HOUSEHOLD AIR POLLUTION AND CHILDHOOD BRONCHIAL ASTHMA NEW ONSET RISK IN KOTA BHARU KELANTAN: THE DETERMINANTS AND MODELLING

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by

DR MUHAMMAD NAIM BIN IBRAHIM

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TABLE OF CONTENTS

LIST OF MANUSCRIPTS

Throughout my Doctor of Public Health (DrPH) course, three manuscripts were successfully prepared in alignment with the study's objectives. One manuscript has been published, and two others are awaiting submission to a Web of Science-indexed journal. Additionally, two presentations related to the research were delivered at international conferences.

First manuscript

(Corresponding to the first research objective)

Development, Validation, and Reliability Analysis of the Household-Related Air Pollution on the Childhood Bronchial Asthma Onset Checklist (HAPBAC-Checklist)

Muhammad Naim Ibrahim[1], Nik Rosmawati Nik Husain[1], Mohamad Ikram Ilias[2], Kueh Y. Cheng[3], Norzaihan Hassan[4], Nurul Ainun Hamzah[5], Norazlin Idris[1], Khairul Azuan Che Azid[6]

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Second manuscript

(Corresponding to the second research objective)

Early Life Exposure to Household Air Pollution and Childhood Bronchial Asthma: Insights from a Case-Control Study in Kota Bharu Kelantan

Muhammad Naim Ibrahim[1], Nik Rosmawati Nik Husain[1], Mohamad Ikram Ilias[2], Kueh Y. Cheng[3], Norzaihan Hassan[4], Nurul Ainun Hamzah[5], Maizun Mohd Zain[6], Mariana Daud[7], Siti Romaino Mohd Nor[8], Norazlin Idris[1], Khairul Azuan Che Azid[9]

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Third manuscript

(Corresponding to the third and fourth research objectives)

Factors Associated with Childhood Bronchial Asthma and Risk Modelling Attributable to Household Air Pollution in Kota Bharu Kelantan

Muhammad Naim Ibrahim[1], Nik Rosmawati Nik Husain[1], Mohamad Ikram Ilias[2], Kueh Y. Cheng[3], Norzaihan Hassan[4], Nurul Ainun Hamzah[5], Maizun Mohd Zain[6], Mariana Daud[7], Siti Romaino Mohd Nor[8], Norazlin Idris[1], Khairul Azuan Che Azid[9]

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LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF APPENDICES

LIST OF SYMBOLS

%	Percentage
=	Equal to
>	More than
<	Less than
≥	More than and equal to
≤	Less than and equal to
±	Plus or minus
:	Ratio
N	Population size
n	Sample size
m	Ratio between two groups
α	Alpha
β	Beta
κ	Cohen's kappa value
p	*p*-value
P_0	Proportion of observed agreement

Pe	Proportion of chance agreement
&	And
^{o}C	Degree Celsius
M	Meter
mg	Milligram
µg	Microgram
kg	kilogram
$	Dollar

LIST OF ABBREVIATIONS

AdjOR	Adjusted odds ratio
AdjRR	Adjusted relative risk
BA	Bronchial asthma
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CO	Carbon monoxide
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CVI	Content validity index
DNA	Deoxyribonucleic acid
DOE	Department of Environment Malaysia
DOSH	Department of Occupational Safety and Health
DOSM	Department of Statistics Malaysia
EHRC	Environmental Health Research Centre
EIA	Environmental Impact Assessment
EPA	Environmental Protection Agency

FMS	Family medicine physician
FVI	Face validity index
HAPBAC-Checklist	Household-Related Air Pollution on Childhood BA Onset Checklist
HEPA	High-efficiency particulate air (filter)
H_2S	Hydrogen sulphide
HC	Health clinic
HR	Hazard ratio
HRPZII	Hospital Raja Perempuan Zainab II
HPUSM	Hospital Pakar Universiti Sains Malaysia
I-CVI	Item-level content validity index
I-FVI	Item-level face validity index
ISAAC	International Study of Asthma and Allergies in Children
KSHD	Kelantan State Health Department
MeSH	Medical Subject Headings
MREC	Medical Research & Ethics Committee
MOH	Ministry of Health
NGO	Non-governmental organisation

NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
O_3	Ozone
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbons
PEFR	Peak expiratory flow rates
KBDHO	Kota Bharu District Health Office
PM	Particulate matter
$PM_{2.5}$	Fine particulate matter with diameter 2.5 micrometres or less
PM_{10}	Particulate matter with diameter 10 micrometres or less
ppm	Parts per million
RCT	Randomised controlled trial
RM	Ringgit Malaysia
ROC	Receiver operating characteristic
RR	Relative risk
RSV	Respiratory syncytial virus
S-CVI	Scale-level content validity index

S-CVI/Ave	Scale-level content validity index based on the averaged method
SD	Standard deviation
SDA	Sabouraud Dextrose Agar
SDG	Sustainable Development Goal
S-FVI	Scale-level face validity index
S-FVI/Ave	Scale-level face validity index based on the averaged method
SME	Small-medium enterprise
SPSS	Statistical Package for the Social Sciences
SO_x	Sulphur oxides
VIF	Variance inflation factor
VOCs	Volatile organic compounds
VIF	Variance inflation factor
Vs	Versus
UK	United Kingdom
UNICEF	United Nations Children's Fund
USA	United States of America
USM	Universiti Sains Malaysia

WHO	World Health Organization

ABSTRAK

Pencemaran Udara Kediaman dan Risiko Kejadian Baharu Asma Bronkial Kanak-Kanak di Kota Bharu, Kelantan: Penentu dan Pemodelan

Latar belakang: Pembangunan yang pesat dan perindustrian telah menyebabkan peningkatan pencemaran alam sekitar, meningkatkan kerentanan kanak-kanak terhadap asma bronkial (BA). Faktor persekitaran, termasuk peningkatan penggunaan produk isi rumah dan pencemaran luar yang kurang dikawal, memainkan peranan utama dalam trend ini. Walaupun risikonya semakin meningkat, kajian yang berfokus secara lokal mengenai faktor penyumbang berkaitan isi rumah terhadap BA kanak-kanak masih terhad. Oleh itu, kajian ini bertujuan untuk menjelaskan hubungan antara pencemaran udara isi rumah dan risiko kejadian BA kanak-kanak di Kota Bharu, Kelantan. Ia merangkumi pembangunan, pengesahan, dan analisis kebolehpercayaan HAPBAC-Checklist, serta mengenal pasti penentu kejadian BA kanak-kanak dan pemodelannya.

Metodologi: Kajian ini dilaksanakan melalui dua fasa, dari Mac 2023 hingga April 2024. Fasa pertama melibatkan pembangunan dan pengesahan HAPBAC-Checklist, yang terdiri daripada empat peringkat: 1) pembangunan senarai semak 2) pengesahan kandungan 3) pengesahan muka dan 4) analisa kebolehpercayaan (analisa persetujuan Kappa). Fasa kedua menggunakan kajian kes-kawalan yang melibatkan 194 kanak-kanak; 97 kes BA yang baru didiagnosis dan 97 kawalan, di Kota Bharu, Kelantan. Data dikumpulkan menggunakan HAPBAC-Checklist dan pengukuran kualiti udara. Analisis deskriptif dan regresi logistik dijalankan bagi mengenal pasti

faktor yang berkaitan dengan BA kanak-kanak serta membangunkan model ramalan yang tepat untuk meramalkan risiko kejadian baharu BA kanak-kanak.

Keputusan: Senarai Semak HAPBAC yang telah disahkan akhir terdiri daripada lima domain (sosiodemografi, sejarah keluarga atopi, sejarah perubatan kanak-kanak, atribut kediaman, dan atribut luar) dengan 59 item. Skor I-CVI (0.83 hingga 1.00) menunjukkan kaitan yang baik dan nilai S-CVI (0.90) adalah memuaskan. I-FVI (≥0.83) dan S-FVI (0.96) menunjukkan bahawa senarai semak mudah difahami. Analisis kebolehpercayaan kappa bagi lima domain yang digabungkan adalah 0.88 (95% CI: 0.81, 0.95; p<0.001). Kajian kes-kawalan mendapati bahawa isi rumah dalam kumpulan kes mempunyai peratusan yang lebih tinggi bagi merokok dalam rumah, haiwan peliharaan di dalam rumah, perabot kayu baharu, serta pelbagai atribut lain. Bagi persekitaran luar, kumpulan kes lebih cenderung meletakkan kenderaan berhampiran rumah, menggunakan dapur kayu dan lebih dekat dengan sumber pencemaran seperti jalan utama dan kawasan pembakaran sampah. Pengukuran kualiti udara menunjukkan tahap pencemaran yang lebih tinggi dalam isi rumah kumpulan kes. Regresi logistik berganda mendedahkan determinan yang signifikan iaitu usia kanak-kanak yang lebih muda (AdjOR: 0.67, 95% CI: 0.50, 0.89; p=0.007), ibu dengan sejarah atopi (AdjOR: 5.18, 95% CI: 1.54, 17.38; p=0.009), dan adik-beradik dengan sejarah atopi (AdjOR: 4.88, 95% CI: 1.51, 15.78; p=0.008); Atribut kediaman: merokok dalam rumah (AdjOR: 5.64, 95% CI: 1.95, 16.29; p=0.001), haiwan peliharaan (AdjOR: 3.65, 95% CI: 1.21, 11.04; p=0.022), cat rumah dalam satu tahun (AdjOR: 9.25, 95% CI: 1.56, 54.91; p=0.014), dapur yang kurang ventilasi (AdjOR: 12.28, 95% CI: 2.80, 53.87; p=0.001), menggoreng makanan kerap (AdjOR: 14.15, 95% CI: 3.01, 66.48; p=0.001), penggunaan dapur kayu (AdjOR: 17.84, 95% CI: 1.29, 247.20; p=0.032) dan penggunaan wangian (AdjOR: 7.54, 95%

CI: 2.23, 25.51; p=0.001); Atribut luar: berhampiran jalan utama (AdjOR: 0.99, 95% CI: 0.98, 0.99; p=0.001), dan haiwan peliharaan atau ternakan berhampiran (AdjOR: 5.62, 95% CI: 1.82, 17.38; p=0.003); dan, Pengukuran kualiti udara: tahap PM_{10} dalam rumah yang tinggi (AdjOR: 1.03, 95% CI: 1.02, 1.05; p<0.001) dan spora *Aspergillus* (AdjOR: 1.08, 95% CI: 1.01, 1.16; p=0.048). Model ramalan yang dibangunkan daripada 14 penentu ini menunjukkan kesesuaian yang sangat baik (kurva ROC = 0.947; 95% CI: 0.92, 0.97), dengan keupayaan yang berkesan dalam meramalkan kejadian BA kanak-kanak.

Rumusan: HAPBAC-Checklist ialah alat baharu yang direka khusus untuk mengenalpasti faktor isi rumah dan persekitaran luar yang dikenal pasti secara lokal yang mempengaruhi BA. Penentu yang meluas ini menekankan keperluan mendesak untuk mencegah BA kanak-kanak. Kajian ini mengesyorkan dasar yang mempromosikan persekitaran hidup yang lebih sihat, insentif untuk amalan yang lebih selamat, pengawalseliaan yang lebih ketat terhadap produk isi rumah, serta advokasi kesihatan mengenai faktor risiko utama.

Kata kunci: Kanak-kanak, asma, penentu, Kota Bharu, isi rumah, kediaman, pencemaran udara

ABSTRACT

Household Air Pollution and Childhood Bronchial Asthma New Onset Risk in Kota Bharu Kelantan: The Determinants and Modelling

Background: Rapid urbanisation and industrialisation have led to increasing environmental pollution, heightening children's vulnerability to bronchial asthma (BA). Environmental factors, including rising household product consumption and poorly regulated outdoor pollution, play a key role in this trend. Despite the growing risk, locally focused studies on household-related contributors to childhood BA remain limited. Therefore, this study aims to elucidate the relationship between household air pollution and the risk of childhood BA onset in Kota Bharu, Kelantan. It includes the development, validation, and reliability analysis of the HAPBAC-Checklist, as well as identifying the determinants of childhood BA onset and modelling them.

Methodology: The study was conducted through two phases, from March 2023 to April 2024. The first phase involved the development and validation of the HAPBAC-Checklist, which included four stages: 1) the development of the checklist 2) content validation 3) face validation and 4) reliability analysis (kappa agreement analysis). Then, the second phase employed a case-control study involving 194 children; 97 newly diagnosed BA cases and 97 controls, in Kota Bharu, Kelantan. Data were collected using the HAPBAC-Checklist and air quality measurements. Descriptive analysis and logistic regression identified factors linked to childhood BA new onset, which were then used to develop accurate predictive models.

Results: The final validated HAPBAC-Checklist consists of five domains (sociodemographic, family history of atopy, child’s medical history, household

attributes, and outdoor attributes) with 59 items. The I-CVI scores indicated good relevancy (value ranged from 0.83 to 1.00), and the S-CVI value was satisfactory (value of 0.94). The I-FVI (at least 0.83) and the S-FVI (value of 0.96) indicating the checklist was easily understood. The kappa analysis for reliability testing for five domains combined was 0.88 (95% CI: 0.81, 0.95; p<0.001). A case-control study found that case group had a higher proportion of indoor smoking, indoor pets, new wooden furniture, and other household attributes. As for outdoor, the case group had a higher proportion vehicle near their homes, use outdoor wood stoves, and live closer to pollution sources such as major roads and garbage burning. Air quality measurements indicated higher pollutant levels among households in the case group. Multiple logistic regression revealed the significant determinants were younger age (AdjOR: 0.67, 95% CI: 0.50, 0.89; p=0.007), mother with history of atopy (AdjOR: 5.18, 95% CI: 1.54, 17.38; p=0.009), and sibling with history of atopy (AdjOR: 4.88, 95% CI: 1.51, 15.78; p=0.008); Household attributes: indoor smoking (AdjOR: 5.64, 95% CI: 1.95, 16.29; p=0.001), indoor pets (AdjOR: 3.65, 95% CI: 1.21, 11.04; p=0.022), recent home painting (AdjOR: 9.25, 95% CI: 1.56, 54.91; p=0.014), poorly ventilated kitchens (AdjOR: 12.28, 95% CI: 2.80, 53.87; p=0.001), frequent frying (AdjOR: 14.15, 95% CI: 3.01, 66.48; p=0.001), wood stove use indoor (AdjOR: 17.84, 95% CI: 1.29, 247.20; p=0.032) and fragrance indoor (AdjOR: 7.54, 95% CI: 2.23, 25.51; p=0.001); Outdoor attributes: proximity to main roads (AdjOR: 0.99, 95% CI: 0.98, 0.99; p=0.001) and nearby livestock or outdoor pets (AdjOR: 5.62, 95% CI: 1.82, 17.38; p=0.003); and air quality measurement: elevated levels of indoor PM_{10} (AdjOR: 1.03, 95% CI: 1.02, 1.05; p<0.001) and *Aspergillus* spores (AdjOR: 1.08, 95% CI: 1.01, 1.16; p=0.048). The predictive model developed from these 14 determinants

showed an excellent fit (ROC curve = 0.947; 95% CI: 0.92, 0.97), effectively predicting childhood BA onset.

Conclusion: The HAPBAC-Checklist is a novel tool specifically tailored to address locally identified household and outdoor factors influencing BA. The widespread determinants underscore the urgent need to prevent childhood BA. This study recommends policies promoting healthier living environments, incentives for safer practices, stricter regulation of household products, and health advocacy on key risk factors.

Keywords: Children, asthma, determinants, Kota Bharu, household, indoor, air pollution

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CHAPTER 1

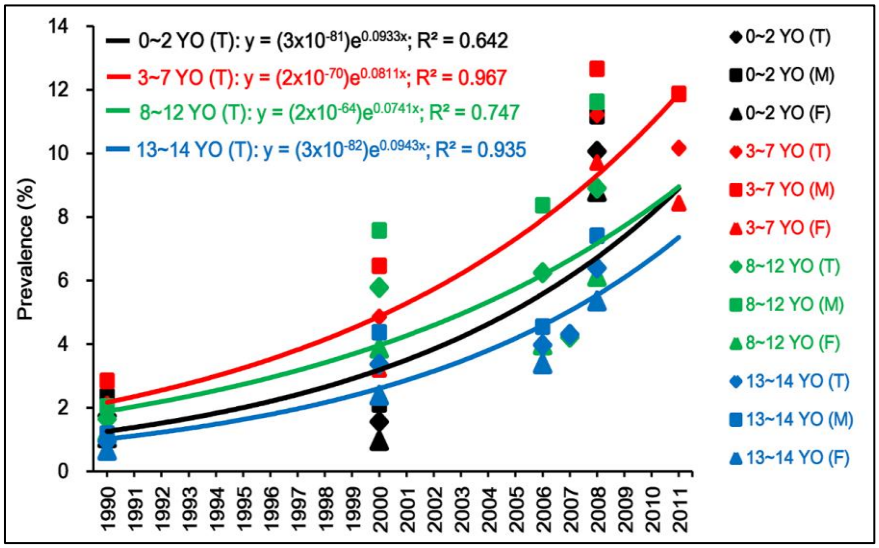
INTRODUCTION

1.1 Background

Asthma is one of the most prevalent chronic diseases globally, affecting both children and adults. Characterised by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, asthma poses a significant public health challenge (GINA, 2019). Recognising its global impact, bronchial asthma (BA) among children has been prioritised within the World Health Organization (WHO) Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) and integrated into the United Nations 2030 Agenda for Sustainable Development (WHO, 2022a). These initiatives highlight the importance of addressing asthma as part of broader efforts to combat chronic diseases and promote global health equity.

The global incidence of asthma has shown a notable increase, rising by 13.0% to 37 million cases in 2019 compared to 2010 (Lancet, 2020). Currently, asthma affects more than 300 million individuals worldwide, with a disproportionately higher prevalence observed in children compared to adults (Stern *et al.*, 2020). For instance, the global prevalence of childhood BA is 9.4%, compared to 7.7% in adults. In the United States of America (USA), 8.4% of children are affected, compared to 7.7% of adults, while in Australia, the prevalence is even higher, with 16.0% of children affected versus 8.0% of adults (Dharmage *et al.*, 2019). In Malaysia, the prevalence of BA has risen sharply, increasing by 50.0%, from 4.7% in 1996 to 7.1% in 2011 (IKU, 2011). Notably, the prevalence of childhood BA continues to rise across all age groups, as shown in **Figure 1.1**. It demonstrates that from newborns to early adolescents in

Shanghai, China, the prevalence has increased in an almost exponential trend from 1990 to 2011.



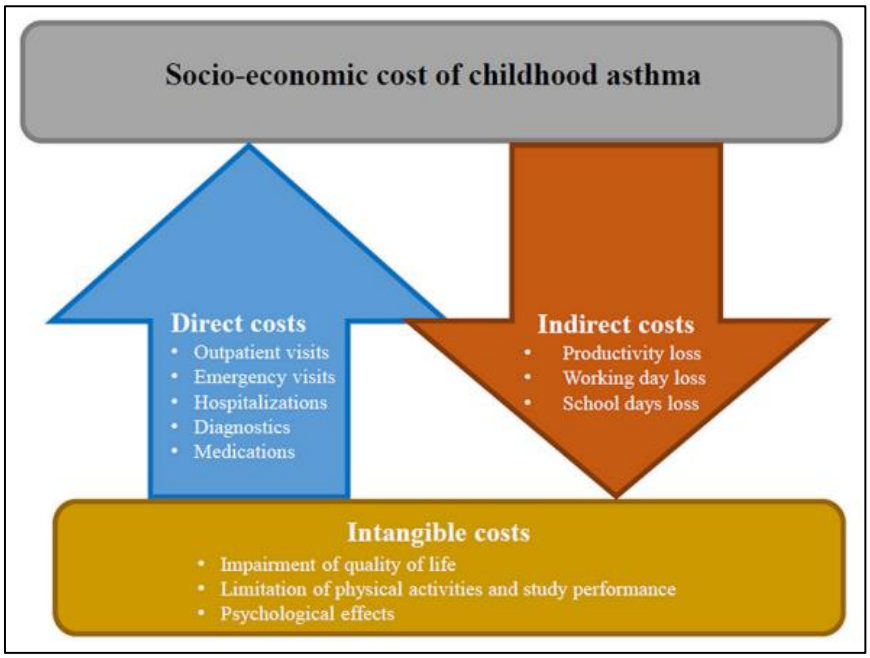
(Source: Huang et al., 2015)

Figure 1.1: The prevalence of childhood BA according to age group in Shanghai, China from the year 1990 to 2011

Childhood BA is the leading cause of hospitalisations among children, with rates at least twice as high as those seen in adults (Ioana and Cezmi, 2014). The disease significantly impacts children's daily lives, resulting in frequent school absences and disruptions to parental work schedules. Beyond the physical symptoms, asthma impairs quality of life, limits physical activities, and adversely affects academic performance. It is also associated with psychological challenges, such as anxiety and depression. Moreover, children with asthma are at a 60.0% increased risk of developing chronic obstructive pulmonary disease (COPD) in adulthood (Ferrante and La Grutta, 2018).

The burden of childhood BA extends beyond health, imposing substantial socioeconomic consequences. These effects are evident in both direct costs, such as medical expenses, and indirect costs to the child and parents, as well as intangible

costs, including psychological effects. This is illustrated in **Figure 1.2**. Over the next 20 years, the global economic burden of asthma is projected to exceed US$900 billion. Given these substantial costs, childhood BA is regarded as the second most critical respiratory disease after COPD, underscoring the need for targeted interventions and effective management strategies of childhood BA (Agache and Akdis, 2021).



(Source: Ferrante and La Grutta, 2018)

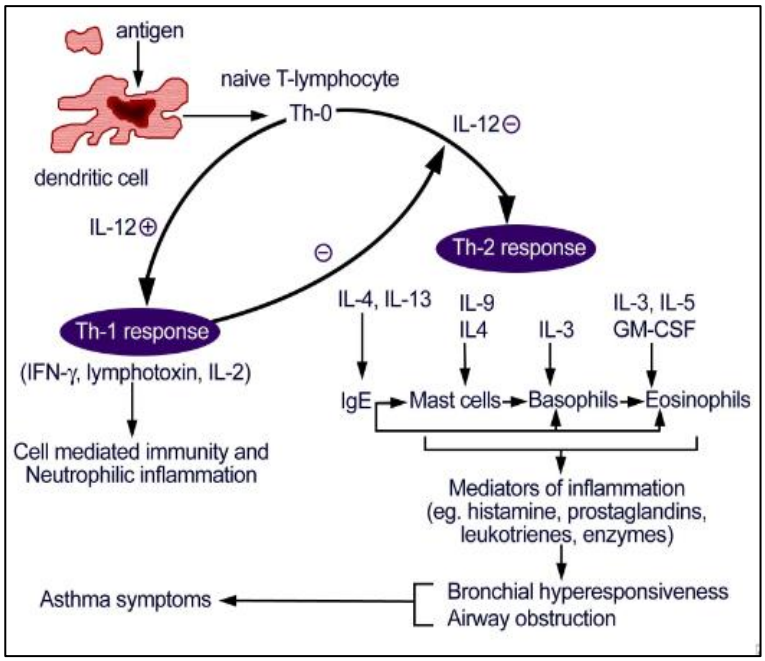
Figure 1.2: Socioeconomic cost of childhood BA: direct, indirect and intangible cost

1.2 Pathophysiology and onset of childhood BA

Asthma is a heterogeneous disease that manifests differently among individuals, particularly in children. It can be classified into various phenotypes based on clinical characteristics, triggers, inflammatory patterns, and response to treatment. Clinical phenotypes of asthma are defined by observable traits rather than genetic makeup. Studies indicate that approximately 60.0 to 80.0% of children with asthma have allergic asthma, which is characterised by hypersensitivity to environmental allergens such as pollen, dust mites, and pet dander (Agache and Akdis, 2021). This

subtype is often associated with other allergic conditions, including eczema and allergic rhinitis. Exercise-induced bronchoconstriction (EIB), previously known as exercise-induced asthma, is another common manifestation among children with asthma. The prevalence varying based on physical activity levels and asthma severity. EIB is characterised by narrowing of the airways during or after exercise, leading to symptoms such as coughing, wheezing, and shortness of breath. Notably, it can also occur in those without a prior asthma diagnosis (Malewska-Kaczmarek *et al*., 2023). In contrast, late-onset asthma, occupational asthma, and other subtypes are more common in adults and are typically associated with workplace exposure, environmental irritants, or specific occupational hazards. These forms of asthma are uncommon in children (Foppiano and Schaub, 2023).

The onset of childhood BA, particularly allergic phenotype is often triggered by specific environmental antigens, leading to complex cytokine and lymphocyte responses that provoke inflammatory reactions, as shown in **Figure 1.3**. The reaction characterised by an inflammatory disorder of the airways leads to widespread airflow limitation with resulting signs and symptoms such as dyspnoea, chest discomfort, wheezing, panic and anxiety and occasionally respiratory arrest (GINA, 2019). No single gold-standard test can be used to diagnose childhood BA accurately. Instead, the diagnosis is based on the symptoms, characteristics, and patterns with evidence of variability in airflow limitation in the presence of airway inflammation and positive response to the treatment (Martin *et al.*, 2022).



(Source: Michael, 2022)

Figure 1.3: Pathogenesis of bronchial asthma

1.3 Environmental exposure to childhood BA onset

The rising prevalence of childhood BA is attributed to a complex interplay of factors, particularly the interaction between genetic predisposition and environmental exposures. Asthma is a heterogeneous disease influenced by varying degrees of genetic and environmental contributions, with individual susceptibility playing a significant role. Genetic heritability estimates for childhood BA range from 35.0 to 75.0%, with higher values observed among boys and in cases of early-onset asthma (Polderman *et al.*, 2015). Recent twin studies provide further insight, revealing that genetic factors account for approximately 24.0 to 34.0% of the variability in childhood BA onset. In contrast, environmental factors appear to play a more substantial role, contributing between 66.0 to 76.0% (Thomsen, 2014; Thomsen *et al.*, 2010).

Gene heritability estimates for childhood BA have remained relatively stable in developed countries. However, the incidence of childhood BA has increased

several-fold over the past century. This trend underscores the substantial influence of environmental factors on disease onset. Rapid urbanization has introduced a range of environmental changes, including increased exposure to air pollutants, allergens, climate fluctuations, and biodiversity loss, all of which contribute to the rising prevalence of asthma. Moreover, the heightened levels of greenhouse gases lead to changes in temperature and atmospheric chemistry, further intensifying air pollution (Cecchi *et al.*, 2018). Environmental exposures during early life shape immune health and play a key role in asthma onset. These exposures can influence gene expression, with air pollution, for example, causing DNA demethylation, which promotes asthma development in children. Such epigenetic changes may also be transmitted from mother to child, highlighting the need to address modifiable environmental factors to reduce asthma risk (Somineni *et al.*, 2016; Yang *et al.*, 2017).

1.4 Household air pollution exposure to childhood BA onset

Household air quality plays a vital role in children's well-being and performance. The immediate attention of previous research is focused on the air quality in institutions like preschools and school environments, but it only represents 27.0% of their daily schedule (Lizana *et al.*, 2020). According to Habre *et al.* (2014), young children in urban areas spend 80.0 to 90.0% of their time at home, supposing a higher percentage of exposure to a broad portfolio of household air pollutants. The gaining popularity of indoor games and video games and parents' concern about outdoor hazards lead to these children's lifestyle changes (Zach, 2022).

Most common household air pollutants are associated with occupancy activities such as cooking, cleaning, smoking, pets and indoor combustion. Studies in different countries, including Malaysia, have found that household air pollution levels

were up to five times higher than outdoor air, mainly due to poor ventilation and various household attributes (Ibiyeye *et al.*, 2015; Nishihama *et al.*, 2021; Sun *et al.*, 2019). The outdoor sources also can affect household air quality and cannot be neglected when studying household air pollution (Leung, 2015). Residents within proximity of heavy traffic, industrial, farming activities and many others are at risk of poor household air quality (Shrestha *et al.*, 2019). The pollutant enters a house through open windows and doors or is transported by the occupant.

Household air pollution has grown more attention as evidence of everyday household products attributed to childhood BA onset (Lizana *et al.*, 2020). Many houses were found to have poor housekeeping practices and designs, leading to more accumulated allergens and pollutants. Meanwhile, institutions like preschools or schools are actively monitored and well-regulated for indoor air pollution. Institutions also represent about 12.0% of the daily inhaled dose of pollutants compared to higher contribution found at house indoors, 88.0%, which puts a higher risk of childhood BA onset (Lizana *et al.*, 2020). High humidity and tropical climate in Malaysia also encourage mould growth at home and become a risk for childhood BA onset (Wahab *et al.*, 2013).

1.5 Problem statement

The prevalence of childhood BA in Malaysia and worldwide is increasing trend. Urbanisation and industrialisation caused a remarkable rise in household air pollution. Besides that, the tropical climate with high humidity substantially encourages mould growth at home. Many pollutants and allergens for childhood BA are household sourced, such as consumer products, smoking, cooking activities, indoor

pets, disinfectants, pesticide use, carpets and many more (Ho and Wu, 2021; Norbäck *et al.*, 2019).

However, the knowledge of household air pollution for childhood BA onset risk in Malaysia is limited. Most studies on indoor air pollution for childhood BA onset in Malaysia were conducted at institutions like preschools and schools. Additionally, research in Malaysia has primarily focused on the west coast of Peninsular Malaysia, with a lack of studies on household environments and respiratory illnesses, particularly childhood BA, in urban areas of the east coast, such as Kota Bharu, Kelantan. Moreover, most environmental checklists or questionnaires have been used to assess the triggering factors in children already diagnosed with asthma; however, none of the established household checklists are designed to assess the risk of new-onset BA in children. Furthermore, previous studies were based on parent or guardian interviews without direct observation or household assessments for indoor air pollution indicators, and limited research quantified air quality parameters in households in Malaysia.

Therefore, limited evidence on the local household attributes to childhood BA makes the prevention efforts ineffective. Healthcare providers and stakeholders have difficulty in proposing evidence-based measurements for childhood BA. Symptomatic children would solely depend on pharmacology treatment without household exposure removal. Hence, the children continue having prolonged episodes of wheezing and later develop into childhood BA.

1.6 Study rationale

This study provides a better understanding of the relationship between household air pollution and childhood BA onset within the local context, particularly in Kota Bharu, Kelantan. As a key commercial and industrial hub on the east coast of Peninsular Malaysia, the town is experiencing rapid urbanisation, high population density, and heavy traffic movement, all of which contribute to environmental pollution (Abdullah *et al*., 2023). By conducting the study, a household assessment checklist for childhood BA onset risk in the local context would be developed and validated. Hence, the checklist would be the first in the country for childhood BA onset risk and substantially benefit following researchers interested in household air pollution and childhood BA.

Despite that, health providers and parents can use the knowledge generated for better allergen and factors identification at the household level. It would allow effective intervention in exposure avoidance and removal. By implementing these findings, childhood BA can be prevented, leading to a reduction in new cases and, consequently, lowering the cost of BA treatment in healthcare facilities. The knowledge also benefits existing childhood BA and other related respiratory illnesses to control their disease by creating a healthy household environment. In addition, the new evidence would enable stakeholders and industries to promote and innovate a better environment for children in Malaysia. It would assist health policy in developing health promotion programs and house regulations. The study would also help private sectors and non-governmental organisations (NGOs) create public awareness of household air quality and childhood BA prevention.

Finally, household air pollution has been listed as a priority research area in the Health Research Priorities for the 12th Malaysia Plan. The study also aligned with the Sustainable Development Goal (SDG) concerning household air pollution, under SDG 3.9.1 for reducing illness from air pollution and SDG 11.6.2 for sustainable living by improving air quality.

1.7 Research questions

1) Is the newly developed checklist for household attributes to childhood BA new onset risk a valid assessment tool?
2) What are the individual characteristics (sociodemographic, family history, medical history) and household attributes related to childhood BA new onset in Kota Bharu?
3) What are the exposures of household air pollutants to childhood BA new onset in Kota Bharu, Kelantan?
4) What are the determinants of childhood BA new onset in Kota Bharu, Kelantan?

1.8 Objectives

1.8.1 General objective

To elucidate the relationship between household air pollution with childhood BA new onset risk in Kota Bharu, Kelantan

1.8.2 Specific objective:

A. Phase 1:

1) To develop and validate the Household-Related Air Pollution on Childhood BA new Onset Checklist (HAPBAC-Checklist).

B. Phase 2:

1) To describe the individual characteristics (sociodemographic, family history, and medical history), household attributes and outdoor attributes of air pollution in relation to childhood BA new onset in Kota Bharu, Kelantan.

2) To determine the exposures of household air pollutants related to childhood BA new onset in Kota Bharu, Kelantan.

3) To determine factors associated with childhood BA new onset in Kota Bharu, Kelantan.

4) To model the childhood BA new onset risk in Kota Bharu, Kelantan, attributable to household air pollution.

1.9 Hypothesis

1) The newly developed checklist (HAPBAC-Checklist) is a valid assessment tool to assess household-related air pollution on childhood BA new onset.

2) There are significant determinants of individual characteristics (sociodemographic, family history, and medical history), household attributes, outdoor attributes, and air quality parameters on childhood BA new onset in Kota Bharu, Kelantan.

CHAPTER 2

LITERATURE REVIEW

A thorough review of the literature was conducted to examine the environmental factors, particularly household air pollution, and their impact on the development of childhood BA. The search was expanded to focus specifically on local household attributes, which are crucial for understanding how specific environmental exposures within the local context influence asthma risk in children. Literature was searched using the journal search engine, mainly PubMed, Scopus, Science Direct, Web ISI, Springer Link and Google Scholar. Recent literature was selected with keywords such as children, asthma, household, home, indoor, and air pollution with their respective MeSH terms. Several searching strategies were applied by using Boolean operators like “AND”, “OR”, and “NOT”.

2.1 Occurrence of childhood BA

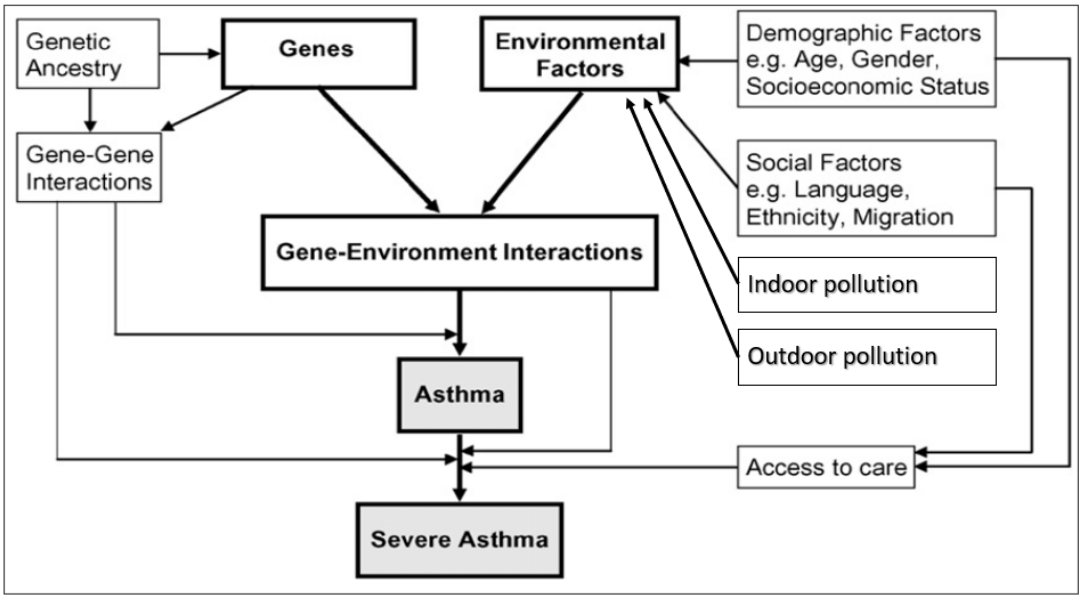
The global incidence of BA has demonstrated an upward trend, with a 13.0% increase observed, rising from 33 million newly diagnosed cases in 2010 to 37 million cases in 2019 (Asher *et al.*, 2021). However, regional variations in incidence trends have been noted; while low- to middle-income countries have experienced a significant surge in new cases, the incidence in some developed countries appears stabilizing (Stern *et al.*, 2020). A substantial proportion of asthma-related morbidity and mortality occurs in low- to middle-income countries, largely attributable to inadequate disease recognition and limited access to healthcare services (To *et al*., 2012).

The occurance of childhood BA is significantly higher in high-income countries compared to developing and low-income nations. For instance, prevalence rates in high-income countries include 15.9% in the USA, 13.1% in the United Arab Emirates, 12.1% in Japan, 11.1% in Australia, 10.1% in the United Kingdom (UK), 10.0% in Spain, and 9.1% in Singapore. In contrast, lower rates are observed in countries such as Malaysia (7.1%), Indonesia (6.7%), Mexico (6.2%), Vietnam (6.0%), and Cambodia (5.0%) (CDC, 2018; Wong *et al.,* 2013). In Malaysia, the incidence of childhood BA has increased significantly, with cases rising by more than 60% over 15 years, from 4.4% in 1995 to 7.1% in 2011 (IKU, 2011). A study involving 2,878 preschool children in Kota Bharu reported a childhood BA prevalence of 9.4% (95% CI: 8.3, 10.4) (Quah *et al.*, 2000). This rising trend in childhood BA prevalence has been accompanied by a parallel increase in other allergic conditions, including allergic rhinitis and eczema (Wong *et al.*, 2013).

Numerous projects and studies have been undertaken globally to investigate the incidence of childhood BA. Prominent examples include the International Study of Asthma and Allergies in Children (ISAAC), the European Community Respiratory Health Survey (ECRHS), the Global Asthma Network (GAN), and various regional studies (Agache and Akdis, 2021). However, challenges in accurately documenting the occurrence of childhood BA persist, primarily due to variations in research methodologies across countries. These discrepancies hinder direct comparisons and complicate the interpretation of temporal trends in the disease's occurrence (Dharmage *et al*., 2019).

2.2 The gene-environmental axis for the development of childhood BA

Childhood BA can manifest at any age; however, its onset typically occurs by age five, a period characterized by critical windows for immune development and allergen sensitization (Lloyd and Saglani, 2019). The aetiology of BA is increasingly understood as the result of complex interactions between genetic predisposition and environmental exposures (Dharmage *et al.*, 2019). These interactions, along with their independent contributions to disease severity, are influenced by multiple determinants, as illustrated in the causal model presented in **Figure 2.1**.



(*Source: Choudhry et al., 2007*)

Figure 2.1: Causal model explaining the gene-environmental axis for the development of childhood BA onset

A notable study by Thomsen *et al*. (2010) examined environmental risks in the development of new asthma. This cohort study, involving a large sample of 21,135 twins across different age groups in Europe, revealed that genetic factors account for 50.0 to 70.0% of the risk of developing childhood BA. The study demonstrated that

the risk of asthma in the co-twin of an affected individual was significantly higher in monozygotic twins compared to dizygotic twins (HR: 2.59; 95% CI: 1.83, 3.68; p<0.001). Additionally, a parental history of BA contributed at least 25.0% to the *et al.* risk of developing the condition, with maternal asthma conferring a higher risk than paternal asthma (OR: 3.04 vs OR: 2.44, p=0.037) (Lim *et al.,* 2010). However, despite the substantial influence of genetic factors, a cohort study involving over 30,000 European children over eight years found that genetic variance explained only 34.0% of childhood BA onset, while environmental factors accounted for 66.0% of the variance (Thomsen, 2014).

Exposure to chemical pollutants early in life has been linked to the early onset of childhood BA. A 14-year longitudinal study conducted among farmers' children in Canada revealed that children raised in rural areas with traditional farming practices had a significantly lower incidence of childhood BA compared to those exposed to modern farming methods (HR: 0.56; 95% CI: 0.41, 0.77; p<0.001) (Parsons *et al*., 2017). Modern farming practices release volatile organic compounds (VOCs) and aerosols from pesticides, herbicides, and fertilizers, increasing children's risk of respiratory irritation and BA. Similarly, a systematic review of studies from Asia-Pacific countries found a 50.0% increase in childhood BA prevalence over a decade, with air pollution as a primary contributing factor (Wong *et al.*, 2013). Modernised households, with airtight designs for energy efficiency, trap indoor pollutants like dust mites, mould, pet dander, and VOCs from synthetic materials, contributing to the rise in childhood BA cases.

Additionally, the use of poorly maintained air conditioning can reduce ventilation by limiting the exchange of indoor and outdoor air, leading to the

accumulation of indoor pollutants and allergens. This can increase exposure to indoor allergens such as dust mites, mould spores, and pet dander, which initiate the development of childhood BA. Young children, who spend 80–90.0% of their time indoors, are particularly vulnerable to these factors, which exacerbate their risk of developing respiratory conditions, including asthma (Habre, 2014).

2.3 Determinants of childhood BA onset

2.3.1 Sociodemographic characteristic

Several sociodemographic determinants have been identified as significant contributors to the onset of childhood BA. Age has been highlighted as a particularly critical factor. A study by Luo *et al.* (2022) found that children under 12 in Sichuan, China, exhibited the highest rates of BA diagnoses, with younger children showing a higher incidence. This finding is consistent with research conducted in Finland, which reported that the incidence of allergic asthma was highest among children, with a rate of 1.8 per 1,000 individuals, compared to 0.6 per 1,000 among individuals aged 50 years and older (Pakkasela *et al*., 2020). These studies underscore the age-dependent nature of asthma incidence, with childhood being a particularly vulnerable period.

Gender has also been identified as a significant determinant in the onset of childhood BA. A study conducted in South Korea involving 215 children found that boys exhibited higher rates of allergen sensitization and elevated immunoglobulin E (IgE) serum levels compared to girls (AdjOR: 5.57; 95% CI: 4.33, 7.07; p=0.005) (Kim *et al.*, 2021). Similarly, a molecular genetics study in Wisconsin, USA, reported a significantly higher genotype-sex interaction for childhood BA among boys compared to girls (p<0.001) (Loisel *et al*., 2011). Additionally, Yung *et al*. (2018) suggested that

boys' relatively smaller airway diameters in proportion to lung volumes further increase their susceptibility to childhood BA. These findings highlight the influence of gender-specific biological and genetic factors in the development of the condition.

A study by Norbäck *et al*. (2021) involving 462 school children in Johor Bharu, Malaysia, identified race as a significant factor in the prevalence of childhood BA. The prevalence was highest among Malay children (15.5%) and lowest among Chinese children (4.3%) (p<0.001). Similarly, a study in the USA comparing two agrarian communities, the Amish and the Hutterites found a significantly higher prevalence of childhood BA among the Hutterites, despite both groups sharing similar agricultural lifestyles and practices (AdjOR: 6.81; 95% CI: 4.40, 8.21; p=0.005) (Stein *et al.*, 2016).

Parental occupation also played a role in the onset of childhood BA. A cohort study in the UK found that occupational exposure to latex, dust, and pesticides among parents increased the risk of childhood BA (AdjOR: 1.22; 95% CI: 1.05, 2.05; p=0.022). An association exists between parental education levels and the development of childhood BA, with lower parental education being linked to higher rates of BA onset. This association may be influenced by factors such as lower health literacy and greater exposure to environmental triggers. Community interventions in Puerto Rico, which focused on parental educational programs about allergens, were effective in reducing allergy-related and respiratory symptoms in children, including those associated with BA (Gill *et al.*, 2022).

Socioeconomic status, particularly household income, was also identified as a significant determinant. A study in Sweden utilising national health records showed that children from the lowest income group had the highest risk of childhood BA onset,

particularly within their first three years of life (HR: 2.07; 95% CI: 1.22, 3.98; p=0.032) (Gong *et al.,* 2014).

A meta-analysis of childhood BA in China revealed that its prevalence was higher in urban areas compared to rural regions. For instance, the prevalence in Beijing was reported at 6.3%, significantly higher than 1.1% in a nearby rural area, while in Guangzhou, it was 6.9% compared to 3.4% in a suburban area (Chen *et al*., 2016). Similarly, a cross-sectional study conducted in Selangor, Malaysia, involving 1,952 school children, found that the prevalence of childhood BA and related symptoms was higher in urban areas (12.5%) than in suburban areas (9.1%) (AdjOR: 1.90; 95% CI: 1.05, 3.52; p=0.040) (Zainal *et al.*, 2014).

A study by Northridge *et al.* (2010) investigated the association between housing typology and the prevalence of childhood asthma in New York City. The study found that children living in private housing had a lower prevalence of asthma compared to those residing in public housing. This disparity was attributed to environmental conditions in public housing, which reported a higher prevalence of asthma-related risk factors, including infestations of cockroaches and rats, as well as structural issues such as water leaks. These findings underscore the role of housing quality in influencing respiratory health outcomes among children.

The house structural type has also been identified as a determinant in the onset of childhood BA. For instance, a study conducted in Hyogo, Japan, involving 1,048 school children, reported that living in structured wooden houses was significantly associated with an increased risk of childhood BA (AdjOR: 2.17; 95% CI: 1.10, 3.61; p<0.05) (Takaoka *et al.*, 2016). Additionally, overcrowded living conditions have been linked to the onset of childhood BA. A study in the USA involving 33,201 households

found that living with more than two people per bedroom was associated with an elevated risk of childhood BA (AdjOR: 1.45; 95% CI: 1.11, 2.04; *p*=0.020) (Hughes *et al.,* 2017). However, a study in Seoul, South Korea, involving 6,919 school children, found no significant association between the number of household occupants and the risk of childhood BA (Choi *et al*., 2012).

2.3.2 Family history of atopy

The Copenhagen Prospective Study on Asthma in Childhood 2010 demonstrated that children have an elevated risk of developing childhood BA when their parents have atopic conditions. Furthermore, the study highlighted that maternal asthma posed a greater risk to the child compared to paternal asthma, underscoring the potential influence of both genetic predisposition and prenatal environmental factors (Schoos *et al*., 2020). This heightened risk is likely attributed to the impact of the prenatal environment, involving mechanisms such as increased maternal inflammation, immune system alterations, and impaired foetal lung development. Additionally, mothers significantly influence early-life exposures, including interactions with allergens and lifestyle choices, further amplifying the risk of asthma in children compared to the influence of paternal asthma (Lebold *et al.*, 2020). Furthermore, the risk of asthma in children was elevated when siblings had a history of atopic condition, likely due to shared genetic factors (Thomsen *et al*., 2010).

2.3.3 Child's medical condition

The onset of childhood BA has been significantly associated with certain medical conditions. A retrospective cohort study conducted in Philadelphia, USA, involving 7,925 infants, reported that prematurity substantially increased the risk of childhood BA onset (AdjOR: 1.68; 95% CI: 1.11, 2.80; *p*=0.005) (Goyal *et al*., 2011).

Similarly, Zhang *et al*. (2018) found that preterm-born children in the USA were significantly associated with an elevated risk of developing childhood BA (AdjOR: 1.64; 95% CI: 1.45, 1.84; p=0.002). Additionally, a nationwide cohort study in Japan revealed that maternal smoking during pregnancy significantly increased the risk of BA and wheezing-related disorders in children by the age of six. Maternal smoking was recognized as a risk factor because it restricts foetal growth, resulting in smaller, more obstruction-prone airways, and alters the immune system, promoting a pro-inflammatory state (Wada *et al.,* 2021).

A meta-analysis conducted by Lodge *et al.* (2015) found that exclusive breastfeeding was associated with an approximately 10.0% reduction in the risk of childhood BA compared to formula feeding. Similarly, a study by Klopp *et al.* (2017) in Canada reported that infants exclusively fed formula had a significantly higher likelihood of developing asthma compared to breastfed infants, with formula-fed babies being 40.0 to 50% more likely to experience asthma or wheezing episodes than those who were exclusively breastfed.

Ho and Wu's (2021) study involving 24,999 primary school children in Taipei, Taiwan, found that 68.8% of children diagnosed with childhood BA had experienced rhinitis within the past 12 months, with a significant association reported (AdjOR: 2.32; 95% CI: 2.13, 2.54; p<0.001). The study also identified eczema as a significant risk factor for childhood BA (AdjOR: 1.93; 95% CI: 1.82, 2.06; p<0.001). Additionally, a history of bronchiolitis and lung infections was found to be a key determinant of childhood BA. A cohort study utilising the Swedish children registry revealed a strong association between pneumonia before the age of five and the onset of childhood BA (AdjOR: 3.38; 95% CI: 3.26, 3.51; p<0.001) (Rhedin *et al.*, 2021).

This finding aligns with Beigelman and Bacharier's (2013) study, which reported that 39.0% of children with a history of respiratory syncytial virus (RSV) bronchiolitis developed childhood BA, compared to only 9.0% of those without a history of RSV bronchiolitis ($p<0.05$).

A meta-analysis involving children reported that the risk of BA increased by 20.0% among overweight children. The study also highlighted a significantly higher prevalence of childhood BA among obese children (26.2%) compared to underweight children (2.5%) (Chen *et al.,* 2013). Additionally, psychological stress has been identified as a determinant of childhood BA. A systematic review found that children exposed to violence, whether by parents or within their neighbourhood, had a significantly increased risk of developing childhood BA (AdjOR: 1.63; 95% CI: 1.17, 3.22; $p=0.030$) (Exley *et al*., 2015). Furthermore, a study conducted in Denmark involving 147,829 children reported that psychological stressors, such as the loss of a close relative, bullying, or housing instability, were significantly associated with childhood BA (HR: 1.54; 95% CI: 1.23, 1.92; $p=0.005$) (Liu *et al*., 2013).

2.3.4 Household attributes

Several household air pollutants have been identified as significant determinants of childhood BA. Smoking, in particular, has been strongly associated with an increased risk of BA symptoms in children. A cross-sectional study involving 234 school children in Kedah and Melaka, Malaysia, found that parental smoking at home was significantly linked to BA symptoms in children (AdjOR: 3.27; 95% CI: 1.15, 9.34; $p<0.05$). The study also reported that any household member who smoked was independently associated with childhood BA symptoms (AdjOR: 3.63; 95% CI: 1.39, 9.50; $p<0.05$) (Zulkifli *et al.,* 2014). Similarly, the International Study of Asthma

and Allergies in Childhood (ISAAC) reported that parental smoking increased the risk of childhood BA onset (AdjOR: 1.56; 95% CI: 1.18, 2.32; p<0.010). Additionally, a meta-analysis by Xian and Chen (2021) identified a significant association between the use of e-cigarettes by parents, both at home and in cars, and childhood BA onset (AdjOR: 1.30; 95% CI: 1.17, 1.45; p<0.05).

A study by Norbäck *et al.* (2021) conducted in Johor Bahru, Malaysia, identified keeping pets indoors, such as cats and dogs, as a significant risk factor for childhood BA onset (AdjOR: 2.12; 95% CI: 1.95, 2.44; p<0.001). Similarly, a study involving 39,782 young children in major cities across China found a significant association between furry pets and BA symptoms (AdjOR: 1.80; 95% CI: 1.42, 2.28; p<0.001) (Lu *et al.,* 2020). Additionally, indoor carpets were identified as another determinant of childhood BA. A study conducted in Kuala Lumpur, Malaysia, by Idris *et al.* (2016) reported that the presence of carpets indoors was significantly associated with childhood BA diagnosis (AdjOR: 2.15; 95% CI: 1.25–3.68; p<0.020).

The presence of mould has been identified as a significant factor associated with childhood BA symptoms. Research involving eight schools in Johor Bahru, Malaysia, found a strong link between mould presence and BA symptoms among 462 students (p<0.001) (Norbäck *et al.*, 2021). Similarly, Chen *et al.* (2011) reported in a Taiwan case-control study that visible mould was a significant determinant of childhood BA diagnosis (AdjOR: 1.75; 95% CI: 1.15, 2.67; p=0.020). The study identified *Aspergillus* as the most common type of mould responsible for asthma in children. Among its species, *Aspergillus* fumigatus is the most frequently associated with childhood asthma, noted for its capacity to provoke airway inflammation and immune sensitization. Other species, such as *Aspergillus flavus*, *Aspergillus niger*, and

Aspergillus terreus, may also contribute to respiratory issues, though their association with asthma is less common. Additionally, other mould species, including *Alternaria*, *Cladosporium*, *Penicillium*, and *Stachybotrys* have been linked to childhood BA, albeit to a lesser extent compared to *Aspergillus fumigatus* (Reponen *et al.*, 2012). The growth of these moulds is typically facilitated by high humidity levels and water damage in buildings, which create conditions conducive to mould proliferation.

In addition to mould, pesticide usage has also been recognized as a contributing factor. Xiao *et al*. (2021), analysing data from the USA National Children's Survey 2018 found that children exposed to household pesticides at least once a month had a higher weighted prevalence of BA (11.9%) compared to those exposed less frequently (8.4%) (p=0.015). A retrospective cohort study conducted in major cities across China reported that the addition of new wooden furniture within the past 12 months was significantly associated with the onset of childhood BA (AdjOR: 1.21; 95% CI: 1.05, 1.40; p<0.050) (Zhang *et al.,* 2018). Similarly, Tang *et al.* (2014) found that new wooden furniture made from non-solid or processed wood posed a significant risk for childhood BA in Fuzhou, China (AdjOR: 2.43; 95% CI: 1.56, 3.79; p=0.010). Additionally, a cross-sectional study by Norbäck *et al*. (2021) among children in Johor Bahru, Malaysia, identified recent indoor home painting as a significant factor associated with childhood BA symptoms (AdjOR: 3.30; 95% CI: 1.56, 3.79; p=0.030).

Using air conditioners has been linked to an increased risk of childhood BA in specific settings. Research from Japan, involving 1,006 households, identified a significant association between air-conditioner use and childhood BA (AdjOR: 1.51; 95% CI: 1.09, 2.33; p=0.040), attributed to poor ventilation and inadequate

maintenance leading to elevated indoor allergen levels (Okada *et al.*, 2022). Conversely, a cross-sectional study in Singapore among 655 households found no significant difference in childhood BA risk between children sleeping in air-conditioned rooms and those exposed to natural ventilation (Zuraimi *et al.*, 2011).

Poor kitchen ventilation has also been recognized as a key risk factor. A cross-sectional study across 3,867 homes in the UK reported that living in houses without windows or mechanical ventilation in the kitchen significantly increased the likelihood of childhood BA onset (AdjOR: 2.20; 95% CI: 1.09, 2.33; p=0.017) (Sharpe *et al*., 2015). A study involving small-size flat-type houses in Hong Kong found that fried cooking practice was significantly associated with childhood BA. The study stated that fumes from hot oil during frying contain various substances, and acrolein was identified as an allergen for the development of childhood BA (Golden and Holm, 2017). The finding was also supported by Jie *et al.* (2013) that cooking oil fume from the kitchen at home was significantly associated with BA symptoms (AdjOR: 2.22; 95% CI: 1.47, 3.36; p<0.001).

The use of wood stoves has been identified as a significant determinant of childhood BA. Kong *et al.* (2015), in a study involving 7,865 children in Tianjin, China, reported that the use of wood stoves and coal as primary cooking fuels significantly increased the likelihood of childhood BA (AdjOR: 2.30; 95% CI: 1.20, 4.49; p<0.05). In contrast, findings from the Australian National Census indicated that 38.2% of households primarily used natural gas for cooking, and the study emphasized that efficient hood ventilation to mitigate gas combustion emissions could reduce the risk of childhood BA onset (Knibbs *et al.,* 2018). Interestingly, the same study by Kong *et al.* (2015) in Tianjin, China, found that gas stoves used for daily cooking were