

**AIRWAY INFLAMMATION IN SCHOOL-AGED
CHILDREN WITH ASTHMA**

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Doctor of Philosophy**

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STATEMENT OF ORIGINALITY

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ABBREVIATIONS

ACS:	Asthma control score
ABS:	Australian bureau of statistics
AHR:	Airway hyperresponsiveness
AI:	Airway inflammation
APCs:	Antigen presenting cells
ASM:	Airway smooth muscle
ATS:	American Thoracic Society
BAL:	Bronchoalveolar lavage
BMI:	Body mass index
CO:	Carbon monoxide
C2R:	Chromatrope 2R
CysLTs:	Cysteinyl leukotrienes
DNA:	Deoxyribonucleic acid
DP:	<i>Dermatophagoides pteronyssinus</i>
DRR:	Dose response ratio
DRS:	Dose response slope
DTT:	Dithiothreitol
EA:	Eosinophilic asthma
EBC:	Exhaled breath condensate
ECP:	Eosinophil Cationic Protein
ED:	Emergency department
EDN:	Eosinophil derived neurotoxin

EIA:	Exercise induced asthma
EIB:	Exercise induced bronchoconstriction
ENO:	Exhaled Nitric oxide
EPO:	Eosinophil peroxidase
EPX:	Eosinophil protein X
ETS:	Environmental tobacco smoke
FeNO:	Fractional exhaled Nitric oxide
FEV ₁ :	Forced expiratory volume in 1 second
FTND:	Fagerstrom test for Nicotine Dependence
FVC:	Forced vital capacity
GM-CSF:	Granulocyte –macrophage colony-stimulating factor
GP:	General practitioner
GRs:	Glucocorticoid receptors
HDAC:	Histone deacetylases
HDM:	House dust mite
ICS:	Inhaled corticosteroids
IFN:	Interferon
IL:	Interleukin
ISAAC:	International Study of Asthma and Allergies in Childhood
cNOS:	constitutive Nitric oxide synthases
iNOS:	inducible Nitric oxide synthases
IQR:	Inter-quartile range
LAK:	Lymphokine-activated killer

LPR:	Late-phase reactions
LPS:	Lipopolysaccharide
MBP:	Major basic protein
MGA:	Mixed granulocytic asthma
MGG:	May Grunwald Giemsa
mRNA:	messenger RNA
NA:	Neutrophilic asthma
NAC:	National Asthma Council
NO:	Nitric oxide
NOS:	Nitric oxide synthases
NO ₂ :	Nitrogen dioxide
NO _x :	Nitrogen oxides
NF-κB:	Nuclear factor- κB
O ₃ :	Ozone
OR:	Odd ratio
PBS:	Phosphate-buffered saline
PC ₂₀ :	Provocative concentration resulting in a 20% fall in FEV ₁
PD ₁₅ :	Provocative dose of hypertonic saline causes to fall FEV ₁ by 15% of the base line
PDGF:	Platelet-derived growth factor
PEF:	Peak expiratory flow
PGA:	Paucigranulocytic asthma
PG:	Prostaglandin

PM:	Particulate matter
PUFAs:	Polyunsaturated fatty acids
pH:	Poition hydrogen Ion concentration
RANTES:	Regulated on activation normal T cell expressed and secreted
RSV:	Respiratory syncytial virus
SD:	Standard deviation
SO ₂ :	Sulphur dioxide
SPT:	Skin prick test
TCC:	Total cell counts
TNF- α :	Tumor necrosis factor α
UK:	United Kingdom
US:	United States
WHO:	World Health Organization

ABSTRACT

Airway inflammation is a key feature of asthma. Currently, airway inflammation can be detected through both invasive and non-invasive methods. Non-invasive methods are safe, feasible and a potentially useful way to assess airway inflammatory markers in both healthy children and children with asthma. In this thesis, a variety of non-invasive markers (induced sputum, exhaled nitric oxide, and exhaled breath condensate) was used to investigate childhood asthma. The aim of the first study was to compare and contrast the different airway markers between healthy children and children with asthma. The second study described the different airway inflammatory phenotypes in children with asthma, and examined clinical predictors of these phenotypes; whereas the third study investigated the effects of environmental tobacco smoke (ETS) exposure on airway inflammation in childhood asthma. The final study assessed the knowledge and attitudes of parents of children with asthma towards passive smoking.

The studies used both cross-sectional and longitudinal designs. Children with stable asthma aged between 7 - 17 years underwent clinical assessment, spirometry, exhaled nitric oxide (FeNO), exhaled breath condensate and sputum induction. Urinary cotinine was assayed to assess tobacco smoke exposure.

These studies have found that children with asthma show differences in both clinical pattern and pathological pattern compared to healthy children. These differences were apparent with elevated FeNO and sputum eosinophils. In children with asthma, there was

heterogeneity of airway inflammation. There were 2 stable inflammatory patterns: eosinophilic asthma and paucigranulocytic asthma. Unlike adult asthma, these phenotypes have different clinical features, which may facilitate detection of the phenotypes in clinical practice.

ETS exposure in children with asthma was common and associated with a non-eosinophilic pattern of airway inflammation. In children who had a change in ETS exposure, sputum eosinophils were decreased whereas sputum neutrophils were increased during ETS exposure compared to a non- ETS exposure period. Fractional exhaled nitric oxide levels were decreased after exposure to ETS compared to those at the time of non-ETS exposure. The severity of asthma was increased in children living with parents who smoked. As a result, parents of children with asthma, especially smoking parents should be more aware about the harmful effects of smoking on their children's health and themselves. Health risk awareness about tobacco smoke helps parental smokers alter their smoking behavior as well as protecting children from ETS exposure.

In conclusion, the important findings of this thesis are the description of the inflammatory phenotypes in childhood asthma, the identification of clinical predictors of these phenotypes and the determination of the effects of ETS exposure on airway inflammatory patterns in childhood asthma. These results should facilitate understanding and management of childhood asthma and prompt treatment studies based on markers of airway inflammation.

