.; Chang, S.Y.; Craig, K.; Rocchio, R.; Bastain, T.; et al. Daily Associations of Air Pollution and Pediatric Asthma Risk Using the Biomedical REAI-Time Health Evaluation (BREATHE) Kit. *Int. J. Environ. Res. Public Health* **2022**, *19*, 3578. [CrossRef] [PubMed]
178. Maeda, S.; Kobayashi, S.; Takahashi, K.; Miyata, S. Association of comorbidities and medications with risk of asthma exacerbation in pediatric patients: A retrospective study using Japanese claims data. *Sci. Rep.* **2022**, *12*, 5509. [CrossRef] [PubMed]
179. Navanandan, N.; Hatoun, J.; Celedon, J.C.; Liu, A.H. Predicting Severe Asthma Exacerbations in Children: Blueprint for Today and Tomorrow. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 2619–2626. [CrossRef]
180. Andrenacci, B.; Ferrante, G.; Roberto, G.; Piacentini, G.; La Grutta, S.; Marseglia, G.L.; Licari, A. Challenges in uncontrolled asthma in pediatrics: Important considerations for the clinician. *Expert. Rev. Clin. Immunol.* **2022**, *18*, 807–821. [CrossRef]
181. Kaplan, A.; Hardjojo, A.; Yu, S.; Price, D. Asthma Across Age: Insights From Primary Care. *Front. Pediatr.* **2019**, *7*, 162. [CrossRef]
182. Huffaker, M.F.; Carchia, M.; Harris, B.U.; Kethman, W.C.; Murphy, T.E.; Sakarovitch, C.C.D.; Qin, F.; Cornfield, D.N. Passive Nocturnal Physiologic Monitoring Enables Early Detection of Exacerbations in Children with Asthma. A Proof-of-Concept Study. *Am. J. Respir. Crit. Care Med.* **2018**, *198*, 320–328. [CrossRef]
183. Hatoun, J.; Correa, E.T.; MacGinnitie, A.J.; Gaffin, J.M.; Vernacchio, L. Development and Validation of the Asthma Exacerbation Risk Score Using Claims Data. *Acad. Pediatr.* **2022**, *22*, 47–54. [CrossRef]
184. Harel-Sterling, M.; Dai, R.; Moraes, T.J.; Boutis, K.; Eiwegger, T.; Narang, I.; Lepine, C.; Brydges, M.G.; Dubeau, A.; Subbarao, P.; et al. Test for respiratory and asthma control in preschool kids in the emergency department as a predictor of wheezing exacerbations. *Pediatr. Pulmonol.* **2020**, *55*, 338–345. [CrossRef] [PubMed]
185. Honkoop, P.J.; Simpson, A.; Bonini, M.; Snoeck-Stroband, J.B.; Meah, S.; Fan Chung, K.; Usmani, O.S.; Fowler, S.; Sont, J.K. MyAirCoach: The use of home-monitoring and mHealth systems to predict deterioration in asthma control and the occurrence of asthma exacerbations; study protocol of an observational study. *BMJ Open* **2017**, *7*, e013935. [CrossRef] [PubMed]
186. Khusial, R.J.; Honkoop, P.J.; Usmani, O.; Soares, M.; Simpson, A.; Biddiscombe, M.; Meah, S.; Bonini, M.; Lalas, A.; Polychronidou, E.; et al. Effectiveness of myAirCoach: A mHealth Self-Management System in Asthma. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 1972–1979.e8. [CrossRef] [PubMed]
187. Bui, A.A.T.; Hosseini, A.; Rocchio, R.; Jacobs, N.; Ross, M.K.; Okelo, S.; Lurmann, F.; Eckel, S.; Dzubur, E.; Dunton, G.; et al. Biomedical REAl-Time Health Evaluation (BREATHE): Toward an mHealth informatics platform. *JAMIA Open* **2020**, *3*, 190–200. [CrossRef] [PubMed]
188. Finkelstein, J.; Jeong, I.C. Machine learning approaches to personalize early prediction of asthma exacerbations. *Ann. N. Y. Acad. Sci.* **2017**, *1387*, 153–165. [CrossRef] [PubMed]
189. Alharbi, E.T.; Nadeem, F.; Cherif, A. Predictive models for personalized asthma attacks based on patient's biosignals and environmental factors: A systematic review. *BMC Med. Inform. Decis. Mak.* **2021**, *21*, 345. [CrossRef] [PubMed]