Artificial intelligence techniques in asthma: a systematic review and critical appraisal of the existing literature

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Artificial intelligence algorithms are able to analyse large amounts of complex data and extract meaningful patterns that can be utilised in clinical practice and contribute to the provision of better care, especially in chronic diseases such as asthma https://bit.ly/2SC6c3q

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ABSTRACT Artificial intelligence (AI) when coupled with large amounts of well characterised data can yield models that are expected to facilitate clinical practice and contribute to the delivery of better care, especially in chronic diseases such as asthma.

The purpose of this paper is to review the utilisation of AI techniques in all aspects of asthma research, *i.e.* from asthma screening and diagnosis, to patient classification and the overall asthma management and treatment, in order to identify trends, draw conclusions and discover potential gaps in the literature.

We conducted a systematic review of the literature using PubMed and DBLP from 1988 up to 2019, yielding 425 articles; after removing duplicate and irrelevant articles, 98 were further selected for detailed review.

The resulting articles were organised in four categories, and subsequently compared based on a set of qualitative and quantitative factors. Overall, we observed an increasing adoption of AI techniques for asthma research, especially within the last decade.

AI is a scientific field that is in the spotlight, especially the last decade. In asthma there are already numerous studies; however, there are certain unmet needs that need to be further elucidated.

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Introduction

Asthma is a common disease affecting an estimated 300 million individuals worldwide; in Europe, about 30 million children and adults less than 45 years old have asthma [1]. It is a major global health problem that imposes a substantial burden on patients, their families and the community. Asthma poses certain challenges that remain largely unmet despite the effort and the research in the respective fields, specifically the following. i) There is no unanimous and widely applicable diagnostic test for asthma, leading to significant underdiagnosis and overdiagnosis [2]. ii) The pathogenesis of asthma is based on the process of gene–environment interaction, yet its specifics remain elusive; this field is currently in the spotlight in view of the new biologic treatments for asthma. iii) Asthma phenotypes remain a controversial subject, due to the discordance in symptomatology, spirometry and response to treatment of individual patients. iv) Asthma exacerbations play a crucial role in the course and management of the disease, incurring significant increase in direct and indirect costs [3].

As in other parts of medicine, there is an increasing interest in artificial intelligence (AI) methodologies to elucidate the aforementioned unmet needs of asthma. AI refers to the software that is able to make a machine intelligent such that it performs human tasks, *i.e.* process, learn and respond to information gained from data. The term is often used in combination with the term "machine learning" that refers to the process followed in order to make a machine learn how to perform a specific task, and in a similar manner as a human to perform better as the experience increases. Both AI and machine learning are data-driven processes whereby the computer or the algorithm is presented with input data and the desired output and "learns" the inherent relations that lead from the input to the output. Similarly, with AI and machine learning, data mining involves the computational and programming steps in order to "mine" large amounts of complex data for meaningful patterns and consequently knowledge. Figure 1 depicts the steps of the data mining process. There are two basic phases within the data mining process: the training and the predicting phase. During the training phase, the machine learning algorithm is fed with input data based on which a model is trained that captures the relations and patterns within the data. During the training phase, the raw input data are subject to a series of preprocessing steps aiming to increase the quality of the data, identify the set of more informative features and omit potentially redundant or irrelevant information. Inherent to the training phase is the process of model evaluation where the parameters of the trained model are further fine tuned in order to procure a well-trained model. In the predicting phase new instances of unknown data are fed as input to the previously trained model and the respective labels are predicted.

AI/machine learning in medicine

Even though AI and machine learning exist as computer science domains for several years, they are two terms that have become radically and widely popular the last few years in a broad and non-specialised audience. This can be attributed to several reasons: their utilisation in daily digital tasks especially pertaining to smartphones (*e.g.* mobile assistant, fingerprint scanner, personalised playlists, *etc.*), the availability of AI and machine learning models to a wider audience with more user-friendly software, the need to discover new knowledge and analyse more effectively large and complex sources of data originating from various domains.

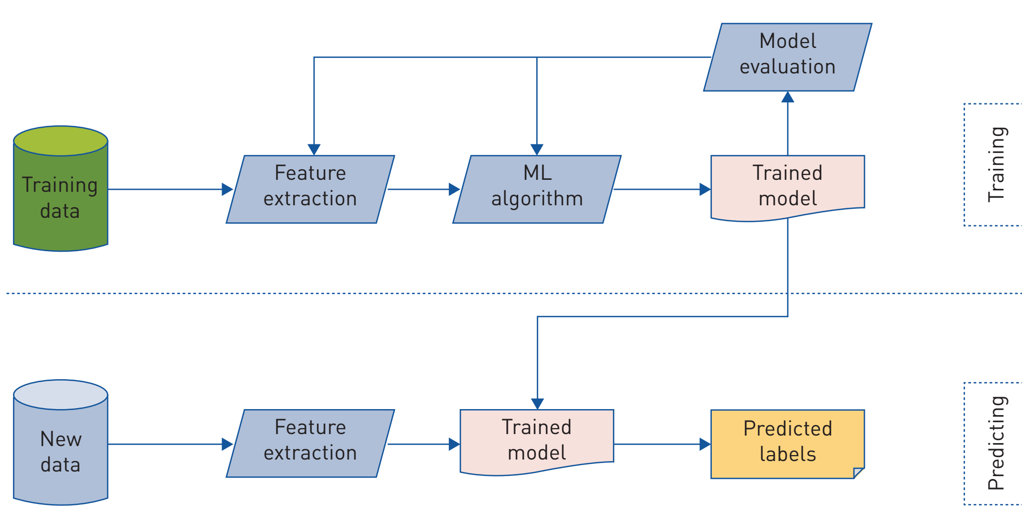

FIGURE 1 Flowchart of the data mining process.

As described previously AI and machine learning models are largely dependent on the available data, and the healthcare domain is producing vast amounts of data that need to be mined for underlying knowledge. Such large and complex datasets incorporating various sources of data, (*e.g.* clinical, imaging, genomic, proteomic, *etc.*) can be effectively analysed with the available AI/machine learning techniques. In the supplementary material, we provide a brief primer on AI/machine learning techniques in order to further facilitate reading of the manuscript. Imaging modalities, such as computed tomography and magnetic resonance imaging scans, used in clinical practice can be effectively analysed by machine learning algorithms [4–7]. Genomic data is another source of enormous and complex information that is being used increasingly in the healthcare domain. Most of these data (*e.g.* single nucleotide polymorphisms, gene expression, *etc.*) produce large amounts of data that are impossible to comprehend; yet the systematic analysis of such data with machine learning techniques has brought about clinically meaningful knowledge for the benefit of patients [8, 9]. The relatively recent boom of high-quality wearable sensors is also producing huge amounts of time-series data that need to be mined efficiently in order to provide clinically relevant information [10, 11].

The distribution of data types analysed with AI algorithms in the literature has been explored in a recent review article [12] suggesting that diagnostic imaging is the most widely employed data source in healthcare-oriented applications of AI, while genomic data and electrodiagnosis constitute emerging data types that are equally appealing for analysis with AI. The authors further explored the leading diseases for which AI algorithms have been employed in the literature, with cancer research being the top field in which AI applications have been developed, followed by diseases of the nervous system as well as cardiovascular diseases [13]. In this analysis, respiratory diseases are way below, with only mediocre adoption of AI techniques.

In the present manuscript, we have systematically searched the literature for articles that employ AI or machine learning techniques in asthma, in an attempt to map the existing literature and identify gaps and areas of interest for future research. First, in the literature review section, we describe the methodological steps in order to acquire all relevant literature. Next, in the machine learning and asthma section, we present our findings from the literature review, and the articles are organised into four major categories to facilitate the critical appraisal of the existing evidence.

Literature review

We systematically searched the literature until May 18, 2019, for articles using AI or machine learning techniques in asthma research. First, we searched DBLP, which is a computer science bibliography website, using the term "asthma". We maintained only journal articles posing no restriction regarding the year of publication. Next, we searched PubMed using the following terms: "artificial intelligence" AND asthma, "machine learning" AND asthma, "data mining" AND asthma, "decision trees" AND asthma, "neural network" AND asthma, "random forests" AND asthma, "support vector machine" AND asthma. The articles from both repositories were then merged and duplicates were removed. All articles were subsequently examined by the authors in order to exclude irrelevant ones; we also omitted articles not written in English. The aforementioned steps are shown in figure 2, resulting eventually in 98 articles. Each of the 98 articles was then assigned to at least one out of the following four categories based on its content and purpose: 1) asthma screening and diagnosis, 2) patient classification, 3) asthma management and monitoring, and 4) asthma treatment.

In figure 3, we present the distribution of studies using AI/machine learning techniques for asthma research, over the course of approximately 30 years, from 1988 up to 2018. As expected during the first and second decade there is minimal use of such techniques for asthma, while from 2010 we observe a considerable and progressive increase.

Artificial intelligence and asthma

In the sections that follow we present the articles retrieved in an organised manner, divided into four categories based on their content and purpose. Specifically, we have split the articles into the following four major contextual categories. 1) Asthma screening and diagnosis. 2) Patient classification. 3) Asthma management and monitoring. 4) Asthma treatment.

The articles from each category are summarised in a separate table where the respective studies can be compared by a set of qualitative and quantitative criteria or characteristics. These tables (tables S3, S4 and S5) are available in the supplementary material of the article. In the sections that follow we provide an overview of the articles comprising each category. Moreover, we have selected some of the most important studies from each category and provide more information. Our aim is to capture the most representative works, focussing on the ones that have been published within the last 5 years, as this is an emerging and developing field with rapid evolution.

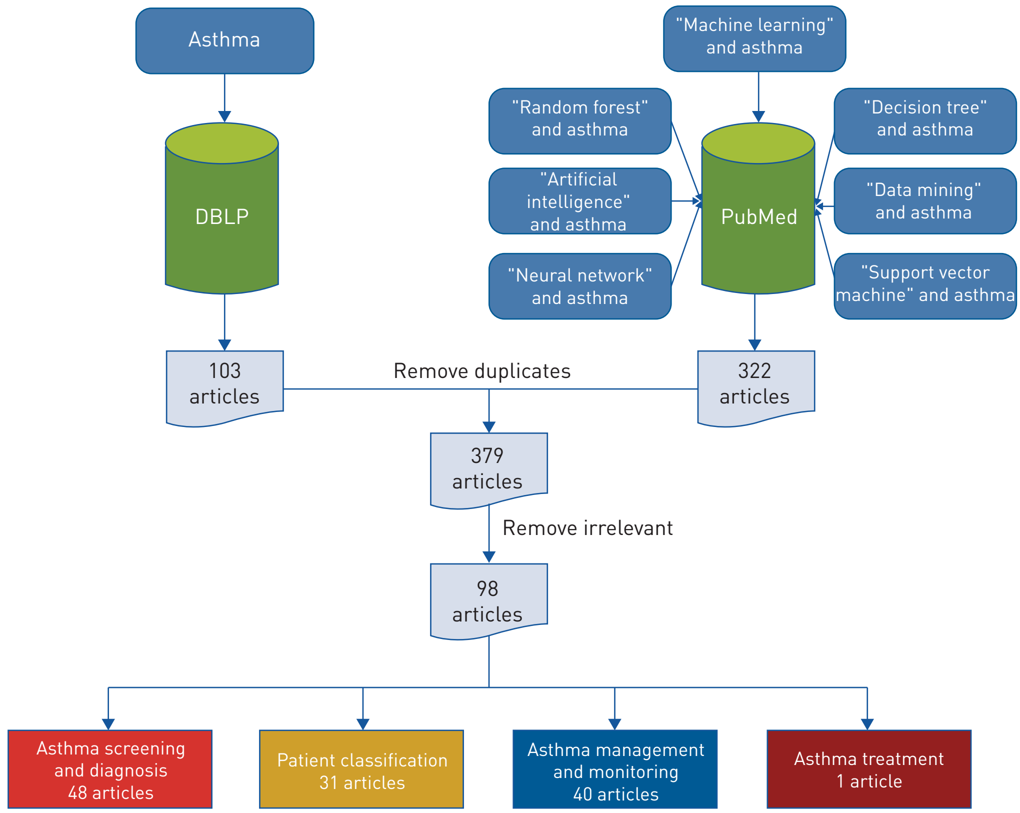

FIGURE 2 Flowchart of the literature search.

In order to facilitate reading of the following sections, we hereby mention some terms that are commonly used in AI/machine learning. Specifically, artificial neural network (ANN), random forest, decision tree, support vector machine (SVM), logistic regression, Bayes network, naïve Bayes, k-nearest neighbours (k-NN), self-organising maps (SOM) and hidden Markov model (HMM) constitute classification algorithms; sensitivity, specificity, accuracy), receiver operating characteristic (ROC) and area under ROC curve (AUC) are performance metrics used for the assessment of AI/machine learning algorithms. Cross

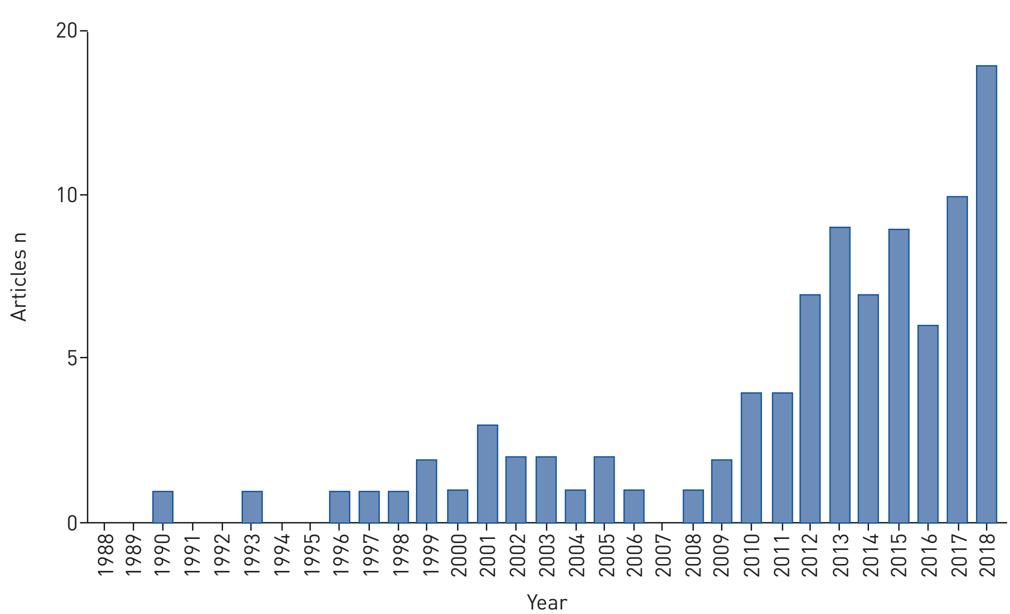

FIGURE 3 Distribution of articles published per year that employed artificial intelligence/machine learning techniques for asthma research.

validation, or its subtype called leave one out CV (LOOCV) are techniques used for AI/machine learning model validation. These terms are summarised in table 1 below. In the supplementary material we provide an exhaustive list of the abbreviations used throughout the manuscript, as well as a primer on AI/machine learning techniques.

Asthma screening and diagnosis

This category is the most populated one and contains 48 articles aiming for the screening or diagnosis of asthma. These studies are summarised in table S3 of the supplementary material. We observe that, in terms of machine learning algorithms, the majority of the studies (20 studies) employ ANNs or variations of ANNs, especially the earlier ones. Support vector machines are used in eight studies, decision trees or random forests are utilised in 11 studies, logistic regression is used in three studies and k-nearest neighbours in two studies. The remaining studies employ other machine learning algorithms, such as HMM, fuzzy logic or naïve Bayes. Overall, we observe that a limited number of machine learning algorithms are employed in the studies contained in the category “Asthma screening and diagnosis”, *i.e.* ANNs, support vector machines, random forests and decision trees. It should be noted that these machine learning algorithms are described in the accompanying supplementary material, as well as some information regarding the evaluation of the reported results. Based on column “sample size”, most of the studies employ tens or hundreds of patients and there are only a few studies that have enrolled larger patient cohorts (only four studies have enrolled >1000 patients).

As expected for the purpose of asthma diagnosis and screening, primarily clinical data have been employed; specifically, these data contain information from the medical history, pattern of symptoms, pulmonary function tests, lung sounds from auscultation, *etc*. Clinical data are employed in 37 studies, out of which 12 explore features pertaining to lung or breath sounds. Similarly, there are studies in this category that exploit questionnaires as well as other clinical and epidemiological features in order to screen certain populations for asthma or identify patients that have a high probability of asthma. Some of the most recently published works employ genetic data (nine studies) in search of predisposing genetic traits for asthma. As for the evaluation methods, 23 studies used variations of cross-validation techniques, of which seven used LOOCV, nine studies performed a train-test split and nine studies used an independent test set. We have selected a few representative studies published within the last 5 years from the category “Asthma screening and diagnosis” that we present briefly hereafter.

Oletic and Bilas [14] used a wearable sensor that recorded signals of respiratory sounds which were subsequently transferred to a smartphone. After certain signal manipulations, an HMM was utilised for respiratory sound classification, aiming primarily to detect wheezing. The resulting model yielded accuracy=94.91%, sensitivity=89.34% and specificity=96.28%. This study shows an emerging trend of smartphone employment in computationally intensive tasks such as the induction of machine learning algorithms in asthma.

Amaral *et al.* [15] explored the contribution of forced oscillation technique (FOT) for the detection of airway obstruction, focussing specifically on patients with asthma. FOT is an oscillation-based technique that captures respiratory mechanics that can assess bronchial hyperresponsiveness in adults and children, and has been shown to be as sensitive as spirometry in detecting impairments to lung function due to smoking or exposure to occupational hazards [16]. It should be noted that FOT is a non-invasive technique that also has the advantage over conventional lung function tests that it does not require the performance of respiratory manoeuvres [16]. However, FOT should be used cautiously and as a complement to spirometry, since its interpretation and reference values remain controversial [17]. In their work Amaral *et al.* [15] employed a series of machine learning algorithms using the FOT parameters as input in order to detect airway obstruction. The best performance was achieved by a k-NN classifier that reached AUC=0.91.

TABLE 1 List of the most commonly used abbreviations in the manuscript

ANN	Artificial neural network
SVM	Support vector machine
k-NN	k-Nearest neighbours
SOM	Self organising map
HMM	Hidden Markov model
ROC	Receiver operating curve
AUC	Area under ROC curve
LOOCV	Leave one out cross validation

In a methodologically different approach KAUR *et al.* [18] utilised a natural language processing (NLP) approach in order to mine health records and identify asthma diagnosis. The resulting algorithm was validated in a cohort of 427 patients and predicted asthma status with sensitivity=86%, specificity=98%, PPV=88% and NPV=98%. Several approaches exist in the literature aiming to screen for asthma based on either the health record or the patient's prescriptions.

SINGH *et al.* [19] measure CO_2 waveforms from capnography in order to discriminate asthmatic and non-asthmatic patients. They extracted a series of features from the capnography signals from 30 non-asthmatic and 43 asthmatic patients; after applying feature selection, the remaining features were fed to a support vector machine which performed very well for the discrimination of the two classes (accuracy=94.52%, sensitivity=97.67% and specificity=90%). Capnography refers to the non-invasive measurement of the partial pressure of CO_2 in exhaled breath expressed as the CO_2 concentration over time. Changes in the CO_2 waveform (capnogram) or the end-tidal CO_2 have been employed for disease diagnosis [20], assessment of disease severity as well as treatment response [21]. Based on the aforementioned results, the authors suggest that capnography may be a promising technique for diagnosing asthma, either alone or coupled with other features. The small dataset used in this study does not allow for proper evaluation of the proposed modality and further analyses in larger datasets are mandatory.

Another interesting work was recently published by SPATHIS and VLAMOS [22] who developed a decision support system for the diagnosis of asthma and chronic obstructive pulmonary disease (COPD). They used as input a set of clinical characteristics (*e.g.* age, sex, sputum production, chest pain, smoking, *etc.*) as well as spirometry in order to detect asthma and COPD; the best performing algorithm in both cases was a random forest classifier that resulted in Precision of 97.7% and 80.3% for the diagnosis of COPD and asthma, respectively. It should be noted that, especially for COPD, the results are quite encouraging given the fact that the employed input features are readily available during a regular pulmonology visit, yet the small number of patients does not allow for firm conclusions.

For a similar purpose as the previous work, TOPALOVIC *et al.* [23] employed spirometry and features from the patients' clinical profile in order to classify patients in 10 different conditions or states (healthy, asthma, COPD, other obstructive, hyperventilation, interstitial lung disease, neuromuscular disorder, pulmonary vascular disorders and upper airway obstruction). Compared with the evaluation by pulmonologists that resulted in correct diagnosis in approximately 38% of the subjects, the proposed machine learning algorithm that utilised a decision tree classifier achieved 68% accuracy. The proposed algorithm performed better in the identification of spirometric patterns (obstructive, restrictive, mixed or normal) and in the most common conditions, such as COPD and asthma.

PANDEY *et al.* [24] acquired nasal brushing samples from 190 patients with asthma and healthy controls and extracted RNA; the expression of 90 genes was recorded and fed to a logistic regression classifier which achieved an impressive AUC of 0.994. Studies employing genomic data have recently emerged in the study of asthma but are gradually being used more widely, and can contribute to the pathogenesis of asthma at the molecular level. In a similar manner, FANG *et al.* [25] analysed gene expression data and came down to 62 genes that could serve as asthma biomarkers. Nasal brushing samples or gene expression data can often be acquired in a minimally invasive manner, nevertheless RNA extraction remains a costly technique.

Finally, the metabolome is another source of biomarkers that has recently been employed in a multitude of fields in medical research. SINHA *et al.* [26] explored the exhaled breath condensate (EBC) from 89 asthmatic subjects and 20 healthy controls and built a random forest classifier in order to differentiate between the two groups. The resulting classifier yielded 80% sensitivity and 75% specificity. Same as before, EBC may be another promising field in the search for non-invasive asthma biomarkers; however, this method needs further standardisation prior to wider clinical application [27].

Patient classification

This category contains 31 studies that aim to classify patients into subgroups based on a series of characteristics. These subgroups refer to asthma severity, asthma phenotypes/endotypes or other classifications of patients. Table S4 of the supplementary material shows a qualitative and quantitative comparison of these studies. In this category, nine studies employed decision trees or random forests, seven studies used ANNs, three studies utilised support vector machines, four studies used logistic regression and the remaining ones employed other machine learning techniques such as k-NN, Bayes network, naïve Bayes, *etc.*

The sample size, as expected, varies significantly among the studies. In terms of input data, 26 studies employ clinical data as input, whereas genomic data either alone or in combination with clinical information are used in six studies, especially in the most recent publications. Variations of the cross-validation technique are primarily used (17 studies) for evaluating the proposed classifications schemes, out of which 10 studies use 10-fold cross validation and three studies employ the LOOCV method; five studies performed evaluation with an independent test set and three studies used the training–testing method.

It is noteworthy that this category "Patient classification" is not the most populated one; however, it is the category that has significant overlap with the other categories. As noted before, every study based on its content could belong in more than one of the available categories. Studies in the category "Patient classification" often belong to other categories as well. Specifically, the task of classifying patients into certain groups is often an important step in the studies even if there are other aims in the respective study.

Identifying subcategories within the broad category of "Patient classification" is not easy. Roughly, the studies in this category could be assigned into the following subcategories: i) asthma severity and ii) asthma phenotypes. Studies in the former subcategory feature a variety of inputs, such as breath/respiratory sounds, asthma control and hospitalisation frequency. Other studies explore the exacerbation severity and classify the patients according to the course of exacerbations or a set of clinical outcomes. Below we present a couple of the most recent and representative studies from the "asthma severity" subcategory.

Van Vilet *et al.* [28] explored the relationship between asthma control and exhaled biomarkers in a paediatric population. Specifically the authors explored the discriminatory ability of fractional nitric oxide (F_{eNO}), volatile organic compounds (VOCs) and cytokines/chemokines towards identifying children with persistently controlled and uncontrolled asthma. A cohort of 96 asthmatic children was followed up for a year and different features sets were fed as input to a random forest aiming to discriminate between the two patient groups. Using solely a set of VOCs resulted in an AUC of 0.86; whereas the addition of the other two inputs did not lead to a more accurate classification.

Nabi *et al.* [29] analysed wheeze sounds from 55 asthmatic patients in order to classify them into three severity classes: *i.e.* mild, moderate and severe. An ensemble classifier yielded the highest PPV of 95%, pinpointing that tracheal-related wheeze sounds were most sensitive and specific predictors of asthma severity levels.

Next, we focus on the second subcategory of the "Patient classification" category, *i.e.* "asthma phenotypes". The studies in this subcategory either explore different patient classes based on a set of input features either genomic and/or clinical; therefore, the patients are clustered based on their inherent characteristics. In the same subcategory, there are studies that classify the employed patients based on their response to treatment. In the next few paragraphs, we present some of the most important and recent studies from this subcategory.

Krautenbacher *et al.* [30] combined a wide range of heterogeneous data, namely questionnaire, diagnostic, genotype, microarray, RT-qPCR, flow cytometry and cytokine data in order to differentiate between three patient phenotypes. The phenotypes under consideration are healthy, mild-to-moderate allergic and nonallergic. The study focussed on a paediatric population of 260 children. The most important variables for classifying childhood asthma phenotypes comprised novel identified genes, namely protein kinase N2 (PKN2), protein tyrosine kinase 2 (PTK2), and alkaline phosphatase, placental (ALPP). Similarly, Fontanella *et al.* [31] explored the relationship between allergic sensitisation and asthma propensity; even though the study primarily aims to serve as a diagnostic tool for asthma, pairwise interactions between immunoglobulin (Ig)E components are used to predict clinical phenotypes.

Williams-DeVane *et al.* [32] utilised a completely data driven approach in order to identify asthma subtypes. The authors employed gene expression data, clinical covariates as well as certain disease indicators and devised a multi-step decision tree aiming to identify asthma endotypes aiming to facilitate the discovery of new mechanisms underlying asthma.

Wu *et al.* [33] explored asthma phenotypes based on patients' response to corticosteroids, using an unsupervised multiview learning approach. The proposed work explored the contribution of 100 clinical, physiological, inflammatory and demographic variables and was validated in a set of 346 adult asthmatic patients. The authors reported that patients with late-onset asthma, low lung function and high baseline eosinophilia showed the best corticosteroid responsiveness, whereas the poorest responsiveness was reported in young, obese females with severe airflow limitation and little eosinophilic inflammation. A similar approach is presented in the paper by Ross *et al.* [34], in which the authors proposed an machine learning algorithm in order to identify paediatric asthma phenotypes based on the patients' response to controller medication. Bronchodilator response and serum eosinophils were found to be the most predictive features of asthma control in the paediatric population under consideration.

Asthma management and monitoring

This category is also quite populated, featuring 40 studies that primarily deal with asthma exacerbations of asthma flare-ups. Table S5 provides an overview of these studies. Regarding machine learning algorithms, 12 studies employed decision trees, random forests or variations of these algorithms; 11 studies utilised ANNs, four studies used support vector machines, three studies employed Bayes network/naïve Bayes algorithms and three used logistic regression.

Interestingly, in this category there are 11 studies employing more than 1000 records, five of which analyse environmental data (*e.g.* air pollution). There are only three studies incorporating genomic data in this category, consequently the majority of the studies encompass either clinical data or environmental/meteorological data or their combination (seven studies). Cross validation was also the main method used for evaluation as reported in 21 studies, of which two used LOOCV; training–testing split was used in eight studies and only four studies performed evaluation on an independent testing set. In this category, we can identify two broad subcategories, namely asthma exacerbation prediction and asthma exacerbation management. The former category refers to models aiming to early identify an exacerbation while the latter contains models that predict the course of the exacerbation and the subsequent management.

Khasha *et al.* [35] utilised expert knowledge in an ensemble classifier in order to detect asthma control level yielding an overall 91.66% accuracy. The algorithm was developed with data collected from 96 asthmatic patients followed-up for a 9-month period. According to the authors, the aim of the proposed model is to serve as a real-time preventive system for asthma control.

In a similar manner, Hosseini *et al.* [36] proposed a platform for real-time assessment of asthma attack risk, based on a set of sensors capturing physiological and environmental data. The collected data are pipelined through a smartphone for analysis to an random forest classifier which identified asthma attacks with an overall accuracy of 80.1%. In another work by Huffaker *et al.* [37], nocturnal recordings of physiological data were obtained from a contactless bed sensor and fed to a random forest model which yielded 87.4% accuracy, 47.2% sensitivity and 96.3% specificity, towards detecting asthma exacerbations. Similarly, for the prediction of asthma exacerbations, Finkelstein *et al.* [38] utilised telemonitoring data which were analysed by an adaptive Bayesian network resulting in perfect classification (*i.e.* 100% accuracy, 100% sensitivity and 100% specificity).

In a methodologically different approach, Ram *et al.* [39] mined a multitude of data coming from Google search interests, Twitter data and environmental data in order to early predict asthma-related emergency department visits; the resulting model yielded 70% precision. Such systems could potentially serve as a means of public health surveillance in order to enhance proactiveness and efficiency of the emergency department. For the same purpose, Khatri *et al.* [40] developed an ANN model in order to predict peak demand days at the emergency department for chronic respiratory diseases.

Another important issue regarding an asthma exacerbation is the decision whether hospitalisation is needed or not. Patel *et al.* [41] proposed an algorithm based on gradient-boosting machines that quantifies the overall risk, and consequently the need for hospitalisation is decided. The algorithm yielded an AUC of 0.84 and the following features were found to be more informative: vital signs, acuity, age, weight, socioeconomic status and weather-related features.

Asthma treatment

The last category contains studies utilising machine learning algorithms for the overall asthma treatment. It is notable that this category contains only one article by Ross *et al.* [34] which has also been mentioned in previous categories. The authors aimed to identify asthma phenotypes based on their response to treatment and, thus, fine tune their patients' treatment. We have intentionally included this hardly populated category in order to highlight the gap in literature in terms of machine learning algorithms used for asthma treatment.

Discussion

Asthma research is gradually picking up on AI/machine learning techniques, following the overall trend of AI/machine learning adoption in healthcare-related studies. Specifically, in figure 3 (Introduction section) we presented the distribution of studies using AI/machine learning techniques for asthma research, over the course of 30 years, *i.e.* from 1988 to 2018. During the first and second decade, there is minimal employment of such techniques for asthma, while from 2010, we observe a considerable and progressive increase. A similar trend has been observed regarding the utilisation of AI/machine learning techniques in other healthcare domains, *e.g.* cancer research [13], whereas in the latter case the number of articles published in each year is almost ten times bigger.

In the “Asthma screening and diagnosis” category we observe that the vast majority of studies have utilised relatively small numbers of patients. Only studies employing questionnaires contain richer patient sets. This observation poses an important question regarding the validity and robustness of the reported results.

As for the “Patient classification” section, the studies employ relatively larger patient cohorts; nevertheless, the reported evaluation metrics are encouraging but not quite perfect yet. Therefore, more data and further analyses are needed in order to obtain more definite answers.

The “Asthma management and monitoring” category is quite heterogeneous in terms of the employed population sizes and the accuracy of the reported results. Specifically, we observe from the respective table S5 that the number of patients or records used in the studies vary significantly from just a couple up to thousands. This has to do with several factors: the type and cost of employed data (genomic, metabolomic, clinical, *etc.*), the focus on specific populations and the scarcity of patients in each patient set, the quality and completeness of gathered information.

It is noteworthy that the last category “Asthma treatment” contains one study, denoting the lack of research currently in this prospect with the employment of machine learning techniques. This can be attributed to the fact that treatment is primarily directed by published guidelines. However, it should be noted that in the field of asthma treatment there is considerable activity in the literature, especially with respect to biologics. According to our literature research, there are currently no studies that exploit machine learning algorithms focussed on the exploration of biologic treatments of asthma. Nevertheless, as the number of approved biologics increases, as also the number of eligible patients, such studies are expected to emerge. The profiles of super-responders to specific biologics currently remain largely elusive, and AI/machine learning could facilitate the discovery of such complex profiles. There is also an increasing interest in the reviewed literature towards severe asthma encompassing machine learning techniques, following the overall trend in asthma research.

Only a small fraction of the studies in the current review utilise large patient cohorts, and even fewer analyse complex data, where AI could be more useful; therefore, AI in asthma research still remains underused, or at least not exploited to its full potential. Furthermore, we observe that in terms of the quantitative and qualitative features we have compared the included studies, there are some similar patterns among them. Specifically, there is considerable utilisation of ANNs and decision trees; whereas, in the most recent studies, random forests are being increasingly used. This trend is to be expected, since ANNs were widely employed in several medical fields due to their superior results. Decision trees are also quite common in health-related studies because they provide reasoning which is often regarded as cornerstone. It should be noted that there is a significant number of studies (*i.e.* 21) focussing on paediatric populations; whereas, the rest include adults, denoting the burden based on age.

It should be highlighted that AI/machine learning techniques are particularly useful for the analysis of large complex datasets, encompassing heterogeneous sources of information. Asthma poses an ideal target for AI/machine learning utilisation, as it is a chronic disease with patients being followed-up for several years and its perturbations can be detected from the cellular level, to the organ level and up to the organism level as a whole. Moreover, environmental factors play a key role in asthma pathogenesis and natural history; therefore, large scale environmental and meteorological data need to be analysed in a complementary manner. Ideally, a theoretical asthma study should capture genomic, metabolomic, clinical and environmental data, in several consecutive time-slices from large and diverse patient cohorts, thus framing all potential asthma effects ranging in scale and time. The resulting highly complex and heterogeneous dataset should be mined with AI techniques aiming to gain new knowledge regarding asthma diagnosis, classification and treatment.

Conclusions

AI/machine learning is undeniably a scientific field that is in the spotlight, especially in the last decade; its utilisation in medical applications is on the rise, and subsequently there is growing interest in the respiratory field and asthma research, as denoted by the literature review conducted in the current work. Further progress is to be expected in respiratory research as more advanced machine learning techniques are gradually used, *e.g.* deep learning. Another issue that affects the combined research of asthma with AI/machine learning techniques is the fruitful communication between computer scientists and clinicians for the identification of the appropriate research questions. In order to deal with those questions more effectively large amounts of high quality and well characterised populations are needed. Finally, there is an unmet need in the identification of treatment responders to different therapeutic approaches, including the selection of an appropriate biologic treatment in severe asthma by predicting a patient’s response based on phenotypic and endotypic characteristics. Artificial intelligence is here to stay in medicine; however, there are certain open issues in asthma that need to be further elucidated.

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References

1 Selroos O, Kupczyk M, Kuna P, *et al.* National and regional asthma programmes in Europe. *Eur Respir Rev* 2015; 24: 474–483.
2 Aaron SD, Boulet LP, Reddel HK, *et al.* Underdiagnosis and overdiagnosis of asthma. *Am J Respir Crit Care Med* 2018; 198: 1012–1020.
3 Bahadori K, Doyle-Waters MM, Marra C, *et al.* Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009; 9: 24.
4 Feng Y, Teh HS, Cai Y. Deep learning for chest radiology: a review. *Curr Radiol Rep* 2019; 7: 25.
5 McBee MP, Awan OA, Colucci AT, *et al.* Deep learning in radiology. *Acad Radiol* 2018; 25: 1472–1480.
6 Angelini E, Dahan S, Shah A. Unravelling machine learning – insights in respiratory medicine. *Eur Respir J* 2019; 54: 1901216.
7 Young AL, Bragman FJS, Rangelov B, *et al.* Disease progression modelling in chronic obstructive pulmonary disease (COPD). *Am J Respir Crit Care Med* 2019; 201: 294–302.
8 Ho DSW, Schierding W, Wake M, *et al.* Machine learning SNP based prediction for precision medicine. *Front Genet* 2019; 10: 267.
9 van IJzendoorn DGP, Szuhai K, Briaire-de Bruijn IH, *et al.* Machine learning analysis of gene expression data reveals novel diagnostic and prognostic biomarkers and identifies therapeutic targets for soft tissue sarcomas. *PLoS Comput Biol* 2019; 15: e1006826.
10 Mauldin TR, Canby ME, Metsis V, *et al.* SmartFall: a smartwatch-based fall detection system using deep learning. *Sensors (Basel)* 2018; 18: 3363.
11 Tison GH, Sanchez JM, Ballinger B, *et al.* Passive detection of atrial fibrillation using a commercially available smartwatch. *JAMA Cardiol* 2018; 3: 409–416.
12 Jiang F, Jiang Y, Zhi H, *et al.* Artificial intelligence in healthcare: past, present and future. *Stroke Vasc Neurol* 2017; 2: 230–243.
13 Kourou K, Exarchos TP, Exarchos KP, *et al.* Machine learning applications in cancer prognosis and prediction. *Comput Struct Biotechnol J* 2015; 13: 8–17.
14 Oletic D, Bilas V. Asthmatic wheeze detection from compressively sensed respiratory sound spectra. *IEEE J Biomed Health Informatics* 2018; 22: 1406–1414.
15 Amaral Jorge LM, Lopes Agnaldo J, Veiga J. High-accuracy detection of airway obstruction in asthma using machine learning algorithms and forced oscillation measurements. *Comput Methods Programs Biomed* 2017; 144: 113–125.
16 Oostveen E, MacLeod D, Lorino H. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Res* 2003; 22: 1026–1041.
17 Shirai T, Kurosawa H. Clinical application of the forced oscillation technique. *Internal Medicine* 2016; 55: 559–566.
18 Kaur Harsheen, Sohn Sunghwan, Wi Chung-Il. Automated chart review utilizing natural language processing algorithm for asthma predictive index. *BMC Pulmonary Medicine* 2018; 18: 34.
19 Singh OP, Palaniappan R, Malarvili M. Automatic quantitative analysis of human respired carbon dioxide waveform for asthma and non-asthma classification using support vector machine. *IEEE Access* 2018; 6: 55245–55256.
20 Bou Chebl R, Madden B, Belsky J. Diagnostic value of end tidal capnography in patients with hyperglycemia in the emergency department. *BMC Emerg Med* 2016; 16: 7.
21 Paiva EF, Paxton JH, O'Neil BJ. The use of end-tidal carbon dioxide (ETCO 2) measurement to guide management of cardiac arrest: A systematic review. *Resuscitation* 2018; 123: 1–7.
22 Spathis D, Vlamos P. Diagnosing asthma and chronic obstructive pulmonary disease with machine learning. *Health Informatics J* 2019; 25: 811–827.
23 Topalovic M, Laval S, Aerts J-M, *et al.* Automated interpretation of pulmonary function tests in adults with respiratory complaints. *Respiration* 2017; 93: 170–178.
24 Pandey G, Pandey OP, Rogers AJ, *et al.* A Nasal brush-based classifier of asthma identified by machine learning analysis of nasal RNA sequence data. *Sci Rep* 2018; 8: 8826.
25 Fang F, Pan J, Li Y, *et al.* Identification of potential transcriptomic markers in developing asthma: An integrative analysis of gene expression profiles. *Mol Immunol* 2017; 92: 38–44.
26 Sinha A, Desiraju K, Aggarwal K, *et al.* Exhaled breath condensate metabolome clusters for endotype discovery in asthma. *J Transl Med* 2017; 15: 262.
27 Horváth I, Barnes PJ, Loukides S, *et al.* A European Respiratory Society technical standard: exhaled biomarkers in lung disease. *Eur Respir* 2017; 49: 1600965.
28 Van Vliet D, Smolinska A, Jöbsis Q. Association between exhaled inflammatory markers and asthma control in children. *J Breath Res* 2016; 10: 016014.
29 Nabi F, Sundaraj K, Lam C, *et al.* Characterization and classification of asthmatic wheeze sounds according to severity level using spectral integrated features. *Comput Biol Med* 2019; 104: 52–61.
30 Krautenbacher N, Flach N, Böck A, *et al.* A strategy for high-dimensional multivariable analysis classifies childhood asthma phenotypes from genetic, immunological, and environmental factors. *Allergy* 2019; 74: 1364–1373.
31 Fontanella S, Frainay C, Murray CS, *et al.* Machine learning to identify pairwise interactions between specific IgE antibodies and their association with asthma: A cross-sectional analysis within a population-based birth cohort. *PLoS Med* 2018; 15: e1002691.
32 Williams-DeVane CR, Reif DM, Cohen H, *et al.* Decision tree-based method for integrating gene expression, demographic, and clinical data to determine disease endotypes. *BMC Systems Biology* 2013; 7: 119.

33 Wu W, Bang S, Bleecker ER, *et al.* Multiview cluster analysis identifies variable corticosteroid response phenotypes in severe asthma. *Am J Respir Crit Care Med* 2019; 199: 1358–1367.
34 Ross MK, Yoon J, van der Schaar A, *et al.* Discovering pediatric asthma phenotypes on the basis of response to controller medication using machine learning. *Ann Am Thorac Soc* 2018; 15: 49–58.
35 Khasha R, Sepehri MM, Mahdaviani SA. An ensemble learning method for asthma control level detection with leveraging medical knowledge-based classifier and supervised learning. *J Med Syst* 2019; 43: 158.
36 Hosseini A, Buonocore CM, Hashemzadeh S, *et al.* Feasibility of a secure wireless sensing smartwatch application for the self-management of pediatric asthma. *Sensors (Basel)* 2017; 17: E1780.
37 Huffaker M, Carchia M, Harris BU, *et al.* Passive nocturnal physiologic monitoring enables early detection of exacerbations in children with asthma. A proof-of-concept study. *Am J Respir Crit Care Med* 2018; 198: 320–328.
38 Finkelstein J, Jeong IC. Machine learning approaches to personalize early prediction of asthma exacerbations. *Ann N Y Acad Sci* 2017; 1387: 153–165.
39 Ram S, Zhang W, Williams M, *et al.* Predicting asthma-related emergency department visits using big data. *IEEE J Biomed Health Inform* 2015; 19: 1216–1223.
40 Khatri KL, Tamil LS. Early detection of peak demand days of chronic respiratory diseases emergency department visits using artificial neural networks. *IEEE J Biomed Health Inform* 2018; 22: 285–290.
41 Patel SJ, Chamberlain DB, Chamberlain JM. A machine learning approach to predicting need for hospitalization for pediatric asthma exacerbation at the time of emergency department triage. *Acad Emerg Med* 2018; 25: 1463–1470.