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Research Progress on Risk Factor in Childhood Asthma: A Systematic Review

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Abstract

Background: Childhood asthma is complex heterogeneous disorder with multiple factors involved in its causation. The basic aim of the study was to accomplish the systemic review of literature elucidating the recent research on risk factors of childhood asthma and its challenging therapies. **Methods:** Data sources: The data for this systematic review was collected from three databases namely PubMed, Science direct and Scopus was used to recoup papers examining the risk factor of childhood asthma and related research progress published from 2011 to 2020. All the included references were manually checked and children under 18 years were part of the study. Inclusion criteria: The studies included were original publication in English, meta-analysis, cross-sectional studies, and cohort/case-control studies. The main study interest was a risk factor of childhood asthma/wheeze and targeted folk was under eighteen children. The keywords used to find the relevant literature were asthma risk factor, asthma, childhood asthma, childhood asthma risk factor, childhood asthma prevention, and asthma therapy. **Results:** Initially, 1051 papers were collected by searching with help of different websites using keywords, and 977 papers were rejected due to irrelevant titles, abstracts, different age groups, and inappropriate estimates. 74 papers were found relevant abstracts which were further studies and more 43 papers were rejected. Finally, 31 papers were met the exact selection criteria. Twenty-two cross-sectional studies, five meta-analyses, and three cohort base studies. Typically increase in risk factor was noticed with OR= 0.60-3.35. **Conclusion:** Multiple factors are associated with childhood asthma, some of them have a positive effect and few have a role in reducing asthma in childhood. Currently, biomarkers are used to assess the disease and for quality treatment but limited numbers of markers can be used in clinical practice for pediatric patients these are blood and sputum eosinophils, serum IgE, periostin, and FeNO, they may be used individual or in combination for better response.

Keywords: Asthma, Childhood Asthma, Risk Factor, Analysis

INTRODUCTION

Globally chronic disorder asthma is well known respiratory disorder with lethal effects on the health of every age group and has a major contribution to increasing the burden of disease.[32] Prevalence of asthma is high in Unite states as 24 million people are facing asthma.[41] In United states asthma prevalence rate has been raised and affect the 3.1% in 1989, 8.3% of the

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population was recorded in 2016.[42] African Americans livening in less developed areas are more prone to an asthma attack while it is also deemed as a worse leading chronic disorder in children.[43] There is a censorious need to tailor asthma more persuasively. Asthma is a multifactorial and heterogeneous disorder associated with many genetic and environmental factors. Global initiative for asthma has conceded the pathophysiological, clinical, and demographical properties that are a pack of obvious asthma phenotypes namely allergic, non-allergic, and late-onset asthma.[44,45] Alteration of environmental exposure is one of the leading causes of developing high prevalence of asthma in the western world.[46] However, few exposures are probable to be important by means of epigenetic mechanism.[47] Asthma might be caused to various environmental exposure likely smoking, respiratory infections48, and multiple dietary factors.49 Lately, much evidence has been concluded the asthma is the causation of interaction among different risk factors.[50] Two domains such as risk and impairment are clearly defined in present guidelines to control asthma, the term risk used to evaluate the assessment of asthma attacks, medication side effects, and disease development.[33,35] we can overcome the burden of asthma in children by reducing the asthma attacks and lifelong adverse findings of childhood asthma.[36,37] The main focus of research on long-lasting outcomes of childhood asthma specifically day by day step toward poorly control, severe asthma with irreversible damage of lung function.[38] As the progress of technology with the advancement in treatment methodology and discovery of new medicines and new biomarkers provided new opportunities to developed technology-oriented individualized treatment strategies. In this way, we can reduce asthma attack and their lifelong effects on an individual's life.[39,40]

MATERIALS AND METHODS

Data sources

The data for this systematic review was collected from three databases namely PubMed, Science Direct and Scopus were used to recoup papers examining the risk factor of childhood asthma and related research progress published from 2011 to 2020. All the included references were manually checked and children under 18 years were the part of the study.

Inclusion criteria

The studies included were original publication in English, meta-analysis, cross-sectional studies, and cohort/case-control studies. The main study interest was a risk factor of childhood asthma/wheeze and targeted folk was under eighteen children. The keywords used to find the relevant literature were asthma risk factor, asthma, childhood asthma, childhood asthma risk factor, childhood asthma prevention, and asthma therapy. All included studies were explained through outcomes and data (odd ratio =OR).

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RESULTS

An overview of selection criteria is given in [Figure1]. Initially, 1051 papers were collected by searching with help of different websites using keywords, and 977 papers were rejected due to irrelevant titles, abstracts, different age groups, and inappropriate estimates. 74 papers were found relevant abstracts which were further studies and more 43 papers were rejected. Finally, 31 papers were met the exact selection criteria. Twenty-two cross-sectional studies, five meta-analyses, and three cohort base studies. These selected studies were explained with different risk facts and interventions in [Table1-3].

Association of different factors with childhood asthma

Exposure to pet animals

Three cross-sectional was identified included one study investigated the risk of asthma during infancy by exposing to indoor pets and found inverse association with risk of asthma (OR value 0.60, 95% CI 0.38-0.96). Exposure to dogs during the initial years of life may increase the risk of allergic rhinitis while cats may reduce the risk of atopic eczema.[2] Similarly, one more study was found with the same findings.[3] Controversy was exists in one publication between the children of school-going age 6-18 years that exposure to cats enhanced risk of asthma and such an environment highly exposed to dogs had a greater contribution to the prevalence of allergy in children.[1]

Exposure to air pollutants

Three cohort study and a meta-analysis was clearly indicated the association with asthma, not one pollutant responsible for asthma. Authors in meta-analysis demonstrated that A higher prevalence of asthma was found in children who had greater exposure to carbon monoxide, nitrogen dioxide, and nitric oxide with variation in odd ratio 1.06, 1.05, and 1.02 respectively, while exposure to Sulphur dioxide (OR = 1.04) triggers the wheeze in children.[4] One cohort study evaluates the exposure to nitrogen dioxide and sulfur dioxide with 2.5 and 10 micrometers, particulate matter and finding shows that higher exposure to an average increase of NO2 5 ppb trigger the asthma risks with confidence intervals 95% Cl = 1.04-1.31.[5] Second study revealed that less the association was observed with asthma in children of age seven years when they had lifelong exposure to different gases including CO, NO2, SO2. Asthma risks were found twice in patients with bronchiolitis with excessive exposure to these gases.[6] Third cohort study was attempted that lifelong exposure to traffic particles had a potent association to develop asthma (OR= 1.25) in children of 0 to 5 years.[7]

Parental smoking

Two meta-analysis was identified associated with asthma, one study elucidated postnatal passive smoking had elevated the 30 to 70% chances of incidence of wheezing promptly in children age less than 2 years (OR = 1.70). The findings of this meta-analysis

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concluded that parental smoking had increased the 20% incidence rate of asthma and wheezing in children.[8] Second meta-analysis concluded that maternal smoking was also linked with risk development of wheezing or asthma in children age six years (OR = 1.3) and data of school-going children was limited. Postnatal had no association with asthma and wheeze.[9]

Dietary exposure

Three studies were identified including a case study of 1276 children including 300 asthma patients concluded that consumption of dairy products 3 to 6 times a week strongly associated with asthma with OR= 0.14 while consumption of meat and nuts daily and double in a week may be significantly linked with asthma. Children of age 3-6 were found less susceptible than 7-13 years to asthma (OR = 3.35), boys were more vulnerable to developed asthma risks (OR= 0.68).[10] A prospective cohort-based study on children of Netherlands by exposing them to a western diet for a duration of 14 months found an increase in association with wheeze at three years.[11] Early introducing fruits to children may decrease the risk to develop asthma at 8 years and by improving the plasma vitamin D could also reduce asthma risk with an OR value of 3.05 while serum vitamin D level had no association with the risk of asthma.[12]

Exposure to Infection

The findings of two studies and one meta-analysis were collected, first, one prospective cohort study concluded that upper respiration did not impose adverse respiratory effect as compared to children with a lower respiratory infection. Children of age 3 to 6 years suffering from lower respiratory infection were more prone to asthma risk (OR = 3.53).[13] the second study outcomes were indicated the strong relationship between early-life respiratory syncytial virus infection and worse respiratory outcomes in children of 0 to 12 years. Infectious child had (OR =3.05, CI = 2.50-3.71) recurrent wheezing and subsequently developed asthma.[15] Meta-analysis consist of 15 original articles and 4 cohort studies concluded that suffering from rhinovirus wheezing during infancy escalate the incident (relative risk, RR = 2.00) of asthma and wheezing in later life.[14]

Medication and asthma

Three publications were elucidated the association of asthma with medicine. The use of antibiotics during prenatal conditions enhances the risk factors to develop asthma OR = 3.1 in children as compared to wheezing had OR value of 1.8 but the use of antibiotics during 1st trimester had no association with asthma and wheezing.[16] Paracetamol was not associated with asthma risk in children.[17] On the other hand Use of paracetamol for 6 months child could develop asthma at 3 years relative risk = 1.13) but not found at 7 years child.[18]

Therapeutic interventions

Three studies related to inhaled corticosteroids recommend lower doses in children to prevent any harmful effect two studies on long-acting beta-

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agonists which cause the relaxation of smooth muscle in the airway, and recommend the use of LABA in combination with ICS to overcome its adverse effects.[25-29] Two studies about leukotriene modifier especially for patients who had greater exposure to smoke.[30,31]

Asthma therapy with biomarkers

Five studies, four articles, and one meta-analysis results were presented in [Table2]. Two biomarkers blood eosinophil count >300/µL and aeroallergen sensitization was used with three medicines and found efficacious control results of ICS in preschool children.[19] Eosinophilic asthma was diagnosed by using serum eosinophils and sputum eosinophils to target the environmental allergen asthma.[20] One meta-analysis support sputum eosinophil could be a better option to treat asthmatic patients. Two studies were about periostin as a biomarker in pediatric asthma.[22,23] An Cochrane review was explained the FeNO effectiveness as a biomarker for children.[24]

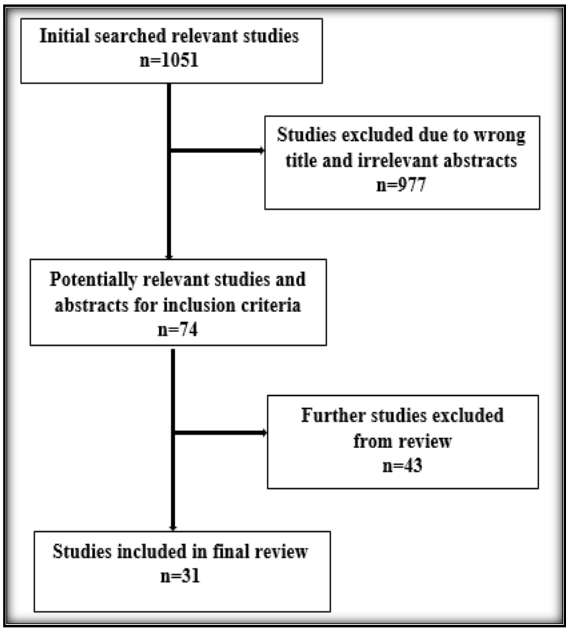

Figure 1: the flow diagram of literature selection process

Table 1: Characteristic of studies included in systematic review

Factors	Authors	Age	Findings
Exposure to pet animals (cats and dogs)	Ojwang et al., 2020 Fretzayas et al., 2013.[2,3]	5 years	High association with OR value 0.60, 95% CI 0.38-0.96
	Song et al., 2014.[1]	6-18 years	Exposure to cats increased the prevalence of asthma and dogs had a contribution to allergy in children
Exposure to air pollutant (carbon mono oxide, nitrous oxide and nitrogen dioxide)	Gasana et al., 2012.[4]	0-16 years	Air pollutants had a strong impact on raising the prevalence of childhood asthma. The odd ratio for nitrous oxide, nitrogen dioxide and carbon mono oxide was 1.02, 1.05, and 1.06 respectively. While SO2 was 1.04.
	Nishimura et al 2013.[5]	First few years of life	Increase of exposure to an average increase of NO2 5 ppb trigger the asthma risks with confidence intervals

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			95% Cl = 1.04- 1.31
	Kim et al., 2013.[6]	7 years	Higher interaction with ozone may enhance the past episodes of bronchiolitis and escalate the chances of asthma in children.
	Patel et al., 2011.[7]	0-5 years	Children could be at greater risk to develop asthma with OR 1.25 when they were exposed to higher traffic density.
Parental smoking	Burke et al., 2012.[8]	0-2 years	Postnatal smokers child were 30 to 70% at risk to develop wheezing (OR = 1.70) and parental smoking increased 20% incidence of asthma and wheeze in children.
	Silvestr et al., 2015.[9]	1.5-16 years	Maternal smoking-induced the risk of asthma and wheezing in children age six years with an odd ratio value of 1.3 and no association of asthma and wheeze was found with postnatal smoking.
Dietary exposure	Hallit et al., 2018.[10]	3-16 years	Consumption of dairy product 3 to 6 times a week strongly associated with asthma with OR= 0.14, Children of age 3-6 were found less susceptible than 7-13 years to asthma (OR = 3.35), boys were more vulnerable to developed asthma risks (OR= 0.68).
	Tromp et al., 2011.[11]	6 months -4 years	Exposure to the western diet may increase the risk of asthma
	Van et al., 2011.[12]	2-8 years	Early life introducing fruits to children may decrease the risk to develop asthma at 8 years and by improving the plasma vitamin D could also, reduce asthma risk with OR value 3.05 while serum vitamin D level had no association with risk of asthma.
Exposure to Infection	Van et al., 2018.[13]	>3-6 years	Early-life exposure to the lower respiratory tract infection consistently lowering the lungs function and increased the asthma risk. (OR= 3.53)
	Liu et al., 2017.[14]	0-3 years	In the first three years of life rhinovirus wheezing illness could escalate the risk of wheezing and asthma in adult age. (relative risk, RR = 2.00)

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	Shi et al., 2020.[15]	0-12 years	Respiratory syncytial virus infection and worse respiratory outcomes in children of 0 to 12 years. The infectious child had (OR =3.05, Cl = 2.50-3.71) recurrent wheezing and subsequently developed asthma
Medication and asthma	Lapin et al., 2015.[16]	0-1 year	Use of prenatal antibiotic enhance the risk factor to develop asthma OR = 3.1 in children as compared to wheezing had OR value of 1.8 but the use of antibiotic during 1st trimester had no association with asthma and wheezing
	Magnus et al., 2018	0-7 years	Use of paracetamol for 6 months child could develop asthma at 3 years (relative risk = 1.13) but not found at 7 years child.
	Heintze et al., 2013	0-5 years	The use of paracetamol had no association in development of wheezing and asthma

Table 2: Role of biomarkers

Authors, year	Studies	Findings
Fitzpatrick et al., 2016.[19]	Asthma therapy with biomarkers (Children were treated with asthma controller medication inhaled daily for 2-8 weeks treatment included corticosteroids, leukotriene receptor antagonists. The response of ICS was targeted through two biomarkers, blood eosinophil count >300/μL and aeroallergen sensitization)	In all treatments best control results for asthma were obtained from ICS used with eosinophil blood count. 42% positive response of aeroallergen sensitized.
deGroot et al., 2015.[20]	Serum and sputum eosinophils was used to diagnose asthma caused by environmental factors.	Sputum eosinophila was found more efficacious as compared to the serum which could be used as a substitute of sputum eosinophila
Petsky et al., 2012.[21]	Compare the inhale corticosteroid, FeNO treatment, and sputum eosinophil in children and adults.	Asthma treatment in children based on sputum eosinophil with ICS shows the effective results rather than FeNO treatment
Scichilone et al., 2016.[22] Anderson et al., 2017.[23]	lgE level and serum periostin level was used as a biomarker in children of age 2, 6 and 11 years to determine the early childhood asthma initiation.	Periostin as biomarker found more frequent for asthma and high level of periostin in children was due to bone

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		turnover.
Petsky et al., 2016.[24]	Fractional exhaled nitric oxide was deemed as a marker to optimize the treatment and may reduce the asthma exacerbations.	The level of FeNO was not effectively associated with asthma therapy in children so, it should recommend as asthma guide therapy

Table 3: Different studies finding in treatment of childhood asthma

Therapeutic interventions	Authors	Findings
Corticosteroids	Boulet et al., 2019.[25]	ICS can be used to treat the acute asthma but in children, it could suppress the hypothalamic-pituitary adrenal axis because of its prolonged treatment.
	Lombard et al., 2012.[26]	Evidence support that children treated with a lower dosage of inhaled corticosteroids suffered from suppression of hypothalamic pituitary adrenal axis.
	Issa et al., 2015.[27]	Pediatric patients treated for six months with a high dose of ICS were found with adrenal suppression.
Long-acting beta agonists (LABA)	Scott et al., 2012.[28]	LABU must use in combination with ICS. The use of LABA alone imposed adverse effects on pediatric patients by increasing the risk of asthma leading to death.
	Busse et al., 2018.[29]	To treat the various asthma endo types use the LABA in combination with ICS was found more effective in children.
Leukotriene modifier	Pacheco et al., 2014.[30] Marcello et al., 2016.[31]	Efficacious results of leukotriene modifiers were obtained for the patients who exposed to smoke. It was also found effective for patients with asthma small airway disease

DISCUSSION

The aim of this systematic review was to collect recent literature on risk factors of childhood asthma and to determine the research progress to treat asthma in children. This study was based on observational studies and found the literature on exposure to environmental factors, tobacco, respiratory infection, and dietary factors. All these factors have an indispensable role in the development of asthma. Exposure of pre-school children to pet animals had an association with asthma that might be suspected to develop asthma at 6 years.[71,72] Pediatric asthma had linked with air pollutants as exposure to air pollutant elevate the risk of asthma and eczema in children.[73,74] Child respiratory disease asthma was linked with parents indoor smoking as well as outdoor smoking,[75] children were more prone to asthma in case of greater exposure to smoke odor.[76]Although a complex relationship exists between various dietary factors and asthma risk,

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a child who took the exclusive breastfeeding for 6 months was less vulnerable to asthma.[77] Prolong breastfeeding did not any adverse effect and no association with asthma.[78]

Secondly, we collected the literature on the therapeutic intervention of asthma that mainly focused on the use of biomarkers and other treatments. Biological markers are indicators that help to assess the disease and measured in an appropriate analytical test system.[51] Biomarkers used in asthma treatment are elucidated above and biological specimens were used to measure asthma in children such as sputum, blood, inhaled breath condensate.[52] However, the most recently used few golden standards to approach the inflammation and remodeling in asthma are bronchial biopsy and BAL with bronchoscopy. Its use for pediatric diagnosis is limited due to adverse effects.[53,54] the use of sputum induction was also found limited especially in children because of the complex method and invasive in nature.[55] now researcher trying to make sure availability of non-invasive childhood asthma markers to diagnosed the inflammation. Potentially biomarkers of asthma can be used to distinguish the inflammatory endo-type (T2- cytokine targeted therapy) that successfully assess and monitor the disease progression.[56-58] In pre-school children FeNO can be used as a predictive factor of new pediatric patients,[79] it is considered a surrogate marker to identify asthma in children.[80] In the case of severe asthma, biomarkers could be used in combination or single to assess the severity of the disease.

The current inception of biomarkers includes the sputum eosinophils, serum IgE, periostin, and FeNO.[59-61] Eosinophils are a central driver of T2 inflammation in children with severe asthma and had a critical role in chronic inflammation.[62-66] A better response of ICS therapy was indicated with the presence of blood eosinophilia and high FeNO, although the poor response was measured for oral corticosteroid therapy.[67,68] One more study concluded that the best predictor response to ICS was obtained through the blood eosinophil count and aeroallergen sanitization in preschool children,[69] such finding helped to tailor treatment of preschool asthma children.[70]

CONCLUSION

Childhood asthma deemed a challenging disease as it has various endo-types. Multiple factors are associated with childhood asthma, some of them have positive effects and few have a role in reducing asthma in childhood. Currently, biomarkers are used to assess the disease and for quality treatment but limited numbers of markers can be used in clinical practice for pediatric patients these are blood and sputum eosinophils, serum IgE, periostin, and FeNO, they may be used individual or in combination for better response.

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