AIRWAY INFLAMMATION IN SCHOOL-AGED CHILDREN WITH ASTHMA

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STATEMENT OF ORIGINALITY

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I hereby certify that the work embodied in this Thesis is the result of original research, the greater part of which was completed subsequent to admission to candidature for the degree (except in cases where the Committee has granted approval for credit to be granted from previous candidature at another institution).

Signature: ……..Date…….

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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:	*Dermatophagoides pteronyssinus*
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

NOx: Nitrogen oxides

NF-kB: Nuclear factor- kB

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
SO2:	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.