Medisch Spectrum Twente
een santeon ziekenhuis

UNIVERSITY OF TWENTE.

# Pediatric Respiratory Exacerbation Detection - Innovating Asthma Care with Artificial Intelligence (PREDICTA)

## AN AI MODEL TO PREDICT PEDIATRIC ASTHMA EXACERBATIONS AND PERSONALIZED RISK FACTORS


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**Abstract**

**Introduction**

Pediatric asthma is a common childhood disease significantly impacting quality of life. Current management is inadequate, resulting in a high prevalence of uncontrolled asthma in children, who face increased risks of unpredictable exacerbations from various factors. The numerous demographic, clinical, and environmental factors influencing exacerbations, combined with their complex interactions, underscore the need for machine learning (ML) to identify predictive patterns. However, existing ML models lack generalizability and clinical implementation. Therefore, the PREDICTA study aims to develop an ML model for predicting asthma exacerbations that fits into regular pediatric asthma care.

**Methods**

This research comprised three parts, the first involved an exploratory literature review to identify ML studies for predicting pediatric asthma exacerbations. The second part was a retrospective simulation study to develop LSTM and XGBoost modelz for predicting pediatric asthma exacerbations. It used electronic patient data from MST, covering 3.5 years and including patient characteristics, clinical and environmental outcomes, and healthcare utilization. Severe asthma exacerbations were defined as hospitalizations requiring prednisone or salbutamol nebulization, while moderate exacerbations involved the same treatments without hospitalization. The third part involved interviews with six pediatricians about their definitions, expectations, and trust in an ML model for predicting asthma exacerbations.

**Results and Discussion**

The literature review revealed a predominant use of XGBoost models, while LSTMs remain underutilized. Key challenges to model accuracy and clinical use included unstandardized definitions, limited input factors, and inconsistent performance metrics. In the simulation study, the LSTM and XGBoost models had low predictive power (sensitivity XGBoost: 0.11, LSTM: indeterminate) due to class imbalance (129 exacerbations present versus 2.3 million absent). The LSTM offered personalized, time-dependent predictions, while the XGBoost struggled with individualized predictions. Interviews revealed that pediatricians expect a model to identify individual risk factors, support decision-making, and present results transparently. Three applications were highlighted: 1) a personal risk dashboard for patient self-management, 2) a risk dashboard for pediatricians during outpatient visits, and 3) an eHealth monitoring tool for at-risk patients.

**Conclusion**

This research emphasizes the need to standardize asthma exacerbation definitions, as variability hinders model comparisons and accuracy. The low number of exacerbations challenges model performance, but improving input factors, optimizing parameters, and addressing class imbalance can enhance it. Enhancing model explainability is crucial for future research and should involve healthcare professionals and patients. The three proposed applications have the potential to enhance and personalize asthma management, allowing for a more effective, patient-centered approach to managing pediatric asthma.

**Keywords**

Pediatric asthma, asthma exacerbation, prediction, Machine Learning, healthcare professional involvement

# Contents

# 1 Introduction

## 1.1 Pediatric Asthma

Pediatric asthma is a prevalent chronic respiratory condition affecting children and young adolescents up to 20 years, with an estimated prevalence of approximately 7% in the Netherlands [1, 2]. Asthma is characterized by clinical manifestations, including inspiratory and expiratory wheezing, dyspnea, and cough [3, 4]. The clinical manifestation can be chronic and acute and shows an episodic character.

The pathophysiology of asthma involves a chronic inflammatory process triggered by a complex combination of possible factors and triggers, which differ for each patient [3, 4]. Following exposure to these triggering elements, inflammatory mediators are released within the airways, setting off a cascade of events that contribute to the acute and chronic symptoms of asthma. This includes the contraction of smooth muscles, increased mucus secretion, increased vascular permeability, and edema of lung tissue. These combined effects result in bronchoconstriction and subsequent airway obstruction.

### 1.1.1 Asthma Exacerbation

In the Global Initiative for Asthma (GINA) guidelines, an asthma exacerbation is defined as "an episode characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness, and progressive decrease in lung function, i.e. it represents a change from the patient's usual status that is sufficient to require a change in treatment" [5].

Asthma exacerbations in children have a high clinical impact due to the immediate health risks and the long-term consequences [6]. The acute effects of asthma exacerbations include (severe) respiratory distress, increased hospitalizations, and substantial disruption to daily life, including missed school days and reduced physical activity [7–9]. Preventing exacerbations during childhood is crucial, as it allows for less time spent ill, leading to improved physical and social development. Moreover, effective management in the early stage significantly decreases the risk of chronic disease in adulthood. The high prevalence of uncontrolled asthma further underscores the urgent need for innovative strategies to enhance pediatric asthma management [10].

The GINA definition of asthma exacerbations is rather broad, making it susceptible to various interpretations in the literature. Furthermore, only the official statement by the American Thoracic Society (ATS) and European Respiratory Society (ERS) distinguishes between adult and pediatric asthma exacerbation definitions [11]. They highlight that a moderate asthma exacerbation in pediatric asthma is treated with an increased dose of inhaled corticosteroids (ICS) instead of systemic corticosteroids. The switch to systemic corticosteroids defines a severe asthma exacerbation.

### 1.1.2 Pediatric Asthma Care

As highlighted in the GINA guidelines, the primary objective of asthma treatment is to achieve sufficient symptom control while minimizing the risks of asthma-related mortality, exacerbations, airflow limitation, and treatment-related side effects [12]. The patient's needs and priorities complement this overarching treatment objective.

The medication for pediatric asthma treatment can be divided into controller and reliever medication. The controller medication is focused on the long-term treatment of inflammation and the reliever medication is focused on acute relief of symptoms. Furthermore, multiple aspects can influence asthma management such as therapy adherence to the controller medication, inhalation technique, perception of symptoms, education, environmental control, lifestyle, comorbidity management, and allergen exposure control [13–21]. The great variety and varying impact of these influencing factors result in the high complexity of pediatric asthma management.

## 1.2 Artificial Intelligence

Artificial Intelligence (AI) encompasses a diverse field in computer science dedicated to developing intelligent systems capable of performing tasks traditionally requiring human intelligence [22]. AI has demonstrated remarkable capabilities in learning patterns from vast and diverse datasets [23, 24]. Within the broad definition of AI, Machine Learning (ML) is a specialized branch where statistical models learn patterns from data to accomplish specific tasks such as prediction and categorization [23, 24]. In recent

years, ML models have grown significantly in medicine, leveraging their capacity to handle vast and multi-dimensional datasets [23,25].

### 1.2.1 Predicting Asthma Exacerbations

The evolving landscape foresees enhancements through electronic data collection [22,26]. Zhang et al. foresee that electronic data collection utilizing smartphone apps linked to digital spirometers and inhalers can further enhance the predictive capabilities of ML algorithms [22]. However, further studies are crucial to determine whether these advancements translate into improved clinical outcomes and assess the cost-effectiveness of predictive algorithms for conditions like asthma [22,25].

Asthma exacerbations substantially burden the affected individuals and contribute significantly to healthcare utilization and costs [27]. Understanding the influencing factors and their magnitude on asthma exacerbations is crucial for developing effective preventive strategies [28]. The complexity of these factors highlights the need for sophisticated analytical tools. Given the multifactorial nature of asthma exacerbations, the application of ML to analyze big data holds great promise in identifying complex relationships and predictive patterns [22,29,30]. The ability of ML models to discern subtle interactions among various contributing factors can provide an opportunity to advance our understanding of the dynamics leading to asthma exacerbations and provide predictions over time.

Moreover, Van Smeden et al. emphasize the importance of a well-defined prediction horizon, the time window within which predictions are relevant and actionable [31]. There is no consensus on the optimal prediction horizon for pediatric asthma exacerbation corresponding to the window of reversibility of imminent exacerbation which also shows an interpatient variability. The proposed range varies from hours to days and weeks [31,32]. This variability affects model accuracy and hinders clinical integration.

Existing prediction models for pediatric asthma exacerbation use various AI methodologies, focusing on single-domain analyses such as genetic, comorbid, biological, environmental, or social factors [28]. These models fail to incorporate the complex interplay between these domains, limiting their predictive power. These models have not been integrated into standard clinical care [32]. This highlights a research gap between understanding domain interplays and practical AI model implementation in clinical settings.

### 1.2.2 Explainable AI

Explainable AI (XAI) focuses on making AI models transparent and understandable, which is crucial for effective implementation in healthcare settings [33–35]. Current machine learning models lack generalization and practical applicability in predicting pediatric asthma exacerbations due to minimal input from healthcare professionals and their "black box" nature, producing outputs without clear reasoning [32,36]. This lack of transparency undermines trust and limits clinical integration, highlighting the need for XAI to provide decision-making insights [33,35]. Most research has prioritized algorithmic development over a user-centered design approach, emphasizing the importance of explainability in building clinicians' trust and confirming AI's practical utility in clinical settings, specifically for the patient as individual [34,37,38]. Involving healthcare professionals in the design process ensures that AI systems meet clinical needs, ethical standards, and workflow requirements, leading to more effective and user-friendly integration [36,39–41].

## 1.3 Research Objective

The significant impact of asthma exacerbations and the high prevalence of uncontrolled asthma underscore the urgent need for innovative approaches to enhance asthma management [10]. Moreover, prediction and prevention of asthma exacerbations are needed to advance and tailor asthma management as current clinical practice lacks the tools to disentangle and timely identify personal signals preluding asthma exacerbations [42]. Improving insight into the multitude of factors influencing asthma exacerbations is crucial for developing effective preventive strategies [28,30].

Thus, this research aims to develop an AI model for predicting pediatric asthma exacerbations that can be applied to regular asthma care in the pediatric department. Furthermore, this AI model can determine the personal risk factors at play in the build-up to an asthma exacerbation for each patient.

This research is divided into three sequential parts. The first part consists of literature research, the second part focuses on simulating machine learning models, and the third part consists of interviews with healthcare professionals.

The research questions of the first part aim to answer the following questions from the literature:

- What machine learning models are used in the literature to predict pediatric asthma exacerbations?
- What definitions of asthma exacerbation are used in the literature?
- What time horizons for predicting asthma exacerbations are achieved in the literature?

The research questions of the second part aim to answer the following questions from the machine learning model simulations:

- What is the performance of machine learning models in predicting pediatric asthma exacerbations?
- How can machine learning models determine risk factors for the individual patient?
- What is the predictive impact of the definition of asthma exacerbations?
- What time horizon for predicting asthma exacerbations can be achieved?

The research questions of the third part aim to answer the following questions from the interviews:

- How would healthcare professionals define asthma exacerbations?
- What time horizons are most useful according to healthcare professionals?
- How do healthcare professionals prefer to integrate asthma exacerbation prediction into their clinical workflow?

The first part is presented in Chapters 3, 4, 5, the second part in Chapters 6, 7, 8, and the third part in Chapters 9, 10, 11. In Chapter 12, a general discussion and conclusion are presented, integrating insights from all three parts to provide an overview of the findings.

# 2 Background

## 2.1 Asthma Exacerbation

As mentioned before, the general definition of an asthma exacerbation as set by the GINA guidelines is rather broad [5]. To demonstrate the range of interpretations, several definitions from various studies are shown in Table 2.1, highlighting the differences in the comprehensiveness of each definition. Notably, the only definitions tailored to pediatric asthma exacerbations are the definitions mentioned by Reddel et al. [43]. A more extensive explanation of each definition is shown in Appendix A.

Table 2.1: The different definitions of asthma exacerbations throughout the literature.

| | Reddel et al. [11] | Altman et al. [44] | Murray et al. [28] | Helen et al. [45] | GINA 2024 [12] | Virchow et al. [46] |
|---|---|---|---|---|---|---|
| Increase in symptoms | Moderate exacerbation | | Significant exacerbation | | Exacerbation | Moderate exacerbation |
| Decrease in lung function | Moderate exacerbation | | | Exacerbation | | Moderate exacerbation |
| Change in daily controller medication | Severe exacerbation | | | Moderate exacerbation | Exacerbation | |
| Need of systemic corticosteroids | Severe exacerbation | Exacerbation | Significant exacerbation | Severe exacerbation | | |
| Hospital admission | | Exacerbation | Severe exacerbation | | | |
| Life-threatening | | | Severe exacerbation | | | |
| Emergency room visit | Severe/moderate exacerbation | | | | | Moderate exacerbation |
| Increase in reliever medication | Moderate exacerbation | | | | | Moderate exacerbation |
| Nocturnal awakening | | | | | | Moderate exacerbation |

The criteria increase in asthma symptoms and the need for systemic corticosteroids are used most in the literature although the definition varies from asthma exacerbation to moderate, significant asthma exacerbation, and severe asthma exacerbations. Interestingly, the need for systemic corticosteroids is classified as a significant asthma exacerbation together with the criterium of an increase in symptoms by Murray et al. but classified as severe asthma exacerbation by Helen et al. and Reddel et al. [11, 28, 45]. Furthermore, a distinction is made between a hospital admission and an emergency visit as the severity of the asthma exacerbation is greater for a hospital admission than for an emergency visit. Moreover, three criteria are based on medication usage, two on healthcare utilization, and two on asthma symptoms. The criteria based on the asthma symptoms are mostly classified as the less severe asthma exacerbation [44, 46]. Lastly, the criterion based on the decrease in lung function classifies the asthma exacerbation as moderate. However, Reddel et al. and Virchow et al. do not provide a clear cut-off value, making it difficult to distinguish between a loss of asthma control and a progression into a more severe exacerbation.

## 2.2 Asthma Management

### 2.2.1 Pharmacological Asthma Management

The medication as part of pediatric asthma treatment consists of controller and reliever medication [5]. Inhalation corticosteroids (ICS) are controller medications and aim to reduce airway inflammation, control asthma symptoms, and reduce overall risks of asthma exacerbation and a further decline in lung function. Reliever medication seeks to provide relief of acute asthma symptoms. Reliever medication includes either short-acting beta-agonists (SABA) or a combination of ICS and formoterol. The mechanism of reliever medications involves the relaxation of smooth muscles in the airway, effectively widening the airway for immediate symptom relief. The approach of combining reliever and controller medication is more compatible with daily practice and not only addresses the underlying inflammatory processes but also provides tailored relief for acute symptoms. Furthermore, treating asthma exacerbations consists of repetitive rapid-acting reliever medication, introduction to systemic corticosteroids such as prednisolone or prednisone, and flow oxygen supplementation.

### 2.2.2 Non-Pharmacological Asthma Management

Therapy adherence and proper inhalation technique are crucial for effective asthma management [16–18, 47, 48]. Non-adherence and incorrect inhalation technique are associated with lower medication deposition in the lungs, resulting in lower asthma control [16, 17]. The variable and episodic nature of asthma, along with challenges like steroid phobia and the lack of immediate relief from inhaled controller medications, complicates medication adherence [16, 18].

Self-management and education are essential aspects of effective asthma management [17, 49–51]. Asthma self-management empowers patients to achieve treatment goals, monitor and manage symptoms, and adapt to lifestyle changes associated with chronic illness by avoiding triggers and maximizing therapy adherence [52]. Education on asthma (management) plays a vital role in equipping patients with the motivation, skills, and confidence needed to control their asthma through self-management [50, 53].

Symptom perception is critical in asthma management as it affects self-management, e.g. how patients recognize and respond to their symptoms [15, 54]. Accurate perception is key for early detection and timely management of asthma exacerbations.

Managing comorbidities is crucial for effective asthma management, as they impact asthma control [21, 51]. Asthma comorbidities include obesity, (non-) allergic rhinitis, chronic rhinosinusitis, obstructive sleep apnea, dysfunctional breathing, inducible laryngeal obstruction, and bronchiectasis [19, 21, 51]. Allergic rhinitis can lead to worsened asthma control and increased asthma symptoms. Additionally, inducible laryngeal obstructions and dysfunctional breathing reduce exercise tolerance, impacting asthma control. Effective asthma management must therefore include management of comorbidities.

Allergen and environmental control are critical components of effective asthma management [20, 55, 56]. Major allergens like house dust mites, pets, molds, and pollen play a significant role in asthma, and continued exposure can exacerbate asthma symptoms. Allergen avoidance can reduce clinical symptoms, particularly in patients with allergic rhinitis [57]. Additionally, indoor air pollutants and viral infections further complicate asthma control [55]. Therefore, allergen and (home) environmental control are essential aspects of asthma management by reducing asthma symptoms [20, 55–57].

Lifestyle and exercise are crucial in asthma management, as they significantly impact asthma control [19, 58, 59]. Decreased physical activity, poor nutrition, and obesity contribute to asthma symptoms and poor asthma control [19, 59]. While exercise can trigger bronchoconstriction, it is safe and beneficial for pediatric asthma patients [59]. Furthermore, dietary choices, such as consuming a Western diet high in saturated fats, may worsen asthma symptoms, while a Mediterranean diet rich in fruits and vegetables increases asthma control [19]. Thus, integrating a healthy lifestyle and regular exercise into asthma management is essential.

### 2.2.3 Exercise Challenge Test

In Medisch Spectrum Twente children with asthma visit the AIRCON (Astma Inspanning & Research Centrum Oost Nederland) approximately once a year as part of standard care. During this visit lung function, bronchial hyperactivity to an exercise test, and reversibility after reliever medication are measured. The AIRCON consists of a climate-controlled room in which children complete an exercise provocation test under a temperature approximating 10 Celsius. For assessing lung function, spirometry and forced oscillation techniques are used. After baseline measurements, the child exercises for six minutes in the

climate room at sub-maximal intensity [60]. Lung function measurements are assessed at certain times after the exercise test. The last measurement is executed after bronchodilator inhalation to assess the reversibility of bronchoconstriction.

This comprehensive aircon test is used as a diagnostic tool for diagnosing pediatric asthma as well as common comorbidities. These comorbidities include (non-)allergic rhinitis (prevalence up to 90% [61,62]), dysfunctional breathing (prevalence up to 30 % [63,64]), physical deconditioning (prevalence 38% [65]), and exercise-induced laryngeal obstruction (no specific prevalence known in pediatric asthma population [21]). Furthermore, this test allows for assessing asthma control, perception, and exercise tolerance in a close to real-life setting to further target asthma management.

#### 2.2.4 eHealth Pediatric Asthma Care

Electronic health (eHealth) is defined by Eysenbach as "an emerging field in the intersection of medical informatics, public health, and business, referring to health services and information delivered or enhanced through the Internet and related technologies [66]. eHealth constitutes a dynamic domain within health services and information and spans various domains such as digital apps, telemedicine, electronic health records, medication tracking, and clinical decision support systems [67,68].

Effective asthma care demands timeliness, accuracy, and patient-tailoring [67]. eHealth applications have the potential to facilitate proactive care, offering easily accessible and personalized asthma action plans, particularly beneficial for patients unresponsive to standard treatments and at a higher risk of asthma exacerbations. Furthermore, technology-supported home care tailored to the individual child and healthcare system can complement scheduled hospital evaluations [69]. eHealth asthma care, appearing both technically and clinically feasible, enables safe remote care and proves beneficial for pediatric asthma care regarding health outcomes and healthcare utilization [70]. Notably, home monitoring of physiological parameters correlates with pediatrician-assessed asthma control, as indicated by a constructed multivariate model, showcasing the high potential for monitoring asthma control and allowing healthcare professionals to assess it at home [71]. eHealth can aid in therapy by allowing for at-home measurement of treatment response and compliance and determining personalized asthma action plans [67,68]. Moreover, eHealth can be implemented as a monitoring tool to assess physiological parameters correlating with asthma control [69,71]. Also, the loss of asthma control can be timely anticipated using eHealth care [67].

Pediatric asthma care in Medisch Spectrum Twente (MST) is complemented with eHealth care through the Puffer app [69]. The Puffer application features a chat function for approachable and easy-access consultation with a healthcare professional with expertise in pediatric asthma, improving education, skills, and self-management. Moreover, it allows the patients to send pictures and videos for a more objective asthma symptom evaluation. Additionally, digital spirometers can be employed at home, with results conveniently transmitted via the Puffer app, enabling at-home lung function assessments. Presently, 45 patients are enrolled in the Puffer app.

The CIRCUS study is currently ongoing in the MST hospital [72]. This study is a cohort multiple randomized controlled trial (cmRCT) to assess risk factors in asthma management and compare the effects of eHealth interventions. This study will help discern risk factors and novel cues of asthma exacerbations, uniquely compare effective scalable eHealth solutions, and improve overall pediatric asthma management and care.

### 2.3 Machine Learning Models

Machine Learning (ML) is a specialized branch of artificial intelligence where statistical models learn patterns from data to accomplish specific tasks such as prediction and categorization [23,24,73].

ML algorithms can be broadly classified into unsupervised and supervised learning approaches [74,75]. While unsupervised learning enables the exploration of patterns and labels in patient samples without predefined labels, supervised learning operates on labeled data to make predictions on new samples [76]. In unsupervised learning, the algorithm identifies inherent structures and relationships within the data, revealing patterns that may not be apparent. In contrast, supervised learning uses a labeled dataset, where the algorithm learns from known outcomes to make predictions on new, unlabeled samples. The goal is to discover a pattern from the training data that can be applied to new, unseen samples to make predictions or classifications [73,77]. Thus, the model performance is greatly influenced by the labeling quality and outcome definition [78].

### 2.3.1 Model Categories

Probabilistic models, like Bayesian Networks (BN), Lasso Logistic Regression (LLR), and Multinomial Logistic Regression (MLR), make predictions by handling uncertainties and relationships between variables [77, 79]. BNs solve predictive problems using conditional probabilities and robustly handle noisy input data [79]. These ML models are mostly used for clustering and classification tasks.

Decision Trees (DT) and Random Forests (RF) split data recursively to make decisions, with RFs improving accuracy by averaging results from multiple trees [75, 77]. Each tree consists of nodes and branches, where nodes represent to-be-classified attributes, and branches represent values used to make decisions.

Ensemble methods, such as Gradient Boosting Models (GBM) and eXtreme Gradient Boosting (XGBoost), sequentially train multiple weak learners, each improving on the errors of the previous ones [77, 80–82]. It is based on the assumption that multiple weak classifiers create one strong classifier which has learned from all previous classification errors. This method primarily improves model performance [81, 83].

Neural networks, including Artificial Neural Networks (ANN) and Long Short-Term Memory (LSTM) models, learn complex patterns through interconnected nodes [77]. They consist of algorithms that recognize underlying associations in a dataset similar to the human brain. LSTMs excel in sequential data analysis and capture long-term dependencies [84–86]. Their ability to handle irregular data and missing values makes them valuable in clinical settings.

Support Vector Machines (SVMs) apply kernel-based methods to perform linear and non-linear classification simultaneously by identifying optimal hyperplanes for separating classes [75, 77]. These models draw margins between classes with a maximum distance to minimize the classification error.

### 2.3.2 Performance Metrics

The area under the ROC curve (AU-ROC) is a widely used performance metric in the literature [87, 88]. It evaluates the model's ability to differentiate between classes across all thresholds, making it independent of any specific decision threshold [88, 89]. AU-ROC is also interpreted straightforwardly, with higher values indicating better class discrimination. It remains unaffected by class prevalence, thus maintaining performance consistency even in cases of class imbalance, though this may not fully reflect real-world scenarios [90].

Other common metrics include sensitivity (or recall), specificity, and accuracy, which are often presented together [75, 87, 91]. Sensitivity measures the proportion of correctly identified true positives (TPs) to false negatives (FNs). It can be calculated using the following formula:

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}. \tag{2.1}$$

Both sensitivity and specificity are independent of prevalence, making them reliable in imbalanced datasets [90]. The specificity reflects the model's ability to correctly identify the true negatives (TNs) in relation to false positives (FPs) and can be calculated using:

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}. \tag{2.2}$$

Accuracy reflects the overall proportion of correct predictions and is calculated using true positives, true negatives, false positives, and false negatives:

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}} \tag{2.3}$$

In contrast, precision (or positive predictive value) measures the proportion of true positive results among all positive predictions made by the model, indicating the accuracy of the positive predictions. It depends on class prevalence, making it particularly useful when dealing with class imbalance. It can be calculated using:

$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}}. \tag{2.4}$$

Like the AUC-ROC, the AUC-PR assesses the trade-off between precision and recall but is particularly useful for imbalanced datasets [92,93]. It provides a clearer view of model performance by focusing on the precision-recall trade-off. It is less affected by the number of correctly predicted negatives, making it less likely to exaggerate performance in cases of class imbalance [90,92–94].

The F1 score combines precision and recall into a single metric, balancing both aspects to provide a comprehensive evaluation, especially important when dealing with imbalanced class distributions [87,95]. It is the weighted mean of precision and recall, reflecting the model's ability to manage both false positives and false negatives effectively [90,95]. It can be calculated using:

$$\text{F1 score} = 2 \times \frac{\text{TP}}{2\text{TP} + \text{FP} + \text{FN}}. \tag{2.5}$$

### 2.3.3 Explainability

Explainability regarding the input features most important for the prediction can be performed in several ways of which the most used are presented here.

Feature permutation involves permuting the values of a feature and observing the impact on the model's performance [96–98]. A significant increase in model error following permutation indicates that the feature is important for prediction.

SHAP (SHapley Additive exPlanations) assigns each feature a value that represents its contribution to the prediction [99,100]. By using kernel-based SHAP, feature importance can be computed for a specific patient and also averaged across the whole population.

Gradient boosting models (GBMs), such as XGBoost, offer built-in feature importance metrics [83, 101], including gain (the improvement in accuracy from a feature split), frequency (how often a feature is used), and coverage (the number of samples affected by a feature's splits) which give a global importance score.

For model-agnostic local feature importance, Local Interpretable Model-agnostic Explanations (LIME) can be employed [83,102]. LIME generates a synthetic dataset near the observation of interest and trains a surrogate interpretable model to explain predictions locally. Similarly, Diverse Counterfactual Explanations (DiCE) can be employed for model-agnostic counterfactual explanations [103]. DiCE generates multiple diverse counterfactual instances by minimally altering feature values to show how small changes in the input could lead to a different prediction, providing insight into the model's decision boundaries.

In deep learning models, techniques such as integrated gradients and attention mechanisms can enhance interpretability [104]. Integrated gradients attribute a model's predictions to individual input features by integrating gradients along a path from a baseline input. Attention mechanisms, commonly used in sequence models like LSTMs, highlight which parts of the input sequence the model focuses on for making predictions.

Model uncertainty estimation methods, such as Monte Carlo Dropout, also contribute to explainability by quantifying the model's confidence in its predictions [105].

## 2.4 Factors influencing Asthma Exacerbations

Factors in various domains, including genetic, comorbid, biological, external, environmental, social, and psychological factors contribute to the heightened risk of recurrent asthma exacerbations in children [28].

### 2.4.1 Demographics

Within the literature, gender distinctions have been identified as a factor influencing the likelihood of an asthma exacerbation [106,107]. Boys demonstrate heightened susceptibility until puberty, after which females are predisposed to acute asthma exacerbations throughout their lives [108,109].

Finally, social factors, such as lower socioeconomic status, are recognized as contributors to the risk of asthma exacerbation [108,110,111]. The reasons for this are likely intricate, encompassing either poor nutrition, exposure to cigarette smoke, air pollution, or a combination of these factors. Additionally, a history of cigarette smoking, tobacco exposure, and e-cigarettes is associated with an increased risk [106, 112,113]. Moreover, race and ethnicity can influence the risk of asthma exacerbation with non-Hispanic black children and African American children having a greater risk of asthma exacerbation, but this is mostly investigated in the United States [30,106,107,114,115].

Furthermore, genetic risk factors can influence the asthma exacerbation risk in children as genome-based studies identified genes predisposing to asthma exacerbations [116,117]. Exacerbation-prone asthma is a phenotype characterized by metabolic dysfunction which has been associated with elevated levels of IL-6, which along with eosinophils, has been shown to predict asthma exacerbation risk [116]. Moreover, gene-environment interactions add complexity to the genetic factors influencing asthma, with evidence suggesting that these interactions play a role in the severity of rhinovirus-triggered asthma exacerbations [118]. Overall, the genetic predisposition to asthma exacerbations is driven by a complex interplay of intrinsic asthma-related genes and external environmental factors.

### 2.4.2 Clinical Factors

Children with poorly controlled asthma have a significantly higher risk of asthma exacerbations, underscoring the importance of consistent therapy adherence [30,119]. The frequent use of reliever medication, particularly salbutamol, for more than two days in two weeks on top of controller medication, is a strong predictor of future severe asthma exacerbations [30,120]. Poor adherence to asthma treatment, including improper use of inhaled medications and devices, is linked to an increased risk of asthma exacerbations and hospital admissions [16,18,30,121–124].

Comorbidities amplifying the risk of asthma exacerbations include obesity, which has been associated with poor asthma control and severe asthma exacerbations [30,106,115,125,126]. Rhinitis, both allergic and non-allergic, contributes to poorer asthma control and a higher frequency of asthma exacerbations which can be indicated with IgE as biomarker [21,106,119,126–128]. Chronic stress and anxiety are also important factors that can exacerbate asthma symptoms [30,115,129,130].

Previous asthma exacerbations are strong predictors of future asthma exacerbations [30,119,125,131,132]. The odds for a second asthma exacerbation do not necessarily increase with increasing severity of an initial exacerbation. [131]. The use of oral corticosteroids and emergency department visits or hospitalizations for asthma symptoms in the past year are significant indicators of a heightened risk for subsequent asthma exacerbations [30]. Biomarkers such as blood eosinophil counts and serum IL-6 levels have been associated with an increased risk of asthma exacerbations [30,115,133–137]. Additionally, higher fractional exhaled nitric oxide (FeNO) levels could indicate a higher risk of asthma exacerbation but its predictive power is low [138,139]. However, evidence remains conflicting, and specific volatile organic compounds (VOCs) patterns in exhaled breath, have shown promise in predicting asthma exacerbations [30,109,140]. Lastly, vitamin D insufficiency has been associated with worse lung function and poor asthma control, although supplementation has not significantly improved the time to the next severe asthma exacerbation [141,142].

Spirometry measures, particularly a lower $FEV_1$% predicted, are strongly associated with an increased risk of asthma exacerbations in the subsequent year [30,138,143]. Furthermore, the ratio between $FEV_1$ and FVC had some predictive power for severe asthma exacerbations in children [144] Reversibility to bronchodilators measured in spirometry heightens the risk of an asthma exacerbation [145,146]. Oscillometry measures such as the resistance at 5Hz, the resistance difference at 5Hz and 20Hz, the reactance at 5Hz, and the area under the reactance curve yield some predictive power for predicting asthma exacerbations [144,147]

### 2.4.3 Environmental Factors

Environmental factors contributing to asthma exacerbations include urbanization, which increases outdoor pollution and is particularly evident in high-income countries [113,117,148]. Air pollution, specifically particulate matter ($PM_{2.5}$), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), and ozone ($O_3$), is a significant risk factor for asthma exacerbations in children [30,44,115,119,149]. Even short-term exposure to high concentrations of these pollutants can significantly elevate the risk of an asthma exacerbation [150]. Lastly, exposure to smoke is another critical environmental factor, as it is associated with worsening lung function, decreased response to treatment, and increased emergency department visits for asthma [115,119,151].

Viral infections, particularly human rhinovirus (HRV), are well-established triggers of asthma exacerbations in children and may serve as a biomarker for imminent attacks [30,115,119,152–154]. Other respiratory viruses, such as respiratory syncytial virus (RSV), influenza, and parainfluenza, also contribute to frequent wheezing and severe exacerbations in early childhood, often acting alone or in combination [115,155,156]. Additionally, the return to school in autumn is associated with a rise in asthma exacerbations, linked to rhinovirus infections and a lack of consistent medication use at school [108].

Exposure to allergens not only triggers asthma symptoms but also interacts with viruses, further increasing the risk of asthma exacerbations, particularly in children [30,44,115,119,149]. Elevated allergen exposure, including pollens influenced by wind speed and rainfall, can heighten airway inflammation, induce symptoms, and raise the likelihood of asthma exacerbations [57, 157, 158]. Seasonal variations also play a role, with exacerbations peaking in late spring due to high grass pollen counts and increased humidity and a second peak occurring around the end of the hay fever season [30].

Meteorological data influences the risk of asthma exacerbations [152, 159]. Cold temperatures and extreme weather conditions are independent predictors of asthma exacerbations, with lower temperatures particularly associated with higher hospital admission rates for asthma [160, 161]. Humidity and temperature also hold predictive power for predicting asthma exacerbations [156]. Additionally, weather-related triggers such as pollen, wind speed, and rainfall are linked to increased asthma exacerbations in children [152].

# 3 Methods - Literature Study

## 3.1 Literature Research

The literature research was conducted with a scoping approach and aimed to identify relevant studies on machine learning models for predicting pediatric asthma exacerbations. This scoping literature research included studies without restriction on publication date. The inclusion criteria are:

- Article is written in English
- Full text of the article is available
- Article is an original research
- Use of an ML model
- Predictions within the asthma domain (e.g. asthma exacerbations, loss of asthma control, asthma deterioration, or asthma symptoms)
- Inclusion of either children, adults, or both

The search, finalized at the beginning of March 2024, included articles from PubMed, Scopus, and Google Scholar. The key search terms are shown in Appendix B.

## 3.2 Data Extraction

The data extraction consisted of article characteristics, machine learning model characteristics, input data, outcome definition, population characteristics, time horizon, and performance metrics. This is further elaborated in Table 3.1.

## 3.3 Data Analysis

Articles are categorized into three distinct groups based on their relevance to the research objectives. This categorization is determined by the study populations' age range and the models' outcome definitions. For further objectification, the criteria are further elaborated in Table 3.2. This approach ensures that only the most relevant studies, directly addressing the research objectives, are highlighted in the results.

For each extracted domain, the results are systematically presented using tables and figures, supplemented with a descriptive analysis to provide context and interpretation. The visualization of the models' input characteristics is shown as either present or not present, categorized by the different domains. The values of the most used model's performance metrics are visually presented.

Assessing the quality of the included articles is beyond the scope of this literature review, which primarily focuses on examining the range of models used in the literature.

Table 3.1: Data extraction of the literature research.

| **Extraction domain** | **Elaboration*** |
|---|---|
| Article characteristics | Year of publication |
| Machine learning model characteristics | Number of ML methods, different types of ML methods, best-performing ML method (if multiple methods are presented) |
| Input data | General description of included input domains |
| Input data: demographics domain | Use of age, sex, gender, ethnicity, race, and language |
| Input data: clinical measurements and vital signs | Use of weight, height, BMI, respiratory rate, heart rate, saturation, blood pressure, temperature, eosinophils, IgE, and other |
| Input data: asthma characteristics | Use of medication, ACT, symptoms, asthma history, medical history, lung function (spirometry), FeNO, VOC, tobacco exposure, and family history |
| Input data: comorbidities | Use of allergies, eczema, obesity, and general comorbidities |
| Input data: healthcare utilization | Use of previous exacerbation, ER visits, ER arrival mode, number of outpatient visits, number of hospitalizations, and other |
| Input data: social data | Use of home area, housing conditions, insurance, household income, and other |
| Input data: environmental data | Use of air pollution, meteorological data, pollen data, virus data, and other |
| Input data: at-home measurements | Use of at-home symptoms and at-home spirometry |
| Outcome definition | Description of defined outcome |
| Population characteristics | Number of included patients, age range of included patients |
| Time horizon | Presence and the exact value of time horizon |
| Performance metrics | Use and the exact value of AU-ROC, sensitivity, specificity, accuracy, recall, positive predictive value, negative predictive value, AU-PR, and F1 score |
| * ML = Machine Learning, BMI = Body Mass Index, ACT = Asthma Control Test, FeNO = Fractional exhaled Nitric Oxide, VOC = Volatile Organic Compounds, ER = Emergency Room, AU-ROC = Areau Under the Receiver Operator Curve, AU-PR = Area Under the Precision-Recall curve | |

Table 3.2: Criteria for articles' assessment of relevance.

| | **Study populations' age range** | **Models' outcome definitions** |
|---|---|---|
| **Highly relevant** | Pediatric | Asthma exacerbation, hospitalization for exacerbation, or ER visit for exacerbation |
| **Moderately relevant** | Pediatric and adults | Asthma control, asthma symptoms, general hospitalizations, general ER visits |
| **Least relevant** | Adults or unknown | Asthma persistence, asthma scores, severity of asthma exacerbation |

# 4 Results - Literature Study

## 4.1 General Results

The number of found articles was not saved in this study. A total of 63 articles were included in the literature research, of which 16 were excluded during data extraction for not meeting the assessment of relevance criteria. In total, 13 articles were classified as highly relevant, 20 as moderately relevant, and 14 as least relevant. The highly applicable articles primarily focus on asthma exacerbation outcomes within pediatric or mixed-age populations. The moderately relevant articles generally use asthma exacerbation outcomes in adult populations only or hospitalization outcomes (Table C.4 in Appendix C). The least relevant articles include those articles using outcomes such as asthma control, symptoms, severity of asthma exacerbation, and readmissions (Table C.6 in Appendix C). The characteristics of the highly relevant articles, including the population details, machine learning methods, outcome definitions, and time horizon, are summarized in Table 4.1.

The 13 highly relevant articles range from 2007 to 2023, with 6 published in the last 5 years. The machine learning method most used is the gradient boosting models, which include the XGBoost models, followed by random forest models.

The outcomes are asthma exacerbations (moderate or severe), criteria for asthma exacerbations (hospitalization, emergency room visit, or systemic corticosteroids), or non-defined asthma exacerbations. The non-defined asthma exacerbation is used the most as the outcome, in 6 out of 13 articles. The age range starts between 2, 6, or even 15 and ends at 18. Five articles did not mention the age range specifically, two of these articles included both children and adults. The number of included patients varies greatly from less than 100 in five articles to a few thousand in three articles and even a few ten thousand in two. For most of the articles, the time horizon of the prediction was not mentioned. In three articles, the prediction's time horizon was set at 365 days; in one article, predictions were presented on multiple time horizons; 30, 90, and 120 days.

## 4.2 Input Results

Figure 4.1 shows the demographics, clinical characteristics, asthma characteristics, and comorbidities used as input for the machine learning models in the highly relevant articles. Table C.1 in Appendix C shows the tabular data. The definitions of input features are elaborated in Appendix D.

Most models use age and sex as demographic input for their model. Alternatively to sex, two models use gender. Four models use ethnicity as input of which two additionally use race. Respiratory rate, saturation, weight, and heart rate are the most used clinical measurements and vital signs. Furthermore, two models from the same group use blood pressure, temperature, eosinophils, immunoglobulin E, and X-rays as input features. Only one model used genome data as input data. Medication, spirometry measures, volatile exhaled compounds, asthma history, asthma symptoms, and fractional exhaled nitric oxide are the most used asthma characteristics. The asthma control questionnaire and the GINA symptoms score are both scores focussed on asthma symptoms and are used in three models. Allergies are the most used comorbidities as input for the machine learning models. Overall, there is a variety in the number of used input features for each model. The models by Luo et al. [168] and [169] use the highest number of input features overall (both 19 features in total) and also the most demographics and the most clinical measurements and vital signs. The models by van Vliet et al. [139] and [140] use the most asthma characteristics and relatively more input features than the other models. The model by Hurst et al. uses the most comorbidities as input for their model.

Figure 4.2 shows the healthcare utilization, social data, environmental data, and at-home measurements used as input for the machine learning models in the literature. Table C.2 in Appendix C shows the tabular data of this figure.

The input features from the four domains shown in Figure 4.2 are relatively less used than the input features shown in Figure 4.1. Three models use healthcare utilization, varying from emergency room visits, outpatient visits, and hospitalizations to billing codes and chief complaints. Four models include social data mostly using home area and insurance data. Three models include environmental data using air pollution, meteorological, virus, and climate data. Three models include at-home measurements of spirometry and symptoms. The model of Patel et al. uses the most social and environmental input data [166].

Table 4.1: The highly relevant literature comparison of machine learning models for predicting pediatric asthma exacerbations.

| **Source** | **ML methods*** | **Outcome*** | **Age range (number of patients)** | **Time horizon** |
|---|---|---|---|---|
| Dexheimer et al. 2007 [162] | BN, SVM, ANN | Asthma exacerbation (not further defined) | 2 – 18 (4023) | - |
| Lee et al. 2011 [163] | DT | Asthma exacerbation (not further defined) | Children (33) | - |
| Xu et al. 2011 [164] | RF | Hospitalization or ER visit | Children (417) | - |
| Robroeks et al. 2013 [165] | SVM | Moderate to severe asthma exacerbations | 6 – 16 (40) | - |
| Van Vliet et al. 2015 [139] | Conditional models | Moderate to severe asthma exacerbations following Reddel et al [43] | 6 – 18 (94) | - |
| Van Vliet et al. 2017 [140] | RF | Asthma exacerbation (not further defined) | 6 – 18 (96) | - |
| Patel et al. 2018 [166] | DT, RF, LLR, GBM | Hospitalization and receiving systemic corticosteroids | 2 – 18 (29392) | - |
| Kim et al. 2020 [167] | LSTM, MNL | Risk for asthma exacerbation | 6 – 14 (14) | - |
| Luo et al. 2020 [168] | XGBoost | Hospitalization or ER visit | Children and adults (unknown) | 365 days |
| Luo et al. 2020b [169] | XGBoost | Hospitalization or ER visit | Children and adults (unknown) | 365 days |
| Hurst et al. 2022 [152] | LLR, RF, XGBoost | Asthma exacerbation (not further defined) | 5 – 18 (5982) | 30, 90, 180 days |
| Hozawa et al. 2022 [170] | XGBoost | Asthma exacerbation (not further defined) | 15 – 18 (42685) | 365 days |
| Mandana et al. 2023 [171] | RF | Asthma exacerbation (not further defined) | Children (2042) | - |
| * BN = Bayesian Network, SVM = Support Vector Machine, ANN = Artificial Neural Network, DT = Decision Tree, RF = Random Forest, LLR = Lasso Logistic Regression, GBM = Gradient Boosting Models, LSTM = Long-Short Term Memory, MNL = MultiNomal Logistic, XGBoost = eXtreme Gradient Boosting, ER = Emergency Room | | | | |

The overall number of input features used in the model varies greatly as the model by Lee et al. [163] only incorporates 3 input features whereas both the models of Luo et al. [168] and [169] use 19 input features. The number of features for each model is shown in Figure C.1 in Appendix C. The mean number of features used is 9.7 features with a standard deviation of 5.5 features.

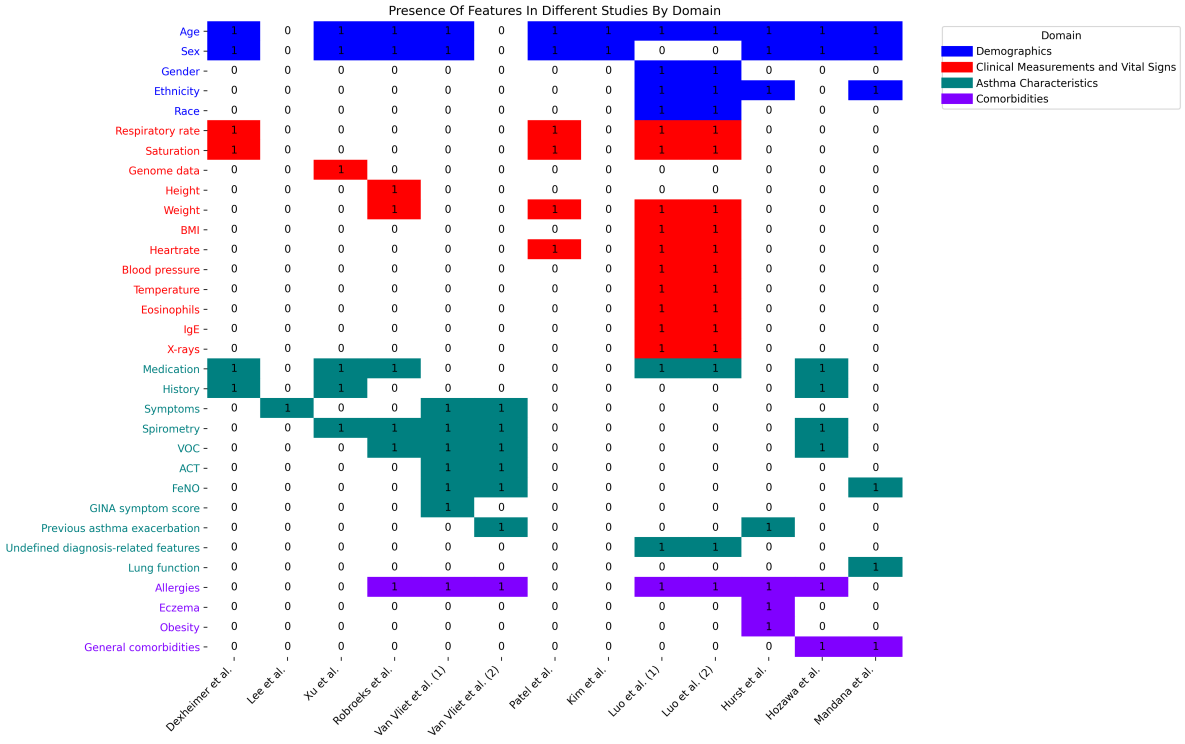


Figure 4.1: The input characteristics of the machine learning methods of the demographic, clinical, and asthma characteristics, and comorbidities domain. BMI = Body Mass Index, IgE = Immunoglobulin E, VOC = Volatile Exhaled Compounds, ACT = Asthma Control Test, and FeNO = Fractional Exhaled Nitric Oxide

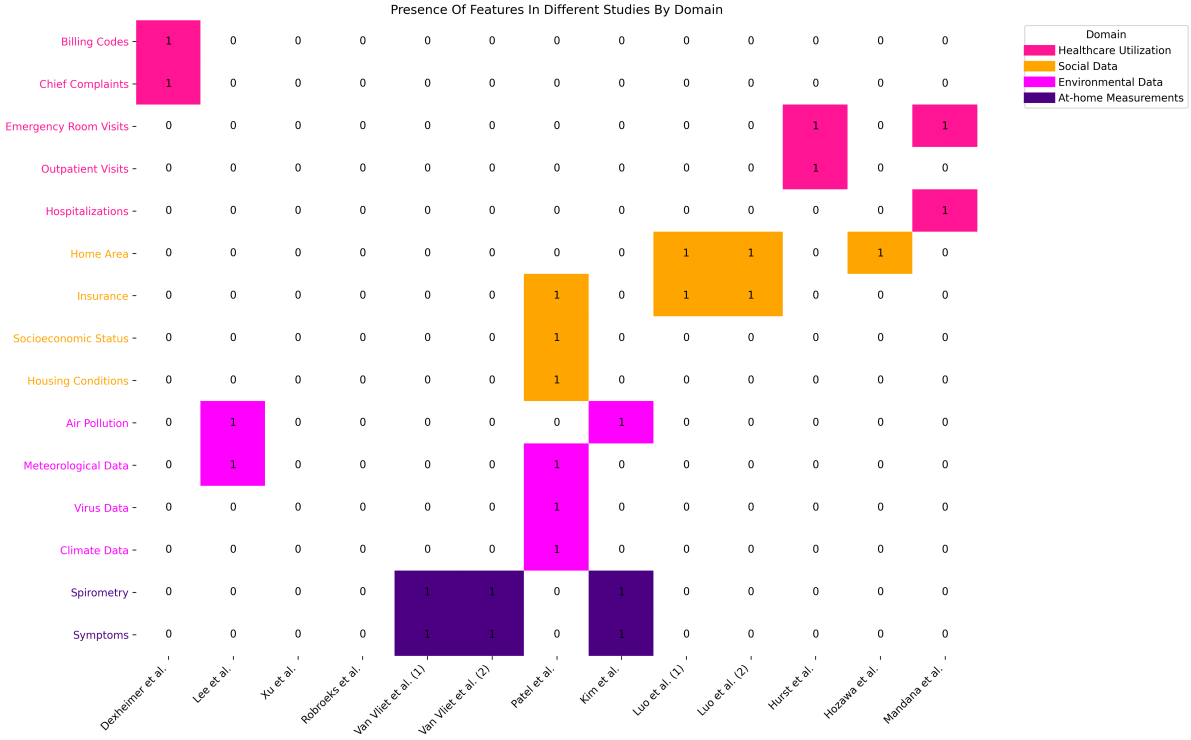


Figure 4.2: The input characteristics of the machine learning methods of the healthcare utilization, social, environmental, and at-home measurements domain.

## 4.3 Model Performance

Figure 4.3 shows the values of the model performances of the machine learning models in the highly applicable category. Table C.3 in Appendix C shows the tabular data.

The most used model performance metrics are the area under the receiver operating curve (AUC) (8 articles), sensitivity (7 articles), specificity (6 articles), and accuracy (6 articles). The AUC ranges from 59% to 96%, the sensitivity from 52% to 100%, specificity from 67% to 93%, and accuracy from 52% to 90%. Positive predictive value (PPV) was only presented in two articles. The negative predictive value, positive likelihood ratio, and negative likelihood ratio were model performance metrics only presented in one article and are therefore only shown in Table C.3 in Appendix C.

None of the models in the literature applied explainable AI to explain the model and reveal the predictive power of input features.

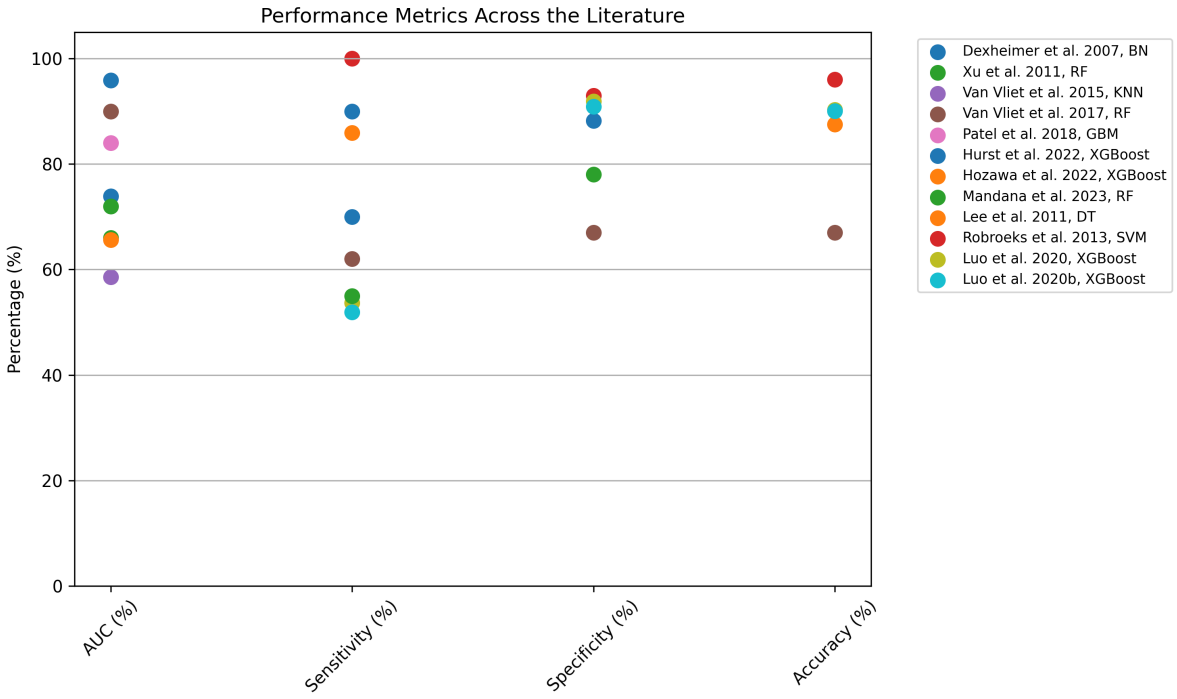


Figure 4.3: The model performance of the best-performing model for the most applicable articles. AUC = Area Under the receiver operating Curve, BN = Bayesian Network, RF = Random Forest, KNN = K-Nearest Neighbors, GBM = Gradient Boosting Model, XGBoost = eXtreme Gradient Boosting, SVM = Support Vector Machine, DT = Decision Tree.

# 5 Discussion and Conclusion - Literature Study

## 5.1 Discussion on General Model Characteristics

The literature research reveals that the most frequently utilized models for predicting asthma exacerbations are gradient boosting models (GBM), particularly XGBoost, alongside random forest (RF) models. A notable challenge arises from the varying definitions of asthma exacerbations for its prediction (see Table 2.1), leading to broad and sometimes ambiguous outcomes within the literature (see Table 4.1). Additionally, many studies lack clarity regarding the time horizon of their predictions, which can hinder clinical applicability.

Comparing the most used ML models based on their theoretic principles reveals their distinct strengths in handling complex datasets, addressing class imbalances, and managing overfitting for asthma exacerbation classification. GBMs, including XGBoost, are particularly effective for asthma exacerbation classification due to their capacity to handle complex, high-dimensional datasets and their robustness in scenarios involving class imbalances [81, 172]. GBMs excel by iteratively combining weak learners to build strong predictive models, making them particularly suitable for high-bias or unbalanced datasets [81, 82, 172]. XGBoost enhances this approach by incorporating strategies to reduce overfitting and optimize training speed, demonstrating scalability and efficiency [81]. Despite these advantages, GBMs are more prone to overfitting if not properly regularized, and their computational demands can be significant, particularly with larger datasets [172]. RFs are similarly advantageous, offering high performance with default hyperparameters and resilience across various class imbalance scenarios [81, 85]. Their efficiency in managing large input features with minimal preprocessing makes them well-suited for datasets that include missing values [172]. However, RFs computational demand can escalate with larger datasets, which is a potential disadvantage. A relatively unused model in pediatric asthma exacerbation is the Long Short-Term Memory (LSTM) model. This model is well-suited for capturing the long-term relationship of features at play in asthma [84–86]. Additionally, LSTM models require no feature engineering making it easier to implement [85, 86]. Nonetheless, the complexity of LSTMs necessitates time-series data, posing practical limitations.

The asthma exacerbation definitions vary greatly through the included studies. The models by Robroeks et al. [165] and van Vliet et al. [139] both defined asthma exacerbations as moderate to severe. However, as defined by Reddel et al. moderate and severe asthma exacerbations are rather different as a severe asthma exacerbation requires hospitalization and a moderate exacerbation requires a step-up in controller medication [45]. Further, models developed by Lee et al. [163], Luo et al. [168] and [169], and Patel et al. [166] utilize hospitalization or emergency room (ER) visits as definitions for asthma exacerbations. As detailed in the literature (Table 2.1), hospitalizations are typically associated with severe exacerbations, whereas ER visits often indicate moderate to severe exacerbations. This suggests that these four models may effectively merge two categories of asthma exacerbations. Although research has not yet fully explored the implications of using different categories of asthma exacerbations, the current models may combine patterns for predicting moderate and severe exacerbations. This blending of patterns could influence the predictions' accuracy. The variety in patient numbers used for model training poses another challenge for the asthma exacerbation definition. The varying age ranges in the included populations may impact model performance, as studies indicate that the risk of hospitalization for severe asthma exacerbations decreases with age [157, 173, 174]. Children under five years old are more likely to be hospitalized due to their smaller lung capacity and more pronounced symptoms [157].

The reviews by Ekpo et al. [175] and Rodriguez-Martinez et al. [176], focused on pediatric asthma prediction, indicated a wide range in children's ages across studies, with many studies not reporting age specifics; however, neither review examined the impact of this variation. Other reviews, such as those by Tsang et al. [177], Molfino et al. [178], Xiong et al. [32], Budiarto et al. [179], Khanam et al. [180], and Sarikloglou et al. [30], did not specifically address the age of included patients and did not focus explicitly on pediatric asthma. Given the higher risk of hospitalization for severe asthma exacerbation in younger children [157, 173, 174], future research should prioritize age group distinctions within the study population. For more meaningful comparisons of simulation results across studies, every study must report both age groups and their distribution relative to asthma exacerbations in the findings.

The absence of a clearly defined time horizon in many articles limits clinical applicability, as it restricts clinicians' ability to anticipate and intervene during potential exacerbations effectively. Of the four studies reporting the time horizon of the prediction, three studies used a time horizon of 365 days (models by

Luo et al. [168] and [169], and model by Hozawa et al. [170]). These predictions are thus more focused on the long-term control of asthma rather than acute asthma exacerbations. Hurst et al. [152] presented predictions on multiple time horizons: 30, 90, and 180 days. These time horizons reflect both the acute and long-term variability of asthma control.

The prediction of exacerbations is also explored in other chronic conditions, such as inflammatory bowel disease (IBD) and chronic obstructive pulmonary disease (COPD). Similar to the models employed in asthma exacerbation prediction, methods like XGBoost, random forests (RF), and neural networks are commonly utilized in the literature [181–185]. Notably, only Gan et al. [185] provided insights into the most important features for predictions, while the other studies lacked explanations regarding prediction mechanisms and feature significance. Furthermore, these models primarily focused on population-level predictions rather than personalized assessments. Zeng et al. were the only researchers to specify a one-year prediction horizon [181].

## 5.2 Discussion on Input Features

The input data for the models was categorized into eight domains: demographics, clinical measurements and vital signs, asthma characteristics, comorbidities, healthcare utilization, social data, environmental data, and at-home measurements. Most models predominantly utilized the categories of demographics, clinical measurements and vital signs, asthma characteristics, and comorbidities, which is expected given that these domains contain well-established risk factors [30] and are relatively easy to extract from electronic health records. Healthcare utilization data, such as prior hospitalizations and ER visits, was used in four models as the primary outcome (models by Xu et al. [164], Luo et al. [168] and [169], and [166]). From these four models, only the model by Patel et al. [166] used healthcare utilization as input for the model. The exclusion of this input data could impact model performance as past healthcare utilization could be highly predictive of future hospitalizations or ER visits [30, 131].

The social domain, although less explored in the context of asthma exacerbations, could play a significant role as a secondary risk factor; for example, lower socioeconomic status can lead to higher tobacco exposure, which is linked to increased risk of asthma exacerbation [106, 111]. Despite the strong evidence linking environmental factors to asthma exacerbations [57, 117, 152], this domain remains underutilized in the models, likely due to logistical challenges in data collection and the lack of personalized environmental exposure data. Environmental data is typically collected from local measurement stations, making it difficult to accurately reflect an individual patient's exposure. Finally, at-home measurements, which could provide valuable real-time data, are only used in two highly relevant studies (and three moderately relevant studies) for predicting pediatric asthma exacerbations but are used for assessing technology development and patient clustering as indicated by the review of Tsang et al. [177].

Most articles in this research primarily focus on specific domains, neglecting the integration of multiple domains (see Figure 4.1 and Figure 4.2. This limitation may significantly impact model performance, as it fails to capture the interplay of features from different domains. A more holistic approach that considers interactions across various domains could enhance the predictive accuracy and robustness of the models as it shows increased prediction accuracy compared to single domain prediction [42, 186].

## 5.3 Discussion on Model Performance

The area under the ROC curve (AUC) is a widely used performance metric in the highly applicable articles and the literature at large [88]. AUC is also interpreted straightforwardly, with higher values indicating better class discrimination. Other common metrics include sensitivity (or recall), specificity, and accuracy, which are often presented together [91]. Both sensitivity and specificity are independent of prevalence, making them reliable in imbalanced datasets, which are often used in asthma exacerbation prediction [90].

In evaluating model performance, two additional performance metrics are not presented in any of the articles; the area under the precision-recall curve (AUC-PR) and the F1 score. These performance metrics are less known from statistical analyses and therefore often neglected in machine learning studies. Nevertheless, the AUC-PR and F1 score could give a clearer view of model performance in unbalanced datasets [90, 90, 92, 95].

Although de Hond et al. advise reporting AUC values for clinical predictions without labeling the interpretation, an AUC value below 75% is mostly considered moderate to poor, and an AUC above 90% excellent [187]. Most models show moderate to poor AUC except the models by Patel et al. [166], van Vliet et al. [140], and Dexheimer et al. [162] with an AUC between 84% and 96% (see Figure 4.3). As for

the sensitivity performance metrics, the models show poor sensitivity indicating misidentifying asthma exacerbations as no asthma exacerbation. Sensitivity is a trade-off with specificity in which the latter shows the ability to identify the absence of an asthma exacerbation. In the case of asthma exacerbation, the sensitivity should be favored above specificity.

None of the models included in this study utilized XAI techniques to clarify the relevance of each input feature in predicting asthma exacerbations. Consequently, the importance of these features remains undetermined, limiting the model's clinical applicability and trustworthiness. This lack of transparency is a critical concern because, without insight into how and why specific features influence predictions, clinicians may be reluctant to incorporate AI recommendations into treatment decisions [32,36]. XAI techniques, such as SHAP, LIME, or Grad-CAM (Gradient Class Activation Mapping), can offer feature-level explanations that enable clinicians to understand the factors most strongly associated with exacerbation risk [188]. Establishing input feature relevance is therefore essential to foster confidence in AI predictions, empowering clinicians to interpret model outputs in a way that supports personalized, informed decision-making in pediatric asthma management. XAI techniques are gradually used more in healthcare, though their use remains limited. For instance, 25 of the 33 studies on cardiovascular disease risk prediction incorporated XAI methods in the review by Teshale et al. [189], while only 5 of 22 studies applied XAI for comorbidity prediction as shown in the review by Alsaleh et al. [190]. Similarly, a review by Loh et al. [191] highlights that only 99 studies used XAI across healthcare applications between 2018 and March 2022. This limited adoption underscores the need for further integration of XAI to enhance transparency and trust in predictive models across a wider range of medical conditions.

No direct correlation is apparent between the most commonly used models (GBM, XGBoost, RF) and their performance outcomes (see Figure 4.3). This indicates that model selection is likely driven more by usability, personal experience, and specific model features rather than performance alone. Additionally, there is no clear relationship between the number of patients included in a model and its performance. This lack of correlation may be due to variations in input characteristics, model types, and outcome definitions, which complicate direct comparisons. Similarly, the number of input features is not consistently correlated with model performance, likely due to model setup and data differences. The absence of clear correlations between model type, sample size, and feature numbers with performance highlights the need for future research to pinpoint that specifically the choice (and number) of input features and the ML model choice most significantly impact predictive accuracy.

## 5.4 Strengts and Limitations

This review is a pioneering exploration into input feature domains, explainability, and time horizons in machine learning models for predicting pediatric asthma exacerbations, addressing an age group often underrepresented in ML studies. By identifying commonly used input features, highlighting research gaps such as the limited integration of multi-domain data, and including social and environmental factors this review provides a comprehensive scope that pinpoints areas to enhance model accuracy and clinical relevance [42,186]. The focus on explainability further underscores the importance of transparency, which is crucial for building trust among healthcare professionals and promoting clinical adoption [33–35]. Additionally, the review identifies issues with inconsistent definitions of asthma exacerbations and prediction time horizons, which complicate model comparison and evaluation. Furthermore, one assessor performed the articles' relevance assessment, which resulted in uniformity of assessment criteria application. This reduced the potential for inter-assessor variability and allowed for a more focused approach.

A limitation of this review is that it did not strictly follow the PRISMA guidelines for systematic reviews [192]. As a result, certain relevant studies may have been missed, limiting the comprehensiveness of the review. Additionally, the relevance assessment was subjectively conducted due to an absence of well-defined inclusion criteria, as many studies did not provide clear definitions for their outcomes or specify the age ranges of their populations. Furthermore, as this field is rapidly advancing, the literature search was completed in March 2024, meaning studies published after that date are not reflected in the analysis. Future reviews would benefit from adhering more closely to systematic review guidelines and including up-to-date literature to provide a more current perspective on this evolving field.

As highlighted by Allgaier et al. [188], patients generally have a limited understanding of commonly used explainability methods. The understanding of these methods among pediatricians has yet to be studied, making it an important focus for future research. Enhancing explainability is crucial for fostering trust in predictive models among pediatricians. Many included studies did not specify a prediction time horizon. Future reviews could focus on examining prediction horizons beyond the scope of pediatric asthma. Prediction horizon generally impacts prediction accuracy [193]. For COPD (Chronic Obstructive

Pulmonary Disease), similar prediction horizons are often used without simulations to assess the effects of the chosen horizon [194]. In adult asthma exacerbation prediction, prediction horizons vary widely, ranging from 4 to 30 months [195]. This indicates that specific applications and impact of prediction horizons remain underexplored and could be an important focus for future reviews. Finally, the clinical implementation of predictive models was beyond the scope of this review. However, as Kothalawala et al. [196] reported in 2020, no prediction models had yet been implemented in pediatric asthma care. Given the recent increase in research on ML models, it would be valuable to investigate which models have since reached clinical practice. The research questions for future research are composed in Table 5.1.

Table 5.1: Research questions for future literature review studies.

| |
|---|
| Which XAI techniques are most favorably received in predictive asthma models? |
| What time horizons are used in general exacerbation prediction across multiple conditions? |
| Which prediction models are clinically implemented in (pediatric) asthma care? |

## 5.5 Conclusions

There is significant variation in how asthma exacerbations are defined across studies, ranging from hospitalization and ER visits to non-specific asthma exacerbations. This lack of standardization complicates comparisons across models and may affect the accuracy and applicability of the predictions. Furthermore, many studies fail to specify crucial details such as the prediction's time horizon and the population characteristics. This omission limits the clinical applicability of the models.

Most models rely on demographic, clinical, asthma characteristics, and comorbidity data, which are readily available from electronic health records. However, not many models utilize social, environmental, and at-home measurement data despite their potential predictive power. Furthermore, most models focus on specific domains, neglecting the integration of multiple domains. Incorporating factors from multiple domains could lead to more accurate and contextually relevant models.

Gradient Boosting Models, including XGBoost, and Random Forests are the most commonly used machine learning methods for predicting pediatric asthma exacerbations. These models are favored because they can handle complex datasets and deliver strong predictive performance. However, promising models like LSTMs remain underutilized. The choice of model often seems to be driven more by factors like usability and specific features than by performance metrics alone.

The area under the ROC curve is the most frequently used performance metric, with most models demonstrating moderate to poor performance. Other metrics like sensitivity, specificity, and accuracy are commonly reported whereas the area under the precision-recall curve and F1 score, particularly useful in handling imbalanced datasets, are rarely used.

Finally, the limited use of XAI techniques further restricts these models' clinical potential, as a lack of transparency in feature importance hinders clinicians' trust and ability to apply model outputs in practice. Increasing model interpretability is essential to building clinically useful models that support informed decision-making.

# 6 Methods - Simulation Study

## 6.1 Study Design and Population

The simulation study aims to develop an ML model for predicting asthma exacerbations and determining personal risk factors. Furthermore, the asthma exacerbation definitions and time horizon are explored.

The study uses a retrospective patient dataset encompassing all pediatric patients from November 11th, 2020 (the start of the electronic patient dossier) until April 1st, 2024 (the start of the CIRCUS study). The inclusion criteria include the diagnosis treatment code (diagnose-behandelcombinatie DBC 3202) corresponding to asthma and under treatment at the pediatrics department at MST.

## 6.2 Data Acquisition and Processing

The retrospective patient data is obtained through a non-WMO request (non-WMO approval acquired from the non-WMO committee at the MST on February 23$^{th}$, 2024). The patient data is retrieved on the 1st of July, 2024 through automated SQL (Structured Query Language) code. The patient data is structured based on electronic patient file segments such as allergies, appointments, and prescribed medication. The description of all electronic patient file segments is shown in Apprendix E. For each segment, a CSV (comma-separated values) file is saved to a secure database. The ICT department sets up usernames and passwords to restrict database access to researchers only. The CSV files on the server are loaded and preprocessed using Microsoft Visual Studio 2022 Version 17.11.2 (Microsoft Corporation, Redmond, Washington, United States). The ecological data CSV files are manually copied from a local laptop to the server using a USB stick.

The dataset encompasses a comprehensive array of demographic, social, clinical, and environmental data, as seen in Table 6.1. The number of comorbidities shown is derived from the patient's medical history and the number of asthma exacerbations following the definitions stated in Table 6.2. The highlighted variables are incorporated into the model. A more comprehensive elaboration on the measured ecological data is shown in Appendix F.

One dataset containing all different input data is constructed with a daily frequency. the variables with multiple values in one day are averaged into one variable. The variables that do not have a daily value (applicable for most variables) are padded with daily values (-9999) to ensure that the value is not interfering with real physiological data and can be detected as a padding value by the model. The dichotomous variables are padded with the original value to match the length of the time frame.

## 6.3 Model Development

Following the results from the literature review, an LSTM and XGBoost model are compared. Both models are implemented in Python 3.9, the XGBoost model is implemented using the Skicit-Learn package [197], and the LSTM model using the Tensorflow package [198].

The experiments and model training were conducted on a virtual machine on the server. The virtual machine type used was Standard D8s v3, belonging to the V1 generation and featuring a 64-bit architecture. The machine was equipped with 8 virtual CPUs and 32 GiB of RAM, running on Windows Server 2022 Datacenter as the operating system. These specifications were chosen to ensure sufficient computational resources for the machine learning tasks performed, balancing performance and cost within the project's constraints.

Generative AI (ChatGPT) is utilized to help in debugging the code.

### 6.3.1 Model Characteristics

The LSTM model incorporates a masking layer to handle missing or padded data, ensuring no interference with the learning process of the padded value. The model's core consists of multiple LSTM layers, which capture long-term dependencies in the data. These layers allow the model to learn from sequential information. To prevent overfitting, dropout layers are incorporated, which randomly omit certain connections during training. This regularization technique enhances the model's generalization ability when exposed to new data. The output layer uses an activation function that maps the model's predictions to a probability of the set outcome. The model is trained using an adaptive optimizer, efficiently adjusting

learning rates during model training. Additionally, class weights are applied during model construction to account for the class imbalance, ensuring the model gives proper attention to each class based on their prevalence in the dataset. In addition to the performance metrics, the computational times of the training and testing process are measured. The LSTM model is switched to a multi-class classification model for classifying the severity of the asthma exacerbation. A softmax activation function is incorporated in the output layer, mapping the model's predictions to a probability distribution across the three classes (no asthma exacerbation, moderate asthma exacerbation, and severe asthma exacerbation). The model's core remains the same.

The XGBoost model is designed for dichotomous prediction of asthma exacerbations. The time series data are flattened, transforming each patient's sequence of timesteps into a tabular format for the model. XGBoost's tree-based classifier is employed to handle this structured data. In addition to standard performance metrics, both training and testing times are recorded to assess the model's computational efficiency.

### 6.3.2 Asthma Exacerbation Definition

Different definitions of asthma exacerbations are considered in which a distinction is made between moderate and severe asthma exacerbations (see Table 6.2). Firstly, severe asthma exacerbations are used as a dichotomous outcome in which a severe asthma exacerbation is defined as a hospitalization AND the prescription of systemic corticosteroids OR nebulization of reliever medication (the exact descriptions for the derivation of hospitalization and medication are shown in Appendix G). The presence of a severe asthma exacerbation is indicated as 1, absence as 0. Secondly, both asthma exacerbation classifications are considered. A moderate asthma exacerbation is defined as an ER visit OR outpatient visit AND the prescription of systemic corticosteroids OR nebulization of reliever medication. The presence of a severe asthma exacerbation is indicated as 2, a moderate asthma exacerbation as 1, and the absence of both as 0.

### 6.3.3 Training and Testing

The complete dataset is split into 80% training and 20% testing datasets. When splitting the data into training and testing sets, randomness is involved in selecting which data go into each set. This randomness can lead to different results each time the code is run, affecting the reproducibility of experiments. A seed value was set for the random number generator used during the data split to ensure consistent splits. This ensures a consistent split across different script runs, making the results reproducible. It also allows for a fair comparison between the LSTM and XGBoost models.

## 6.4 Data Analysis

The data analysis is performed for both the LSTM and XGBoost models for both the dichotomous and multiclass predictions.

The predictions are shown as patient-specific and averaged over the whole population. The patient-specific predictions are shown for one particular patient with known asthma exacerbations each time to improve consistency. Monte Carlo simulations are employed to run the model 20 times, allowing for the determination of the mean and standard deviation of the predictions, which serves as a measure of the model's uncertainty. The models' performance on different time horizons is assessed through the mean and standard deviation of the predictions, derived through the Monte Carlo simulations.

### 6.4.1 Model Statistics

Following the results from the literature review, the following metrics are used to assess models' performances; area under the receiver-operator curve (AU-ROC), sensitivity, specificity, accuracy, area under the precision-recall curve (AU-PR), and F1 score.

### 6.4.2 Explainability - Risk Factors

The 10 most important risk factors were determined for one specific patient and averaged across the whole population. In the LSTM model's predictions, both feature permutation and SHAP were implemented. Feature permutation was applied on the whole time range, SHAP only at the last timestep of the model's prediction. The XGBoost model has a built-in feature importance function and is applied on the whole time range.

Table 6.1: The data acquired in this study. The green highlighted input data are currently taken into account in the simulation.

| Variable | Description |
|---|---|
| **Demographic data** | |
| Date of birth | Birth month and birth year |
| Postal code | |
| Sex | |
| Ethnicity | |
| Weight, height, and BMI | |
| **Clinical data** | |
| Asthma-related history | Medical history, sports, hobbies, and sleep patterns |
| Comorbidities | |
| Medication usage | Prescribed medication and retrieved medication from pharmacy |
| Allergies | Inhalation allergies and food allergies |
| Blood tests | IgE, CRP, eosinophils, IgMs, leucocytes, neutrophils, basophils, lymphocytes, and monocytes |
| Radiology reports | Reports on X-ray, MRI, and CT-scans |
| Healthcare professionals | General Physician, main practitioners, and co-practitioners |
| Asthma control | (C-)ACT score |
| Healthcare utilization | Hospital admission, outpatient visits, diagnostic tests, telephonic consultations, ambulant care levels, total healthcare costs, and patient additional costs |
| Lung Function | Spirometry and Forced Oscillation Techniques |
| AIRCON | Lung function, perception scores, and therapy compliance |
| eHealth | Chat data, at-home (C-)ACT scores, at-home spirometry measures, and perception scores |
| **Environmental data** | |
| Daily pollen counts | Common grass, tree, and plant pollen in the Netherlands |
| Air quality | Common air quality measured in the Netherlands |
| Virus data | Common virus infections measured in the Netherlands |
| Weather data | Common weather metrics measured in the Netherlands |

Table 6.2: The considered outcome definitions of the machine learning model.

| Asthma Exacerbation Classification | Condition 1 | Condition 2 | Result |
|---|---|---|---|
| Severe | Hospitalization | Prescription of systemic corticosteroids OR nebulization of reliever medication | Severe asthma exacerbation if both condition 1 AND condition 2 are met |
| Moderate | ER visit OR outpatient visit | Prescription of systemic corticosteroids OR nebulization of reliever medication | Moderate asthma exacerbation if both condition 1 AND condition 2 are met |

# 7 Results - Simulation Study

## 7.1 Patient Characteristics

A total of 1858 patients are included in this study, their characteristics are found in Table 7.1. The population's age is shown for the start and endpoint of the patient dataset. Figure 7.1 shows the total

Table 7.1: The patients' characteristics.

| | |
|---|---|
| Age at November 11th, 2020 in mean (std) | 7.6 (5.2) |
| Age at April 1st, 2024 in mean (std) | 11.0 (5.2) |
| Sex in number males (%) | 1097 (59%) |
| Comorbidities in number (%) | |
| * Eczema | * 30 (2%) |
| * (Non-)allergic rhinitis | * 36 (2%) |
| * Dysfunctional breathing | * 64 (3%) |
| Asthma exacerbations in number | 129 |
| * Severe | * 71 |
| * Moderate | * 58 |

number of asthma exacerbations in the dataset as a function of the patient's age for severe and moderate asthma exacerbations. In the dichotomous asthma exacerbation prediction, the definition of a severe asthma exacerbation is used as the outcome. The mean age of severe asthma exacerbation is 7.2 years, the standard deviation is 4.2 years. The mean age of moderate asthma exacerbation is 9.6 years, the standard deviation is 4.6 years.

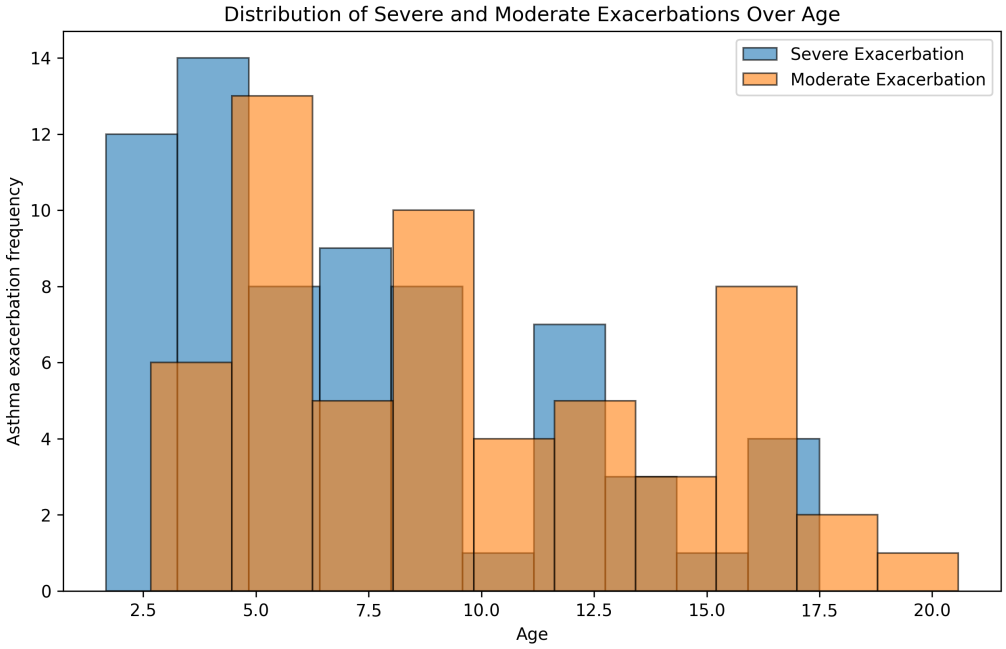


Figure 7.1: The number of asthma exacerbations as a function of the patient's age for the dichotomous classification of asthma exacerbation.

## 7.2 General Results of Models Simulations

The model performance's differences between the LSTM and XGBoost model for the dichotomous prediction can be seen in Table 7.2. The training and testing time of the LSTM model is higher than the XGBoost model. The test loss can not be determined in the XGBoost model. The test accuracy of both models is equal. The AU-ROC, AU-PR, sensitivity, specificity, and F1 score could not be determined in the LSTM model.

Table 7.2: Performance metrics of the dichotomous prediction using the LSTM and XGBoost models.

| **Model performance metric** | **LSTM model** | **XGBoost model** |
|---|---|---|
| Training time (seconds) | 525 | 8 |
| Testing time (seconds) | 4 | 1 |
| Test loss | 0.001 | - |
| Test accuracy | 0.999 | 0.999 |
| Test AU-ROC | Indeterminate | 0.979 |
| Test AU-PR | Indeterminate | 0.050 |
| Test sensitivity | Indeterminate | 0.111 |
| Test specificity | Indeterminate | 0.999 |
| F1 score | Indeterminate | 0.133 |

Figures 7.2 and 7.3 show the Monte Carlo simulation of the LSTM model for one specific patient and averaged across the whole population respectively. For one patient, the mean prediction for an asthma exacerbation is 0.24 with a standard deviation of 0.06. For the whole population, the mean prediction of an asthma exacerbation is lower than for the specific patient with a mean of 0.0006, and a standard deviation of 0.003. Figure 7.4 shows the Monte Carlo predictions of the XGBoost simulation averaged across the whole population. The mean prediction of an asthma exacerbation is 0.0003, similar to the population prediction of the LSTM model.

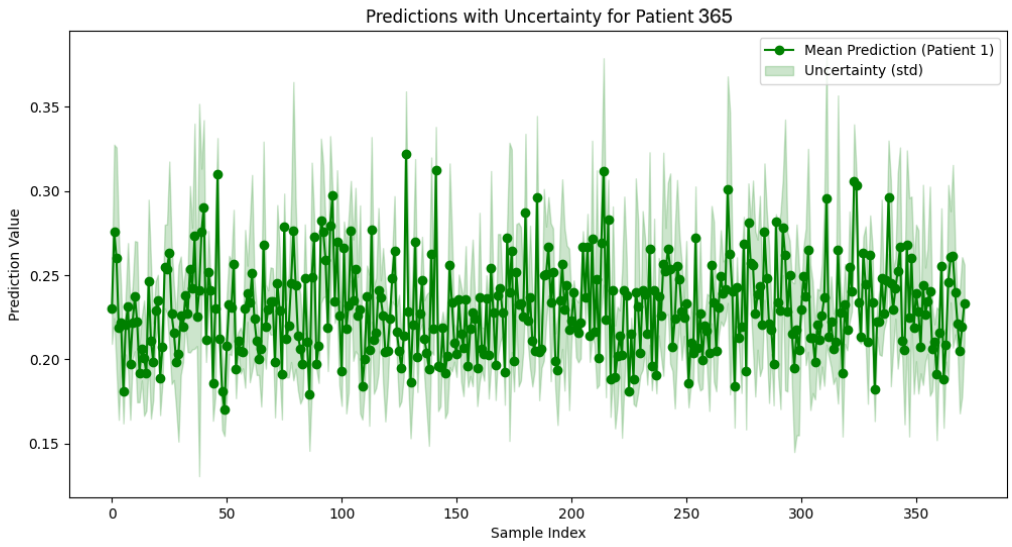


Figure 7.2: The prediction of asthma exacerbations for one specific patient over sample index (time). The mean and standard deviation are derived using 20 Monte Carlo simulations. The y-axis represents the prediction value of an asthma exacerbation (e.g. 0.25 corresponds to a 25% chance of an asthma exacerbation).

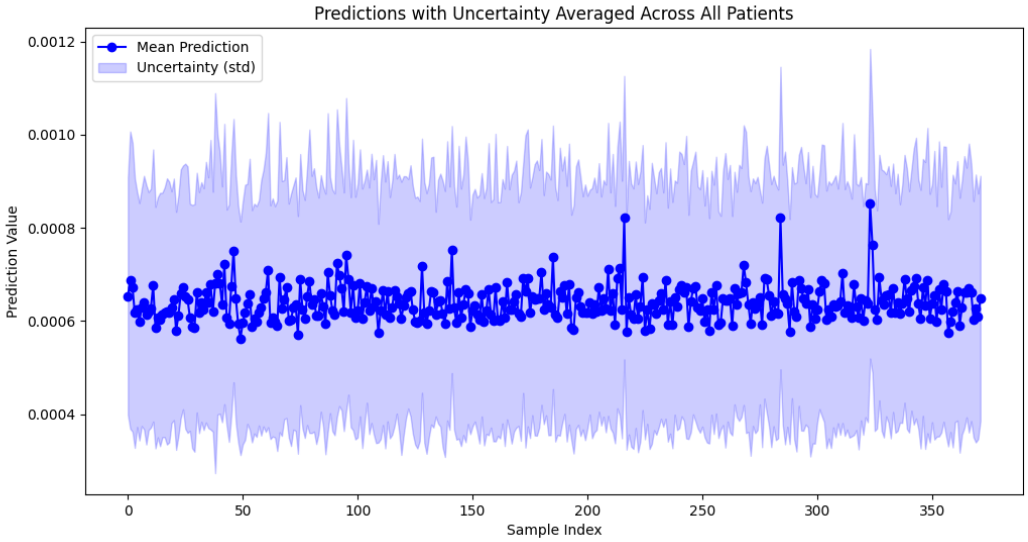


Figure 7.3: The prediction of asthma exacerbations averaged across the whole population over sample index (time). The mean and standard deviation are derived using 20 Monte Carlo simulations. The y-axis represents the prediction value of an asthma exacerbation (e.g. 0.0006 corresponds to a 0.06% chance of an asthma exacerbation).

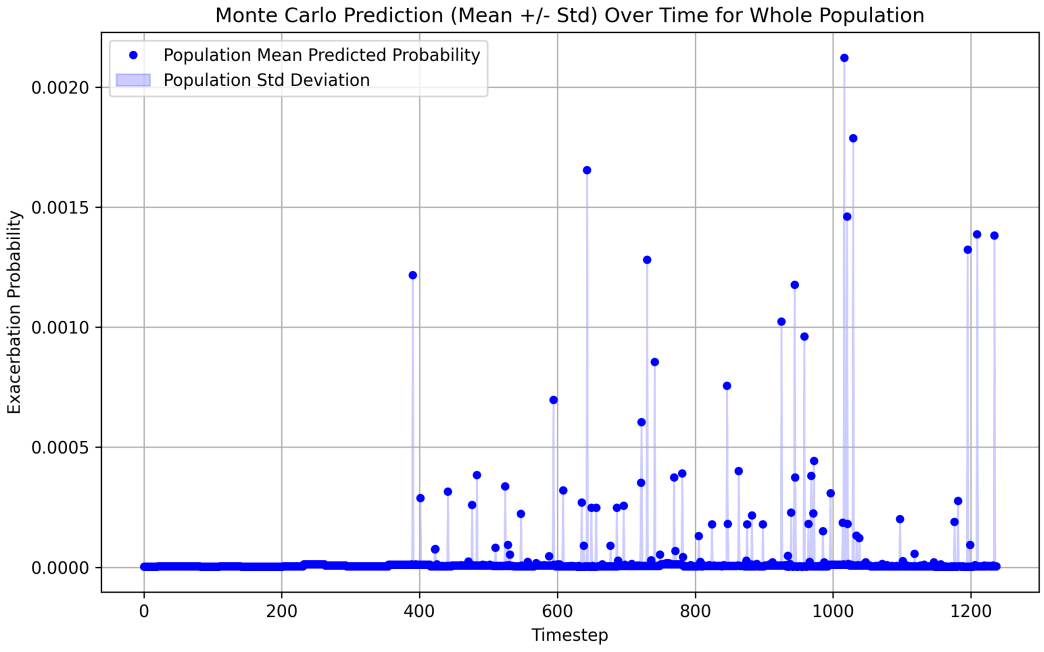


Figure 7.4: The prediction of asthma exacerbations averaged across the whole population over timesteps (time). The mean and standard deviation are derived using 20 Monte Carlo simulations. The y-axis represents the exacerbation probability of an asthma exacerbation (e.g. 0.0010 corresponds to a 0.1% chance of an asthma exacerbation).

Figure 7.5 shows the 10 input features with the highest predictive power determined by feature permutation of the LSTM model, Figure 7.6 determined by SHAP. It can be seen that there is a difference in the feature importance derived from the different methods. The input features derived by feature permutation all have a positive correlation to the prediction of asthma exacerbation, e.g. the presence of pet allergy indicates a higher risk of asthma exacerbations. The BMI, weight, and height have a negative

correlation with the asthma exacerbation prediction, indicating that lower values for these input features pose a lower risk of asthma exacerbations.

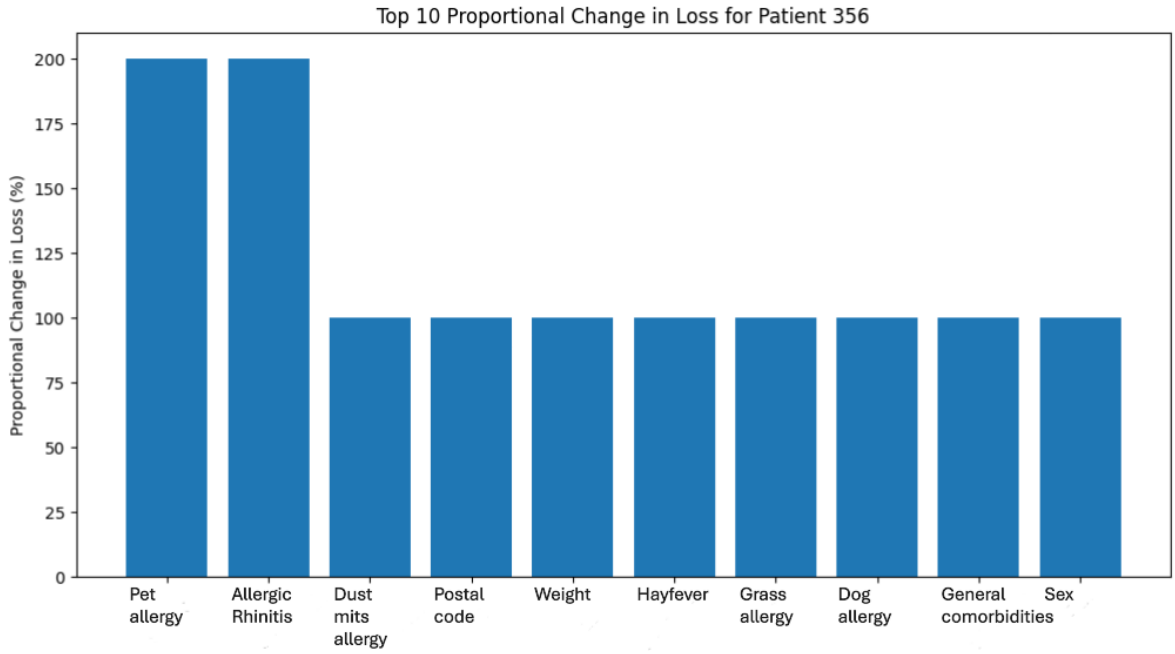


Figure 7.5: The feature importance of the input features determined for one specific patient using feature permutation of the LSTM model.

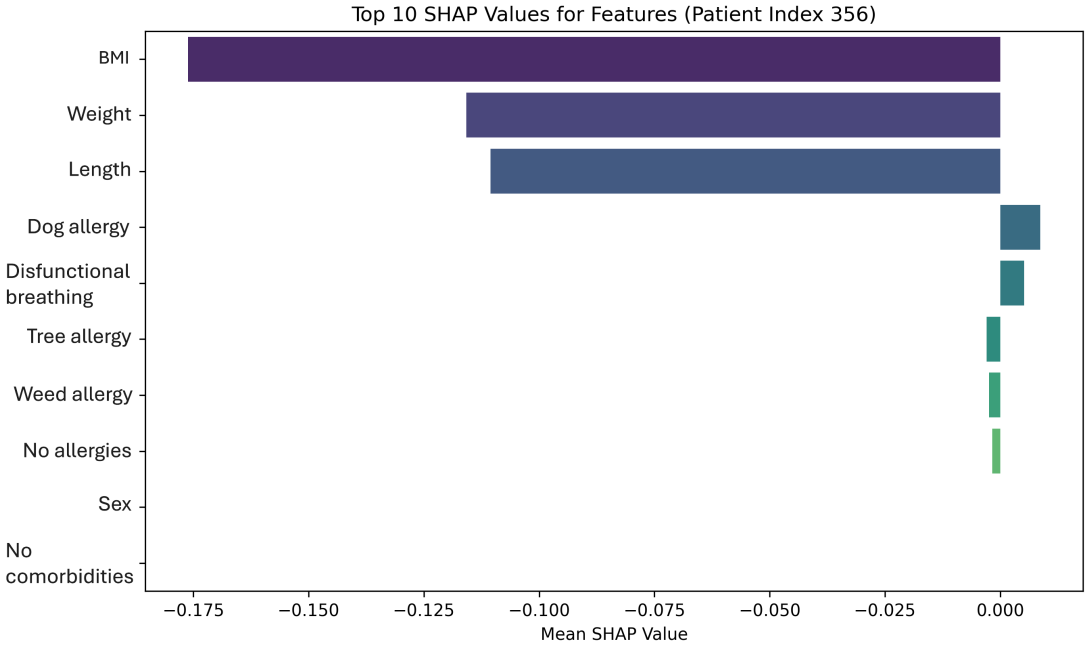


Figure 7.6: The feature importance of the input features determined for one specific patient using SHAP on the LSTM model.

The 10 most important features averaged over the whole population determined using feature permutation of the LSTM model are obesity and grass allergy positively correlated and cat allergy, no comorbidities, dust mite allergy, weed allergy, allergic rhinitis, rodent allergy, non-allergic rhinitis, and postal

code negatively correlated (Figure H.1 in Appendix H). The 10 most important features determined using SHAP are all negatively correlated and include BMI, weight, length, tree allergy, dysfunctional breathing, rodent allergy, hay fever, dust mite allergy, age, and no comorbidities (Figure H.2 in Appendix H).

Figure 7.7 shows the global feature importance of the XGBoost model. These features have a positive correlation with a higher asthma exacerbation prediction. Indicating that the presence of a dust mite allergy results in a higher asthma exacerbation risk, contrary to the SHAP feature importance derived by the LSTM model.

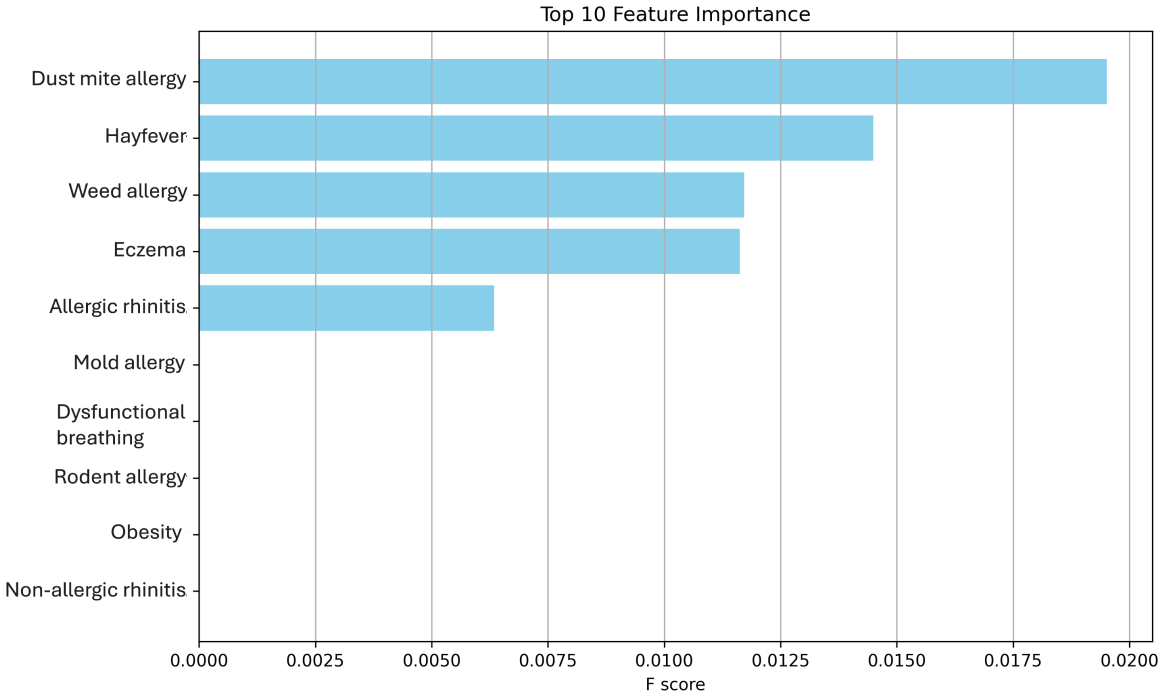


Figure 7.7: The global feature importance of the XGBoost model predictions.

## 7.3 Results of Outcome Definitions Simulations

The model performance's differences between the LSTM and XGBoost model for the multiclass prediction can be seen in Table 7.3. The training time of the LSTM model is higher than the XGBoost model, with the testing time higher as well. The test loss can not be determined in the XGBoost model. The test accuracy of both models is similar. The AU-ROC, AU-PR, sensitivity, specificity, and F1 score could not be determined in the LSTM model.

Table 7.3: Performance metrics of the multiclass prediction using the LSTM and XGBoost models.

| **Model performance metric** | **LSTM model** | **XGBoost model** |
|---|---|---|
| Training time (seconds) | 714 | 25 |
| Testing time (seconds) | 5 | 1 |
| Test loss | 0.607 | - |
| Test accuracy | 0.975 | 0.999 |
| Test AU-ROC | Indeterminate | 0.934 |
| Test AU-PR | Indeterminate | 0.351 |
| Test sensitivity | Indeterminate | 0.333 |
| Test specificity | Indeterminate | 0.666 |
| F1 score | Indeterminate | 0.999 |

Figure 7.8 shows the LSTM model's prediction of all classes for one specific patient over time, and Figure 7.9 shows it averaged across the whole population. For a particular patient, the highest prediction is for no asthma exacerbation at approximately 70%, which decreases when the prediction for a moderate asthma exacerbation increases. The risk for a severe asthma exacerbation stays similar over time around 20%. In the predictions averaged across the whole population, the prediction for moderate asthma exacerbations has the highest probability at approximately 45%. Again, the prediction for severe asthma exacerbation has the lowest probability at around 10%. Starting at the end of 2021, the probability of moderate asthma exacerbation decreases as the probability of no asthma exacerbations increases.

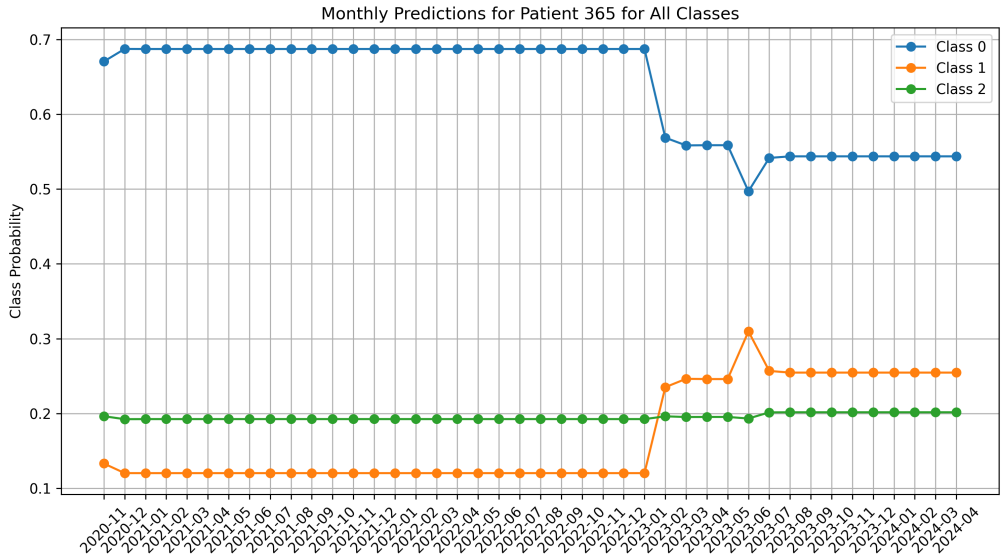


Figure 7.8: The LSTM model's predictions for the three classes for one specific patient over time. The y-axis represents the class probability, where 0 corresponds to no asthma exacerbation, 1 to moderate asthma exacerbation, and 2 to severe asthma exacerbation (e.g. 0.20 for class 2 corresponds to a 20% chance of a severe asthma exacerbation).

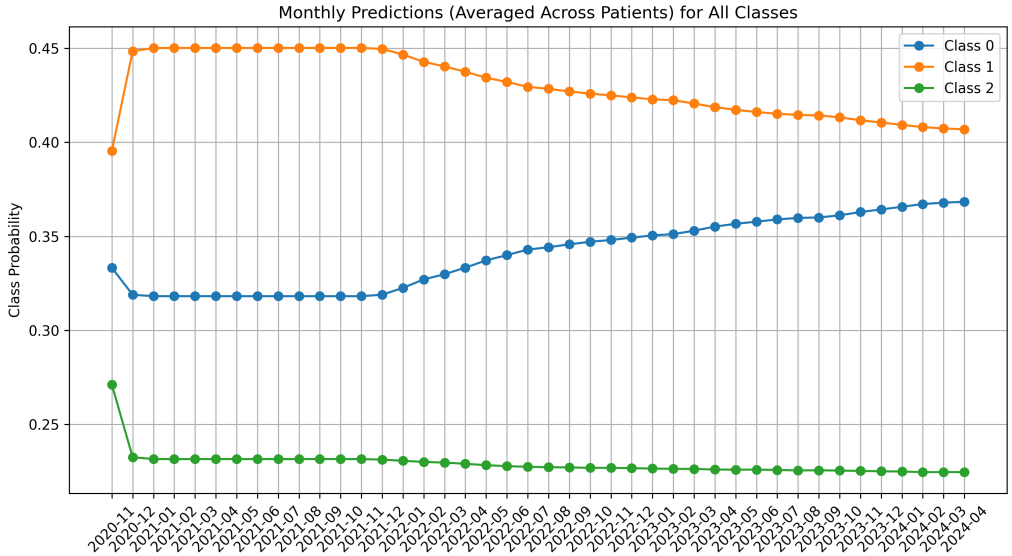


Figure 7.9: The LSTM model's predictions for the three classes averaged across the whole population over time. The y-axis represents the class probability, where 0 corresponds to no asthma exacerbation, 1 to moderate asthma exacerbation, and 2 to severe asthma exacerbation (e.g. 0.45 for class 1 corresponds to a 45% chance of a moderate asthma exacerbation).

Figure 7.10 shows the XGBoost model's prediction of all classes averaged across the whole population over time. The prediction for no asthma exacerbation stays the same at almost 100% probability, while both the moderate and severe asthma exacerbation are approximately at 0%. The indication of moderate exacerbation is at the same level as the severe asthma exacerbation, which is why it cannot be seen in the Figure.

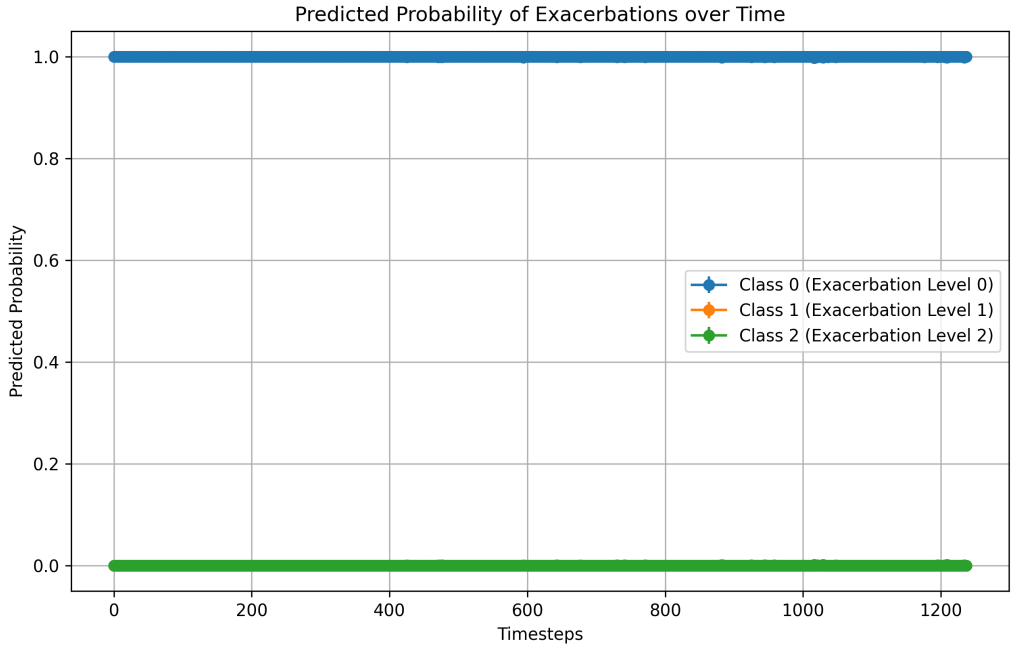


Figure 7.10: The XGBoost model's predictions for the three classes averaged across the whole population over time. The y-axis represents the predicted probability, where 0 corresponds to no asthma exacerbation, 1 to moderate asthma exacerbation, and 2 to severe asthma exacerbation (e.g. 1 for class 0 corresponds to a 100% chance of no asthma exacerbation).

## 7.4 Results of Time Horizon Simulations

Figure 7.11 shows the 7-day forecasted prediction for one patient, and Figure 7.12 the 28-day forecasted prediction. It can be seen that for both time horizons, the asthma exacerbation predictions stay equal over time in mean and standard deviation. The mean asthma exacerbation risk for 7 days is 0.397 with a standard deviation of 0.395 and for 28 days 0.48 with a standard deviation of 0.46. The time horizon predictions for the population are shown in Appendix H, Figure H.3 shows the 7-day forecasted prediction, and Figure H.4 shows the 28-day forecasted prediction.

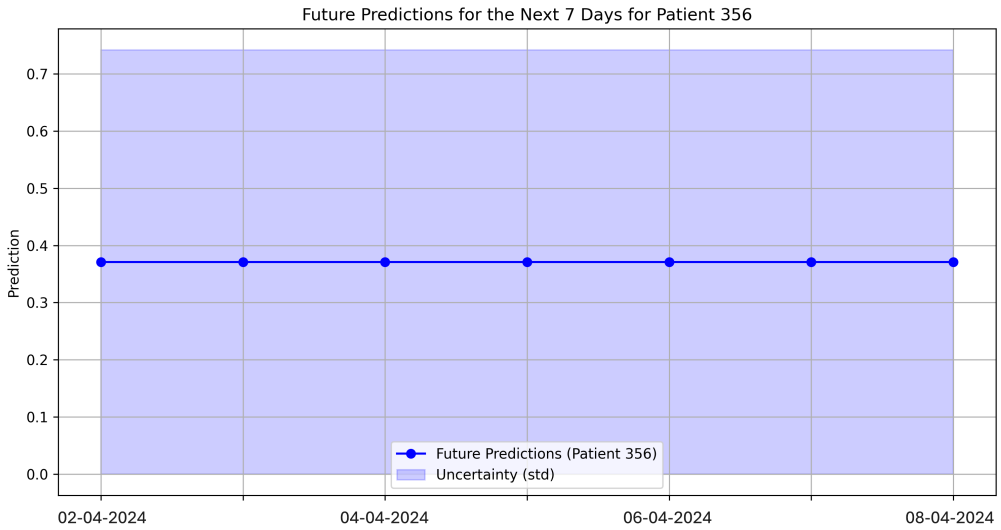


Figure 7.11: The prediction of asthma exacerbations in one specific patient 7 days ahead of the time frame with the mean and standard deviation. The y-axis represents the prediction of an asthma exacerbation (e.g. 0.4 corresponds to a 40% chance of an asthma exacerbation).

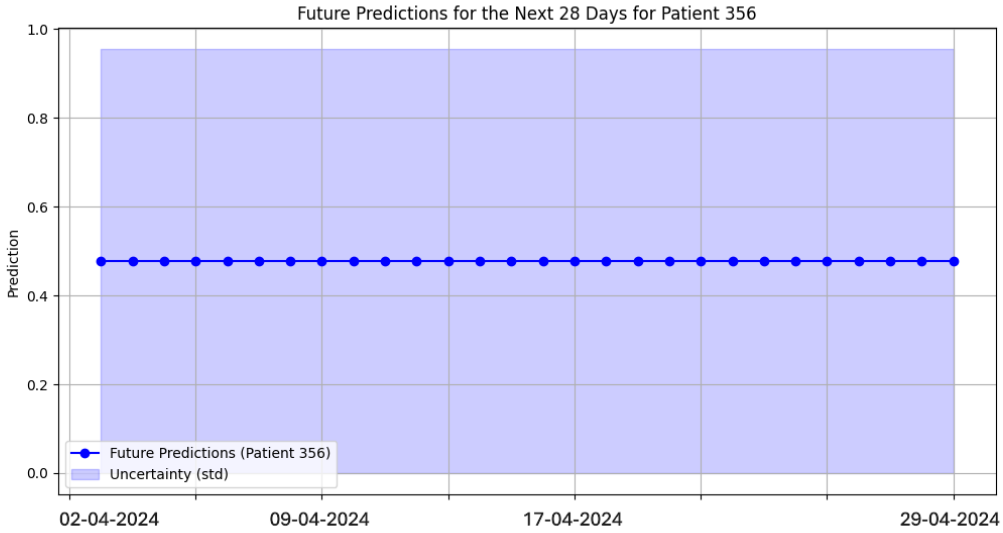


Figure 7.12: The prediction of asthma exacerbations in one specific patient 28 days ahead of the time frame with the mean and standard deviation. The y-axis represents the prediction of an asthma exacerbation (e.g. 0.45 corresponds to a 45% chance of an asthma exacerbation).

# 8 Discussion and Conclusion - Simulation Study

## 8.1 Discussion on Model Simulations

The simulation study reveals that the XGboost and LSTM model architecture allows for asthma exacerbation prediction but that the prediction's accuracy fails with the current input variables. The LSTM model's simulation revealed personalized predictions, whereas the XGBoost model's simulation in this study only revealed population-level predictions. The personal and population risk factors of the LSTM's predictions were determined using both feature permutation and SHAP but were inconclusive due to low accuracy. The risk factors of the XGBoost's predictions were determined on a global level using the built-in function of XGBoost. Due to the limited accuracy, the outcome definition and time horizon simulations did not yield significant results in this study. However, the LSTM's and XGBoost's model architecture allows for multiclass prediction and future prediction

This research's results show that the distribution of severe and moderate asthma exacerbations is not evenly spread across age groups (Figure 7.1), which may introduce bias in the predictions. Additionally, the number of asthma exacerbations is low in general (Table 7.1); among the 2.3 million data points from 1858 patients and 1238 time steps, only 71 are labeled as severe and 58 as moderate asthma exacerbations. This class imbalance poses a significant challenge for accurate prediction.

Comparing the performance metrics of the LSTM model to those of the XGBoost model is difficult because many metrics could not be determined for the LSTM model (Table 7.2 and Table 7.3). While the LSTM model's training time is notably longer than the XGBoost model's, this could be attributed to the XGBoost model only making predictions at the population level, not on a patient-specific basis. Though the accuracy appears high, it is misleading due to class imbalance. More insightful metrics, such as AU-PR, sensitivity, and F1 score, reveal that both models struggle to accurately predict asthma exacerbations (dichotomous and multiclass) with the current input variables. Furthermore, in the individual asthma exacerbation predictions of the LSTM model, the standard deviation across multiple Monte Carlo simulation runs is reasonable for individual patients (Figure 7.2) but quite large across the entire population for both the LSTM and XGBoost models (Figure 7.3 and Figure 7.4). However, further interpretation is limited due to the overall low accuracy of the models.

Feature importance varies between the two methods applied to the LSTM model, as shown by the differences in feature permutation and SHAP results (Figure 7.5 and Figure 7.6). This discrepancy may stem from the models' low accuracy. Notably, XGBoost's feature importance remained consistent in each simulation (Figure 7.7), indicating robustness, but its global feature importance is not suited for patient-specific predictions as they are on a general level [83, 101]. The large negative SHAP values in Figure 7.6 for BMI, height, and weight may be a result of these features being among the few variables that change over time, while most other input features are dichotomous. The measurement frequency of a feature influences its SHAP values by affecting how contributions to predictions are captured [**?**]. Features measured frequently (e.g., daily) reflect more variability and dynamic impacts, while infrequently measured features (e.g., quarterly) may not adequately represent temporal effects, potentially skewing their perceived importance.

The LSTM model's class prediction for a specific patient seems reasonable, as the risk for no asthma exacerbation is the highest and decreases at certain points that the risk of a moderate asthma exacerbation increases (Figure 7.8). Interestingly, the LSTM model's class prediction values averaged across the whole population show a higher probability for moderate exacerbation than for no exacerbation (Figure 7.9). This may result from the significant class imbalance, where moderate and severe exacerbations are much less frequent than no exacerbation.

Finally, while the LSTM model incorporates the concept of time and can predict across different time horizons, the XGBoost model cannot. Despite this advantage, the LSTM model does not deliver realistic forecasts for 7- or 28-day predictions, as the model's output remains unchanged over time (Figure 7.11 and Figure 7.12). This constant prediction may stem from several factors, including insufficient temporal features that fail to capture daily variations and a lack of variation in the training samples [199]. Moreover, the high standard deviation across the forecasts points to substantial uncertainty in the predictions.

## 8.2 Strengths

This research has several strengths that set it apart from existing work in the field. With a sample size of 1858 patients, the study utilizes an average number of patients as compared to the other models in the literature (Table 4.1). Computational demands, while not often mentioned in comparable studies, were manageable in this case (Table 7.2 and Table 7.3). This indicates the potential for optimizing the model's accuracy. However, the current models did not incorporate all input variables, decreasing the computational demands. Notably, this work pioneers in comparing model performance based on changes in exacerbation definitions, an area that has seen little attention. Furthermore, the model's incorporation of a time horizon simulation distinguishes it as an early step toward potential clinical application, unlike most models in the literature that do not consider time-based predictions. While models developed by Luo et al. [168,169] and Hozawa et al. [170] utilized a broad time horizon of 365 days, this study adopts a 7 and 28-day time frame, which aligns with the approach taken by Hurst et al. [152]. This shorter time horizon enhances the applicability of the model in clinical settings.

## 8.3 Limitations

This research has several limitations that could impact the models' performance in predicting pediatric asthma exacerbations. The number of comorbidities and allergies included in the model was lower than expected, likely since these were based on only one aspect of the medical patient file, which made them highly dependent on how thoroughly healthcare professionals filled in the records. The completeness and quality of the database entries were outside the scope of this research but could be important factors to incorporate in future research. Additionally, environmental data was deliberately excluded from the day-by-day prediction model due to its significantly higher measurement frequency than other features, which disproportionately influenced the model's outcomes. Due to time constraints, several important risk factors known from the literature, such as symptom scores, lung function, therapy adherence, and tobacco exposure, were not included [30,112,113,147]. This omission likely contributed to the model's lack of accuracy in predicting asthma exacerbations. Further, all patients in the dataset were from a single hospital, which could introduce bias and limit the generalizability of the model's predictions to broader populations [41].

Another limitation of this research is the strict definitions of asthma exacerbations, which may have led to a small number of identified cases in the dataset as the prevalence of severe asthma exacerbations following these criteria is low in this dataset. Although class weights were applied in the LSTM model to address the class imbalance, the LSTM model could still not accurately predict the asthma exacerbations. These strict criteria might have excluded patients who experienced less severe exacerbations but were sent home with a reliever medication scheme (*salbutamol afbouwschema*).

While the accuracy of the LSTM and XGBoost models appear high (Table 7.2 and Table 7.3), this is primarily due to the correct predictions of the absence of asthma exacerbations. Since the asthma exacerbations occurrence is so low, the misclassification of these events constitutes a relatively small portion of all predictions across patients and timesteps, resulting in a high overall accuracy. Another explanation lies in the models' daily prediction setup, while the patient-related features were recorded at a much lower frequency (monthly at best), making it hard for the model to accurately predict events daily [199]. As a result, the model failed to identify any asthma exacerbations, leading to zero true positives and consequently, performance metrics that returned indeterminate values for the LSTM model. Lastly, the time horizon predictions have not yet been checked against prospective data, and while this is currently irrelevant given the model's inability to predict asthma exacerbations, it remains an area that needs to be addressed in future work.

In this simulation study, the proposed XGBoost was not able to determine personalized predictions but the literature shows that the model's architecture does allow personalized predictions [200]. In this simulation study, the LSTM was able to make personalized predictions. Furthermore, the LSTM model understands the concept of time and can directly predict a time horizon. The XGBoost model has no concept of time and rather works with a sequence of values, rather than a time series this makes it less suitable for forecasting predictions [77,81,200].

## 8.4 Future Directives

Future directives for this research include several key areas for improvement and expansion. First, to achieve the objectives of this research the model's input variables should be extended to the available input variables from the electronic health record and at-home measurements. Second, the asthma exacerbation definition, prediction time horizon, and personalized risk factors should be assessed again based on the inclusion of all the input variables.

Furthermore, given the correlation between electronic health record completeness and patient health status [201], data quality assessments should be integrated into model development. For example, the completeness of electronic health records can be evaluated using the Data Completeness Analysis Package [202], and overall data quality can be assessed using the Aggregate Data Quality score proposed by Salati et al. [203]. Further improvements involve incorporating additional risk factors known from the literature, such as symptom scoring, therapy adherence, and lung function measurements [30, 147]. Lastly, implementing natural language processing (NLP) techniques, such as Word2Vector [204] or BERT (Bidirectional Encoder Representations from Transformers) models, could enhance the analysis of medical reports on tobacco exposure and facilitate tracking of symptom trajectories over time, potentially improving asthma exacerbation prediction [205–208]. This approach has already shown promise in COPD exacerbation predictions [209].

Moreover, optimizing the definition of asthma exacerbation to match the model's clinical application could improve the accuracy and usability. The prediction of severe asthma exacerbation could be more relevant for high-risk patients while the prediction of loss of asthma control could be more relevant to patients with mild asthma and low risk of asthma exacerbation. With this same reasoning, the prediction timing can be matched to the model's clinical application. The severe asthma exacerbation prediction might need a more timely prediction time horizon (daily) whereas the loss of asthma control might suffice with monthly predictions. Future research should focus on the needs of patients and healthcare professionals as well as the effect of the prediction time horizon on the model's accuracy. Incorporating additional monthly questionnaires, such as the (C-)ACT from the CIRCUS study [72], could help assess their possible potential as indicators for predicting and preventing asthma exacerbations.

To effectively address class imbalance, more advanced techniques should be employed in addition to class weights [41, 210]. One effective method is SMOTE (Synthetic Minority Over-sampling Technique), which generates synthetic samples for the minority class, increasing its representation [211]. Additionally, using focal loss can help the model focus on hard-to-classify examples while under-sampling the majority class, or using cluster-based approaches can maintain data distribution while balancing the dataset [212]. Implementing these strategies can significantly improve the model's predictive performance for underrepresented classes.

The model's accuracy can also be improved through hyperparameter optimization [213]. Hyperparameter optimization (tuning) involves adjusting the model architecture's key parameters to enhance predictive performance by systematically selecting the best values for each. Li et al. propose the HELP algorithm, which structures hyperparameter optimization for LSTM models and improves the efficiency of this process [214]. Some hyperparameters that can be optimized include the number of nodes, the number of hidden LSTM layers, units in the dense layer, decay rate, learning rate, batch size, and layer weight.

Another directive is to analyze the entire patient population to identify risk groups sharing similar risk factors [215]. This has shown potential in COPD [216]. Dividing these factors into modifiable and non-modifiable categories will allow for targeted advice to patients on aspects they can actively manage. Additionally, simple models like logistic regression (LR) can be applied as a gold standard for comparison, providing a benchmark to assess the desired accuracy of the model [41, 217].

The research questions for future simulation studies are composed in Table 8.1, with the order reflecting the recommended sequence for the next steps of this project.

Table 8.1: Research questions for future model simulation studies.

| **Improving the models' prediction performance** |
|---|
| What accuracy and sensitivity can be achieved when incorporating all available known risk factors? |
| What is the predictive impact of the definition of asthma exacerbations when incorporating all available known risk factors? |
| What accuracy and sensitivity can be achieved when predicting mild exacerbation or loss of asthma control? |
| What accuracy and sensitivity can be achieved after adjustment for class imbalance? |
| What accuracy and sensitivity can be achieved when optimizing the models' hyperparameters? |
| What time horizon for predicting asthma exacerbations can be achieved when incorporating all available known risk factors? |
| How can the XGBoost model's architecture be fitted to make personalized predictions? |
| **Steps towards clinical implementation** |
| What is the completeness and quality of the input data derived from the electronic health record? |
| What accuracy and sensitivity can be achieved when externally validating the models? |
| What temporal frequency of input variables yields the model's best accuracy? |
| How can risk groups in the patient population be identified using the models' predictions? |

## 8.5 Conclusions

In conclusion, this research highlights the potential of the LSTM model for predicting pediatric asthma exacerbations as its model architecture allows for identifying individual risk factors and predicting individual asthma exacerbation risks over time. With the current XGBoost's model structure, no individual predictions and risk factors could be determined. Additionally, with the current input, the LSTM and XGBoost models struggle with accuracy and sensitivity due to class imbalance and a limited number of asthma exacerbations in the dataset. Therefore, the exact influence of multiple asthma exacerbations and prediction time horizons on the models' accuracy and sensitivity could not be determined. Overall, this study underscores the need for further refinement of the models to improve accuracy by optimizing the input data, class imbalance, and model hyperparameters, thus enhancing their applicability in regular pediatric asthma care. After these refinements, the predictive impact of the multiple asthma exacerbation definitions and prediction time horizons can be assessed.

# 9 Methods - Interview Study

## 9.1 Interviews with Healthcare Professionals

The main goal of the one-on-one semi-structured interviews is to gather insights from a group of pediatricians (n=6) at MST regarding the integration and use of the machine learning model as developed in part 2. Each pediatrician will participate in a one-on-one 30-minute semi-structured interview complemented by follow-up questions. All interviews were conducted in Dutch so the interviewees could speak more easily. Each interviewee granted permission to record the interviews. The questions and quotes in this report are translated into English for better readability. Furthermore, the pediatricians' ages and years of experience as pediatricians are gathered.

Appendix I (in Dutch) shows the structured overview of the interview and the exact questions. The interview begins with a summary of the project to provide context and to allow for even background information for each of the interviewees. The project summary covers the research aim, model input data, and interview goals. The interview is subdivided into multiple research topics, starting with the definition of asthma exacerbations. Subsequently, the model's expectations and requirements are discussed including trusting an AI model, using the AI model as a base for medical policy change, and explainability. Then, the interview continues on the optimal time horizon for the model's predictions from their clinical perspective, aiming to determine the most valuable timing for patient care. Next, possible applications of the model are discussed. Lastly, interviewees can give general input that was not already discussed during the interview.

The interview results are analyzed using a quick, practical approach, focusing on distilling each response to a specific, concrete answer. These responses were then compared across participants to identify any commonalities or differences. This method enabled a straightforward synthesis of key points without in-depth thematic coding. The interview results are presented descriptively and, where possible, supported by objective measures. Additionally, translated quotes are included to enrich the findings.

# 10 Results - Interview Study

A total of six pediatricians are interviewed. The interviewees were (33%) male, and had a mean age of 43 years (standard deviation of 9.5 years), and a mean years of experience as a pediatrician of 13.5 years (standard deviation of 9 years).

## 10.1 Asthma Exacerbation Definition

The interviewed pediatricians primarily defined asthma exacerbations as the acute increase in symptoms. They also emphasized the need for medical intervention as a key distinction between a loss of asthma control and an exacerbation. Additionally, some pediatricians noted that an asthma diagnosis is sometimes made only after an exacerbation, with family history and the patient's clinical status playing a role in the assessment.

*"An asthma exacerbation is an acute episode of heightened symptoms that cannot be solved with their standard reliever medication."*

Feedback on the provided definitions of asthma exacerbation highlighted the use of salbutamol nebulization, which is currently being considered an indicator of an asthma exacerbation. However, this medication is sometimes used to treat conditions like pneumonia or bronchiolitis, complicating its role as a definitive marker for asthma exacerbations. Furthermore, salbutamol inhalators are often used to treat asthma exacerbations and are now omitted from the asthma exacerbation definition. The total doses per day were suggested to differentiate between severe and moderate asthma exacerbations. Healthcare utilization, such as ER visits, was noted to vary significantly among patients, with some seeking care sooner due to anxiety, while others delay seeking care despite more severe symptoms. Hospitalization and step-up in treatment decisions also differ between pediatricians, adding another layer of variability. Lastly, while this research does not account for the rare cases of intensive care hospitalizations, it was mentioned that this omission is acceptable for this patient population. The use of a reliever medication schedule (salbutamol afbouwschema) was suggested as a potential indicator for moderate asthma exacerbations. The step-up in daily controller medication was suggested as a potential indicator for loss of asthma control.

*"The start of systemic corticosteroids like prednisone as a treatment for an asthma exacerbation greatly depends on the attending pediatrician."*

*"I would distinguish a moderate asthma exacerbation from loss of asthma control if a patient uses the highest step on the reliever medication schedule."*

## 10.2 Model Expectations

The pediatricians' expectations are primarily centered on how the model can support their decision-making, with a focus on understanding individual patient risk factors rather than on precise predictions. However, in an outpatient setting, knowing the season when a patient might require more medication could be useful. Additionally, the model's monitoring capability was mentioned to potentially aid in preventing asthma exacerbations by alerting pediatricians to early signs of asthma control loss. Ultimately, the question arose whether incorporating patient-reported outcomes could further enhance the model's quality and make it more acceptable to users by reflecting patient perspectives.

*"I would want the AI model to support me in finding the blind spots in a patient's asthma management."*

*"I want a model that doesn't take up my time but saves me time."*

The desired outcomes from the model's predictions vary. Some pediatricians preferred seeing a percentage risk of an asthma exacerbation along with a summary of the patient's history that supports the prediction, while others were more interested in the personalized risk factors. The presented outcome formats supported this, with 5 out of 6 pediatricians preferring the visualization and 1 favoring the textual explanation. Regarding the number of features displayed, preferences ranged between three and five risk factors, with a distinction between modifiable and fixed risk factors. Furthermore, the possibility to get more information on specific feature importance or predictive values was mentioned to increase explainability. Additionally, it was mentioned that also the absence of certain risk factors could be informative to show. All pediatricians used the descriptive term dashboard for using the model in the clinic.

*"I want to see the patient's risk factors in one glance."*

*"I am seeing all kinds of feature importance values which I do not understand, I need an explanation from the model."*

Overall, pediatricians indicated they would trust the model and incorporate its insights into medical decision-making, provided the identified risk factors are reasonable. An accuracy level of 80% to 90% as well as a sensitivity of 80 % were suggested as acceptable. Four out of six pediatricians did not specify a minimum accuracy level; two described it as needing to be as good as a pediatrician, while the other two felt it could be somewhat less accurate than a pediatrician. Furthermore, two pediatricians mentioned that a pilot phase, where pediatricians could familiarize themselves with the model, would help build trust. For explainability, it was recommended that the model include an option to request further explanation on how the predictions are derived.

*"I expect the AI model to have a broader oversight than the clinician, therefore being more accurate."*

*"I cannot expect the AI model to be always right, I also make mistakes. But I want the model to be approximately as good as the average doctor."*

## 10.3 Prediction Time Horizon

It was mentioned that the prediction time horizon highly depends on the implementation and clinical context. For patients presenting with acute symptoms, the suggested prediction window ranged from 1 to 3 weeks to assess the need for initiating systemic corticosteroids. In contrast, during routine outpatient visits, monthly, quarterly, and biyearly predictions were considered to guide treatment adjustments, allowing pediatricians to step up medication during high-risk months and decrease medication during lower-risk periods. Furthermore, it was suggested that a year timeline be visualized in which the asthma exacerbation risk and the influence of the risk factors over time are presented.

*"I want the AI model to guide me in accurately stepping up the medication when needed and safely stepping down the medication when not needed anymore."*

*"The time horizon of the model's prediction should still leave me some room to do something about a high-risk prediction."*

## 10.4 Model Applications

Four pediatricians proposed an application that involves either the patients, pediatricians, or both receiving an alarm notification when a patient is at high risk for an asthma exacerbation, enabling them to contact each other to discuss further medical management. Two pediatricians also suggested the application to give advice corresponding to the patient's risk factors based on medical guidelines. An additional proposed application was for general practitioners to have the ability to refer the patients back to the GP with additional monitoring.

Four out of six pediatricians favored the proposed eHealth application, and all pediatricians supported its use in both patient-specific contexts and during outpatient visits.

For the patient-specific application, improvements were suggested, such as using a traffic light system to indicate risk levels, with generic advice for an orange alert, while ensuring the option to contact a doctor remains available. It was also suggested that the patient's and parents' educational level should be considered by incorporating icons and images to explain risk factors and advice, making it as simple and accessible as possible. Furthermore, in light of sustainability and data storage, it was mentioned that not all pediatric asthma patients should receive this application, but only those patients interested and who have still some room for improvement in their asthma management. Although another pediatrician mentioned that the application could be offered to every pediatric asthma patient and to let the patient decide whether or not they want to use it, to further promote self-management.

*"This application could stimulate patients to improve their asthma self-management."*

Additionally, it was emphasized that it's important to assess where the greatest benefit can be achieved. EHealth patients are already well-monitored, and many no longer experience exacerbations. In such cases, it raises the question of whether a supplemental eHealth AI model is necessary.

# 11 Discussion and Conclusion - Interview Study

## 11.1 Discussion on Interviews

The interview results provide valuable insights into the expectations, definitions, and potential applications of an AI model designed to predict asthma exacerbations in pediatric patients. The interviewed pediatricians primarily defined asthma exacerbations as an acute increase in symptoms that necessitates medical intervention, distinguishing it from a mere loss of asthma control. However, these clinically oriented aspects are often subjective and challenging to quantify objectively, making it difficult to extract them directly from the data.

Furthermore, pediatricians emphasized the importance of understanding individual patient risk factors rather than relying solely on precise predictions. This highlights the need for a model that supports clinical decision-making by identifying areas where intervention may be required, especially during outpatient visits. This corresponds to the findings of Nair et al. who showed that physicians prefer to have an AI model as a clinical decision support system during the treatment follow-up consultations [218]. Furthermore, the variability in preferred output formats, from risk percentages to detailed explanations of risk factors, indicates that pediatricians may be uncertain about which format would work best in daily clinical practice.

Regarding model trust, the pediatricians suggested that acceptable accuracy levels would range between 80% and 90%, or a sensitivity of 80%. Opinions were evenly split between those who expected the model to perform better than or as accurately as a pediatrician. In contrast, Hummelsberger et al. found that high performance was essential for physicians to consider implementing AI models in practice [219]. The possibility of piloting the model to build confidence and trust among pediatricians aligns with findings that early physician training results in better model understanding [219–222]. Additionally, involving stakeholders early in the AI model development process helps ensure clinical relevance and alignment with the clinical workflow [218, 223].

The pediatricians preferred visual explanations of the model's asthma exacerbation risks alongside personal risk factors. This aligns with literature, as Hughes et al. demonstrate that model explainability enhances trust and awareness of model limitations [224]. Similarly, Lesley et al. found that clinicians favor thorough explanations of predictions, with scientific references further increasing trust and reducing uncertainty [35]. This demand for explainability highlights the value of incorporating user-friendly features. However, Gould et al. reported an even split among clinicians between prioritizing interpretability and model accuracy [225].

The suggested prediction time horizons ranged from a few weeks to multiple months and were highly dependent on the corresponding application the pediatrician proposed. The prediction of acute symptoms was mentioned for the prediction time horizon of a few weeks and the prediction of long-term asthma control for a couple of months. The prediction of a couple of months corresponds to the prediction time horizon of Hurst et al. [152] who showed prediction time horizons of one, three, and six months. The proposed year timeline corresponds to the prediction time horizons of Luo et al. [168], [169], and Hozawa et al. [170]. Weekly predictions of (asthma) exacerbation risk or associated risk factors have not yet been explored in the literature. This may be due to the practical challenges involved, as weekly predictions would require input variables measured at intervals shorter than a week. These intervals could, however, be made possible through eHealth devices that measure key input variables at home [177].

The proposed patient-specific application, featuring a traffic light system for assessing asthma exacerbation risk, was met with interest. However, concerns were raised about its utility for well-monitored patients who no longer experience exacerbations. This suggests that the AI model should focus on patients who may benefit from additional asthma management support. For well-monitored patients without current symptoms, a simple 'all clear' message indicating that their asthma is under control could be more appropriate, alongside general asthma management tips. When the risk of an exacerbation increases, the application could then highlight the specific risk factors needing attention. This approach ensures that the AI model remains both targeted and adaptable to individual patient needs, aligning with findings in the literature that show AI-based applications can improve self-management skills and increase healthcare engagement [226–228]. Such a system could empower patients to actively manage their asthma.

## 11.2 Strengths

A key strength of this research lies in its close collaboration with pediatricians, fostering a sense of involvement and accountability in the model's development. By interviewing pediatricians and incorporating their expectations and clinical perspectives, this research bridges the gap between simulation studies of the ML models and their clinical application, enhancing both motivation and willingness for adoption [220]. The structured interview format ensured consistency, with each pediatrician answering the same questions, strengthening the gathered insights' reliability. Additionally, the study considered a diverse range of participants in terms of age and years of clinical experience, yielding a well-rounded understanding of the potential for model implementation in pediatric asthma care [35]. This diversity also highlights the need for ongoing design iterations with clinicians and other users to address specific needs, from model design to system integration and the overall implementation process [218]. Creating 'AI alignment', or 'human-AI cooperation,' between AI design and the end users' values and needs is crucial to its success [222].

## 11.3 Limitations

One limitation of this research is the involvement of a limited number of pediatricians, all from a single hospital, which may introduce bias and limit the generalizability of the findings. Additionally, one of the pediatricians had a higher baseline knowledge due to their prior involvement in the research, potentially influencing their responses. While structured interviews were used to mitigate this bias, it may still have impacted the uniformity of perspectives gathered. The interview results are presented descriptively, which aligns with the purpose of this study but could benefit from thematic analysis to reveal deeper, underlying themes. Such themes might align with those identified by Gould et al., who outlined three main themes expectations (responsibility, judgment, process), empowerment (understanding, values, power), and partnership (trust, awareness, prognosis), each offering valuable subthemes that could further enrich our understanding [225].

## 11.4 Future Directives

For future research, it is important to interview a broader range of pediatricians, including technical physicians, nurse specialists, and asthma nurses, who may also use the model in practice. To improve the generalizability of the findings, interviews should be conducted across multiple hospitals. Additionally, involving all potential end-users, including patients, in the interview process will provide valuable insights into the model's real-world applications. Expanding the research to include focus groups and use cases will further enhance understanding and ensure the model's practicality in clinical settings. The research questions for future simulation studies are composed in Table 11.1.

Table 11.1: Research questions for future interview studies.

| |
|---|
| What key themes emerge from pediatricians' perspectives on implementing AI models for asthma management? |
| How do technical physicians, nurse specialists, and asthma nurses prefer to integrate asthma exacerbation into their clinical workflow? |
| How do patients (and their parents) prefer to use an AI model in their asthma management? |
| What practical considerations impact healthcare professionals' and patients' engagement with an AI application during a pilot phase? |

## 11.5 Conclusion

This study explored the expectations, definitions, and potential applications of an AI model for predicting asthma exacerbations in pediatric asthma patients, based on insights from pediatricians. Asthma exacerbations were consistently defined as acute episodes that require medical intervention, highlighting the need for precise criteria to distinguish between exacerbation and loss of asthma control. The time horizon for predictions was recognized as highly context-dependent, with weekly predictions being useful for acute care and monthly predictions preferred in outpatient settings for adjusting long-term management strategies.

Pediatricians emphasized the importance of a model that supports decision-making by identifying personalized risk factors, rather than focusing solely on prediction accuracy. Model transparency and explainability were also deemed crucial, with pediatricians expressing a preference for visualizations with the possibility of further explanations. The applications for providing patients insight into their risk factors and supporting pediatricians during outpatient visits were favored and could improve asthma management.

# 12 General Discussion and Conclusion

## 12.1 Principal Findings

This research aimed to develop an AI model for predicting pediatric asthma exacerbations that can be integrated into routine pediatric asthma care within the pediatric department while identifying personal risk factors for each patient. This research consisted of three parts; a literature review, a simulation study, and an interview study.

The exploratory literature review revealed considerable variability in how asthma exacerbations are defined across studies, complicating model comparisons and potentially affecting prediction accuracy. Most models primarily utilized demographic and clinical data from electronic health records, yet often overlooked social, environmental, and at-home factors that could enhance predictive capability. While Gradient Boosting Models and Random Forests were frequently chosen for their capacity to handle complex data, the promising potential of LSTMs remained underutilized.

The simulation study highlighted the potential of the LSTM model, which identified personalized risk factors and predicted individual asthma exacerbation risks over time. These capabilities were lacking in the current XGBoost model. Both models encountered challenges with accuracy and sensitivity due to class imbalance and a limited number of asthma exacerbations in the dataset. This indicates a need for model improvements, such as refined input data, techniques for compensating class imbalances, and hyperparameter optimization, to increase accuracy and applicability in pediatric asthma care. These refinements could also enable more precise evaluations of the influence of various exacerbation definitions and prediction time horizons.

The interview study showed pediatricians' insight into the necessity for model transparency and personalized risk factor identification to support clinical decision-making. Pediatricians consistently defined exacerbations as acute episodes requiring medical intervention, emphasizing the need for clear criteria to distinguish them from general loss of asthma control. They identified different prediction time horizons for specific contexts, with weekly predictions suitable for acute care and monthly predictions beneficial for long-term asthma management.

## 12.2 Future Directives

This research adopted a clinically focused approach, beyond predicting pediatric asthma exacerbations to emphasize practical implementation in pediatric asthma care. This approach collaborates with pediatricians and focuses on explainability rather than solely on performance metrics. This study aimed to create a more comprehensive and clinically applicable model for managing pediatric asthma exacerbations by evaluating various machine learning models, refining asthma definitions, and testing different prediction time horizons. A broader approach is used to predict exacerbations and incorporate diverse risk factors to provide a holistic view of patient health [42, 186]. The interviews helped identify key applications for the AI model, including a personal risk dashboard for patients, a dashboard for pediatricians to support outpatient care, and an eHealth tool to enhance the monitoring of high-risk patients. Each of these applications will guide the model's structure and parameters, as each requires different features. For example, an outpatient visit tool could enhance accuracy with less frequent predictions (e.g. monthly) while an eHealth tool might rely on more frequent at-home measurements. These eHealth applications can be evaluated by healthcare professionals in pilot studies with concept applications.

Explainability emerged as a central theme across all three research parts. The exploratory literature review highlighted that none of the existing models included explainability, which limits their clinical utility [33, 34, 41]. The simulation study demonstrated that the LSTM model could provide personalized identification of individual risk factors, supporting model explainability, while the XGBoost models illustrated the global importance of input features. Interviews with pediatricians revealed a strong preference for visual explanations of model predictions that highlight risk factors, with a clear distinction between modifiable risk factors (treatable traits) and non-modifiable risk factors. Thus, the literature and interview studies underscored the importance of model explainability, while the simulation study confirmed the LSTM model's capability to support it. Future research should aim to determine optimal explainability techniques for presenting risk factors that are understandable for healthcare professionals and patients, as the literature shows understanding of common explainability techniques is limited [188]. A pilot study involving end-users, including pediatricians and patients, could refine the practical application of these visualizations. Additional details are provided in Appendix J, which outlines a grant

proposal (Pioneers In HealthCare) for an AI-based personal risk dashboard to help patients understand their asthma exacerbation risks and associated risk factors.

The literature study identified models with acceptable to good accuracy and sensitivity; however, these models were unable to continuously predict asthma exacerbations over time. The simulation study also showed satisfactory accuracy, though this was misleading due to an imbalance between specificity and sensitivity. Because asthma exacerbations are relatively infrequent, the model's accuracy is elevated by correctly predicting their absence. However, detecting the presence of exacerbations is most critical, highlighting the need to improve sensitivity. In the interviews, there was no consensus on a specific accuracy threshold for the model; while some suggested acceptable accuracy levels of 80-90% or sensitivity of 80%, others preferred a model that performs at least as well as, if not better than, a pediatrician. Additionally, the specific application of the model could influence the required accuracy level, which was not discussed in interviews. After further refinements, the model's accuracy and sensitivity should be reassessed by pediatricians for each intended use. Furthermore, the definition of asthma exacerbation is closely related to model accuracy. As noted in the literature study, definitions vary significantly between models, making direct comparisons difficult and heavily influencing model accuracy. In the simulation study, a strict definition of severe exacerbation was applied, resulting in fewer exacerbation events in the dataset, leading to class imbalance and lower sensitivity. In the interviews, pediatricians suggested refining moderate asthma exacerbation definitions by using parameters such as a reliever medication schedule (*salbutamol afbouwschema*). Additionally, predicting loss of asthma control by determining increases in daily controller medication was suggested. Although not mentioned in the interviews, other potential indicators of moderate exacerbation could include the initiation of prednisone following a consultation by phone or eHealth contact. With these revised definitions, model accuracy and sensitivity should be reassessed.

As mentioned earlier in this paragraph, three applications of the AI model are determined as further follow-up of this research. These applications are 1) a personal risk dashboard for patients at home, 2) a risk dashboard for pediatricians to support outpatient visits, and 3) an AI-based monitoring tool for eHealth care. The first application, detailed further in Appendix J, aims to empower patients to manage their asthma by showing them their modifiable personal risk factors (treatable traits) for asthma exacerbations [229]. The second application is designed to support pediatricians during outpatient visits, highlighting key risk factors for each patient and predicting the risk of an asthma exacerbation over the coming period (e.g. the months leading up to the next visit). This information allows pediatricians to tailor asthma management based on individualized risk assessments. The third application focuses on enhanced monitoring for high-risk patients in eHealth care, who provide more frequent data through symptom tracking (chat) and, in some cases, at-home spirometry. This enables the AI model to deliver more specific asthma exacerbation predictions on a shorter time horizon (e.g. daily). The identified risk factors from this application can also contribute to a database that matches eHealth interventions to specific risk factors. This database allows healthcare professionals to offer patients targeted eHealth interventions tailored to their most important risk factors, making self-management more efficient, personalized, and effective. Additionally, the model can identify patient subgroups with similar risk profiles, helping prioritize the development of eHealth interventions targeting key risk factors. The effectiveness of these targeted interventions could be evaluated through an RCT study within the CIRCUS cohort [72]. The research questions following each part of this research are shown in Tables 5.1, 8.1, and 11.1. Figure 12.1 shows an overview of the whole project.

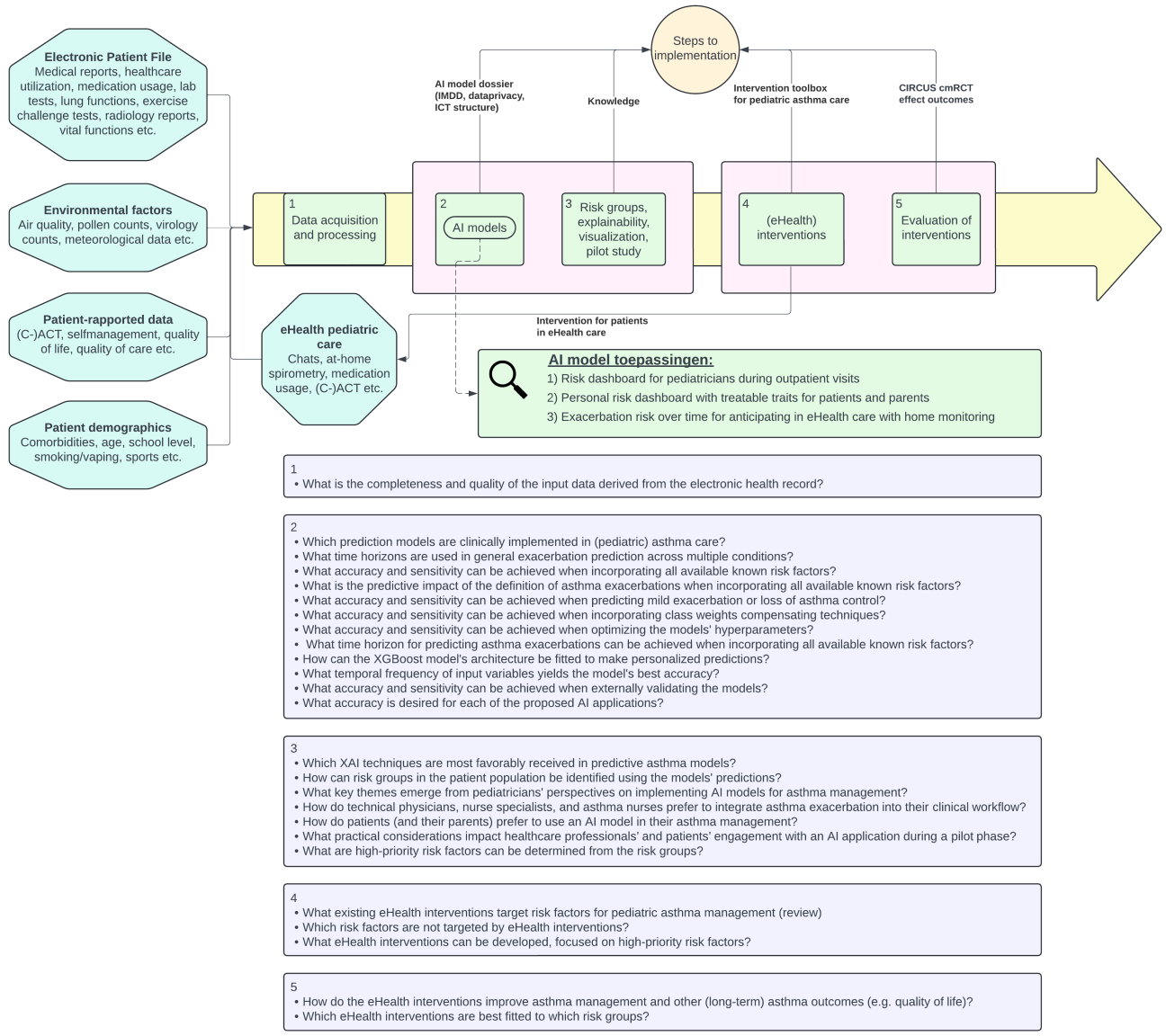


Figure 12.1: An overview of the follow-up projects of the AI model for predicting pediatric asthma exacerbations.

## 12.3 Conclusion

In conclusion, this research represents pioneering work in predicting pediatric asthma exacerbations over time while identifying individualized risk factors, showing potential for clinical application. The proposed model builds on literature-based risk factors and insights from interviews, aligning well with clinical needs to support pediatric asthma management through personalized care.

Future work should focus on enhancing the model's sensitivity in detecting asthma exacerbations by incorporating diverse input data, addressing class imbalances, and optimizing model parameters. These improvements will enable a more accurate assessment of the clinical definitions of asthma exacerbations and enable prediction time horizons tailored to specific applications. Potential applications are 1) a personal risk dashboard for patient self-management, 2) a risk dashboard for pediatricians to guide outpatient visits, and 3) an eHealth monitoring tool. Pilot studies with healthcare professionals and patients will evaluate these applications on their accuracy, clinical utility, and feasibility, ensuring that they deliver actionable insights that enhance both prevention and treatment strategies.

Through these applications, the model offers a pathway toward more responsive and individualized asthma management, ultimately supporting better (long-term) asthma outcomes and empowering patients and clinicians to manage asthma more effectively.

# 13 Dankwoord

Wat een jaar is het geweest... Zoals iedereen mij kent ben ik vanuit mijzelf heel enthousiast en op deze manier ben ik dus ook aan mijn M3 begonnen, en heb ik dit ook wel volgehouden hoor ;). Binnen mijn afstuderen heb ik ontzettend veel geleerd over het onderwerp zelf, het uitvoeren van onderzoek en heel veel over alles wat er rondom onderzoek speelt. Maar ik heb naast al het serieuze leerwerk ook zeker heel veel plezier gehad tijdens mijn afstuderen!

Ik wil graag iedereen bedanken die mij tijdens dit jaar heeft geholpen, op wat voor manier dan ook om dit onderzoek tot een succes te brengen! Allereerst wil ik Mattiènne bedanken voor alle begeleiding die je mij dit jaar hebt gegeven. Van de inhoudelijke discussies tot het pushen van de juiste mensen, maar ook de supervisie van mijn klinische activiteiten bij het aircon en het meegaan naar het congres in Amerika. Naast alle serieuze activiteiten hebben we ook ontzettend veel kunnen lachen; die ene moeilijke wandeling in Salt Lake City of de Saboteur spelletjes in Wenen.

Verder wil ik ook Boony bedanken voor jouw begeleiding tijdens dit jaar. Je hebt mij ontzettend veel geleerd over kinderen in het algemeen, astma en klinisch redeneren. Je staat altijd voor mij klaar om mee te denken, om mijn stukken van feedback te voorzien of om te overleggen over een patiënt. Jouw enthousiasme werkt aanstekelijk en heeft er echt voor gezorgd dat ik met meer vertrouwen de kliniek in kan! Ook heb jij altijd de tijd om het over van alles en nog wat te hebben, zoals je meest recente wielrenrondje of grapjes die we uit willen halen.

Frans jou wil ik ook bedanken voor alle hulp en begeleiding die je hebt geboden tijdens mijn afstuderen. Jij kon altijd echt met een goede kritische blik naar mijn verslagen, onderzoeksvragen of methode kijken, waardoor het onderzoek echt een stuk sterker wordt. Wat ik verder echt ontzettend kan waarderen is dat ik altijd van jou op aan kan; hoe druk je ook bent, je hebt altijd een moment om mijn verslagen te lezen of om een meeting in te plannen, dankjewel hiervoor!

Ik wil daarnaast ook graag de andere leden van mijn afstudeercommissie bedanken; Monique, Lieke en Marijn. Monique ik wil je graag bedanken voor de scherpe feedback die je altijd kunt geven op mijn verslagen, je kijkt er altijd weer met een vernieuwende blik naar, waardoor ik het stuk nog concreter kan maken; voor mijn verslag, het CIRCUS artikel, maar ook voor de subsidie-aanvragen ben je altijd bereid om mee te denken. Lieke ik wil jou ook bedanken voor alle fijne begeleiding (vanaf de M2 al!) tijdens en buiten de intervisies waarin je altijd heel open bent, wilt meedenken en er altijd voor zorgt dat ik weer verder kan. Tot slot wil ik jou nog bedanken Marijn, dat je zo enthousiast en bereidwillig was om mee te lezen (en luisteren) als buitenlid van mijn afstudeercommissie.

Verder wil ik ook iedereen van de Kindergeneeskunde afdeling bedanken. Iedereen hier staat altijd open om mee te denken over het onderzoek of om mee te lopen op de kliniek. Specifiek wil ik ook nog iedereen van het AIRCON team bedanken (Boony, Mark, Mattiènne, Pascal, Pamela en Miranda) voor jullie openheid, betrokkenheid en enthousiasme waarin jullie mij hebben ondersteund in het zelfstandig uitvoeren van de aircon inspanningstesten. Ik voelde mij al snel echt onderdeel van het team en ik kan altijd bij jullie terecht met vragen, leuke verhaaltjes (supertjes!) en soms wat geklaag. Verder wil ik Deborah bedanken voor al jouw betrokkenheid bij mijn afstuderen en alle hulp bij het CIRCUS onderzoek. Tijdens (en na) onze theepauzes kunnen we naast alle belangrijke zaken ook altijd lekker kletsen over eigenlijk alles. Tot slot natuurlijk ook alle stagiaires, naast alle inhoudelijke discussies was er ook altijd tijd om gewoon lekker te kletsen, veel te lachen en leuke dingen samen te doen!

Tot slot wil ik natuurlijk ook nog (mijn) Mark bedanken voor alle steun, aanmoediging en geduld die je mij hebt geboden tijdens mijn afstuderen. Het maakte niet uit met wat voor verhalen, geklaag of dolenthousiasme ik thuis kwam, je was er altijd voor mij. Dit heeft er voor gezorgd dat ik dit jaar zo mooi kan afronden, dankjewel!

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[265] LUMC, "Pollen en hooikoorts."

[266] Elkerliek, "Pollentellingen."

[267] RIVM;, "Luchtmeetnet dataset," 2023.

[268] NVMO, "Nederlandse Vereniging voor Medische Oncologie," 2012.

[269] RIVM, "RecenteVirUitslagen27w — RIVM," 2024.

[270] KNMI, "Dagwaarden van weerstations," 2022.

# Appendix A: Definitions of Asthma Exacerbations

An explanation on the different definitions mentioned in Table 2.1.

Altman et al. use asthma exacerbations as a clinical endpoint by defining it as requiring systemic corticosteroids, hospital admission, or a combination of both [44].

Murray et al. further distinguished loss of asthma control and asthma exacerbation by a limitation of 48 hours for loss of asthma control [28]. Furthermore, a significant asthma exacerbation is defined as troublesome symptoms lasting for at least 48 hours and ultimately resulting in treatment with systemic corticosteroids. A status asthmaticus is defined as a severe asthma exacerbation that cannot be relieved with acute care in an emergency department, that requires hospital admission, and that can be life-threatening.

Helen et al. provide a more elaborate definition of asthma exacerbation [45]. An asthma exacerbation is defined as an event characterized by a change from the patient's previous status which is further divided into severe and moderate asthma exacerbations. A severe asthma exacerbation is defined as an event that requires an acute effort of both patient and physician to avert a serious consequence such as hospitalization and death. A moderate asthma exacerbation is defined as a troublesome event that prompts a need for a modification in treatment. This is clinically specified by being past the patient's standard range of day-to-day variation of asthma.

An official statement from the American Thoracic Society (ATS) and European Respiratory Society (ERS) from Reddel et al. distinguishes between severe, moderate, and mild asthma exacerbations [11]. Severe asthma exacerbations are defined as needing urgent intervention to prevent hospitalization or death. This can be further explained by the use of systemic corticosteroids for at least three days, or an increased dose from a stable maintenance level, and by hospitalization or emergency room visits requiring systemic corticosteroids. Moderate asthma exacerbations are defined as a temporary treatment change to prevent escalation. They are defined by a deterioration in symptoms, decline in lung function, or increased rescue bronchodilator use, persisting for two or more days but not severe enough for systemic corticosteroids or hospitalization. ER visits not requiring systemic corticosteroids may also be classified as moderate. Mild exacerbations lack a justifiable definition as symptoms or flow rate changes are minor and may reflect transient loss of asthma control rather than a precursor to severe exacerbations.

Virchow et al. derive further clinical endpoints for moderate exacerbations using the official statement of the ATS/ERS [46]. They state four criteria and when fulfilling at least two of those that result in a change in treatment, the event is considered a moderate asthma exacerbation. These criteria are 1) nocturnal awakening due to asthma and requiring reliever medication for two consecutive nights or an increase of at least 0.75 in the daily symptom score for two consecutive days, 2) increase of at least 4 puffs a day in reliever medication use on two executive days, 3) increase of at least 20% in PEF or FEV1 on at least two consecutive days, and 4) visit to the emergency room for asthma treatment not requiring systemic corticosteroids.

# Appendix B: Literature Search Strategy

To ensure a comprehensive review of relevant literature, a systematic search strategy was employed across multiple academic databases, including PubMed, Scopus, and Google Scholar. The search aimed to identify studies related to the use of artificial intelligence in predicting pediatric asthma exacerbations.

The following keywords and Boolean operators were used to refine the search:

- ("Artificial Intelligence" OR "AI" OR "Machine Learning" OR "ML" OR "model")
- AND ("predicting" OR "forecasting"
- AND ("asthma exacerbations" OR "asthma attacks")
- AND ("pediatric" OR "child")

Only studies available in English were included. Additionally, the search strategy included reviewing reference lists from key articles to identify further relevant studies.

# Appendix C: Machine Learning Models in the Literature to predict Asthma Exacerbations

## C.1 Highly Relevant ML Models

Table C.1 shows the demographics, clinical characteristics, asthma characteristics, and comorbidities used as input for the machine learning models in the literature categorized as most relevant. The demographics are used most as input for the ML models, followed by asthma characteristics, comorbidities, and clinical measurements. However, the specific features within each domain vary greatly in the asthma characteristics domain.

Table C.2 shows the healthcare utilization, social data, environmental data, and at home-measurements used as input for the machine learning models in the literature categorized as most relevant. It can be seen that these domains are used less as compared to the domains in Table C.1. Healthcare utilization is used in most of the models, but the domains of social, environmental, and at-home data are relatively unused.

Figure C.1 shows the number of input features for each of the included articles. It can be seen that the number of input features varies greatly with a mean of 9.7 features and a standard deviation of 4.6 features.

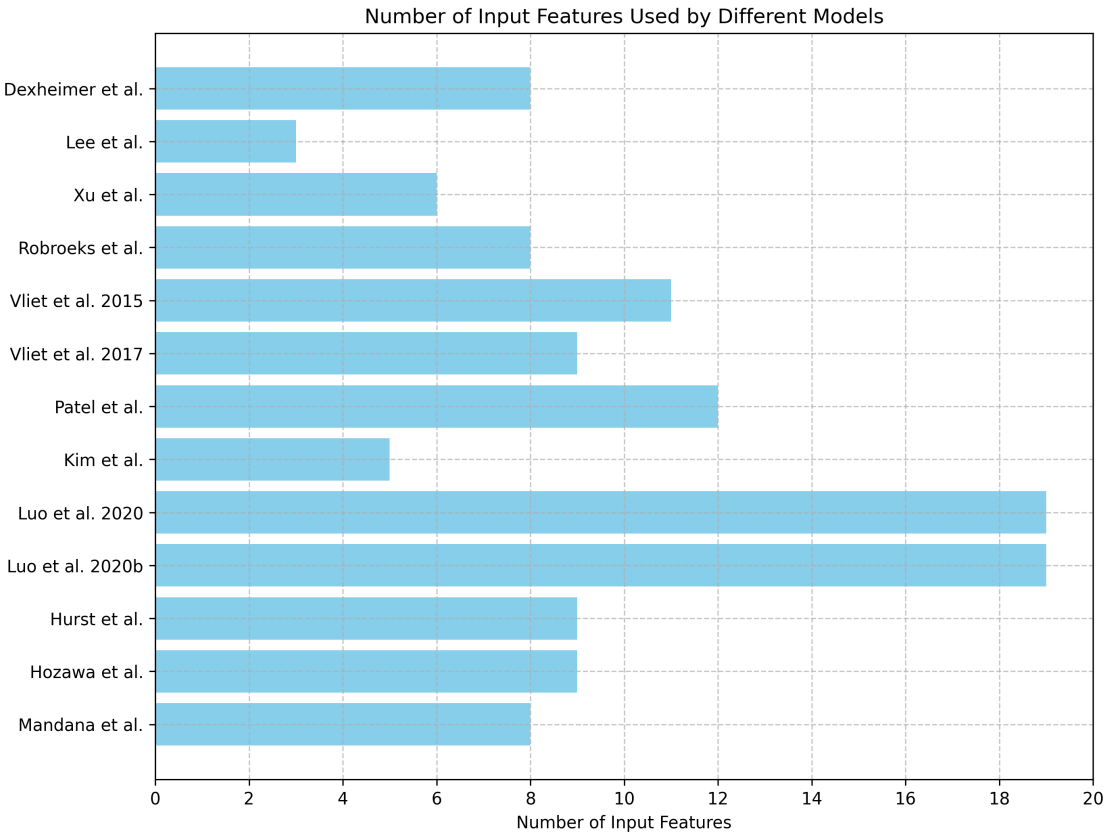



Figure C.1: The number of input features used in the models from the literature.

Table C.3 shows the machine learning methods, best-performing model, outcome definitions, and model performances for each of the highly relevant models. No clear correlation can be determined from the ML method used and the model performance.

Table C.1: The input characteristics of the machine learning methods of the demographic, clinical, and asthma characteristics, and comorbidities domain.

| **Source** | **Demographics** | **Clinical Measurements and Vital Signs*** | **Asthma Characteristics*** | **Comorbidities** |
|---|---|---|---|---|
| Dexheimer et al. [162] | Age, sex | Respiratory rate, saturation | History | - |
| Lee et al. [163] | - | - | Symptoms | - |
| Xu et al. [164] | Age, sex | Genome data | History, spirometry | - |
| Robroeks et al. [165] | Age, sex | Height, weight | Spirometry, VOC | Allergies |
| Van Vliet et al. [139] | Age, sex | - | ACT, symptoms, spirometry, FeNO, VOC, GINA symptom score | Allergies |
| Van Vliet et al. [140] | - | - | ACT, symptoms, spirometry, FeNO, VOC, previous asthma exacerbation | Allergies |
| Patel et al. [166] | Age, sex | Weight, respiratory rate, heart rate, saturation | - | - |
| Kim et al. [167] | Age, sex | - | - | - |
| Luo et al. [168] | Age, gender, ethnicity, race | Weight, BMI, respiratory rate, heart rate, saturation, blood pressure, temperature, eosinophils, IgE, X-rays | Undefined diagnosis-related features | Allergies |
| Luo et al. [169] | Age, gender, ethnicity, race | Weight, BMI, respiratory rate, heart rate, saturation, blood pressure, temperature, eosinophils, IgE, X-rays | Undefined diagnosis-related features | Allergies |
| Hurst et al. [152] | Age, sex, ethnicity | - | Previous asthma exacerbation | Allergies, Eczema, obesity |
| Hozawa et al. [170] | Age, sex | - | History, spirometry, VOC | Allergies, general comorbidities |
| Mandana et al. [171] | Age, sex, ethnicity | - | Lung function, FeNO | General comorbidities |
| * BMI = Body Mass Index, IgE = Immunoglobulin E, VOC = Volatile Exhaled Compounds, ACT = Asthma Control Test, FeNO = Fractional Exhaled Nitric Oxide | | | | |

Table C.2: The input characteristics of the machine learning methods of the healthcare utilization, social, environmental, and at-home measurements domain.

| **Source** | **Healthcare Utilization** | **Social Data** | **Environmental Data*** | **At-home Measurements*** |
|---|---|---|---|---|
| Dexheimer et al. [162] | Medication, billing codes, chief complaints | - | - | - |
| Lee et al. [163] | - | - | Air pollution, meteorological data (humidity, temperature) | - |
| Xu et al. [164] | Medication | - | - | - |
| Robroeks et al. [165] | Medication | - | - | - |
| Van Vliet et al. [139] | - | - | - | Daily spirometry, daily symptoms |
| Van Vliet et al. [140] | - | - | - | FEV1, symptoms |
| Patel et al. [166] | Patient acuity at triage | Housing conditions, insurance, socioeconomic status | Meteorological data, virus data (community viral load data), climate data | - |
| Kim et al. [167] | - | - | Air pollution (PM2.5, PM10) | Bidaily PEF, asthma questionnaires |
| Luo et al. [168] | Medication | Home area, insurance | - | - |
| Luo et al. [169] | Medication | Home area, insurance | - | - |
| Hurst et al. [152] | Emergency room visits, outpatient visits | - | - | - |
| Hozawa et al. [170] | Medication | Home area | - | - |
| Mandana et al. [171] | Emergency room visits, hospitalizations | - | - | - |
| * PM2.5 = Particulate Matter 2.5, PM10 = Particulate Matter 10, FEV1 = Forced Expiratory Volume in 1 second, and PEF = Peak Expiratory Flow | | | | |

Table C.3: The model metrics of the highly relevant literature models. The machine learning models in *Italic font* were the best-performing models in those articles, only those model performances are presented in the table.

| **Source** | **ML methods*** | **Outcome*** | **Model performance*** |
|---|---|---|---|
| Dexheimer et al. 2007 [162] | *BN*, SVM, ANN | Exacerbation (not further defined) | AUC 95.9%, sensitivity 90%, specificity 88.2%, PPV 44.7%, NPV 98.9%, PLR 7.69, NLR 0.11 |
| Lee et al. 2011 [163] | DT | Exacerbation (not further defined) | Accuracy 87.52%, Sensitivity 85.59% |
| Xu et al. 2011 [164] | RF | Hospitalization or ER visit | AUC 66% |
| Robroeks et al. 2013 [165] | SVM | Moderate to severe exacerbations | Sensitivity 100%, specificity 93%, accuracy 96% |
| Van Vliet et al. 2015 [139] | KNN | Moderate to severe exacerbations following Reddel et al. | AUC 58.54%, accuracy 52% |
| Van Vliet et al. 2017 [140] | RF | Exacerbation (not further defined) | AUC 90%, sensitivity 62%, specificity 67%, accuracy 67% |
| Patel et al. 2018 [166] | DT, RF, LLR, *GBM* | Hospitalization and receiving systemic corticosteroids | AUC 84% |
| Kim et al. 2020 [167] | *LSTM*, MNL | Risk for exacerbation | PPV no exact value |
| Luo et al. 2020 [168] | XGBoost | Hospitalization or ER visit | Sensitivity 53.7%, specificity 91.93%, accuracy 90.31% |
| Luo et al. 2020b [169] | XGBoost | Hospitalization or ER visit | Sensitivity 51.9%, specificity 90.91%, accuracy 90.08% |
| Hurst et al. 2022 [152] | LLR, RF, *XGBoost* | Exacerbation (not further defined) | AUC 73.9%, sensitivity 70%, PPV 13.8% |
| Hozawa et al. 2022 [170] | XGBoost | Exacerbation (not further defined) | AUC 65.6% |
| Mandana et al. 2023 [171] | RF | Exacerbation (not further defined) | AUC 72%, sensitivity 55%, specificity 78% |

* BN = Bayesian Network, SVM = Support Vector Machine, ANN = Artificial Neural Network, DT = Decision Tree, RF = Random Forest, KNN = K-Nearest Neighbor, LLR = Lasso Logistic Regression, GBM = Gradient Boosting Model, LSTM = Long-Short Term Memory, MNL = MultiNomial Logistic Regression, XGBoost = eXtreme Gradient Boosting, ER = Emergency Room, AUC = Area under the Receiver-Operative Curve, PPV = Positive Predictive Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio

## C.2 Moderately Relevant ML Models

Table C.4 shows the article characteristics, population details, time horizon, and outcome definitions of the moderately relevant machine learning models. It can be seen that a great variety of ML methods is applied in this category as is the same in the outcome definition. The definitions in this category are more focused on measures of asthma control rather than asthma exacerbations. Furthermore, the models with an asthma exacerbation as an outcome did not further define this outcome and only included adults in their studies. The time horizon presented in some of the studies ranges greatly from only two weeks to one year. The comparison of these models on clinical applicability is therefore rather difficult.

Table C.4: The moderately relevant literature comparison of machine learning models for predicting pediatric asthma exacerbations.

| **Source** | **ML methods*** | **Outcome*** | **Age range (nr. of patients)** | **Time horizon** |
|---|---|---|---|---|
| Lieu et al. 1998 [230] | DT | Hospitalization or ER visit | 0 – 14 (16520) | - |
| Luo et al. 2015 [231] | MBDS, SVM, DL, NB, KNN, RF | Asthma control deterioration | 2 – 8 (210) | - |
| Hosseini et al. 2017 [232] | RF | Risk of asthma exacerbations | Child and adult (2) | - |
| Das et al. 2017 [233] | LR, DT, RF, SVM | Frequent ER use (more than 2) | Children (2691) | - |
| Deng et al. 2019 [234] | GBM | Asthma symptoms | Children (4548) | - |
| Xiang et al. 2020 [84] | ANN | Asthma exacerbation (not further defined) | Adults (31433) | 365 days |
| Cobian et al. 2020 [235] | semi-Markov | Asthma exacerbation (not further defined) | Adults (28101) | 90 days |
| Tong et al. 2021 [236] | XGBoost | Hospitalization or ER for asthma | Adults (Unknown) | 365 days |
| Sills et al. 2021 [237] | RF, LR, autoML | Hospitalization from ER visit | Children (9069) | - |
| Lisspers et al. 2021 [238] | XGBoost, RF, LightGBM, GLM-Net | Asthma exacerbation (not further defined) | Adults (29396) | 15 days |
| Zein et al. 2021 [239] | LR, RF, Light-GBM | Non-severe and severe asthma exacerbation | Adults (12093) | 28 days |
| Haque et al. 2021 [240] | DNN | ACT score | Unknown (10) | - |
| Seol et al. 2021 [241] | BN | Asthma exacerbation within 1 year of start study | Children (99) | - |
| Hogan et al. 2022 [242] | Cox, LR, ANN | Asthma exacerbation readmission within 180 days after diagnosis | 5 – 18 (18489) | 180 days |
| Lugogo et al. 2022 [243] | GBM | Moderate and severe asthma exacerbation | Adults (360) | - |

Continued on next page

Table C.4: (Continued) The moderately relevant literature comparison of machine learning models for predicting pediatric asthma exacerbations.

| Source | ML methods | Outcome | Age range (nr. of patients) | Time horizon |
|---|---|---|---|---|
| Alsaad et al. 2022 [244] | RNN (BiLSTM, BiGRU, RETAIN), LR | Risk for (repeated) ER visits | 0 – 18 (87413) | - |
| Hond et al. 2022 [245] | XGBoost, SVM, LR | Severe asthma exacerbation | Adults (266) | - |
| Inselman et al. 2023 [246] | GLMnet, RF, XGBoost | Asthma exacerbation (not further defined) | Adults (3057) | 180 days |
| Gorham et al. 2023 [247] | LLR | Asthma emergency risk score | 2 – 18 (26008) | - |
| Huang et al. 2023 [248] | XGBoost | Predictors of asthma exacerbation | Adults (7922) | - |
| * DT = Decision Tree, MBDS = , SVM = Support Vector Machine, DL = Deep Learning, NB = Naïve Bayes, KNN = K-Nearest Neighbor, RF = Random Forest, LR = Logistic Regression, GBM = Gradient Boosting model, ANN = Artificial Neural Network, MBDS = MultiBoost with Decision Stumps, GLM = Gradient Light model, DNN = Deep Neural Network Regression, RNN = Recurrent Neural Network, BiLSTM = Bidirectional Long-Short Term Memory, BiGRU = Bidirectional Gated Recurrent Unit, RETAIN = REverse Time AttentIoN model, LLR = Lasso Logistic Regression, ER = Emergency Room | | | | |

Figure C.2 shows the input data used in the moderately relevant machine learning models. Overall, input features in the demographics domain are used most, followed by features from the asthma characteristics and clinical measurements & vital signs domains. The input feature medication in the asthma characteristics domain is by far the most used within this domain, followed by tobacco exposure and the asthma control test (ACT). Moreover, as opposed to the comorbidities used in the highly relevant models (see Figure 4.1), the general comorbidities are the most used and not the allergies.

Table C.5 shows the machine learning methods, best-performing model, outcome definitions, and model performances for each of the moderately relevant models. It shows that multiple ML methods are used, but no correlation can directly be determined between the ML method and the model performance or the definition of the model's outcome.

Table C.5: The model metrics of the moderately relevant literature models. The machine learning models in *Italic font* were the best-performing models in those articles, only those model performances are presented in the table.

| Source | ML methods | Outcome | Model performance |
|---|---|---|---|
| Lieu et al. 1998 [230] | DT | Hospitalization or ER visit | Sensitivity (32%), specificity (94%), PPV (7%) |
| Luo et al. 2015 [231] | *MBDS*, SVM, DL, NB, KNN, RF | Asthma control deterioration | AUC (75.7%), sensitivity (73.8%), specificity (71.4%), accuracy (71.8%) |
| Hosseini et al. 2017 [232] | RF | Risk of asthma exacerbations | Accuracy (80.1%) |
| Das et al. 2017 [233] | *LR*, DT, RF, SVM | Frequent ER use (more than 2) | AUC (86%), sensitivity (23%), PPV (56%), calibration (13%) |

Continued on next page

**Table C.5 – continued from previous page**

| Source | ML methods* | Outcome | Model performance* |
|---|---|---|---|
| Deng et al. 2019 [234] | GBM | Asthma symptoms | AUC (78%) |
| Xiang et al. 2020 [84] | ANN | Asthma exacerbation (not further defined) | AUC (70.03%) |
| Cobian et al. 2020 [235] | semi-Markov | Asthma exacerbation (not further defined) | AUC (77%) |
| Tong et al. 2021 [236] | XGBoost | Hospitalization or ER for asthma | AUC (90.2%), sensitivity (70.2%), specificity (90.91%), accuracy (90.6%) |
| Sills et al. 2021 [237] | *RF*, LR | Hospitalization from ER visit | AUC (91.4%) |
| Lisspers et al. 2021 [238] | *XGBoost*, LightGBM, RF, GLMNet | Asthma exacerbation (not further defined) | AUC (0.7%) |
| Zein et al. 2021 [239] | LR, RF, *Light GBM* | Non-severe and severe asthma exacerbation | AUC (85%) |
| Haque et al. 2021 [240] | DNN | ACT score | Sensitivity (94%), Mean absolute error (0.2), Mean squared error (0.9) |
| Seol et al. 2021 [249] | BN | Asthma exacerbation within 1 year of study | No model performance given |
| Hogan et al. 2022 [242] | Cox, LR, *ANN* | Asthma exacerbation readmission within 180 days after diagnosis | AUC (63.7%) |
| Lugogo et al. 2022 [243] | GBM | Moderate and severe asthma exacerbation | AUC (83%) |
| Alsaad et al. 2022 [244] | *RNN* (BiLSTM, BiGRU, RETAIN), LR | Risk for (repeated) ER visits | AUC (85%), AU PR-curve (74%), F1-score (0.61) |
| Hond et al. 2022 [245] | XGBoost, SVM, *LR* | Severe asthma exacerbation | AUC (85%), sensitivity (59%), accuracy (89%), PPV (2%), NPV (100%) |
| Inselman et al. 2023 [246] | GLMnet, RF, *XGBoost* | Asthma exacerbation (not further defined) | AUC (74%) |
| Gorham et al. 2023 [247] | LASSO | Asthma emergency risk score | AUC (73.7%) |
| Huang et al. 2023 [248] | XGBoost | Predictors of asthma exacerbation | AUC (73.7%), sensitivity (96%), NPV (96.7%) |

* DT = Decision Tree, MBDS = MultiBoost with Decision Stumps, SVM = Support Vector Machine, NB = Naïve Bayes, KNN = K-Nearest Neighbor, RF = Random Forest, LR = Logistic Regression, GBM = Gradient Boosting model, ANN = Artificial Neural Network, DNN = Deep Neural Network, RNN = Recurrent Neural Network, BiLSTM = Bidirectional Long-Short Term Memory, BiGRU = Bidirectional Gated Recurrent Unit, RETAIN = REverse Time AttentIoN model, LLR = Lasso Logistic Regression, PPV = Positive Predictive Value, AUC = Area Under the Receiver-Operating Curve, AU-PR = Area Under the Precision-Recall Curve, NPV = Negative Predictive Value

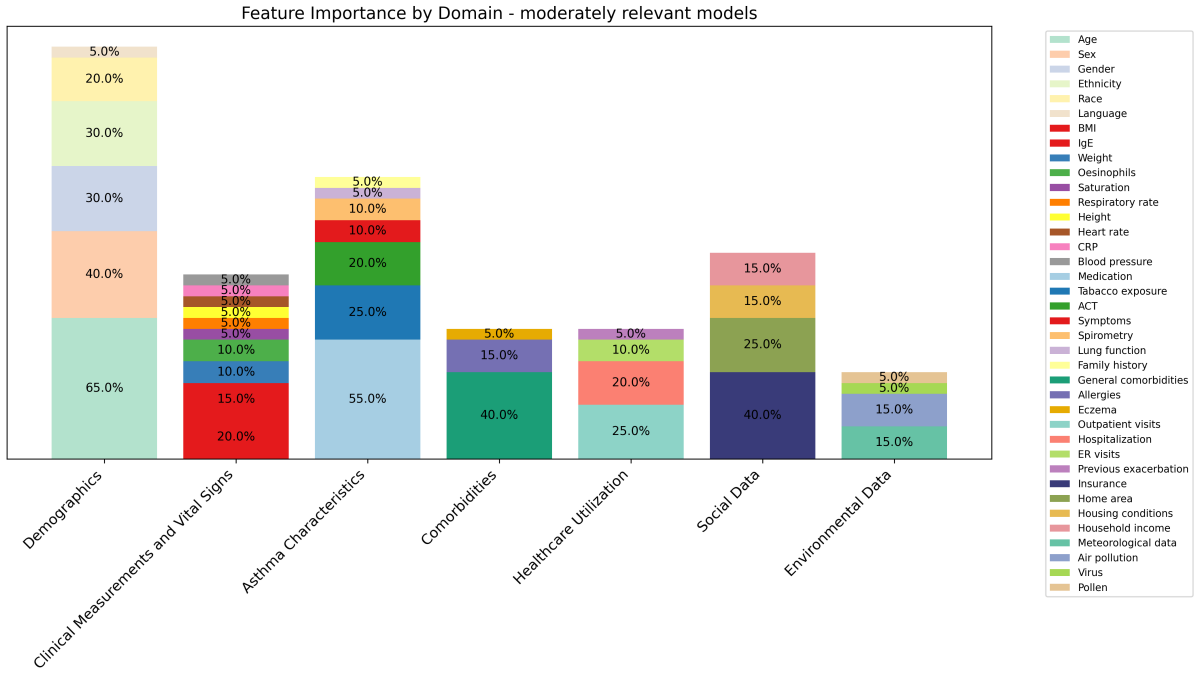



Figure C.2: The input data for the moderately relevant machine learning models per input domain. The frequency of the input data is shown as a percentage of the total number of articles in this category (n=21).

## C.3 Least Relevant ML Models

Table C.6 shows the article characteristics, population details, time horizon, and outcome definitions of the least relevant machine learning models. A great variety of ML methods is used in the literature, similar to the ML methods used in the highly and moderately relevant models. The outcomes used in this category are very broad focussing on asthma control, risk factors, severity of the asthma exacerbation, or the persistence of asthma. The age range varies greatly in this category as is the number of included patients, starting at only 16 patients and reaching 100 thousand. No model in this category presented a time horizon.

Figure C.3 shows the input data used in the moderately relevant machine learning models. Overall, input features in asthma characteristics, clinical measurements & vital signs, and demographics domains are used most. In this category of models, the features from the asthma characteristics domain are used most, as opposed to the highly and moderately relevant models in which demographics are used most. The asthma characteristics are followed by the clinical measurements & vital signs, and demographics. In the asthma characteristics domain, again medication is the most used feature. The domains of healthcare utilization, social data, and environmental data are rarely used and the domain of at-home measurements is not used at all.

Table C.7 shows the machine learning methods, best-performing model, outcome definitions, and model performances for each of the moderately relevant models. Again, no correlation can be seen between the ML methods used in these articles and their model performance.

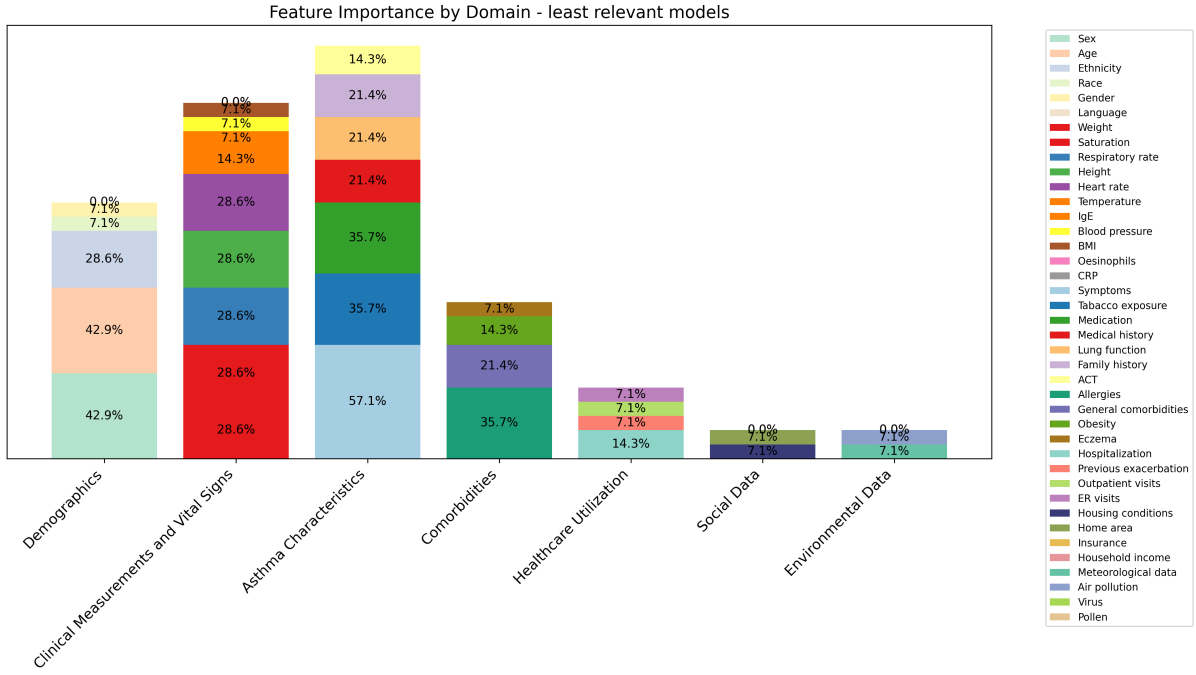



Figure C.3: The input data for the least relevant machine learning models per input domain. The frequency of the input data is shown as a percentage of the total number of articles in this category (n=21).

Table C.6: The least relevant literature comparison of machine learning models for predicting pediatric asthma exacerbations.

| **Source** | **ML methods*** | **Outcome*** | **Age range (number of patients)** | **Time horizon** |
|---|---|---|---|---|
| Farion et al. 2010 [250] | DT | Severity of asthma exacerbation after ER presentation | 1 – 17 (341) | - |
| Farion et al. 2013 [251] | NB, DT, SVM | Severity of asthma exacerbation | Children (291) | - |
| Chatzimichail et al. 2013 [252] | SVM | Asthma outcome (not further defined) | 7 – 14 (112) | - |
| Blakey et al. 2017 [253] | LR | Risk of recurrent asthma exacerbation | 12 – 80 (118981) | - |
| Goto et al. 2018 [254] | LLR, RM, XGBoost, DNN | Risk of hospitalization for asthma or COPD | Adults (3206) | - |
| Spyroglou et al. 2018 [255] | NB | Asthma persistence | Children (147) | - |
| Huffakker et al. 2018 [256] | RF | Asthma symptoms | 5 – 18 (16) | - |
| Khasha et al. 2019 [257] | MNLR, SVM, RF, XGBoost, KNN, DT, GN | Asthma control level | 5+ (96) | - |
| Harvey et al. 2019 [258] | KNN, LR, DT, RF, NB | Asthma development | Children (Unknown) | - |
| Messinger et al. 2019 [259] | ANN | Objective respiratory score for asthma | Children (128) | - |
| Deliu et al. 2020 [260] | LR | Risk factors for asthma exacerbation | Children (887) | - |
| Bose et al. 2021 [261] | XGBoost, NB, LR, KNN, RF | Asthma persistence | 5 – 10 (9934) | - |
| Lan et al. 2021 [262] | RF, DT | ED or inpatient visits for respiratory issues, including asthma | Unknown (Unknown) | - |
| Halner et al. 2021 [263] | RF | Need for additional systemic corticosteroids and/or antibiotics, hospital readmission, or death within 30 days of initial asthma exacerbation | Adults (81) | - |
| Overgaard et al. 2022 [264] | LR, SVM, RF, GN | Asthma exacerbation risk | 6 – 17 (Unknown) | - |

* DT = Decision Tree, NB = Naive Bayes, SVM = Support Vector Machine, LR = Logistic Regression, LLR = Lasso Logistic Regression, XGBoost = eXtreme Gradient Boosting, DNN = Deep Neural Network, RF = Random Forest, MNLR = MultinNomial Logistic Regression, KNN = K-Nearest Neighbor, ANN = Artificial Neural Network, ER = Emergency Room, COPD = Chronic Obstructive Pulmonary Disease

Table C.7: The model metrics of the least relevant literature models. The machine learning models in *Italic font* were the best-performing models in those articles, only those model performances are presented in the table.

| **Source** | **ML methods*** | **Outcome*** | **Model performance*** |
|---|---|---|---|
| Farion et al. 2010 [250] | DT | Severity of asthma exacerbation after ER presentation | AUC (83%), sensitivity (84%), specificity (71%), Brier score (0.18) |
| Farion et al. 2013 [251] | *NB*, DT, SVM | Severity of asthma exacerbation | Accuracy (70.7%) |
| Chatzimichail et al. 2013 [252] | SVM | Asthma outcome (not further defined) | Sensitivity (95.45%), specificity (95.59%), accuracy (95.54%) |
| Blakey et al. 2017 [253] | LR | Risk of recurrent asthma exacerbation | AUC (86.7%) |
| Goto et al. 2018 [254] | LLR, *RF*, XGBoost, DNN | Risk of hospitalization for asthma or COPD | Sensitivity (75%), C-statistics (0.83), Reclassification improvement (92%) |
| Spyroglou et al. 2018 [255] | BN | Asthma persistence | Sensitivity (87.25%), specificity (85.52%), accuracy (86.37%) |
| Huffakker et al. 2018 [256] | RF | Asthma symptoms | Sensitivity (47.2%), specificity (96.3%), accuracy (87.4%) |
| Khasha et al. 2019 [257] | MNLR, SVM, RF, *XGBoost*, KNN, DT, GN | Asthma control level | Accuracy (91.66%) |
| Harvey et al. 2019 [258] | KNN, LR, DT, *RF*, NB | Asthma development | Accuracy (90.9%) |
| Messinger et al. 2019 [259] | ANN | Objective respiratory score for asthma | Accuracy (80%) |
| Bose et al. 2021 [261] | *XGBoost*, NB, LR, KNN, RF | Asthma persistence | Average NPV-Specificity area (0.43) |
| Lan et al. 2021 [262] | RF, DT | ED or inpatient visits for respiratory issues, including asthma | No model performance given |
| Halner et al. 2021 [263] | RF | Need for additional systemic corticosteroids and/or antibiotics, hospital readmission or death within 30 days of initial asthma exacerbation | AUC (68%) |
| Overgaard et al. 2022 [264] | LR, SVM, *RF*, GN | Asthma exacerbation risk | AUC (80%) |

* DT = Decision Tree, NB = Naive Bayes, SVM = Support Vector Machine, LR = Logistic Regression, LLR = Lasso Logistic Regression, XGBoost = eXtreme Gradient Boosting, DNN = Deep Neural Network, RF = Random Forest, MNLR = MultinNomial Logistic Regression, KNN = K-Nearest Neighbor, ANN = Artificial Neural Network, ER = Emergency Room, COPD = Chronic Obstructive Pulmonary Disease, AUC = Areau Under the Receiver-Operating Curve, NPV = Negative Predictive Value

## Appendix D: Definition of Input Features

- Demographic domain
  - Age: age either in years, months, or days
  - Sex: female or male
  - Gender: more broad gender identities including bigender, genderfluid, etc.
  - Ethnicity: caucasian, African American, etc
  - Race: white, black, Asian, etc
- Clinical measurements and vital signs domain
  - Respiratory rate, saturation, heart rate, blood pressure: (dis)continuously measured
  - Genome data: presence of specific genes or more broad genome data
  - Height, weight, BMI, temperature: measured in either the hospital or at-home setting
  - Eosinophils, Ige: measured value or labeled as elevated/normal
  - X-rays: image or conclusion
- Asthma characteristics
  - Medication: prescribed, retrieved, or a measure of taken medication
  - History: dichotomous annotation of asthma-related history (symptoms, cues, triggers, etc)
  - Symptoms: description or dichotomous annotation of previous or present symptoms
  - Spirometry, VOC, FeNO: specific values or conclusion
  - ACT (asthma control test), GINA symptom score: total score or individual question answers
  - Previous asthma exacerbation: dichotomous or time series
  - Undefined diagnosis-related features: not further defined in the literature
  - Lung function: undefined lung function; values or conclusion
- Comorbidities
  - Allergies, eczema, obesity: dichotomous annotation, time series, severity
  - General comorbidities: dichotomous annotation or number of comorbidities
- Healthcare utilization
  - Billing codes, chief complaints: mentioned as such in electronic patient file
  - ER visits, outpatient visits, hospitalizations: dichotomous annotation, time series or duration
- Social data
  - Home area: description of the district, categorized based on income, or area code
  - Insurance: dichotomous annotation of healthcare insurance, type, additional insurance
  - Socioeconomic status: categorization based on income
  - Housing conditions: dichotomous annotation of air quality, neighborhood type, mold presence
- Environmental data:
  - Air pollution, meteorological data, climate data: time series of closest measurement station
  - Virus data: time series based on dichotomous annotation or closest measurements station
- At-home measurements
  - Spirometry: specific values or conclusion
  - Symptoms: description or dichotomous annotation of previous or present symptoms

# Appendix E: Electronic Patient File Segments

The electronic patient file is divided into the following segments:

- Appointments: outpatient visits categorized per department, containing information regarding date and time of appointment, date time registered, healthcare professional, location, appointment type, and dichotomous annotation of show/no show
- Allergies: allergy name and registration date
- Practitioner: name of practitioner, type of practitioner, start date practitioner
- Medical report (*naslag*): report text per subsection: requested additional tests, additional tests description, current medication, advises, allergies, anamnesis, medical policy, medical course (*beloop*), complications, conclusions, correspondence, diagnosis, endoscopic report, family anamnesis, functional tests description, informed consent, intoxication, lab tests description, physical examination, medication, microbiology, nuclear tests description, *overdracht*, other actions, differential diagnoses, pathology tests description, radiology tests description, reason of visit, summary, social anamnesis, tracts anamnesis, performed operation (*uitgevoerde verrichting*), vital functions, medical history
- Documents: creation date, send date, specialty, document type, author, co-author, document text
- Function tests: date of function test, dichotomous annotation of show/no show, description of functional test, report of functional tests, performer of functional test
- General practitioners: name of practitioner, type of practitioner
- Lab tests: lab measurement name, lab measurement type, lab measurement value, date of retrieval, date of result
- Pharmacy request (*LSP*): medication, dosage, type, delivered until, start date, stop date, route of medication administration
- Prescribed medication: medication, dosage, type, delivered until, start date, stop date, route of medication administration, practitioner name
- Medical points of interest: practitioner name, practitioner specialty, medical points of interest text, start date, registration date, dichotomous annotation of expiration
- Measurements: measurement date time, measurement value, measurement label, measurement description, measurement unit, extra information
- Questionnaires: questionnaire name, questionnaire subquestions, answers to subquestions, date time of answers, questionnaire category
- Demographics: birth year, birth month, sex, postal code, diagnosis
- Operations (*verrichtingen*): DBC (*diagnose-behandelcombinatie* number, start year, start month, date of operation, operator, number of operations, operation description
- Radiology: date of radiology test, date of conclusion input, dichotomous annotation performed yes/no, operation number, indication, conclusions, healthcare professional
- Medical history: medical history, corresponding DBC, healthcare professional, healthcare professional specialty, registration date, dichotomous annotation of expiration, medical history type

# Appendix F: Elaboration on Environmental Data

The daily pollen counts are measured through Leiden University Medical Center and Elkerliek Hospital [265, 266]. The measured pollen are seen in Table F.1.

Table F.1: The measured grass, tree, and plant pollen, measured trough [265, 266].

| | | | |
|---|---|---|---|
| Poaceae | Hornbeam | Sea-buckthorn | Apiaceae |
| Cyperaceae | Beech | Holly | Brassicaceae |
| Hazel | Oak | Elder | Rumex |
| Alder | Horse-chestnut | Privet | Plantago |
| Cypress | Walnut | Juncaceae | Urtica |
| Iep | Maple | Ericaceae | Amaranthaceae |
| Poplar | Platanus | Rosaceae | Artemisia |
| Ash | Pine tree | Ragged-Robin | Hops |
| Willow | Sweet-chestnut | Asteraceae | |
| Birch | Linden | Buttercup | |

The air quality metrics are measured through the RIVM [267] and are seen in Table F.2.

Table F.2: The measured quality metrics, measured through [267].

| | | | |
|---|---|---|---|
| Ammonia | Naphthalene | Particulate matter 10 | Toluene |
| Benzene | Nitric oxide | Particulate matter 2.5 | Ultra-fine particles |
| Carbon monoxide | Nitrogen dioxide | Soot | Xylene |
| Hydrogen sulfide | Ozone | Sulfur dioxide | |

The virological data is measured through the NVMO and RIVM [268, 269] and is measured in the number of positive tests. The measured viruses are seen in Table F.3.

The meteorological data is measured through the KNMI [270] and is seen in Table F.4.

Table F.3: The measured virologic data, measured through [268, 269].

| | | |
|---|---|---|
| Adenovirus 40/41 | Hepatitis C virus | Parainfluenza virus type 1 |
| Adenovirus no type | Hepatitis D virus | Parainfluenza virus type 2 |
| Adenovirus not 40/41 | Hepatitis E virus | Parainfluenza virus type 3 |
| Astrovirus | Human immunodeficiency virus type 1 | Parainfluenza virus type 4 |
| Bocavirus | Human immunodeficiency virus type 2 | Parechovirus |
| Chikungunya virus | Human metapneumovirus | Parvovirus |
| Chlamydia no type | Human T-lymphotropic virus | Respiratory syncytial virus |
| Chlamydia no type possible | Influenza A virus | Rhinovirus |
| Chlamydia pneumoniae | Influenza B virus | Rickettsiae |
| Chlamydia psittaci | Influenza C virus | Rotavirus |
| Chlamydia trachomatis | Measles virus | Rubella virus |
| Corona virus excluding SARS-CoV-2 | Mumphs virus | Sapovirus |
| Coxiella burnetii | Mycoplasma pneumonia | Sars-CoV-2 |
| Enterovirus | Norovirus | West Nile virus |
| Hantavirus | Other | Zika virus |
| Hepatitis A virus | Parainfluenza virus no type | |
| Hepatitis B virus | Parainfluenza virus no type possible | |

Table F.4: The meteorological weather data, measured through [270].

| | |
|---|---|
| Mean wind direction (every hour) | Rain duration |
| Mean wind velocity (every hour) | The daily sum of rain amount |
| Daily mean wind velocity | Daily maximum rain amount and timing |
| Highest daily mean wind velocity and timing | Daily mean atmospheric pressure |
| Highest gust and timing | Daily maximum atmospheric pressure and timing |
| Daily mean temperature | Daily minimum atmospheric pressure and timing |
| Daily minimum temperature and timing | Minimum sight and timing |
| Daily maximum temperature and timing | Maximum sight and timing |
| Daily minimum temperature at 10 cm height and timing | Daily mean cloud cover |
| Sunshine duration | Daily mean humidity |
| Percentage of sunshine duration | Daily maximum humidity and timing |
| Global duration | Daily minimum humidity and timing |

# Appendix G: Elaboration on Outcome Definition

The definition of hospitalizations in operations (*verrichtingen*) is (in Dutch) *Klinische opname*.

The definitions of ER visits are enumerated below (in Dutch):

- Spoedeisende hulp contact buiten de SEH afdeling, elders in het ziekenhuis.
- spoedeisendehulp-contact buiten spoedeisende hulp afdeling
- eerste consult op spoedeisende hulp afdeling
- herhaalconsult op spoedeisende hulp afdeling

In the medication list, the systemic corticosteroids are listed as (in Dutch):

- PREDNISOLON SANDOZ TABLET 20MG
- PREDNISOLON CAPSULE 25MG
- PREDNISOLON DRANK 5MG/ML
- PREDNISOLON TABLET 20MG
- PREDNISOLON 25 mg
- PREDNISOLON DRANK 1MG/ML DMB
- PREDNISOLON DRANK 5MG/ML CEB
- PREDNISOLON DRANK 5MG/ML DMB
- PREDNISOLON SANDOZ TABLET 30MG
- PREDNISOLON TEVA TABLET 20MG
- PREDNISOLON TABLET 30MG
- PREDNISOLON DRANK 5MG/ML ACE
- PREDNISOLON CF TABLET 5MG
- PREDNISOLON MYLAN TABLET 30MG
- PREDNISOLON TEVA TABLET 30MG
- PREDNISOLON TEVA TABLET 5MG
- PREDNISOLON SANDOZ TABLET 5MG
- PREDNISOLON MYLAN TABLET 20MG
- PREDNISOLON RP TABLET 5MG
- PREDNISOLON DRANK 1MG/ML
- PREDNISOLON DRANK 1MG/ML CEB
- PREDNISOLON TABLET 5MG
- PREDNISOLON DRANK 1MG/ML ACE
- PREDNISON TABLET 20MG
- PREDNISOLON 25 mg/2 ml
- PREDNISOLON 25 mg/1 ml

In the medication list, the nebulizations are listed as (in Dutch):

- SALBUTAMOL VERNEVELVLST 1MG/ML PATR 2,5ML
- IPRATROPIUM VERNEVELVLST 250UG/ML PATR 2ML
- SALBUTAMOL/IPRATROPIUM VERNEVELVLST 1/0,2MG/ML FL
- IPRATRO BR/SALBUT SDZ UD VERNOPL 0,5/2,5MG FL2,5ML

- SALAMOL STERI-NEB VERNOPL 2MG/ML AMPUL 2,5ML
- ATROVENT UNIT DOSE VERNEVELOPL 125MCG/ML FL 2ML
- SALBUTAMOL 5 mg/50 ml (0,1 mg/ml) (pomp: 5mg=50ml)
- SALBUTAMOL INJVLST 0,5MG/ML AMP 1ML
- IPRATRO BR/SALBUT CIP UD VERNOPL 0,5/2,5MG FL2,5ML
- SALBUTAMOL VERNEVELVLST 1,25 MG/ED 2,5 ML (import)
- SALBUTAMOL INFOPL CONC 1MG/ML AMP 5ML
- SALBUTAMOL VERNEVELVLST 5MG/ML
- ATROVENT UNIT DOSE VERNEVELOPL 250MCG/ML FL 2ML
- BUDESONIDE TEVA STERI-NEB VERNS 0,125MG/ML AMP 2ML
- SALBUTAMOL/IPRATROPIUM VERNEVELVLST 1/0,1MG/ML
- SALBUTAMOL/IPRATROPIUM 1 ml

# Appendix H: Additional Model Results

Figure H.1 shows the most important features in the prediction averaged across the whole population determined through feature permutation, Figure H.2 determined through SHAP. The most input features from the feature permutation are obesity, grass allergy, age, no comorbidities, dust mite allergy, weed allergy, allergic rhinitis, rodent allergy, non-allergic rhinitis, and postal code. The most important features from the SHAP are BMI, weight, length, tree allergy, dysfunctional breathing, rodent allergy, hayfever, dust mite allergy, age, and no comorbidities.

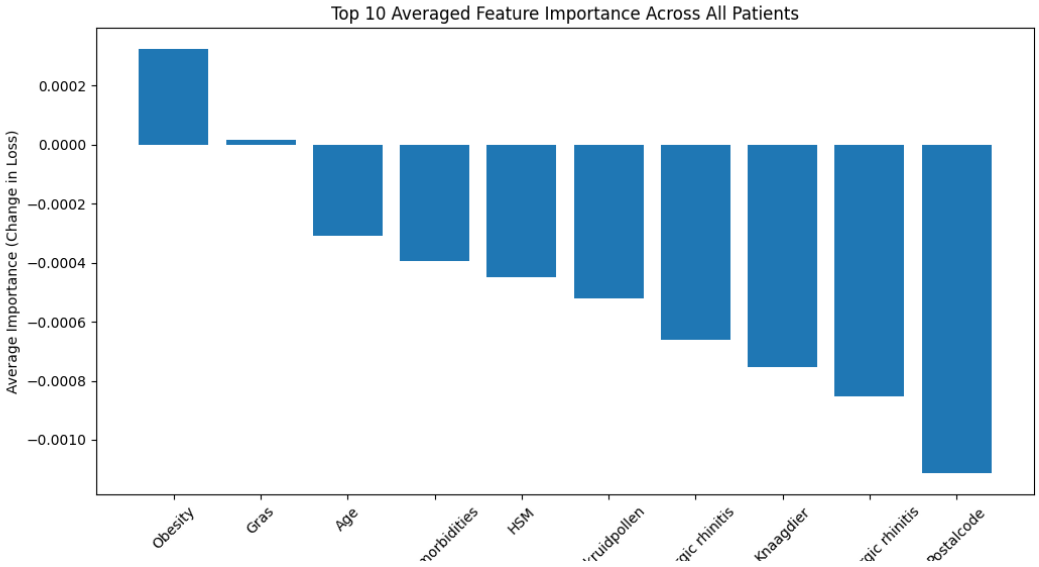



Figure H.1: The feature importance of the input features averaged across the whole population using feature permutation.

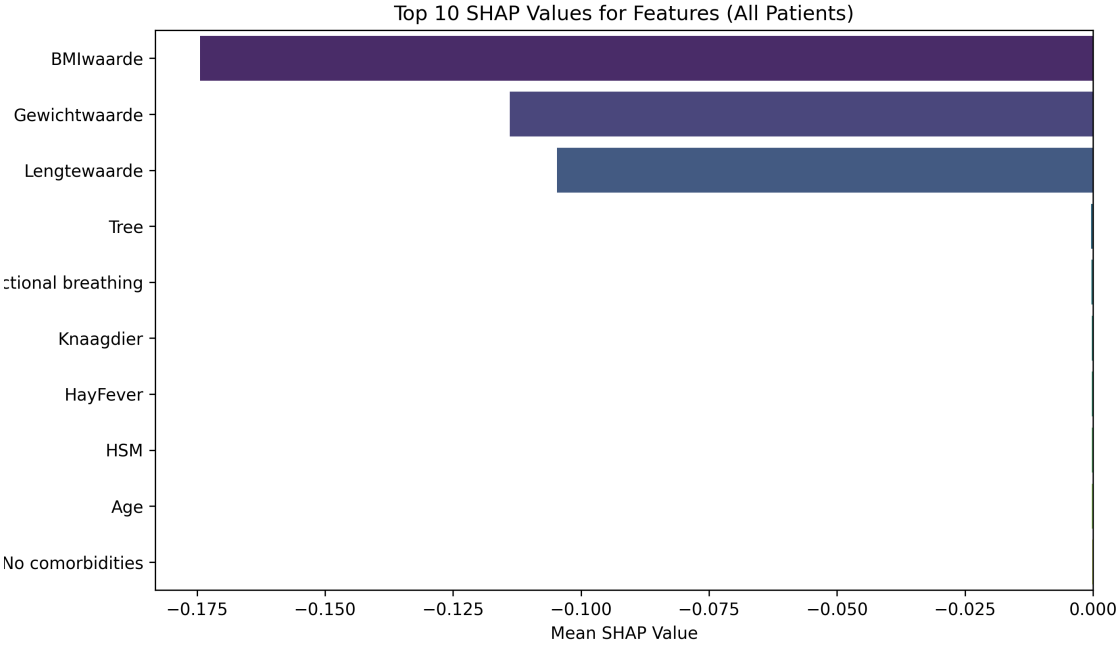



Figure H.2: The feature importance of the input features averaged across the whole population using SHAP.

Figure H.3 shows the 7-day forecasted prediction of dichotomous asthma exacerbation averaged across the whole population, Figure H.4 the 28-day forecasted prediction both.

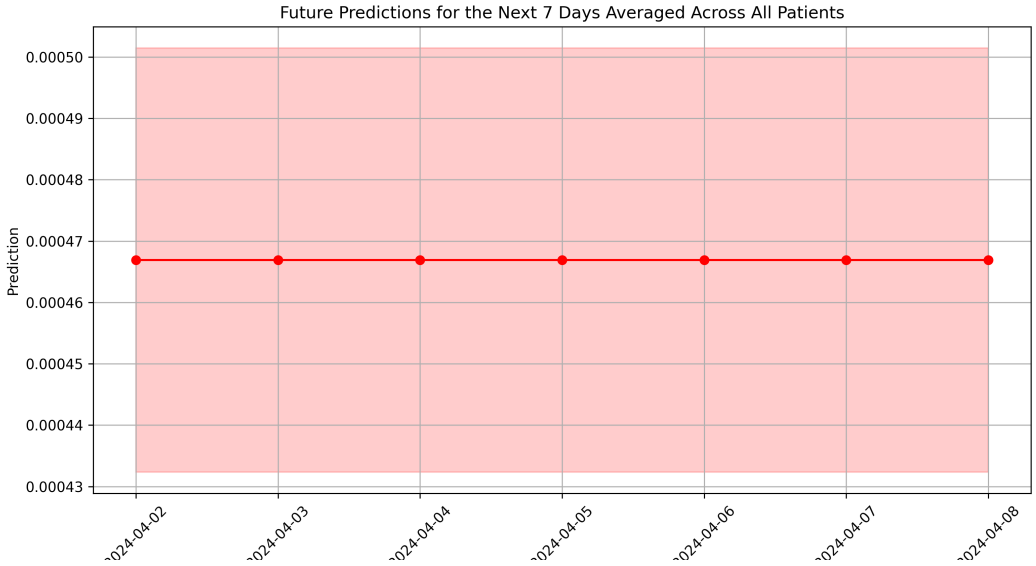



Figure H.3: The 7-day forecasted prediction of asthma exacerbation averaged across the whole population. The mean and standard deviation are shown. The y-axis represents the prediction of an asthma exacerbation (e.g. 0.00047 corresponds to a 0.047% chance of an asthma exacerbation).

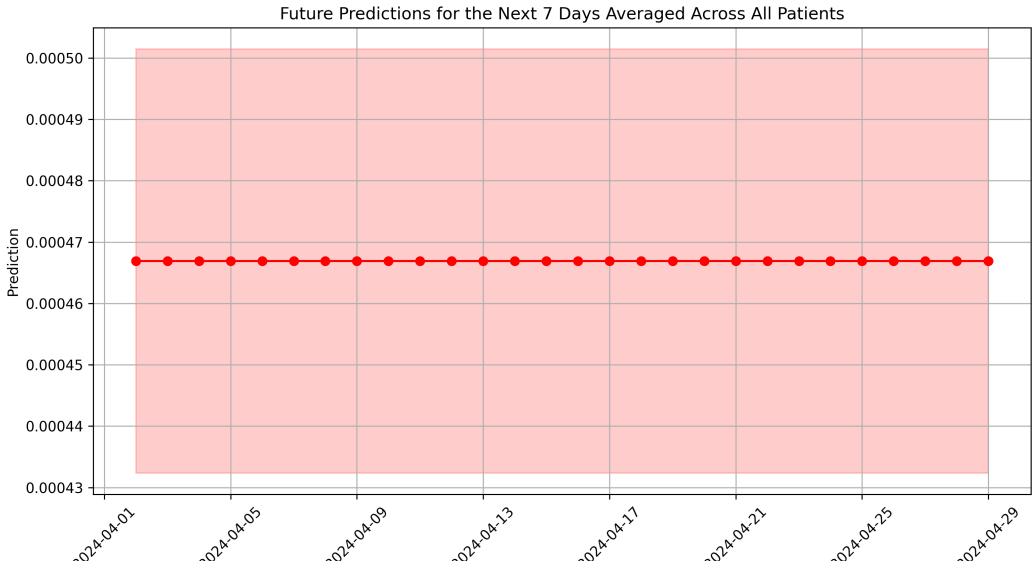



Figure H.4: The 28-day forecasted prediction of asthma exacerbation averaged across the whole population.The mean and standard deviation are shown. The y-axis represents the prediction of an asthma exacerbation (e.g. 0.00047 corresponds to a 0.047% chance of an asthma exacerbation).

# Appendix I: Interview Structure Outline

Het hoofddoel van de interviews is om inzichten te verzamelen van kinderartsen over de integratie van een AI-model dat astma-exacerbaties bij kinderen voorspelt.

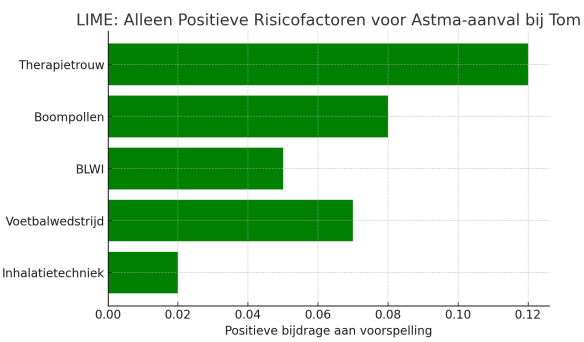
Binnen dit onderzoek ben ik bezig met het ontwikkelen van een AI model om astma exacerbaties bij kinderen te voorspellen en hierin de persoonlijke risicofactoren te bepalen. Voor dit model gebruik ik alle medische gegevens van de patiënten uit HiX, maar ook algemene gegevens zoals het weer, pollentellingen, luchtkwaliteit en virologie data. Voor de gehele populatie zijn er veel risicofactoren bekend, maar juist de bijdrage van elk van deze risicofactoren voor elke individuele patiënten zijn vaak nog onbekend. Om er ook voor te zorgen dat het uiteindelijk een model wordt dat jij als kinderarts ook zou kunnen en willen gebruiken interview ik een aantal kinderartsen om jullie visie en verwachtingen in kaart te brengen.

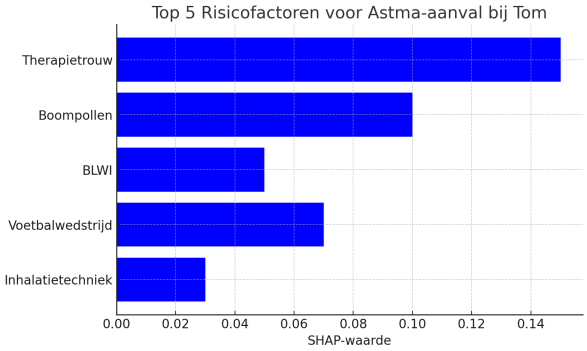
Table I.1: Interview structure of the semi-structured interviews.

| **Onderzoeksonderwerp** | **Interview vraag** |
|---|---|
| Astma exacerbatie definitie | Welke definitie van astma exacerbatie zou jij willen gebruiken voor het voorspel model?<br>In dit onderzoek maak ik voor nu onderscheid tussen ernstige en matige exacerbaties:<br>Matig: presentatie SEH of poli met start prednison of salbutamol vernevelingen<br>Ernstig: ziekenhuisopname met start prednison of salbutamol vernevelingen<br>Wat vind je van deze definities en het onderscheid tussen de twee?<br>Hoe zou je deze definities aan willen passen? |
| Model verwachtingen | Wat zijn je verwachtingen van dit AI model?<br>Hoe zou je dit AI model willen gebruiken op de poli?<br>Wat zou je van dit model willen weten/zien als uitkomst?<br>Waar zou je de resultaten van dit AI model willen zien?<br>Hoe zou je de resultaten willen zien?<br>Voorbeelden XAI uitkomsten laten zien bij de volgende casus: patiënt Tom heeft een kans van 40% op een astma exacerbatie en zijn 5 belangrijkste risicofactoren zijn therapietrouw, boompollen, BLWI, voetbalwedstrijd en inhalatietechniek.<br>Hoe zou je de waarde voor kans op exacerbatie willen zien?<br>Hoeveel van de belangrijkste risicofactoren zou je willen zien?<br>Hoe zou je willen zien hoe belangrijk een risicofactor is?<br>Hoe accuraat verwacht je dat het model is?<br>Zou je dit model vertrouwen en op de resultaten je beleid aan durven passen? |
| Voorspellingstijd | In welk(e) tijdsbestek(ken) voor een astma exacerbatie wil je de voorspelling van het model krijgen?<br>Hoe zou je beleid aan willen/kunnen passen op basis van een voorspelling op dat tijdsbestek? |
| Continued on next page | |

Table I.1: Interview structure of the semi-structured interviews (continued).

| **Onderzoeksonderwerp** | **Interview vraag** |
|---|---|
| Model toepassingen | In wat voor applicatie zou jij het AI model willen gebruiken?<br>Voor nu hebben we drie applicaties gedefinieerd:<br>1) AI model voor op de poli; geeft bij elke patiënt de belangrijkste risicofactoren en het risico op astma exacerbatie in een bepaalde tijdsduur<br>2) AI model voor eHealth zorg; voorspelling astma exacerbatie over tijd bij de intensievere monitoring van at-risk patiënten<br>3) AI model voor patiënten thuis: stoplicht als indicatie kans op astma exacerbatie met hierbij de belangrijkste beïnvloedbare risicofactoren<br>Wat vind je van deze applicaties en zou je de modellen op deze manier willen gebruiken? |
| Overig | Heb je nog andere aspecten die belangrijk vindt die nog niet aan bod zijn gekomen? |




"Het AI model voorspelt een astma exacerbatie voor Tom in de komende 3 weken met een kans van 40%. De 5 belangrijkste risicofactoren voor Tom zijn: therapietrouw (0.14 op basis van [specifieke methode]), aanwezigheid boompollen (0.10), voetbalwedstrijd (0.9), BLWI (0.5) en inhalatietechniek (0.3)."

# Appendix J: Pioneers in HealthCare (PIHC) Subsidy Call - Personal Risk Dashboard

**Titel**
PREVENT (Persoonlijke risico evaluatie van astma exacerbatie op basis van multimodale data m.b.v. AI)

**Publieke samenvatting**
Instabiel kinderastma komt veel voor, en kan leiden tot ernstige aanvallen en ziekenhuisopnames. Het risico op een aanval wordt door veel factoren beïnvloed, zoals allergenen, virusinfecties, medicijngebruik, weersveranderingen etc. De bijdrage van verschillende factoren op het risico op een astma aanval is voor een individueel kind vaak niet direct evident. In dit project verzamelen we deze factoren over de tijd in relatie tot klachten en longfunctie en ontwikkelen we m.b.v. geavanceerde kunstmatige intelligentie (AI) technieken een persoonlijk risico dashboard. Dit biedt artsen en patiënten inzicht in de belangrijkste risicofactoren, waardoor astma beter, tijdiger en gerichter kan worden behandeld.

**Klinische en maatschappelijke relevantie**
Kinderastma is een chronisch ziektebeeld dat bij ongeveer 7% van de Nederlandse kinderen voorkomt. Astma heeft een grote impact op de kwaliteit van leven, ze kunnen niet goed fysiek meekomen met hun leeftijdsgenoten, slapen vaak slecht en hebben meer schoolverzuim. Ongecontroleerd astma verhoogt het risico op astma aanvallen waarvoor ziekenhuisopnames noodzakelijk kunnen zijn. Er worden steeds meer factoren ontdekt die een rol spelen in het uitlokken van aanvallen. Sommige factoren zijn patiëntgerelateerd, zoals BMI, therapietrouw, longfunctie schommelingen, comorbiditeiten, zelfmanagement en symptoomperceptie. Andere omgeving gerelateerd, zoals meteorologische omstandigheden, pollen, luchtkwaliteit en virusdata [1]. In de dagelijkse klinische praktijk wordt aan de hand van klachten over de tijd en klinische observaties gekeken welke factoren het astma beïnvloeden. Het is echter vaak lastig om op empirische wijze te ontrafelen welke combinatie van factoren voor een individuele patiënt het meest bijdragen. Daarom wordt (volgens de huidige GINA-richtlijnen) veelal gekozen voor een generieke aanpak van behandeling en brede trigger vermijding. Met de opkomst van AI-technieken die diverse datasoorten over tijd analyseren, en de groeiende kwaliteit van databronnen binnen en buiten het elektronisch patiëntendossier, kunnen we het leerproces voor patiënten en zorgprofessionals versnellen en verbeteren. Door de unieke eHealth data van het MST met thuismetingen (klachtenpatroon, therapietrouw en longfuncties) te gebruiken, kunnen monitoring en behandeling nog gerichter worden ondersteund. Onderzoeksvraag: Hoe kan een AI-model patiëntgerichte risicofactoren en de kans op een astma aanval voorspellen en weergeven in een persoonlijk risico dashboard? Binnen dit project willen we dit persoonlijke risico dashboard op zo'n manier inzetten dat deze impact heeft voor de patiënt en ouders, door alleen de risicofactoren te laten zien die de patiënt zelf kan verbeteren (treatable traits), zoals het trouw innemen van de puffen. Hierdoor krijgt de patiënt de mogelijkheid en motivatie om zelf controle te nemen over zijn/haar astma management [2]. Verder geeft het de kinderarts handvatten voor het verbeteren van het astma management samen met de patiënt. De toegevoegde waarde is dat het astma management overzichtelijker wordt waarbij de complexiteit van de uitlokkende factoren wordt doorgrond. Hierbij kunnen eHealth interventies ingezet worden passend bij de persoonlijke risicofactoren, waardoor de astmazorg doelmatiger wordt.

**Uitdaging**
Dit project valt onder de categorie "Technologisch pionieren in de zorg" omdat we een LSTM-model (Long-Short Term Memory) gaan ontwikkelen, optimaliseren en evalueren voor de predictie van astma aanvallen bij kinderen om de kinderastmazorg te personaliseren. De huidige literatuur laat een grote variatie in modeltypes, input data en uitkomstmaten zien waarbij LSTM-modellen een opmars laten zien voor het maken van tijdsgebonden voorspellingen [3]. Deze modellen zijn echter nog niet eerder ingezet in de (kinder)astmazorg en missen de personalisatie en de klinische uitlegbaarheid die nodig is voor toepassing in de praktijk. Vanuit de lopende masterthesis van Tamara Ruuls is er een opzet gemaakt voor een LSTM-model, dat de kans op astma aanvallen en persoonlijke risicofactoren voorspelt. Om de verdere ontwikkeling en implementatie mogelijk te maken moeten de volgende technologisch-wetenschappelijke uitdagingen in dit project worden overbrugd:

1. Datasoorten: Het combineren van continue en discrete variabelen maakt de LSTM-architectuur complexer doordat er verschillende modellagen nodig zijn om deze datatypes te integreren.
2. Tijdsindicatie: De voorspellingstermijn vaststellen, toegespitst op het klinische doel.

3. Accuraatheid: We onderzoeken of een sensitiviteit van 90% haalbaar is, met als doel deze zo hoog mogelijk te krijgen. Het correct voorspellen van astma aanvallen is namelijk belangrijker dan het voorspellen van het uitblijven ervan.

4. Generaliseerbaarheid: Het model moet breed inzetbaar zijn, waarvoor validatie (intern en extern) nodig is. Om toekomstige opschaling te faciliteren, gebruiken we (inter)nationale informatiestandaarden zoals SNOMED CT en LOINC.

5. Visualisatie: De modeluitkomsten moeten duidelijk en begrijpelijk worden gepresenteerd aan patiënten, ouders en zorgverleners in een persoonlijk risico dashboard. Voor het weergeven van de persoonlijke risicofactoren zetten we explainable AI-technieken zoals SHAP, LIME of LSTM attention layers in om de belangrijkste input variabelen voor de voorspelling te ontrafelen.

**Synergie tussen de technologische en klinische partners**
De synergie tussen de technologische en klinische partners van dit consortium is essentieel voor het succes van dit project, waarbij de expertises van de partners elkaar aanvullen. Tamara Ruuls is expert in het LSTM-model en de optimalisatie en validatie hiervan. Zij zal het project coördineren en de verbindende schakel vormen tussen de verschillende partners. Dr. Boony Thio en dr. Mattiènne van der Kamp (MST) brengen ervaring in de klinische kinderastmazorg aangevuld met de implementatie van het eHealth zorgpad in de kinderastmazorg, waar al jarenlang continue data wordt verzameld. Hiermee dragen zij bij aan de complexiteit en uitgebreidheid van de input data voor het model alsook de aansluiting van het persoonlijk risico dashboard op de huidige kinderastmazorg. Prof. Monique Tabak (UT) heeft expertise op het gebied van monitoring en shared decision support in eHealth technologie wat bijdraagt aan o.a. het opstellen van de requirementsanalyse en het uitvoeren van de pilot studie. Verder coördineert zij het RESAMPLE project, gericht op AI-modellen voor COPD-patiënten, wat potentiële samenwerkingen teweeg kan brengen. Anouk Veldhuis, MSc en ing. Jeroen Geerdink (ZGT), met een bewezen trackrecord in AI-implementatie in de zorg, zullen samen met hun junior onderzoeker een sterke adviserende rol vervullen voor de model optimalisatie en generalisatie. Daniëlle Ekkel, MSc en Cornelieke Graat-van Steenbeek, MSc, van het AI-lab in het MST, dragen bij met expertise in wet- en regelgeving omtrent AI en dataprivacy. De externe validatie zal plaatsvinden d.m.v. data uit DZ en ZGT, hierbij zal Tamara het voortouw nemen en samenwerken met kinderarts drs. Monique Gorissen (DZ) met haar jarenlange ervaring als kinderarts en met onderzoek. Monique de Jong-Rouweler, MSc en dr. Vera Bulsink vanuit het Waarde gedreven zorg team brengen expertise in de opschaling van projecten naar Santeon ziekenhuizen en in de data-gedreven evaluatie van de effecten op de zorg. Evidencio is een softwarebedrijf in de regio dat gespecialiseerd is in het ontwikkelen en implementeren van AI-algoritmes in de zorg met hierbij ook veel ervaring op het gebied van wet- en regelgeving en beschikbare standaarden rondom AI-software als medisch hulpmiddel. Zij zullen vanaf de start van het project aansluiten en waken dat alle processtappen volgens de huidige standaarden gedocumenteerd worden zodat de implementatie versneld kan worden. Het MST is de aangewezen plek om dit project te leiden, omdat dit onderzoek plaatsvindt binnen de uitgebreide (eHealth) kinderastma onderzoekslijn. Hierbij is dit onderzoek een nieuwe tak gericht op het optimaliseren, personaliseren en efficiënter maken van de kinderastmazorg.

**Plan van aanpak**
Er wordt in dit onderzoek gebruik gemaakt van data vanuit twee reeds goedgekeurde studies:

- PREDICTA: In het MST wordt retrospectieve data van de volledige populatie kinderastmapatiënten ($>$ 1800) verzameld. De dataset omvat medische, milieu en eHealth data.
- CIRCUS: In het MST wordt prospectieve data verzameld van 300 patiënten (30% van de MST jaarpopulatie) in de CIRCUS studie, een cohort multiple randomized controlled trial (cmRCT). De studie verzamelt naast de data van de PREDICTA studie ook maandelijks.

Vervolgens zal dit onderzoek in vier opvolgende fases worden uitgevoerd (zie Figuur J.1);

1. Model optimalisatie; Het optimaliseren van het AI-model tot maximale sensitiviteit. Toevoegen van input data, zoals textmining van de medische naslag, therapietrouw, eHealth data en longfunctiemetingen over tijd. Verder uitvoeren van hyperparameter tuning o.b.v. het aantal nodes, units in de dense laag, epochs, batch size en gewicht van lagen. Daarnaast ook het optimaliseren van de frequentie van de continue variabelen (dagelijks, wekelijks of maandelijks).

2. Model generalisatie; Het generaliseren van het AI-model d.m.v. interne validatie (CIRCUS studie, MST) en externa validatie (retrospectieve data, ZGT en DZ). Hiervoor wordt allereerst een niet-WMO aanvraag geschreven voor de externa validatie.

3. Model applicatie; Opstellen van een requirementsanalyse voor een persoonlijk risico dashboard (d.m.v. de methodiek gepresenteerd door van Velsen [4]). De requirementsanalyse wordt opgesteld o.b.v. 2 focusgroepen van 1) 10 kinderartsen (5 van MST en 5 van DZ) en 2) 10 deelnemers van het patiëntenpanel (5 kinderen en 5 ouders). Op basis hiervan wordt een concept applicatie van het persoonlijk risico dashboard gebouwd.

4. Pilot studie; Het testen van de applicatie met de eindgebruikers. Hiervoor wordt een pilot studie opgezet waarvoor een niet-WMO aanvraag geschreven wordt. De pilot studie bestaat uit 2 focusgroepen die tweemaal de applicatie evalueren; 1) bestaat uit 10 kinderartsen (MST en DZ) en 2) uit 10 deelnemers van het patiëntenpanel (MST). In de pilot studie wordt het persoonlijk risico dashboard van 5 geanonimiseerde digital twins getoond, waarbij de interactie met de applicatie wordt gemeten via audio-video opnames en de deelnemers via een semigestructureerd beoordelingsformulier het dashboard evalueren op o.a. gebruiksvriendelijkheid, toepasbaarheid en verbeterpunten. Op basis van deze resultaten wordt de applicatie verbeterd en opnieuw geëvalueerd. Op basis van deze resultaten wordt een stappenplan tot implementatie uitgewerkt.

De betrokken partijen en de leidende partij in dikgedrukte stijl zijn weergegeven alsmede de tijdsplanning in onderstaand figuur. Tamara zal hierin de coördinator zijn.

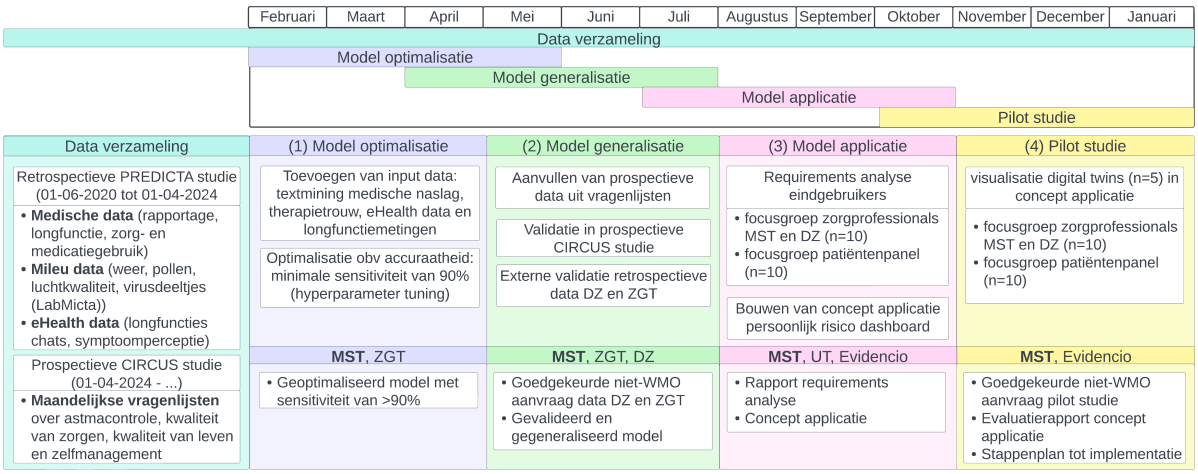



Figure J.1: De tijdlijn van het project.

**Verwachte korte termijn doelstellingen, resultaten en uitkomsten van het project**
Dit onderzoek zal resulteren in 1) een geoptimaliseerd AI-model die 2) gegeneraliseerd wordt o.b.v. interne en externa validatie. Er wordt in samenwerking met de eindgebruikers een 3) requirementsanalyse rapport opgesteld vanuit waar er een 4) concept applicatie opgesteld wordt die een persoonlijk risico dashboard geeft van risicofactoren en de kans op een astma aanval. Deze concept applicatie wordt in een pilot studie geëvalueerd om de 5) evaluatie rapport op te stellen en tot een 6) stappenplan tot implementatie te komen. Binnen dit onderzoek worden vier HBO en WO (student)projecten ingezet op 1) het uitvoeren van de hyperparameter tuning (model optimalisatie), 2) het uitvoeren van de interne validatie, 3) het uitvoeren van de focusgroep met het patiëntenpanel (requirementsanalyse) en 4) het opzetten van de pilot studie. De kennisdisseminatie van de 4 verschillende stappen van dit project zal plaatsvinden middels posters of mondelinge presentaties op internationale AI en (kinder)long congressen of symposia en publicatie(s) in een Q1 tijdschrift. Hierbij zullen de partners een workshop organiseren over de toepassing van het model en het persoonlijk risico dashboard op het European Respiratory Congress (ERS). Verder zal er kennisgeving aan de doelgroep zijn d.m.v. het patiëntenpanel, de CIRCUS studie nieuwsbrief en patiënt-verenigingen (Longfonds, VND). Ook is er kennisgeving aan collega's via instellingsnieuwsbrieven, websites, TechMed, zorgmarkt en wetenschapsdagen, met verdere verspreiding via het Reggeborgh Research Fellowship netwerk.

**Duurzame samenwerking, voortzetting van het project**
MST (kindergeneeskunde, AI-lab en Waarde Gedreven Zorg team) en UT (BSS vakgroep en eCMC) hebben een sterke samenwerking door eerdere succesvolle projecten. Dit project breidt de samenwerking uit met ZGT, dat ervaring heeft in AI-implementaties. Binnen MST werken technisch geneeskundigen en kinderartsen samen aan zorginnovaties en waarborgen ze de klinische toepassing van AI-modellen.

De CIRCUS-studie, goedgekeurd in februari 2024, biedt een raamwerk voor een toekomstige RCT-studie om de effectiviteit van het persoonlijk risico dashboard te evalueren. De reeds bestaande internationale samenwerking (BLOOM consortium) met MST en UT gericht op het verbeteren van lange termijn uitkomsten en zelfmanagement voor kinderen met chronische aandoeningen via eHealth zoekt actief naar vervolgfinanciering waarbinnen dit project ook kan vallen, waaronder EU Horizon-subsidieaanvragen. Dit onderzoek valt binnen de huidige onderzoekslijn gericht op het verbeteren van de kinderastmazorg middels eHealth applicaties. Binnen deze onderzoekslijn wordt actief gezocht naar vervolgsubsidies zoals het stichting astma bestrijding, ZonMW doelmatigheidonderzoek en MedZO. Het model biedt potentie tot uitbreiding naar andere afdelingen zoals longgeneeskunde. De bestaande ICT-infrastructuur maakt veilige analyse van patiëntgegevens mogelijk en biedt mogelijkheid voor implementatie in Santeon ziekenhuizen via het waarde gedreven zorg team.

**Impact op de zorg en lange termijn uitkomsten**
De duurzame inzet van het eHealth zorgpad geeft reeds kwalitatieve verbetering (verbeterde astma uitkomsten en zelfmanagement) en doelmatigheid van de huidige kinderastmazorg [5]. Het AI-model biedt zorgverleners, patiënten en ouders inzicht in persoonlijke risicofactoren voor astma aanvallen. Hierdoor kunnen monitoring en behandeling gepersonaliseerd en minimaal belastend worden ingezet d.m.v. passende eHealth interventies. Dit kan leiden tot minder klachten, betere kwaliteit van leven, en een afname van zorgverbruik waarbij zelfregie van patiënten wordt versterkt. Deze effecten kunnen in een opvolgende RCT-effectstudie worden geobjectiveerd. Daarna kan bij succesvol doorlopen o.b.v. de documentatie en betrokkenheid van Evidencio worden overgaan tot valorisatie en implementatie. De doelgroep is de gehele kinderastmapopulatie (per jaar ongeveer 1000 kinderen in het MST). Via waarde gedreven zorg (standaardiseren, personaliseren en digitaliseren) worden de impact en medische zorguitkomsten geëvalueerd en kan er een zorgpad ontworpen worden waarbij eHealth interventies ingezet worden passend bij de persoonlijke risicofactoren om de astmazorg doelmatiger te maken. Dit sluit ook aan bij de IZA-doelstellingen voor zorgtransformatie en versterking van zelfregie. Benchmarking met andere ziekenhuizen borgt de kwaliteit van de zorg. Naast de innovatieve ontwikkelingen wordt dit project ook wetenschappelijk ingebed middels het promotie traject van Tamara Ruuls, wat de kans op toekomstige opname van de resultaten in behandelrichtlijnen voor astma vergroot.

**(Potentie tot) valorisatie of implementatie**
Bij de start van dit project is er reeds een AI-model met TRL2 dat binnen het project ontwikkeld zal worden tot TRL6 in de pilotstudie. Het uiteindelijke product zal vallen onder de EU AI Act en de MDR klasse IIa, waarvoor wordt samengewerkt met Evidencio waarbij dit model opgenomen kan worden in hun bibliotheek van (MDR-gecertificeerde) medische algoritmes. De resultaten van dit onderzoek kunnen een basis vormen voor het ontwikkelen van een businessplan in samenwerking met eCMC, NovelT en de verschillende partners. Daarnaast worden partijen zoals de patiëntverenigingen actief op de hoogte gehouden om de aansluiting op de behoeften van patiënten te waarborgen en te versterken, met het oog op een succesvolle toekomstige implementatie. Hierbij wordt de infrastructuur zo opgesteld dat deze gemakkelijk uit te breiden is naar andere ziekenhuizen.

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