



Queensland University of Technology
Brisbane Australia

This is the author's version of a work that was submitted/accepted for publication in the following source:

Blake, Tamara L
(2019)

Spirometry and Fractional Exhaled Nitric Oxide (FeNO) Reference Values for Indigenous Australians.

PhD

by Publication,
Queensland University of Technology.

This file was downloaded from: <https://eprints.qut.edu.au/131824/>

Notice: *Changes introduced as a result of publishing processes such as copy-editing and formatting may not be reflected in this document. For a definitive version of this work, please refer to the published source:*

<https://doi.org/10.5204/thesis.eprints.131824>

**SPIROMETRY AND FRACTIONAL EXHALED NITRIC
OXIDE (FENO) REFERENCE VALUES FOR
INDIGENOUS AUSTRALIANS**

**Tamara Louise Blake
BBSc (Hons), MCISc**

Submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy

School of Public Health and Social Work
Faculty of Health
Queensland University of Technology
2019

Keywords

Australia, Aboriginal, Torres Strait Islander, children, spirometry, reference equations, Fractional Exhaled Nitric Oxide (FeNO), cut-off values

Abstract

Background: Spirometry and fractional exhaled nitric oxide (FeNO) are globally used lung function tests that help to determine the absence or presence of many lung conditions. Both are easy to perform and can be completed using portable devices, making it possible to transport to rural and remote locations. Reference values are used in clinical tests to indicate the normal range of test results in healthy individuals. The use of appropriate and validated reference values is essential for interpreting spirometry and FeNO. Incorrect reference values can result in inaccurate interpretation and misclassification of disease presence/absence which can impede best practice care and effect disease progression. Reference values for these tests have been well established for Caucasian populations and for a number of other ethnicities but not for Aboriginal and/or Torres Strait Islander (Indigenous) Australians. Given that respiratory diseases continue to significantly impact the lives of Indigenous Australians, it is important to develop and use appropriate reference values for these tests in this population.

The primary aim of my PhD is to determine the suitability of currently available reference values for interpreting spirometry and FeNO results of Indigenous Australian children and young adults (according to current American Thoracic Society [ATS] and European Respiratory Society [ERS] guidelines). The secondary aim will be to determine if there is a difference in lung function results

between Indigenous Australian ethnic groups; that is participants who identify as Aboriginal, Torres Strait Islander or Aboriginal and Torres Strait Islander (Both). Finally, self-reported and medical record information is frequently used in research studies to assess if participants meet inclusion or exclusion criteria. This PhD will therefore provide data on the agreement between information sources for respiratory and atopic conditions that influence the identification of 'healthy' Indigenous Australian children and young adults for these lung function tests.

Methods: This research is a cross-sectional study and consists of participants who were recruited from nine communities throughout Queensland and the Northern Territory. Eligible participants were recruited from schools and the general community. Consented participants performed spirometry and FeNO measurements according to international guidelines by trained respiratory scientists. Medical history and tobacco smoke exposure for each participant was sought by questionnaires (self-reported) and medical records (from health care centres and hospitals) in order to identify participants who were eligible for the final 'healthy' dataset (no respiratory and/or smoking history).

Descriptive analyses were used to summarize all data. The study population was described as a total cohort and by participants' identified ethnicity, with selected characteristics expressed as proportions and/or means/medians with corresponding standard deviation (SD) or inter-quartile ranges (IQR), dependent on data distribution (normal or skewed). Differences between ethnic groups were

assessed using χ^2 tests for proportions, Kruskal-Wallis tests for means (conditional on assumptions of normality) and non-parametric tests for any non-normally distributed data. All analyses were performed using Stata15 software.

Kappa analysis was used to determine the agreement between self-reported and medical record sources for asthma, bronchiectasis, pneumonia, allergic rhinitis and eczema so as to determine the most accurate source for identification of 'healthy' participants for the final dataset. The Global Lung Function Initiative (GLI) software was used to determine the appropriateness of existing GLI equations ('Caucasian', 'African-American' and 'Other/Mixed') for our 'healthy' Indigenous Australian spirometry data. For FeNO, the distribution and percent of 'healthy' participants considered positive for inflammation was compared to existing published guidelines as outlined by the ATS, National Institute for Health and Care Excellence (NICE), British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) and Global Initiative for Asthma (GINA) guidelines.

Results: When examining the agreement between information sources we found pneumonia and eczema were more commonly identified in medical records while asthma, bronchiectasis and allergic rhinitis were more commonly self-reported. There was moderate agreement for asthma and bronchiectasis between self-reported and medical record evidence ($\kappa=0.53$, 95% CI 0.45-0.61 and $\kappa=0.52$, 0.25-0.80 respectively). In contrast, agreement for eczema was fair, while agreement for pneumonia and allergic rhinitis was poor. These results suggest that

accurate health history of some conditions in this population may be better achieved by examining medical records rather than relying solely on self-reporting. As a result of this, both information sources were used to identify 'healthy' participants for this research.

A total of 930 'healthy' participants met inclusion criteria for determining spirometry reference values for Indigenous Australians. There was no statistically significant difference in mean FEV₁ or FVC z-scores between the three Indigenous ethnic groups for males or females. However, for males only, there was a statistically significant difference between Torres Strait Islander and Both ethnic groups for FEV₁/FVC% (Bonferroni corrected $p=0.041$). Of the available GLI-2012 reference equations, the 'Other/Mixed' reference equation provided the best overall fit for Indigenous Australian children and young adults (3-25 years) compared to 'Caucasian' and 'African-American'. Mean z-scores for all parameters were close to 0, SD close to 1 and approximately 5% of participants had z-scores <-1.64 and >1.64 when using the 'Other/Mixed' equation.

There was no statistically significant difference in the distribution of FeNO results between 603 'healthy' (that is no asthma or atopy history) Aboriginal and/or Torres Strait Islander participants. For participants <12 years ($n=390$), 7.2% had FeNO values in the 'inflammatory' zone when using the ATS, NICE or BTS/SIGN cut-off value (>35 ppb), however only 3.8% were identified when using the GINA guidelines (cut-off value >50 ppb). Respective values for those aged 12-16 years

(n=213), were 9.9% when using the NICE or BTS/SIGN cut-off value and 4.7% when using the ATS or GINA cut-off value (>35 ppb vs. >50 ppb). Therefore, the GINA recommended cut-off value of 50 ppb appears to be the most appropriate for identifying healthy individuals and considering abnormality amongst Indigenous Australians.

Conclusion: My PhD is the first study to quantify a number of 'healthy' lung function parameters that meet current international guidelines for Australian Indigenous children and young adults. Furthermore, this is the first study to report any data on the lung function of Torres Strait Islander participants. This research has shown that it is appropriate to use the GLI 'Other/Mixed' equation when performing spirometry and that the GINA guidelines should be used when interpreting FeNO results of Indigenous Australians. Use of these reference values will help to improve the accuracy of test interpretation, and aid in diagnosis and clinical care for this population. A number of additional areas for future research have been identified which will further help to improve the generalisability of results.

Thesis Formatting

This thesis is a collection of five articles that have been published or accepted for publication at appropriate journals. The articles have been arranged to ensure a logical flow throughout the thesis. All articles have been reformatted using the Vancouver referencing style and reconfigured to Word so as to ensure a consistent format for readers. Furthermore, tables and figures have been numbered sequentially as they appear in the thesis.

Table of Contents

Keywords.....	i
Abstract	ii
Thesis Formatting.....	vii
Table of Contents	viii
List of Figures.....	xi
List of Tables.....	xii
List of Abbreviations.....	xiii
List of Publications.....	xvi
List of Presentations	xviii
Statement of Original Authorship	xx
Acknowledgements	xxi
Chapter 1: Introduction.....	1
1.1 Literature review.....	1
1.2 Research aims and questions.....	23
1.3 Research setting.....	25
1.4 Significance of research	26
1.5 Definition of terms	28
1.6 Thesis outline	28
Chapter 2: Spirometry reference values in Indigenous Australians: a systematic review (Article 1)	30
2.1 Abstract	32
2.2 Introduction	34
2.3 Methods.....	36
2.4 Results	38
2.5 Discussion.....	47
2.6 Conclusions	51
2.7 Acknowledgements.....	52
Chapter 3: Does ethnicity influence fractional exhaled nitric oxide (FeNO) in healthy individuals? a systematic review (Article 2).....	53
3.1 Abstract	55
3.2 Introduction	57
3.3 Methods.....	59
3.4 Results	61

3.5	Discussion	73
3.6	Conclusions	79
3.7	Acknowledgements	80
Chapter 4: Research methodology		81
4.1	Introduction	81
4.2	Ethics approval.....	81
4.3	Research plan	82
4.4	Data collection	86
4.5	Data analysis	90
4.6	Feedback to communities	95
Chapter 5: How does parent/self-reporting of common respiratory conditions compare with medical records among Aboriginal and Torres Strait Islander (Indigenous) children and young adults (Article 3).....		97
5.1	Abstract.....	99
5.2	Introduction	101
5.3	Materials and methods.....	103
5.4	Results.....	106
5.5	Discussion	108
5.6	Conclusion	113
5.7	Acknowledgements	113
Chapter 6: Global Lung Function Initiative (GLI)-2012 'Other/Mixed' spirometry reference equation provides the best overall fit for Australian Aboriginal and/or Torres Strait Islander children and young adults (Article 4).....		115
6.1	Abstract.....	117
6.2	Introduction	119
6.3	Materials and methods.....	120
6.4	Results.....	124
6.5	Discussion	133
6.6	Conclusion	137
6.7	Acknowledgements	138
Chapter 7: Fractional exhaled nitric oxide (FeNO) values in Indigenous Australians aged 3-16 years (Article 5)		139
7.1	Abstract.....	141
7.2	Introduction	143
7.3	Materials and methods.....	145
7.4	Results.....	149
7.5	Discussion	155

7.6	Conclusion	160
7.7	Acknowledgments.....	160
Chapter 8: Conclusion		163
8.1	Introduction	163
8.2	Summary of findings	163
8.3	Strengths and limitations	169
8.4	Implications and recommendations	173
8.5	Impact of research to date.....	180
Bibliography		183
Appendices.....		197
Appendix A Article 1 Supplement file: Search strategy for systematic review		197
Appendix B Indigenous Respiratory Reference Value (IRRV) Study Information Sheet		198
Appendix C Indigenous Respiratory Reference Value (IRRV) Study Consent Form		200
Appendix D Respiratory and health questionnaire		201
Appendix E ISAAC questionnaire.....		203
Appendix F Medical chart form		206
Appendix G Article 3 Supplement file: Study protocol.....		208
Appendix H Article 4 Supplement file: Z-score scatterplots		213
Appendix I Article 5 Supplement file: Asthma within 12 months		217
Appendix J Co-author contribution statements for manuscripts		218

List of Figures

Figure 1.1 Spirometry outputs measuring volume and flow	8
Figure 1.2 Flow diagram showing outline of thesis	29
Figure 2.1 PRISMA flowchart of included/excluded articles for Australian Indigenous spirometry systematic review.....	39
Figure 3.1 Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) flowchart of included/excluded articles for FeNO systematic review	62
Figure 3.2 Distribution of FeNO (geometric mean and estimated 5 th and 95 th percentiles) for non-Caucasian samples of children (≤ 12 years)	72
Figure 3.3 Distribution of FeNO (geometric mean and estimated 5 th and 95 th percentiles) for non-Caucasian samples of adults (> 12 years).....	73
Figure 4.1: Included study sites within Australia	83
Figure 6.1 Exclusion criteria to identify ‘healthy’ Indigenous Australian spirometry data.....	124
Figure 6.2 Distribution of z-scores for Australian Indigenous males and females separated according to ethnicity, using Global Lung function Initiative ‘Other/Mixed’ equation.....	131
Figure 6.3 Distribution of z-scores for males and females as a combined cohort, using Global Lung Function Initiative ‘Other/Mixed’ equation	133
Figure 7.1 Flow diagram depicting exclusion criteria used to identify participants for analysis and separation of according to asthma and/or atopy history	148
Figure 7.2 Box and whisker plots of FeNO for ‘healthy’ (no asthma or atopy) Australian Indigenous participants < 12 years (n=390) separated according to ethnicity	151
Figure 7.3 Box and whisker plots of FeNO for ‘healthy’ (no asthma or atopy) Australian Indigenous participants 12-16 years (n=213) separated according to ethnicity	152
Figure 7.4 Box and whisker plots of FeNO for Australian Indigenous participants < 12 years (n=534) separated according to asthma and/or atopy history	154
Figure 7.5 Box and whisker plots of FeNO for Australian Indigenous participants 12-16 years (n=314) separated according to asthma and/or atopy history	155

List of Tables

Table 1.1 Potential errors in interpretation of spirometry data when extrapolating reference sets beyond the demographics of the reference population	11
Table 1.2 Cut-off values for FeNO measurements of children and adults	16
Table 2.1 Description of the nine included studies.....	41
Table 2.2 Comparison of spirometry results between Indigenous Australians and people of European ancestry	44
Table 2.3 Suitability of Indigenous spirometry data for developing healthy reference values, according to current ATS/ERS and GLI criteria.....	46
Table 2.4 Interpretation of lung function results using five different reference equations.....	49
Table 3.1 Description of studies included in review	65
Table 3.2 FeNO result variation of ethnic populations against Caucasian data	70
Table 3.3 Clinical implications for interpretation based on current ATS guidelines	77
Table 5.1 Participant demographics.....	106
Table 5.2 Agreement between self-reported and medical record diagnoses	107
Table 6.1 Cohort demographics	125
Table 6.2 Suitability of GLI equations for Australian Indigenous males and females (according to ethnicity)	129
Table 6.3 Suitability of GLI equations for Australian Indigenous males and females (combined cohort).....	132
Table 7.1 Current FeNO guidelines	145
Table 7.2 Cohort demographics	150

List of Abbreviations

AHR	airway hyper-responsiveness
ANOVA	analysis of variance
ANZSRS	Australia and New Zealand Society of Respiratory Science
ARI	acute respiratory infections
ATS	American Thoracic Society
Both	Aboriginal and Torres Strait Islander
BSA	body surface area
BTS	British Thoracic Society
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	c-reactive protein
CT	computed tomography
eCO	exhaled carbon monoxide
ECP	eosinophil cationic protein
ERS	European Respiratory Society
FEF _{25-75%}	forced expiratory volume between 25% and 75% of FVC
FeNO	fractional exhaled nitric oxide
FEV ₁	forced expiratory volume in 1 second
FEV ₁ /FVC%	percentage of FVC expelled in the first second
FVC	forced vital capacity
GINA	Global Initiative for Asthma

GLI	Global Lung Function Initiative
HREC	Human Research Ethics Committee
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IgG	immunoglobulin G
Indigenous	Aboriginal and/or Torres Strait Islander
IROC	Indigenous Respiratory Outreach Care
ISAAC	International Study of Asthma and Allergies in Childhood
K	Cohen's kappa
LLN	lower limit of normal
LR	linear regression
MLR	multiple linear regression
MR	medical records
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Survey
NICE	National Institute for Health and Care Excellence
NO	nitric oxide
NT	Northern Territory
PEF	peak expiratory flow
ppb	parts per billion
ppm	parts per million
QLD	Queensland
RSD	residual standard deviation

RV	residual volume
SD	standard deviation
SR	self-reported
SIGN	Scottish Intercollegiate Guidelines Network
TLC	total lung capacity
TSANZ	Thoracic Society of Australia and New Zealand
ULN	upper limit of normal
URI	upper respiratory tract infection
USA	United States of America

List of Publications

Published papers

1. Blake TL, Chang AB, Petsky HL, Rodwell LT, Brown MG, Hill DC, Thompson B, McElrea MS. Spirometry reference values in Indigenous Australians: a systematic review. *Medical Journal of Australia*. 2016; 205(1): 35-40
2. Blake TL, Chang AB, Chatfield MD, Rodwell LT, Brown MG, Hill DC, McElrea MS. Does Ethnicity Influence Fractional Exhaled Nitric Oxide in Healthy Individuals? A Systematic Review. *CHEST*. 2017; 152(1): 40-50
3. Blake TL, Chang AB, Chatfield MD, Marchant JM, Petsky HL, McElrea MS. Fractional exhaled nitric oxide (FeNO) values in Aboriginal and Torres Strait Islander (Indigenous) Australians aged 3-16 years. *CHEST*. 2019; doi:10.1016/j.chest.2019.02.401
4. Blake TL, Chang AB, Chatfield MD, Marchant JM, Petsky HL, McElrea MS. How does parent/self-reporting of common respiratory conditions compare with medical records among Aboriginal and Torres Strait Islander (Indigenous) children and young adults? *Journal of Paediatrics and Child Health*. 2019; doi:10.1111/jpc.14490

Accepted (In press)

5. Blake TL, Chang AB, Chatfield MD, Marchant JM, McElrea MS. Global Lung Function Initiative (GLI)-2012 'Other/Mixed' spirometry reference equation provides the best overall fit for Australian Aboriginal and/or Torres Strait Islander children and young adults. *Respirology*. 2019

List of Presentations

1. Blake TL, Chang AB, Rodwell LT, Brown MG, Hill DC, Petsky HL & McElrea MS.
Spirometric references values in Indigenous Australians: a systematic review.
[Oral] Thoracic Society of Australia and New Zealand/Australian and New Zealand Society of Respiratory Science 2015 Conference, Gold Coast, Australia
2. Blake TL, Chang AB, Rodwell LT, Brown MG, Hill DC, Petsky HL & McElrea MS.
Ethnicity as a determinant of fractional exhaled nitric oxide (FeNO) in adults and children: a systematic review. [Oral] Thoracic Society of Australia and New Zealand/Australian and New Zealand Society of Respiratory Science 2015 Conference, Gold Coast, Australia
3. Blake TL, Petsky HL, Chang AB, Peacock B & McElrea MS. Fractional exhaled nitric oxide (FeNO) levels in Aboriginal and Torres Strait Islander Australians.
[Oral] Thoracic Society of Australia and New Zealand/Australian and New Zealand Society of Respiratory Science 2016 Conference, Perth, Australia
4. Blake TL, Chatfield MD, Chang AB, Petsky HL & McElrea MS. Assessing the suitability of FeNO cut-off ranges for Aboriginal and/or Torres Strait Islander children and young adults. [Oral] Thoracic Society of Australia and New Zealand/Australian and New Zealand Society of Respiratory Science 2018 Conference, Adelaide, Australia

5. Blake TL, Chatfield MD, Chang AB, Petsky HL, Marchant JM & McElrea MS.
Spirometry reference values for Australian Aboriginal and Torres Strait
Islander (Indigenous) children and young adults. [Oral] European Respiratory
Society 2018 Conference, Paris
6. Blake TL, Chatfield MD, Chang AB, Petsky HL, Marchant JM & McElrea MS.
Self-reported and medical chart histories of Australian Aboriginal and Torres
Strait Islander (Indigenous) children and young adults. [Poster]. European
Respiratory Society 2018 Conference, Paris

Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signature: [QUT Verified Signature](#)

Date: 10-Jul-2019

Acknowledgements

This PhD would not have been possible without the expert knowledge, guidance and support provided to me by my supervisors; Dr Margaret McElrea, Prof Anne Chang, A/Prof Mark Chatfield, Dr Helen Petsky and A/Prof Julie Marchant. Marg and Anne – words cannot express my thanks to you both for the journey you have taken me on over the last few years. You have challenged, inspired and encouraged me to push through and have cultivated a deep respect and love of research. I will always be thankful to you. Mark – thank you for your patience in teaching me statistics and answering my obscure, often daft questions. Never would I have thought that I would grow to love graphs so much! Helen and Julie – I really appreciated the time you both took to check in with me and lend a friendly ear whenever I felt overwhelmed. You have all been such an amazing group of individuals to learn from.

This study was facilitated by grants provided to the Indigenous Respiratory Outreach Care (IROC) Program from the (i) Aboriginal and Torres Strait Islander Health Unit (Queensland Health), (ii) NHMRC Centre for Research Excellence for Indigenous Children and (iii) The Prince Charles Hospital Foundation New Investigator grant. Completion of this thesis would not have possible without the support provided to me from the Centre for Children's Health Research, the Institute of Health and Biomedical Innovation and Queensland University of Technology. I would like to acknowledge the financial assistance (scholarship)

provided to me by the NHMRC Postgraduate Scholarship program, a supervisor top-up scholarship and a QUT Faculty of Health top-up scholarship.

To the participants, families, communities, schools, health services and research assistants that participated in this research, I thank you from the bottom of my heart. Thank you to the Elders who welcomed us into their communities and entrusted their members to us.

The success of this research would not have been possible without the support and dedication of the IROC team, in particular, Brian Peacock and Allan Takken. Thank you for your invaluable knowledge and guidance, and being there for the early starts, long days, crazy car rides and hilarious conversations (sometimes at my expense). Special thanks also to Deearne Dodd, Gale Collins and Jeleacha Hopkins-Lincolne for their help with recruitment. Thank you also to the many respiratory scientists (Marg, Leanne, Sean, Petra, Craig and Jessica) and research members (Gabrielle, Lesley, Erin and Cate) who have helped with collecting this data.

Thank you to everyone in the CAARG and RiOAR teams at CCHR for looking out for me over the past few years. I have really appreciated the offers for coffee, help when programs decided to not work, laughs and bad jokes. I am lucky to have worked closely with a great group of caring people. Thank you to all the other PhD students I've met and travelled on this incredible journey with – Claire, Samantha,

Rebecca, Kerry, Yolanda, Sophie, Kaley and Vikas. Your understanding and support often when you were busy with your own tasks have been a life saver and I wish you all the best for the rest of your journeys.

I cannot express my deepest thanks (and apologies) enough to Sean for being my sounding board at work particularly in the last year. You've been such an understanding friend and I appreciate the time you took to check in on me. To my second family – Liz, Aaron and the munchkins – thank you for always checking up on me to make sure I wasn't asleep at my desk, and especially for squeezing in last minute dinner catch-ups, non-PhD conversations and play time whenever I was available.

Finally, thank you to my beautiful family – Mum, Dad, Stephanie, Jacqueline, Tony and the twins. This has been one of the most challenging things I have done and I would not have made it without you. Thank for your understanding when I was distracted/busy, giving me a roof over my head and meals when I needed it, good company and laughs when I had free time and most importantly, your unwavering belief that I would eventually make it.

Honourable mentions must also go to coffee, chocolate and wine!

Chapter 1: Introduction

1.1 Literature review

While there are recent improvements in Indigenous health outcomes attributable to national and state programs such as *Closing the Gap, Aboriginal and Torres Strait Islander Chronic Disease Fund* and *Health for Life*,¹ Aboriginal and Torres Strait Islander (here forth collectively referred to as Indigenous) Australians have a lower life expectancy than non-Indigenous Australians with approximately 12% of deaths attributable to lung diseases.^{1,2} Furthermore, acute and chronic respiratory illnesses (such as asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD), and pneumonia) are significant contributors to the morbidity of Indigenous Australians across all ages.

1.1.1 Burden of respiratory disease in Australian Indigenous children and adults

Recent data indicates that two thirds of Indigenous Australians die before 65 years of age, with respiratory diseases being one of the leading contributors to mortality – 4th behind circulatory disease, endocrine disorders and neoplasms.^{2,3} Mortality rates attributable to respiratory diseases are currently 3.6 times higher³ for Indigenous Australians than non-Indigenous Australians. Deaths from respiratory illness remain one of the most common preventable causes of death in Indigenous children in the 0-1 year age group with mortality rates being 2 times higher than non-Indigenous Australian children.² Morbidity rates due to acute and chronic respiratory diseases, in Indigenous Australians are among the highest

published rates in the world.^{4,5} In fact, respiratory illnesses are the most common self-reported chronic illness in Indigenous people.² Furthermore, approximately 10% of Indigenous Australian hospitalisations are due to respiratory diseases.² During 2011-2013, the rate of hospitalisation for respiratory disease of Indigenous Australians compared to non-Indigenous was five times higher for those aged 45-54 years and roughly four times higher for those aged 55 years and over.² When adjusted for differences in age, the hospitalisation rate for respiratory diseases are currently 2.4 times higher for Indigenous Australians than non-Indigenous Australians.²

Asthma contributes considerably to the morbidity and high hospitalisation rates within Indigenous communities.² Asthma is currently the highest self-reported respiratory condition at 18% and, in fact, has increased from previous data.² Some studies have reported the prevalence of asthma within the Indigenous population to be higher than non-Indigenous Australians.^{2,6} Asthma is associated with chronic inflammation and hyper-responsiveness of the airways which causes characteristic symptoms of wheeze, shortness of breath and bronchoconstriction. Delayed diagnosis and inadequate treatment of asthma can severely impact a child's overall health and day to day functioning.² Furthermore, a high number of hospitalisations due to suboptimal asthma management and/or severe and prolonged symptoms has been shown to be associated with poorer lung health which continues into adulthood.⁷

Australian Indigenous children have some of the highest published rates in the world for both pneumonia⁴ and bronchiectasis.⁸ Bacterial or viral in nature, pneumonia causes inflammation of the alveoli (air sacs) resulting in a build-up of pus or fluid which hinders gas exchange. Pneumonia is of particular concern for very young children and the elderly, and may require lengthy hospital admissions.⁹ Bronchiectasis is described as irreversible dilation and thickening of the bronchi and is caused by chronic inflammation and infections (bacterial or viral).¹⁰ Both of these diagnoses are associated with reduced lung function in adulthood.¹¹⁻¹³ In Indigenous-specific data, a cross-sectional study of Indigenous children 8-14 years old demonstrated that being hospitalised more than once for a chest infection was associated with a significant reduction in lung function later in childhood.¹⁴ Similarly Indigenous children hospitalised with pneumonia are up to 15 times more likely to develop bronchiectasis than children who have not had pneumonia requiring hospitalisation.^{15,16} It is known that Indigenous adults with bronchiectasis often die prematurely, in their third or fourth decade of life.¹⁷

COPD is characterised by airway inflammation and airflow obstruction that is not fully reversible.¹⁸ The reported prevalence of COPD amongst Indigenous Australians varies from 17 to 54% depending on the studied location.^{3,19} The development of COPD is affected by smoking status, poor nutrition and growth during early childhood, lung infections in early life and other environmental exposures such as air pollution.^{18,20} These factors are all common in Indigenous communities. For example, the incidence of tobacco use by Indigenous Australians

still remains a significant factor for several chronic conditions, contributing to 17% of the health gap.^{19,21} Recent data indicates that 44% of Indigenous people over the age of 15 years are current smokers.²² When compared to other Indigenous populations around the world, Australian Indigenous people have a higher prevalence of COPD across all age groups for both males and females.²³

Hence, respiratory disease is a higher burden for Indigenous Australians when compared to non-Indigenous Australians. This premature mortality and high burden of chronic disease in Indigenous Australians demands a strong focus on early diagnosis and treatment of respiratory disease to improve quality of life and to reduce the health gap. Many factors are required to reduce the burden of lung disease in Indigenous Australians including an accurate diagnosis followed by reliable disease monitoring of lung conditions.

1.1.2 Diagnosing and monitoring respiratory illness

A variety of tests are used to objectively and definitively diagnose lung disease as well as to determine severity. Typically these include the use of radiology (such as chest computed tomography (CT) scans and chest X-rays), ultrasound scanning and a variety of lung function tests. Use of these tests however is often dependent on availability of resources and equipment, as well appropriately trained technicians.^{24,25} For example, radiology is generally not portable and rural/remote primary health centres are unlikely to have funding to purchase such equipment.

Hence, portable lung function is the most feasible method for ensuring accurate diagnosis and monitoring of respiratory diseases outside of the hospital setting.

Several lung function tests are available today to assist in the diagnosis, treatment and monitoring of respiratory illnesses. Internationally, spirometry is the most commonly performed respiratory function test as it is relatively easy to perform and acts as a quick screening tool for general respiratory health.²⁶ Another simple test is the measurement of fractional exhaled nitric oxide (FeNO).²⁷ Both spirometry and FeNO are standardised lung function tests that have established reference values for Caucasians and can be performed on equipment that is easily transported.

Despite the widespread use of spirometry and increasing use of FeNO throughout clinical practice, there are no established normal reference values for either spirometry or FeNO for Indigenous Australian children or adults. The lack of reference values makes it difficult for clinicians to accurately identify abnormal lung function results in Indigenous Australians. A set of reference values for spirometry and FeNO in healthy children of Aboriginal and Torres Strait Islander descent will greatly aid in the diagnosis and clinical care of respiratory conditions in this group.

1.1.3 The utility of spirometry

What is spirometry?

Spirometry is the most established lung function test and results can help differentiate normal lung function from abnormalities affecting airflow and lung size. It is indicated as a diagnostic tool to assess lung function when respiratory symptoms are present, and is very useful for monitoring therapeutic interventions, progression of disease and adverse reactions to treatment.²⁶ In fact, spirometry is the international gold standard for diagnosing and monitoring airway obstruction such as seen in COPD.¹⁸ Similarly, pre- and post-bronchodilator spirometry testing is an essential component of measuring and monitoring severity of reactive airways conditions, such as in asthma.

An important feature of spirometry testing is that under appropriate conditions, it can successfully be performed by preschool children as young as 3 years old,^{28,29} children/adolescents³⁰ and senior adults.³¹ The reliability of this technique is dependent on using standardised equipment, data acquisition and interpretation methods, as well as being performed by appropriately trained staff.^{26,32} The American Thoracic Society (ATS) and European Respiratory Society (ERS) have published joint statements regarding spirometry testing and its interpretation.^{26,33} These statements are acknowledged by clinicians in Australia and by the Thoracic Society of Australia and New Zealand (TSANZ) and the Australian and New Zealand Society of Respiratory Science (ANZSRS) as the standard for spirometry testing.

How is spirometry performed

The ATS/ERS guidelines require that height and weight be measured without shoes prior to performing spirometry. Relevant clinical information, such as smoking and current medications, should be noted at the time of testing. The individual is instructed to sit in an upright position, wearing a nose peg and with lips tightly sealed around the mouthpiece. After a maximum inspiration to total lung capacity (TLC), the air is forcefully exhaled until the lung contains only the residual volume (RV). A spirometer measures the volume and flow of the exhaled air (Figure 1.1) recording several key parameters including:

- Forced expiratory volume in one second (FEV_1): The maximal volume (in litres) of air exhaled in the first second of a forced expiration from a position of full inspiration.²⁶ FEV_1 is affected by the caliber of the airways and will be decreased when the airways narrow
- Forced vital capacity (FVC): The maximal volume (in litres) of air exhaled with maximally forced effort from a maximal inspiration²⁶
- FEV_1 over FVC ratio ($FEV_1/FVC\%$): Indicates the percentage of air (FVC) expelled in the first second²⁶
- Forced expiratory volume between 25% and 75% of the FVC ($FEF_{25-75\%}$): Mean forced expiratory flow between 25% and 75% of the FVC, also known as the maximum mid-expiratory flow²⁶
- Peak expiratory flow (PEF): Maximum expiratory flow (in litres per second) achieved during from a maximum forced expiration, starting without hesitation and from the point of maximal lung inhalation²⁶

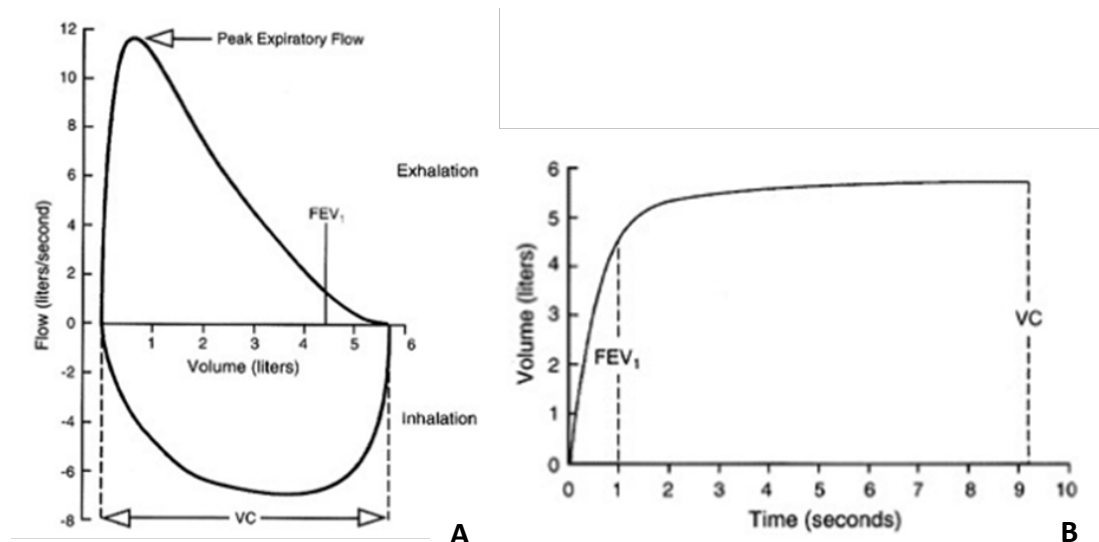


Figure 1.1 Spirometry outputs measuring volume and flow

(A) Flow-volume curve and (B) Volume-time curve³⁴

According to current ATS/ERS guidelines²⁶ an acceptable test requires full inspiration to TLC, a distinct PEF achieved very early during expiration (within 0.16 seconds) and an expiration time of at least six seconds (if patient is older than 10 years of age) or three seconds (if patient is younger than 10 years of age). After three acceptable tests have been achieved they are considered repeatable if the two largest FEV₁ values and the two largest FVC values are each within 0.15 L of each other. Pre-school children can experience difficulty achieving all criteria partly because their lungs empty more rapidly than older children or adults and partly because learning the technique often requires many repeated attempts.³⁵

How is spirometry interpreted?

Results from the parameters outlined above, help to differentiate normal from obstructive, restrictive or mixed obstructive/restrictive lung function patterns.

In obstructive respiratory diseases such as COPD, asthma and bronchiectasis there is a reduction in airflow caused by narrowing of the airways as a result of airway inflammation and increased amounts of mucus. This reduces both FEV_1 and the FEV_1/FVC ratio.³³ With restrictive respiratory diseases such as pulmonary fibrosis and interstitial lung disease, there is a reduction in the FVC (and TLC) with a normal or high FEV_1/FVC ratio.³³ In the presence of concurrent obstructive and restrictive processes (such as fibrosis with COPD), FEV_1 , FVC and the FEV_1/FVC ratio are all reduced.³³

Interpretation of lung function tests requires comparing an individual patient's results to reference values obtained from a representative 'healthy' population that closely match those presenting in a clinical setting (including height, age and sex distribution).^{33,36} The reference population should be a sample of lifetime non-smokers and free of clearly defined respiratory diseases including asthma, bronchitis, COPD and emphysema.^{36,37} These reference values are also commonly referred to as predicted or normal values throughout the literature. Comparison with reference values not only allows for a diagnosis to be made but also aids in measuring disease severity.

An individual's FEV_1 , FVC and FEV_1/FVC ratio can be compared with reference values in several ways:

- By observing whether measured values are above the lower limit of normal (LLN). In respiratory medicine, FEV_1 and FVC results that are low

are more clinically relevant and as such, the LLN is defined by the ATS/ERS as the 5th percentile (-1.64)³⁸

- By expressing the difference between measured and predicted values as a multiple of the residual standard deviation (RSD), also known as the z-score
- By expressing the measured value as a percent of the predicted value

Anthropometric measures have a significant influence on spirometry values. In healthy children aged <7 years, the main determinant of FEV₁ and FVC is height.^{28,29} In older children, height and sex and to a lesser extent age, are the predominant influencing factors.^{31,39} In adults, FEV₁, FVC and FEV₁/FVC ratio are all influenced by height, sex and age.^{31,40,41} A plateau in predicted values occurs during young adulthood (18-25 years)⁴² before beginning a natural decline as an individual ages. Additionally, ethnicity^{31,43-45} as well as socio-economic and environmental influences^{40,46,47} are known to affect spirometry values.

Most reference sets have marked limitations as they do not span the full age range of children and adults that may require spirometry testing. For example, a patients' spirometry results should be compared to a reference set that includes children and young adolescents when their age is <18 years and a set that includes adults when they are over 18 years. Transitioning between different reference equations can result in dramatic changes in lung function reference values especially around the transition ages (childhood to adolescent, adolescent to

adulthood).^{39,48} Furthermore there has been a paucity of reference equations for the extremes of height. Extrapolating reference equations for patients who fall outside the limits of the reference population may introduce significant error when interpreting spirometry results.^{26,33} Table 1.1 illustrates how extrapolating reference sets beyond the study populations demographics can lead to errors. When the measured FEV₁ result is compared to the predicted FEV₁ generated by two reference sets (Eigen 2001²⁸ and Global Lung Function Initiative (GLI)-2012)³¹ that include the particular age and height of the patient, the FEV₁ is interpreted to be within the normal range. However when a reference set, in this case Hibbert 1989³⁹, is extrapolated beyond the height and age range that it covers, the FEV₁ is falsely interpreted as ‘abnormally low’.

Table 1.1 Potential errors in interpretation of spirometry data when extrapolating reference sets beyond the demographics of the reference population

Comparison between different reference sets:			
6 year old boy, 100 cm tall with measured FEV₁ of 0.90 L			
	Eigen 2001²⁸	GLI 2012³¹	Hibbert 1989⁹³
<i>Age Range</i>	<i>3-6 years</i>	<i>3-95 years</i>	<i>8-19 years</i>
<i>Height Range</i>	<i>87-127 cm</i>	<i>50-250 cm</i>	<i>120-190 cm</i>
FEV ₁ Reference Value	0.86 L	0.91 L	1.29 L
LLN for FEV ₁	0.68 L	0.72 L	1.06 L
Measured FEV ₁	0.90 L	0.90 L	0.90 L
% Predicted	105%	99%	70%
Interpretation	Within normal range	Within normal range	Abnormally low i.e. disease present

To overcome the issues of transitioning between different sets of reference equations there has been a push for the development of reference data that applies

across a broad age and height range. The first of these was the National Health and Nutrition Examination Survey (NHANES III)⁴⁹ which tested 7429 individuals between the age of 8-80 years old from the United States of America (USA). Similarly, Stanojevic and colleagues⁵⁰ published reference ranges for ages 4-80 years derived from 3598 Caucasian subjects from the USA, United Kingdom, Belgium and Canada. Despite being necessary studies they still fail to adequately cover the full age range of individuals who may be required to perform spirometry, particularly the very young and very old.

In addition to this, there are still gaps in reference ranges for some of the world's ethnic groups. Many studies have been performed in several Asian, African and European ethnic groups however these are generally specific to either a child or adult population.⁵¹⁻⁵⁴ The GLI has been an international endeavour to develop 'all-age' and multi ethnic reference equations spanning the ages of 3 to 95 years.³¹ GLI reference values are based on 74187 sets of spirometry data from four major ethnic groups; Caucasian, African-American, North-East Asian and South-East Asian.

1.1.4 The utility of Fractional Exhaled Nitric Oxide (FeNO)

What is FeNO?

Nitric oxide (NO) is a gas produced by a variety of cells in the lung including epithelial cells, airway nerves, inflammatory cells (eosinophils, macrophages) and vascular endothelial cells.⁵⁵ When measured in the exhaled breath, termed FeNO, its concentration is used as an indicator of eosinophilic airway inflammation.^{55,56}

The role of NO in airways is varied and includes involvement in several host defence mechanisms, production of airway secretions, regulation of bronchial smooth muscle and ciliary function.⁵⁶ Abnormal FeNO levels have been demonstrated in many respiratory conditions including asthma, COPD, bronchiectasis, cystic fibrosis, sarcoidosis, upper respiratory tract infections and pulmonary hypertension.⁵⁷

Research into FeNO and its potential use in clinical care has increased significantly over the last 20 years. In 1999 the ATS and ERS jointly released recommendations for standardised ways of measuring and reporting exhaled nitric oxide.²⁷ As further research indicated a role for FeNO in diagnosing asthma as well as its ability to monitor airway inflammation and treatment outcomes, these recommendations were updated by the ATS⁵⁸ to include detailed information on interpretation of FeNO results and potential confounding factors.

FeNO testing has many uses in today's clinical setting. Current guidelines recommend measuring FeNO to aid in the diagnosis of eosinophilic asthma phenotypes, identify patients who may benefit from inhaled corticosteroids (anti-inflammatory agent), predict asthma exacerbations, guide adjustments made to steroid doses and to help in the differential diagnosis of respiratory symptoms allowing for better targeting and monitoring of anti-inflammatory treatment.^{58,59} However, it is recommended that FeNO not be used to guide therapy in severe asthmatics (children or adults)^{60,61} as it has not been shown to improve clinical outcomes.

How is FeNO performed?

Measurement of FeNO was first reported in 1993⁶² and is now measured by a simple breath test. A portable hand held NO measuring device is available for use in the clinical setting. The patient either exhales directly into the real-time NO analyser through a connected mouthpiece (the 'online' technique), or into a reservoir that can be connected to the analyser (the 'offline' technique) for later examination. Current ATS/ERS guidelines²⁷ recommend the use of the 'online' technique within the clinical setting as it allows the operator to monitor the exhalation phase ensuring all parameters have been met. The test requires the patient to be seated in an upright position with the head in a neutral relaxed position. The patient is then instructed to inhale through the mouthpiece to TLC and then to exhale completely to RV. Unlike spirometry the exhalation phase should not be forceful. An exhalation flow rate of 50 mLs/second with a back pressure of 10-20 cm H₂O is recommended. These criteria respectively, standardise transit time of air through the airways and assist with velum closure to prevent contamination of expired FeNO with nasal NO. Nasal NO levels are typically higher than the respiratory tract⁶³ and so for this reason nose pegs and a breath hold are discouraged when performing this test.

Results are displayed in parts per billion (ppb) and measurements are repeated until two results are within 5% of each other.²⁷ FeNO is suitable for use in adults of all ages and can be used in children as young as 4 years old.⁶⁴ The major

advantages of using FeNO to test for airway inflammation is the non-invasive nature of the test, ease of repeat measurements and the ease of use compared to other instruments for patients with severe airflow obstruction.^{62,65}

How is FeNO interpreted?

FeNO values have been shown to be influenced by respiratory infections,^{66,67} atopy,^{68,69} age,⁷⁰ genetics,⁷¹ gender,⁶⁸ anthropometry,⁷¹ as well as smoking, environmental and exercise factors.⁷² Other factors which may influence FeNO results include inappropriate technique, exhalation time, flow rate, nasal NO contamination, the NO analyser used as well as use of anti-inflammatory medication. These factors greatly affect the ability to arrive at 'clinically optimal' FeNO levels for children and adults and therefore, predicted values would have limited application in the clinical setting for FeNO testing.⁵⁸ Until the impact of influencing factors on FeNO results is better understood, current guidelines recommend the use of cut-off values.⁵⁸

There are currently four published guidelines – ATS,⁵⁸ National Institute for Health and Care Excellence (NICE),⁷³ British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN)⁷⁴ and Global Initiative for Asthma (GINA)⁷⁵ – that provide recommended cut-off values, discuss the interpretation of FeNO results and make recommendations for management and treatment. There are however differences between these guidelines with respect to the definitions of child vs. adult and the suggested cut-off value that would suggest the presence of

inflammation (Table 1.2) which further influences the use of FeNO in a clinical setting.

Table 1.2 Cut-off values for FeNO measurements of children and adults

	Age	Recommended cut-off value suggestive of inflammation
ATS ⁵⁸	Child <12 yrs. or	>35 ppb
	Adult	>50 ppb
NICE ⁷³	Child <17 yrs. or	≥35 ppb
	Adult	≥40 ppb
BTS/SIGN ⁷⁴	Child <17 yrs. or	≥35 ppb
	Adult	≥40 ppb
GINA ⁷⁵	All ages	>50 ppb

ATS: American Thoracic Society; **BTS/SIGN:** British Thoracic Society/Scottish Intercollegiate Guidelines Network; **GINA:** Global Initiative for Asthma; **NICE:** National Institute for Health and Care Excellence; **ppb:** parts per billion

The use of cut-off values is still heavily debated as several studies have shown a large range of FeNO results for both healthy and asthmatic populations. Grob and Dweik⁷⁶ reported a FeNO range of 10 ppb to 33 ppb in a healthy adult control population, and for asthma, the FeNO geometric mean ranged from 6 ppb to 98 ppb. Similarly one recent study has demonstrated that even in a healthy population free of atopy and asthma, the ULN ranges from 27 ppb to 75 ppb⁷⁷ which overlaps with values obtained from asthmatic populations. It has been suggested that ‘different clinical settings and purposes of measurement’ need to be considered when interpreting exhaled nitric oxide levels⁵⁷ and should factor in current

respiratory symptoms of the patient, prior airways disease diagnosis and other clinically relevant information.⁵⁸

Jacinto *et al.*⁷⁰ also highlighted the difficulty of formulating reference ranges and their subsequent interpretation, especially in adults or children with current respiratory symptoms. It is acknowledged that FeNO values are affected by and should take into account sex, atopy and smoking status, and that reference ranges should be reflective of these factors.^{68,70,78} It is the variety of ways in which various studies have taken these factors into account (including statistically) that makes it difficult to draw comparisons across studies regarding correct or appropriate reference values or ranges to be used.

Jacinto *et al.*⁷⁰ noted that interpretation of FeNO currently involves the use of 'absolute values' in terms of ppb, both clinically and in research, however these values are seldom used in diagnostic tests. The authors suggest the percent predicted of the reference value and Z-score is preferable though further research is needed. There is strong agreement across the literature^{57,58} on the need to develop standardized methods for performing FeNO tests, evaluating FeNO values, and statistically analysing results. Future studies should sample a wider range of ages, focus on specific races or ethnicities and should take into account ethnicity, sex, age as well as numerous anthropometric factors.⁷⁰

Despite the uncertainty regarding meaningful cut-off values, many studies have highlighted the benefits of including FeNO testing in a clinical setting. Firstly, FeNO has been shown to be helpful in diagnosing respiratory diseases (not just asthma) that may be sensitive to inhaled corticosteroid (ICS) treatment. In these studies,⁷⁹⁻⁸³ patients with elevated baseline FeNO values were more likely to respond to ICS treatment compared to those with baseline values in the normal range. Secondly, FeNO has the potential to monitor adherence to asthma medications as it has been shown to respond rapidly and dose-dependently to changes in ICS treatment.⁸⁴⁻⁸⁶ Finally, there is emerging data that suggest FeNO to be helpful in predicting future exacerbations and lung function decline amongst patients with difficult to treat asthma.⁸⁷⁻⁹⁰ These findings suggest that the clinical utility of FeNO may lie more in the personalised management of asthma in an individual rather than as a diagnostic tool.

1.1.5 Influence of ethnicity on lung function

Examining the effect of race and/or ethnicity on lung function is complicated by the fact that 'ethnicity' often includes other influences such as social and cultural,⁴³ socioeconomic status,^{91,92} nutritional status (diet trends),^{46,93} achieved educational level^{40,47,94} and genetic factors from diverse backgrounds.^{95,96} These factors are difficult to quantify and measure. Unlike age or height, it is not yet known what influence ethnicity has in the development, decline and overall lung function of an individual.

Ethnicity and spirometry

As spirometry reference values are dependent on body habitus, it is not surprising that ethnicity (which is one determinant of body habitus) would influence reference values. In the absence of spirometry reference values for a specific ethnic group, interpretation is frequently based on reference sets for Caucasians with or without the application of a 'race correction factor'. The term Caucasian is used to represent 'white' or those with a European heritage. Identifying the effects of ethnicity is further complicated by the diversity of subdivisions within ethnicities; for example Chinese, Indian and Japanese are considered to be of collective Asian descent.⁹⁷

In keeping with current industry guidelines, the GLI³¹ recommends using appropriate race and ethnic specific reference equations, or a race correction factor if one exists, for non-Caucasian individuals. As mentioned, the GLI³¹ presents validated spirometry reference values for Caucasian and three other ethnic groups (African-American, North-East Asian and South-East Asian). More data is required to determine suitable all-age reference values for the Indian subcontinent, Arab, Polynesian, Africa and Latin American countries,³¹ as well as Australian Aboriginal and Torres Strait Islander people.

The GLI report³¹ found that African-American and South-East Asian ethnicities have FEV₁ and FVC values 10-16% lower than Caucasians of similar height. The GLI predicted FEV₁ and FVC values for North-East Asians are however only 1-4% lower

than Caucasians. Furthermore, results from this initiative demonstrated that for these ethnic groups there is a proportionate reduction in FEV₁ and FVC and therefore the FEV₁/FVC ratio is minimally changed compared with Caucasian reference sets. This makes it possible to have a single correction factor across the whole age range for individual ethnic groups. The GLI findings described above are consistent with several earlier reports.^{45,98,99} For example, black Caribbean and Indian children in England have FEV₁ and FVC values up to 17% lower than Caucasian children.¹⁰⁰ While Yang *et al.*¹⁰¹ reported that Chinese and Indian individuals had 13-18% lower volumes for TLC, FVC and FEV₁ than Caucasians.

Reasons why lower reference values are found in some ethnic groups have been investigated but still remain largely unknown. Braun and colleagues¹⁰² conducted a systematic review on 226 articles comparing spirometry in 'other race' groups' to a 'white' population. The articles reviewed had made direct comparisons of lung function values between ethnic groups and had measured FEV₁, FVC and FEV₁/FVC%. The explanations for ethnic differences were grouped into four categories. The categories included inherent differences between racial/ethnic groups (24.3% of articles), anthropometric differences (29.4%), environmental differences (21%) and no explanation of differences (24.3%). Interestingly only 17.3% of papers actually defined the race/ethnicity. The majority of papers (83.6%) claimed that 'other race/ethnic groups' had lower spirometry, 5.8% demonstrated no difference or similar values, 4.4% had higher values and 6.2% had variable results when comparing to a 'white' population.

Kumar *et al.*⁹⁵ investigated the relative effects on lung size of mixed ancestry. Percent African ancestry was determined by genotyping informative markers in all patients across five study groups that self-identified as African-American. In both men and women, there were significant inverse relations between African ancestry and FEV₁ and FVC suggesting that at least some of the ethnic differences between Caucasian and African-Americans may be due to inherent differences. Donnelly *et al.*¹⁰³ investigated the contribution of physical characteristics to lung volume differences between Indian, Chinese and Caucasian subjects. They found Caucasian subjects to have wider chests and therefore greater TLC volumes when compared to Indian and Chinese individuals. The influence of socio-economic and psychological wellbeing is considerably smaller than genetic components and body size⁴⁰ however the impact of overcrowding, access to adequate living facilities and parental employment status have been shown to significantly impact lung function in several ethnic groups.^{47,103}

In light of data indicating an influence of ethnicity on spirometry values and the importance of reference values for clinical interpretation, it is necessary to determine whether currently available spirometry reference values are suitable for Indigenous Australians. My thesis addresses this through research questions 1 and 4 (chapters 2 and 6 respectively).

Ethnicity and FeNO

For FeNO, the mechanism by which ethnicity impacts results for healthy individuals is still largely unknown. Some studies have found there to be differences in the activity of NO synthase (the enzyme essential for NO production) and in allele frequencies of the NO synthase genes between different ethnic groups.¹⁰⁴⁻¹⁰⁶ Other contributing factors may include complex interactions between genetic and biological, and/or environmental factors i.e. diet, second hand smoking, air pollution, and socioeconomic status.^{27,72,107,108} None of these potential factors have been adequately tested in either Caucasian or non-Caucasian populations and preliminary results are inconsistent and require further investigation.

This research does not attempt to identify potential influencing factors on FeNO for this population, but rather to assess the appropriateness of recommended cut-off values for use by Indigenous Australians which are predominantly Caucasian-based. My thesis addresses this through research questions 2 and 5 (chapters 3 and 6 respectively).

1.1.6 Self-reported and medical record health history

Health history is typically obtained through self-reporting or medical record checks. It is well accepted in the literature that neither information source is a perfect method for collecting accurate health history and in fact, can lead to the over- and under-diagnosis of some conditions depending on which information source is used. Self-reported data is an inexpensive way to obtain relevant

information from a patient and can be administered on a national scale (e.g. health surveys). However, it is dependent on accurate patient recall¹⁰⁹ and understanding of conditions.^{110,111} While medical records may be more robust, they can be limited by incomplete/inaccurate recording of diagnostic information¹¹² and the complexities of disease coding.^{113,114}

These data discrepancies can pose significant problems not only to effective monitoring and targeting of conditions that impact Indigenous Australians, but also to research studies that use these information sources as a way of checking if participants meet inclusion/exclusion criteria. Amongst our cohort, we were interested to see whether one information source was more reliable than the other so as to confirm the most accurate process for identifying 'healthy' participants for research questions 4 and 5. Therefore, research question 3 sought to determine the agreement between the data sources for selected respiratory and atopic conditions that continue to impact Indigenous Australians (chapter 5).

1.2 Research aims and questions

In the absence of any Indigenous Australian reference values for spirometry or FeNO, the primary aim of this research is to determine the suitability of currently available reference values for this population. The secondary aim is to determine if there are differences in these lung function results between the three Indigenous Australian ethnic groups; that is, children and young adults who identify as Aboriginal, Torres Strait Islander or Aboriginal and Torres Strait Islander (Both).

Differences between the Indigenous ethnic groups would indicate that different reference values are needed for interpretation. Finally, the tertiary aim is to provide data on the agreement between information sources (self-reported vs. medical records) specific for respiratory and atopic conditions.

The specific research questions that underpin the aims of this PhD study are:

1. Do any of the published spirometry reference value studies for Aboriginal and/or Torres Strait Islander Australians meet current ATS/ERS guidelines?
2. Does ethnicity impact FeNO values and what are the potential implications?
3. How consistent is the information obtained from self-reported and medical records in this population?
4.
 - a) Is there a difference in spirometry values between participants who identify as Aboriginal, Torres Strait Islander or Both?
 - b) Which (if any) of the GLI-2012 reference equations are most suitable for Australian Indigenous children and young adults?

5. a) Is there a difference in FeNO values between participants who identify as Aboriginal, Torres Strait Islander or Both ?

b) Based on the distribution of FeNO values found, can current Caucasian-based FeNO cut-off values be applied to Indigenous children and young adults?

1.3 Research setting

This research was a cross-sectional study that aimed to recruit up to 1800 Aboriginal and Torres Strait Islander children and young adults aged between 3-25 years old from nine urban and remote communities across Queensland and the Northern Territory. This age bracket was targeted for recruitment as improving diagnosis and treatment of paediatric lung disease is likely to have a positive impact into adulthood. Respiratory infections, environmental and cultural factors^{20,92,115} can have significant effects on respiratory health during the lung growth years up to 25 years.⁴²

Study sites included Bamaga, Caboolture, Cherbourg, Dalby, Darwin, Horn Island, Murgon, Thursday Island, and Woorabinda and were examined for homogeneity. These communities are visited regularly by the Indigenous Respiratory Outreach Care (IROC) program specialist clinics. IROC is a Queensland Health funded program that delivers specialist respiratory clinical care and education to Indigenous communities throughout Queensland. The study was

conducted in consultation with, and with approval from, local Aboriginal and Torres Strait Islander Elders and key community members from each community.

Eligible participants were recruited from schools and the general community. Every possible effort was made to recruit as many individuals who fulfilled inclusion criteria. Once schools and key community members were identified, the study packs (which included information sheets, consent forms and questionnaires) were distributed by study staff and locally employed research assistants. Following completion of lung function testing, medical records of participants were checked to record birth details (i.e. gestational age and weight) and to identify any existing respiratory illnesses and related hospitalisations. Detailed methodology for this research is outlined in Chapter 4.

1.4 Significance of research

Although the gap (non-Indigenous vs. Indigenous Australians) in mortality from respiratory diseases has reduced significantly in the last decade,² respiratory diseases continue to directly impact the lives of many Indigenous Australians. Addressing lung health in childhood is a vital step in improving both quality of life and clinical outcomes, and in reducing long-term lung impairment into adulthood.^{116,117} Early diagnosis leading to appropriate management of respiratory diseases is crucial in improving clinical outcomes, as well as preventing unnecessary hospitalisations and the development of chronic lung disease.²⁶ Use of objective measures, such as spirometry and FeNO, aids in early diagnosis and monitoring of

respiratory diseases to guide on-going management.²⁶ As with other clinical measurements, these tests require comparison of an individual's results with 'normal' reference values achieved from a healthy population.³³

Reference values for lung function tests are affected by an individual's age, height, sex and ethnicity.^{30,31,33} While the influence of anthropometric measures (i.e. age, height and sex) are not controversial, the impact of ethnicity is less defined. Differences in lung function results between Caucasian and some non-Caucasian ethnic groups have been well documented in the literature.^{31,46,47} Despite this, ethnic specific reference values for spirometry and FeNO have not been well established for many of the world's ethnic groups, including Aboriginal and Torres Strait Islander Australians.^{118,119}

Given the importance of lung function testing on respiratory diagnosis and treatment, there is a need for accurate and validated reference values for basic lung function tests such as spirometry and FeNO in Indigenous Australians. The inappropriate use of currently available Caucasian reference values could lead to incorrect diagnosis subsequently impacting on treatment and disease progression. A set of Australian Indigenous specific reference values for spirometry and FeNO, which are developed according to current international guidelines, will improve the accuracy of test interpretation, and aid in diagnosis and clinical care.

1.5 Definition of terms

Indigenous Australian: an Aboriginal or Torres Strait Islander person who identifies as an Aboriginal or Torres Strait Islander and is accepted as such by the community in which he (or she) lives

Both: a person who identifies as being both Aboriginal and Torres Strait Islander

1.6 Thesis outline

This thesis consists of eight chapters, five of which are publications. Figure 1.2 outlines the research question and publication (if applicable) related to each chapter (see publication list, page xvi-xvii).

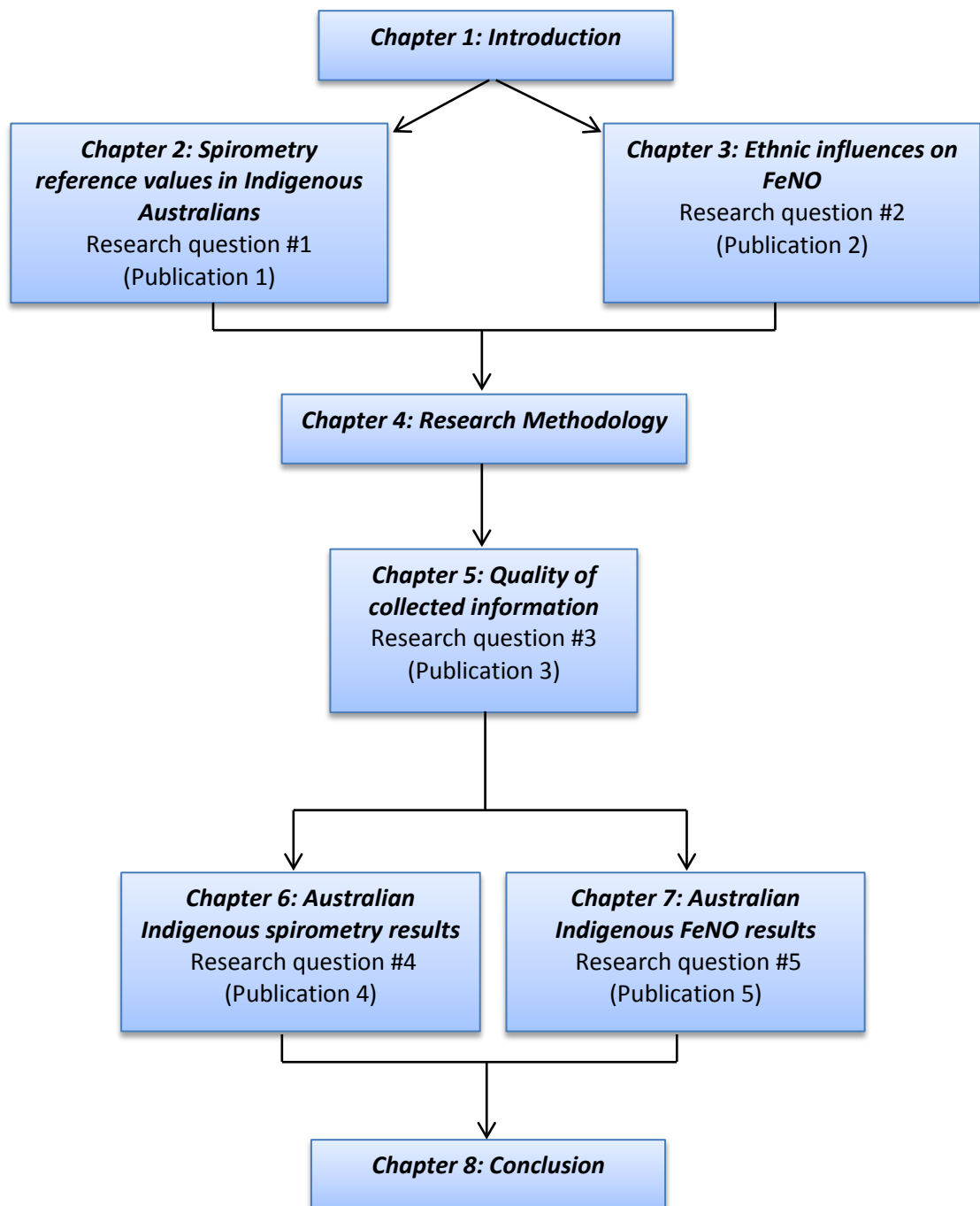


Figure 1.2 Flow diagram showing outline of thesis

Chapter 2: Spirometry reference values in Indigenous Australians: a systematic review (Article 1)

This chapter addresses **research question 1**: “Do any of the published reference value studies for Aboriginal and/or Torres Strait Islander Australians meet current ATS/ERS guidelines?” and consists of the following published article:

Blake TL, Chang AB, Petsky HL, Rodwell LT, Brown MG, Hill DC, Thompson B, McElrea MS. Spirometry reference values in Indigenous Australians: a systematic review. Med J Aust. 2016; 205(1): 35-40

Spirometry is internationally recommended to aid in the diagnosis of many respiratory diseases and to guide on-going management. However, its strength as a diagnostic tool is dependent not only the test being performed correctly but also in results being appropriately interpreted. As previously mentioned (section 1.1.3), a patients’ spirometry results should be compared to reference values obtained from a demographically similar ‘healthy’ population and the use of inappropriate reference values can have harmful ramifications for patients.

To our knowledge this review was the first to systematically examine studies that have measured spirometry in Indigenous Australians, and to evaluate the validity of the reference values used or reference equations developed. We found

that no study met all ATS, ERS or GLI criteria for developing a new or validating an existing reference equation. As such, it is still unknown as to what spirometry reference values should be used for this population. These findings highlighted the urgent need to develop a set of Indigenous Australian-specific reference values to improve the accuracy of test interpretation.

2.1 Abstract

Objective: To evaluate published spirometry data for Australian Aboriginal and Torres Strait Islander (Indigenous) peoples to determine (i) whether their ethnicity influenced spirometry results; and (ii) if any reliable spirometry reference values exist for Indigenous Australians.

Study design: Systematic review of published and grey literature.

Data sources: PubMed and Cochrane Library databases, references of included articles and appropriate grey literature. Last searches were conducted in April 2016.

Study selection: We included any study that performed spirometry on healthy Indigenous Australians and compared their results with those from people of European ancestry. Two authors independently screened titles and abstracts and then reviewed potentially relevant full-text articles for possible inclusion. We used PRISMA systematic review reporting methods to collate data.

Data synthesis: Of a possible 125 studies, 18 full-text articles were reviewed, but only nine fulfilled the inclusion criteria. None specified Torres Strait Islander inclusion. All studies reported lower spirometry values (as much as 30% lower) for Aboriginal people compared with non-Indigenous people. Five studies developed

spirometry reference values for Indigenous Australians; however, none adhered to all participant inclusion and exclusion criteria outlined by the American Thoracic Society and European Respiratory Society. Hence, reported results and subsequent reference values may not be a true representation of spirometry values in healthy Indigenous people.

Conclusions: The lower spirometry values reported for Indigenous Australians may be due to study limitations. Furthermore, there are currently no reliable spirometry reference values for Indigenous Australians that adhere to current guidelines. Developing a set of Indigenous Australian reference values will improve the accuracy of test interpretation and aid in the diagnosis of respiratory disease in this population.

2.2 Introduction

Respiratory illnesses are a significant contributor to the morbidity and mortality of Aboriginal and Torres Strait Islander (Indigenous) Australians across all ages.^{1,120} Previous studies have highlighted the high incidence of respiratory disease in Indigenous Australians.^{4,116} In adults, asthma¹²¹ and chronic obstructive pulmonary disease (COPD)²³ are the greatest contributors to the respiratory burden, with Indigenous Australians being 2.4 times more likely than non-Indigenous Australians to require hospitalisation.²

Spirometry is the most common test²⁶ used to aid the diagnosis and management of respiratory diseases. As with all clinical tests, there are standards for performance and interpretation of results.^{26,33} The latter requires comparing the patient's spirometry values (forced expiratory volume in 1 second [FEV₁] and forced vital capacity [FVC]) against reference values obtained from a representative "healthy" population matched for age, sex, height and ethnicity.^{33,36} The American Thoracic Society (ATS)³⁶ and European Respiratory Society (ERS)¹²² outline criteria for developing spirometry reference values that include recruiting individuals who (i) are lifelong non-smokers, (ii) are free from current respiratory symptoms or a diagnosed respiratory disease, and (iii) have spirometry performed in accordance with ATS/ERS test criteria.²⁶ When validating an existing or new reference set using software developed by the Global Lung Function Initiative (GLI),³¹ it is a requirement to have a minimum of 300 participants who meet these criteria.

Anthropometric measures have a significant influence on spirometry values. While the contribution of (and hence adjustment for) age, height and sex is not controversial, the impact of ethnicity is less well defined. The 2005 ATS/ ERS guidelines²⁶ recommend using ethnic-specific reference values to interpret spirometry results, but these do not exist for many of the world's ethnic groups. The GLI³¹ recently presented validated spirometry reference values for people of European ancestry and three other ethnic groups. African-American and South-East Asian groups were found to have FEV₁ and FVC values 10-16% lower than in people of European ancestry of matching sex, height and age, whereas values in North-East Asians were only 1-4% lower. Use of the correct reference values is important, as comparison against incorrect reference values could misclassify a person as having normal or abnormal lung function, and thus lead to possible misdiagnosis and either deprivation of necessary interventions or unwarranted overtreatment.

Given the high burden of respiratory disease in Indigenous Australians, the variations in ethnic adjustment factors and the implications for clinical care and outcomes, it is important to know how spirometry values in the Indigenous Australian population compare with those among people of European ancestry. This will inform what reference values or adjustment factors should be used. We undertook a systematic review of published and grey literature to explore community-based studies that reported on spirometry in healthy Indigenous Australians. Our objective was to determine whether (i) Aboriginal and Torres Strait Islander ethnicity influenced spirometry results; and (ii) any reliable healthy

reference values or equations for spirometry (based on ATS/ERS guidelines) existed for Indigenous Australians.

2.3 Methods

2.3.1 Search strategy

We identified studies by searching PubMed and Cochrane Library databases with the search text: (spirometry or forced expiratory volume) and (indigenous or native or Aboriginal or Torres Strait Islander) and (lung function or respiratory or pulmonary). The last searches were conducted in April 2016. We set no limit on the earliest date of publications to include. Details of the search strategy are outlined in Appendix A. We also searched bibliographies of included studies and key Indigenous Australian health-related websites (grey literature) to identify possible additional studies.

2.3.2 Eligibility criteria

Studies were included in the review if they: (i) recruited Australian Aboriginal and/or Torres Strait Islander people; (ii) performed spirometry; (iii) compared spirometry results of Indigenous participants with those of other ethnic groups (people of European ancestry or other) or a standard reference range; and (iv) included healthy community members.

Studies were excluded if they: (i) did not include a healthy comparison group; or (ii) were either comment articles or study protocols.

2.3.3 Study selection and data extraction

Two of us (TB and MM) independently reviewed the search results. We identified potentially relevant studies from titles, abstracts or descriptions, then retrieved the full-text articles for review. We used specified criteria to independently select studies from among the full-text articles for inclusion. It was planned that a third person (AC) would adjudicate any disagreements.

Data extracted from each included study were: study location and population source, number of participants and their age range, participants' medical history and smoking status, equipment used and parameters measured, exclusion criteria, comparison of spirometry results with those of a non-Indigenous population, statistical model used and factors examined. It was also noted whether the studies attempted to develop reference equations from their data. Any objective assessments (e.g. chest x-rays and medical examination, skin prick tests, airway hyper-responsiveness [AHR] and white blood cell counts) were also recorded.

We used the most appropriate method to grade the included studies in terms of quality, which was to examine their adherence to current ATS/ERS guidelines for developing or validating reference equations.

2.4 Results

The database search identified 125 potential studies. Of these, 18 full-text publications were obtained for consideration for inclusion. Nine studies were excluded after reviewing the full text, leaving nine articles for inclusion. No further relevant studies were identified through searching bibliographies or the grey literature. Reasons for publication exclusions are shown in Figure 2.1.

2.4.1 Study characteristics

The characteristics of the nine included studies are shown in Table 2.1. The studies took place in multiple locations around Australia: Queensland (3/9), Western Australia (3/9), Northern Territory (2/9), and both Queensland and the Northern Territory (1/9). All participants were recruited from rural and remote communities. Of the nine studies, four involved children and/or adolescents, one study focused solely on adults, and four studies included both children and adults. Overall, the studies recruited individuals aged about 5–85 years, although three of the studies did not record the oldest participant age. Seven of the studies tested participants of Aboriginal descent only, while two studies tested both non-Indigenous and Aboriginal Australians. No study stated inclusion of Torres Strait Islander people.

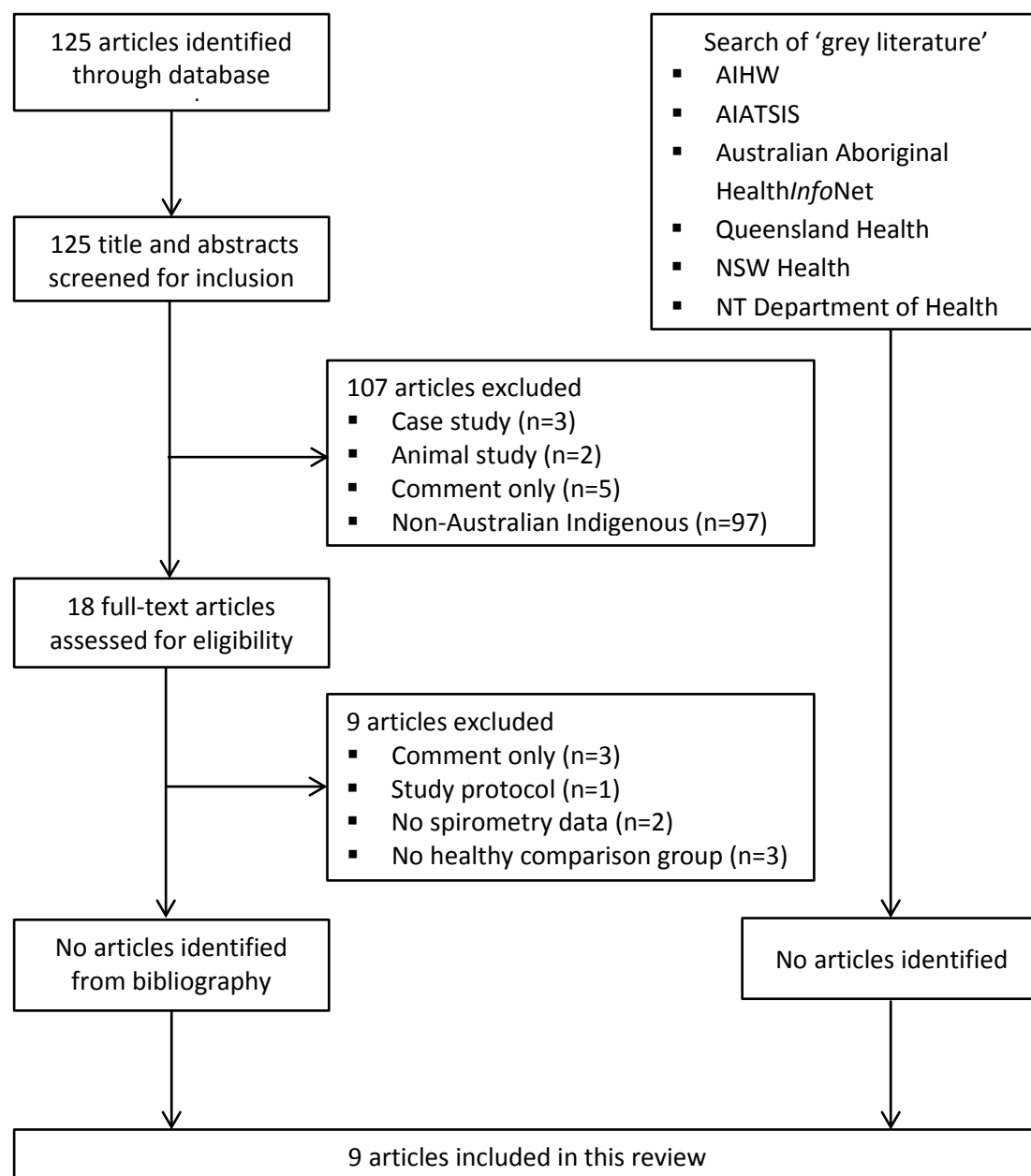


Figure 2.1 PRISMA flowchart of included/excluded articles for Australian Indigenous spirometry systematic review

AIHW: Australian Institute of Health and Welfare; **AIATSIS:** Australian Institute of Aboriginal and Torres Strait Islander Studies; **NSW:** New South Wales; **NT:** Northern Territory

The type and depth of data obtained from the nine studies differed greatly. Atopy was objectively measured in two studies: using the skin prick test in one, and skin prick test and IgE serology in the other. Three studies assessed atopy status

during physical examinations and/or by reviewing medical records, while the remaining four did not report any atopy information.

Respiratory history and current health were assessed using questionnaires and/or AHR tests in three studies, questionnaires and chest x-ray in one study and questionnaires alone in one study. Five studies reviewed medical charts to obtain previous hospitalisation data, and three studies recorded birth history. Physical examinations were undertaken in two studies. Smoking status was recorded in seven studies, but none used objective measures. Three studies used the British Medical Research Council questionnaire to assess previous and current smoking history. Three studies relied on self-reporting of current smoking status only, while one study asked only about mothers' smoking history during pregnancy (maternal smoking).

Table 2.1 Description of the nine included studies

Study/Year	Location	Sample size	Age range (years)	Medical history and other data	Smoking status data	Equipment used	Exclusion criteria in publication	Final sample size
Musk <i>et al.</i> 2008 ¹²³	WA – rural	251	>5	Questionnaire (respiratory), IgG	Questionnaire	Vitalograph	Unable to perform test (n=20)	230
Bucens <i>et al.</i> 2006 ¹⁴	NT – remote and rural	547	8-14	Physical examination, medical chart review	Self-reported (Maternal only)	Vitalograph	Unable to perform test (n=130)	417
Verheijden <i>et al.</i> 2002 ¹²⁴	WA – remote	Not recorded	>5	Questionnaire (respiratory), medical chart review, skin-prick test, AHR, white cell count, IgE	Questionnaire	Vitalograph	Nil	292
Bremner <i>et al.</i> 1998 ¹¹⁵	WA – very remote	225	5-85	Questionnaire (respiratory), skin-prick test, AHR	Questionnaire	Vitalograph	Unable to perform test (n=18)	207 (82<18yrs.) (125≥18yrs.)

Veale <i>et al.</i> 1997 ¹²⁵	Qld and NT – all rural	1161	7-80	Physical examination, AHR	Self-reported	Mijnhardt VRS 2000	Loose/chronic cough, wheeze, positive AHR, unable to perform test (n=134), known respiratory disease	593 (261 <20yrs.) (332 ≥20yrs.)
Thompson <i>et al.</i> 1992 ¹²⁶	Qld – rural	288	>20	Questionnaire (respiratory), medical chart review, chest x-ray	Self-reported	Vitalograph	Known respiratory disease, abnormal chest x-ray, loose cough, unable to perform test (n=2), < 60% lung function	229
Watson <i>et al.</i> 1986 ¹²⁷	NT – remote	154	11-15	Not recorded	Self-reported	Vitalograph	Nil	151
Chandler <i>et al.</i> 1980 ¹²⁸	Qld – remote	92	5-13	Medical chart review (birthweight and weight at 1 year)	Not recorded	Vitalograph	Unable to perform test (n=36)	56
Chandler <i>et al.</i> 1979 ¹²⁹	Qld – rural	Not recorded	5-13	Medical chart review (birthweight and weight at 1 year)	Not recorded	Vitalograph	Nil	203

AHR: airway hyper-responsiveness; **IgE:** immunoglobulin E; **IgG:** immunoglobulin G; **NT:** Northern Territory; **Qld:** Queensland; **WA:** Western Australia

2.4.2 Reported spirometry results

Comparisons of spirometry values of the Indigenous cohorts with other data are summarised in Table 2.2. Of the nine studies, only two^{115,127} directly compared results for Indigenous Australian participants with those of non-Indigenous Australians recruited to the study. The remaining seven studies compared results with previously published data; however, two studies^{14,123} did not specify the reference sets used. All of the studies reported spirometry values in Indigenous people to be lower than those in people of European ancestry. However, there was a large variation in the differences observed. For example, Chandler and colleagues¹²⁸ noted Indigenous FEV₁ and FVC values to be $\leq 15\%$ lower, whereas the studies by Verheijden and colleagues¹²⁴ and Veale and colleagues¹²⁵ reported results to be as much as 30% lower. Musk and colleagues¹²³ and Bucens and colleagues¹⁴ noted that their spirometry results were similar to previous studies and lower than those in people of European ancestry, but did not specify how much lower.

Inconsistencies between the studies in how individuals were excluded from the sample population may have influenced results. Three studies reported no exclusion criteria (see Table 2.1). Six studies specified exclusion criteria, including not being able to perform the spirometry test. Two studies^{125,126} excluded participants with known or current respiratory symptoms or illnesses, but only Thompson and colleagues¹²⁶ confirmed this by reviewing medical charts. No study excluded participants with current or previous smoking history.

Table 2.2 Comparison of spirometry results between Indigenous Australians and people of European ancestry

Study/Year	Statistical model	Factors significant to spirometry results*	Comparison population data	Observed variation (Indigenous Australian vs. European ancestry)
Musk <i>et al.</i> 2008 ¹¹¹	LR	Age, sex, height, weight, smoking	Unknown [†]	Lower (non-specified)
Bucens <i>et al.</i> 2006 ¹⁴	LR	Age, sex, height, birth weight, gestational age, non-Aboriginal ancestry, residence, cough, hospitalisations for respiratory illness	Unknown [†]	Lower (non-specified)
Verheijden <i>et al.</i> 2002 ¹¹²	Chi-squared, student t-tests	Respiratory symptoms, white blood cell count	James <i>et al.</i> ^{130†}	≤ 30% lower
Bremner <i>et al.</i> 1998 ¹⁰³	LR, non-LR	Age, sex, height, race, asthma, wheezing, cough, atopy, AHR	1020 recruited participants [‡]	≤ 25% lower
Veale <i>et al.</i> 1997 ¹¹³	MLR	Age, sex, height, smoking	Gore <i>et al.</i> ^{131†}	≤ 30% lower
Thompson <i>et al.</i> 1992 ¹¹⁴	MLR	Age, sex, height, smoking	Gibson <i>et al.</i> ^{132†}	≤ 25% lower
Watson <i>et al.</i> 1986 ¹¹⁵	MLR	Age, height, sex	246 recruited participants [‡]	≤ 20% lower
Chandler <i>et al.</i> 1980 ¹¹⁶	ANOVA	Age, height, weight	Polgar <i>et al.</i> ^{133†}	≤ 15% lower
Chandler <i>et al.</i> 1979 ¹¹⁷	MLR	Age, height, weight	Polgar <i>et al.</i> ^{121†}	≤ 25% lower

*: Statistically significant; †: Published Caucasian data; ‡: Caucasian participants recruited as part of study; **AHR**: airway hyper-responsiveness; **ANOVA**: analysis of variance; **LR**: linear regressions; **MLR**: multiple linear regressions

All included studies involved prospective cohort groups and all followed appropriate ATS/ERS criteria when performing spirometry. The aims of the studies differed and included observing lung function,¹²⁸ examining influencing factors^{14,123,124} and developing reference equations for spirometry in Indigenous Australians (n=5).^{115,125-127,129} None of the included studies followed all of the ATS/ERS and GLI criteria needed to develop reference equations or validate spirometry results (Table 2.3). Only two studies^{14,125} recruited more than 300 participants, the minimum number required to validate new reference values for an ethnic population, according to GLI criteria.³¹

Table 2.3 Suitability of Indigenous spirometry data for developing healthy reference values, according to current ATS/ERS and GLI criteria

Study/Year	Study aim	ATS/ERS and GLI criteria			Validated according to criteria?
		No smoking history	No respiratory history or symptoms	≥300 participants	
Musk <i>et al.</i> 2008 ¹¹¹	Examine influence of previous infections on lung function	x	x	x	x
Bucens <i>et al.</i> 2006 ¹⁴	Examine influencing factors on lung function	x	x	✓	x
Verheijden <i>et al.</i> 2002 ¹¹²	Examine differences in respiratory health between two communities	x	x	x	x
Bremner <i>et al.</i> 1998 ¹⁰³	Examine prevalence of influencing factors on lung function and compare against data for people of European ancestry	x	x	x	x
Veale <i>et al.</i> 1997 ¹¹³	Develop reference equations	x	✓	✓	x
Thompson <i>et al.</i> 1992 ¹¹⁴	Develop reference equations	x	✓	x	x
Watson <i>et al.</i> 1986 ¹¹⁵	Develop reference equations	x	x	x	x
Chandler <i>et al.</i> 1980 ¹¹⁶	Observe lung function in an Aboriginal community	x	x	x	x
Chandler <i>et al.</i> 1979 ¹¹⁷	Measure residual lung damage from childhood infections and develop reference equations	x	x	x	x

ATS: American Thoracic Society; **ERS:** European Respiratory Society; **GLI:** Global Lung Function Initiative

2.5 Discussion

To our knowledge this is the first systematic review to critically examine studies that have measured spirometry in Indigenous Australians, and to evaluate validity of the reference values used or reference equations developed. All included studies reported lower spirometry values (15-30% lower) in Indigenous Australians compared with people of European ancestry. No study indicated having any Torres Strait Islanders participants. The reported differences seen in these studies are even greater than those observed between many other ethnic populations and people of European ancestry.^{31,44,98-101} However, as none of the studies adhered to the current ATS/ERS and GLI guidelines for spirometry reference data collection in healthy populations, it remains unknown if the reported lower levels reflect the true healthy reference range for Indigenous Australians. Application of the results from these studies to reference values in the clinical setting is therefore not appropriate, and further studies are required to develop suitable Indigenous-specific reference values for this population.

Validated ethnic appropriate reference values are essential for correct interpretation of spirometry results, which subsequently influences diagnosis of disease (e.g. COPD) and the severity of disease (e.g. asthma). We found five studies^{115,125-127,129} that developed reference equations for Aboriginal Australians. However, these studies lacked the rigorous exclusion criteria and appropriate participant numbers essential for developing or validating reference values for spirometry. While most studies excluded participants with respiratory symptoms (i.e. known respiratory conditions, presence of cough or wheeze), no study also

excluded participants who had a history of smoking or evaluated past history adequately. Exclusion of participants who have previously been hospitalised for respiratory infections (especially in childhood) is important as it is well known that these are associated with lower lung function and chronic respiratory diseases such as COPD and bronchiectasis.^{116,117} Furthermore, the sample size of all studies were small, with only two studies^{14,125} recruiting more than 300 participants, the minimum number required by the 2012 GLI guidelines.³¹

Comparison of the reference equations developed in the studies highlights the potential for misinterpreting and misdiagnosing respiratory disease in the Indigenous population (Table 2.4). For example, in a hypothetical scenario, the reference equation for children generated by Watson and colleagues¹²⁷ predicted FEV₁ and FVC values up to 500 mL greater than those in the other three studies that developed reference equations for children.^{115,125,129} Results for predicted FEV₁ and FVC values were also markedly different between the three studies that developed adult reference equations. Thompson and colleagues¹²⁶ predicted FEV₁ and FVC values up to 400 mL and 300 mL greater, respectively, than those predicted by Veale and colleagues¹²⁵ and Bremner and colleagues.¹¹⁵ The end result of these differences is that some of the reference values developed in these studies would report lung function to be normal, while others would indicate the presence of disease in both children and adults.

Table 2.4 Interpretation of lung function results using five different reference equations

	Child scenario: 12 year old boy, 145 cm tall, achieved FEV ₁ =1.85 L		Adult scenario: 25 year old man, 170 cm tall, achieved FEV ₁ =2.70 L	
	Predicted FEV ₁	% predicted, Interpretation*	Predicted FEV ₁	% predicted, Interpretation*
Bremner <i>et al.</i> 1998 ¹⁰³	2.21 L	84% borderline	3.11 L	86% normal
Veale <i>et al.</i> 1997 ¹¹³	2.02 L	92% normal	2.97 L	91% normal
Thompson <i>et al.</i> 1992 ¹¹⁴	N/A	N/A	3.40 L	79% low – disease
Watson <i>et al.</i> 1986 ¹¹⁵	2.57 L	72%†	N/A	N/A
Chandler <i>et al.</i> 1979 ¹¹⁷	2.00 L	93%†	N/A	N/A

*: Interpretation based on lower limit of normal (not shown); †: Insufficient data for calculation of lower limit of normal; **FEV₁**: forced expiratory volume in 1 second; **N/A**: not applicable

The possible reasons given by the studies' authors for the lower spirometry values observed in Indigenous Australians included external factors (i.e., asthma, smoking, cough, repeated childhood infections) affecting lung growth during childhood^{14,115,123} and suboptimal environmental conditions causing a faster decline in lung function during adulthood.^{125,126} Differences between participant recruitment sites were considered the primary factor causing variation in spirometry results in Verheijden and colleagues' study,¹²⁴ as they noted lower spirometry values and more prevalent respiratory symptoms in the desert community compared with the tropical community. These factors, as well as access to quality health care, malnutrition, high levels of smoke exposure, premature birth and low birthweight, have been acknowledged in previous studies⁴⁴⁻⁴⁷ as negatively

influencing respiratory health in these populations. However, the differences observed between the studies in terms of the influence of population differences may have been due to study designs (e.g., rural and remote recruitment, pathogen testing).

Examining the effect of ethnicity on lung function is complicated by the fact that 'ethnicity' often includes other influences such as social and cultural factors,⁴³ socioeconomic status,⁹² nutritional status (diet trends),⁴⁶ achieved educational level⁴⁷ and genetic factors from diverse backgrounds.⁹⁵ These factors are often difficult to quantify and measure. Unlike age or height, it is not yet known what influence ethnicity has on the development, decline and overall state of lung function in an individual. Also, self-identified Indigenous Australians are likely to have a range of Indigenous genetic ancestry, which may further affect interpretation of lung function measurements. It is therefore necessary to examine healthy lung function results from both Aboriginal and Torres Strait Islander populations. Comparison of results between the two populations will determine if a single Indigenous reference equation is clinically appropriate or if two ethnic-specific equations are needed.

All the studies included in this review have important shortcomings that limit the reported findings. In previous studies conducted by members of our group using unadjusted values for spirometry, Indigenous children with lung disease (specifically asthma¹³⁴ and bronchiectasis¹³⁵) often had results within the healthy range for

people of European ancestry. For example, the mean FEV₁ and FVC values in the asthma study were 95% predicted (SD, 18%) and 100% predicted (SD, 17%), respectively.¹³⁴ It is possible that a study that includes only healthy Indigenous Australians (strictly defined and with careful examination of medical history) will find spirometry reference values for Indigenous Australians similar to those for people of European ancestry, or requiring only a small adjustment factor.

Our systematic review also has some limitations. It was restricted to only nine studies and the differences between the studies in terms of methods and reporting of results affected our ability to make direct comparisons between them.

2.6 Conclusions

In conclusion, Indigenous Australians may have a healthy lung function range that differs from that in people of European ancestry, and ethnic-specific spirometry reference values should be investigated according to strict guidelines to ensure proper clinical applicability. While our systematic review found lower lung function values in Indigenous Australians compared with people of European ancestry, there were limitations in all of the studies. None of the studies provided a reliable set of Aboriginal or Torres Strait Islander spirometry reference values that could be validated against ATS/ERS criteria. It therefore remains inconclusive as to what spirometry reference values should be used when testing Indigenous Australians. Given the importance of spirometry testing on respiratory diagnosis and treatment, there is an urgent need for accurate and validated reference values

for Indigenous Australians. The inappropriate use of reference values developed for people of European ancestry could lead to a false-positive or false-negative diagnosis, subsequently affecting treatment and disease progression. Developing a set of Indigenous Australian-specific reference values for spirometry, according to current guidelines, will improve the accuracy of test interpretation, aid in diagnosis and clinical care and reduce morbidity from respiratory disease. Until these reference values are known, health care professionals should be aware of the limitations of using an ethnic correction or adjustment factor when managing Indigenous patients.

2.7 Acknowledgements

The Indigenous Respiratory Outreach Care (IROC) Program received funding under the Queensland Aboriginal and Torres Strait Islander Health Investment Strategy for this work, through the Queensland Aboriginal and Torres Strait Islander Health Unit of Queensland Health. Anne Chang is supported by a National Health and Medical Research Council Practitioner Fellowship (1058213).

Chapter 3: Does ethnicity influence fractional exhaled nitric oxide (FeNO) in healthy individuals? a systematic review (Article 2)

This chapter addresses **research question 2**: “Does ethnicity impact FeNO values and what are the potential implications?” and consists of the following published article:

Blake TL, Chang AB, Chatfield MD, Petsky PL, Rodwell LT, Brown MG, Hill DC, McElrea MS. Does ethnicity influence fractional exhaled nitric oxide (FeNO) in healthy individuals? a systematic review. CHEST. 2017; 152(1): 40-50

Fractional exhaled nitric oxide (FeNO) has been increasingly used as a simple test for assessing eosinophilic airway inflammation and aiding in the management of asthma in both children and adults. However, it is well acknowledged that FeNO values are affected by a range of factors (such as respiratory infections, age, atopy, smoking status, environmental and socioeconomic determinants) that make development of reference equations challenging and at this stage, ineffective for use in the wider population (see section 1.1.4). The potential influence of ‘ethnicity’ on FeNO values has not been widely researched.

To our knowledge this review was the first to explore ethnicity solely as a potential factor influencing FeNO values in healthy adults and children of non-Caucasian ethnic groups. No study has been conducted with Australian Indigenous participants. We found that ethnicity does influence FeNO values and that in some non-Caucasian ethnic groups; this influence may impact clinical interpretation according to current guidelines. These findings highlight the need to evaluate healthy FeNO values of non-Caucasian ethnic groups so as to improve the clinical utility of FeNO.

3.1 Abstract

Background: Fractional exhaled nitric oxide (FeNO) is used clinically as a biomarker of eosinophilic airway inflammation. Awareness of the factors influencing FeNO values is important for valid clinical interpretation.

Methods: We undertook a systematic review of PubMed, Cochrane Library, Scopus, and Web of Science databases and reference lists of included articles to evaluate whether ethnicity influences FeNO values, and to determine if this influence affects clinical interpretation according to current guidelines. We included all studies that performed online FeNO measurements on at least 25 healthy, non-Caucasian individuals, and examined the effect of ethnicity on FeNO.

Results: From 62 potential studies, 12 studies were included. One study recruited only children (<12 years), six studies recruited children and/or adolescents, four studies recruited adults only, and a single study involved children, adolescents, and adults. In total, 16 different ethnic populations representing 11 ethnicities were studied. Ethnicity was considered a significant influencing factor in 10 of the included studies. We found the geometric mean FeNO to be above the normal healthy range in two studies. We also identified five studies in which at least 5% of participants had FeNO results above the age-specific inflammatory ranges.

Conclusion: Ethnicity influences FeNO values, and for some ethnic groups this influence likely affects clinical interpretation according to current guidelines. There

is a need to establish healthy FeNO reference ranges for specific ethnic groups in order to improve clinical application.

3.2 Introduction

Fractional exhaled nitric oxide (FeNO) is regarded as a simple, non-invasive method for assessing eosinophilic airway inflammation.^{58,78,136} Produced by a variety of cells within the lungs, nitric oxide (NO) concentrations are generally low in healthy individuals.⁵⁹ However, high concentrations of NO appear to be involved in non-specific host defence mechanisms (particularly Th2-mediated responses), and chronic inflammatory diseases such as asthma.^{59,137} The American Thoracic Society (ATS) therefore has recommended using FeNO to aid in the diagnosis and monitoring of eosinophilic airway inflammation and asthma, and for identifying steroid responsive individuals whose chronic respiratory symptoms may be due to airway inflammation.⁵⁸

For FeNO to be reliable as a biomarker, it is important to know factors that influence FeNO values. Currently, it is known that FeNO values are influenced by respiratory infections,^{66,67} atopy,^{68,69,138} presence of eosinophils,¹³⁹ age,^{70,140} gender,⁶⁸ height,^{70,77} smoking,^{70,141} environmental factors,^{72,108} and possibly ethnicity.^{58,142,143} Current guidelines recommend the use of cut-off values⁵⁸ which are presently based solely on age. For example, FeNO levels in adolescents and adults (>12 years old) of >50 parts per billion (ppb) suggest that eosinophilic inflammation is present and, in symptomatic patients, potential responsiveness to inhaled corticosteroid (ICS) treatment. The corresponding cut-off value in children (<12 years old) is >35 ppb.⁵⁸ When the individual's FeNO value is in the intermediate range (25-50 ppb for adults and 20-35 ppb for children), it is recommended that "results should be interpreted cautiously and with reference to the clinical

context”.⁵⁸ Eosinophilic inflammation is considered unlikely with FeNO values <25 ppb in adults and adolescents or <20 ppb in children.⁵⁸ Notably, factors important in predicted values of other pulmonary function tests (e.g. sex, height, and ethnicity) were not considered in the recommended cut-off FeNO values.

Since the 1990’s the ATS/ERS (European Respiratory Society) has recommended that respiratory function reference values should be obtained from representative healthy populations that closely match (age, sex, height, and ethnicity) those presenting in the clinical setting.^{33,36} Despite this, there are still little data on normal values in adults and children of non-Caucasian ethnic groups for FeNO. There is strong agreement in the literature^{58,70,76} for the need to develop reference ranges for evaluating FeNO values in these groups. However, there is currently no published systematic review on the influence of ethnicity on FeNO values in healthy children and adults.

Thus, we undertook a systematic review of published literature to explore ethnicity as a potential factor influencing FeNO values in healthy adults and children of non-Caucasian ethnic groups. In this review, ethnicity refers to a group of people who identify with each other based on common ancestral, social, cultural, or national experiences including languages, art, religious symbols, and physical appearance.^{102,144} Our primary objective was to evaluate if ethnicity influenced FeNO levels in studies of healthy cohorts. Given the importance of cut-offs, we also

evaluated if an ethnic influence affected the clinical interpretation according to current guidelines.⁵⁸

3.3 Methods

3.3.1 Search strategy

Studies were identified by searching the PubMed, Cochrane Library, Scopus, and Web of Science databases with the search text: (exhaled nitric oxide or FeNO or eNO) and (race or ethnic or non-Caucasian) and (normal or healthy or well or asymptomatic). Latest searches were performed in December 2016, and there were no language exclusions. Abstracts, reviews, and comments were not included. Reference lists of relevant articles were also searched.

3.3.2 Eligibility criteria

Studies were included in the review if they (i) recruited healthy, non-Caucasian individuals; (ii) explored race or ethnicity as a factor influencing FeNO measurements; (iii) performed FeNO measurements in line with international recommendations; and (iv) identified the type of NO analyser used.

Studies were excluded if they (i) recruited <25 healthy non-Caucasian subjects; (ii) included individuals with chromosomal or other genetic conditions; or (iii) performed offline FeNO measurements.

3.3.3 Study selection and data extraction

Two authors (TB and MM) independently reviewed the searches. Potentially relevant studies were identified from titles, abstracts, and/or descriptions and then retrieved for full review. We also conducted searches of bibliographies to identify additional studies. The authors then independently selected trials for inclusion from the full text using specific criteria. A third person (AC) was available to adjudicate any disagreement.

Data were extracted in duplicate from each study and included the following: study location and population source, number of participants and age range, medical history, smoking status/history, analyser used, exclusion criteria, statistical model used, factors examined and found significant, and measured FeNO levels. The source of clinical information was noted if available. For example, it was noted whether atopy was recorded via clinical history only, self-reported on questionnaires or via formal laboratory testing (IgE).

3.3.4 Statistical analysis

Where possible, the geometric mean and the standard deviation of FeNO were obtained for each population. Assuming that FeNO is log-normally distributed, we estimated the 5th and 95th percentiles for each population making use of the relationship between the standard deviation (SD) on the original scale, the SD on the log scale (σ) and the geometric mean (geomean), that is; $SD^2 = (\exp[\sigma^2] - 1) \times$

$\exp(2 \times \log[\text{geomean}] + \sigma^2)$. All statistical analysis was performed by a statistician (MC) with Stata13 software (StataCorp).

3.4 Results

The search identified 62 potential studies (26 in PubMed, one in Cochrane, 20 in Scopus and 15 in Web of Science). After title and abstract screening, 11 publications were retrieved for full-text review. Two studies were further excluded as they did not contain sufficient FeNO data to comment on. Screening of reference lists identified three studies to be included in the review. This resulted in 12 articles for inclusion. Reasons for paper exclusions are shown in Figure 3.1.

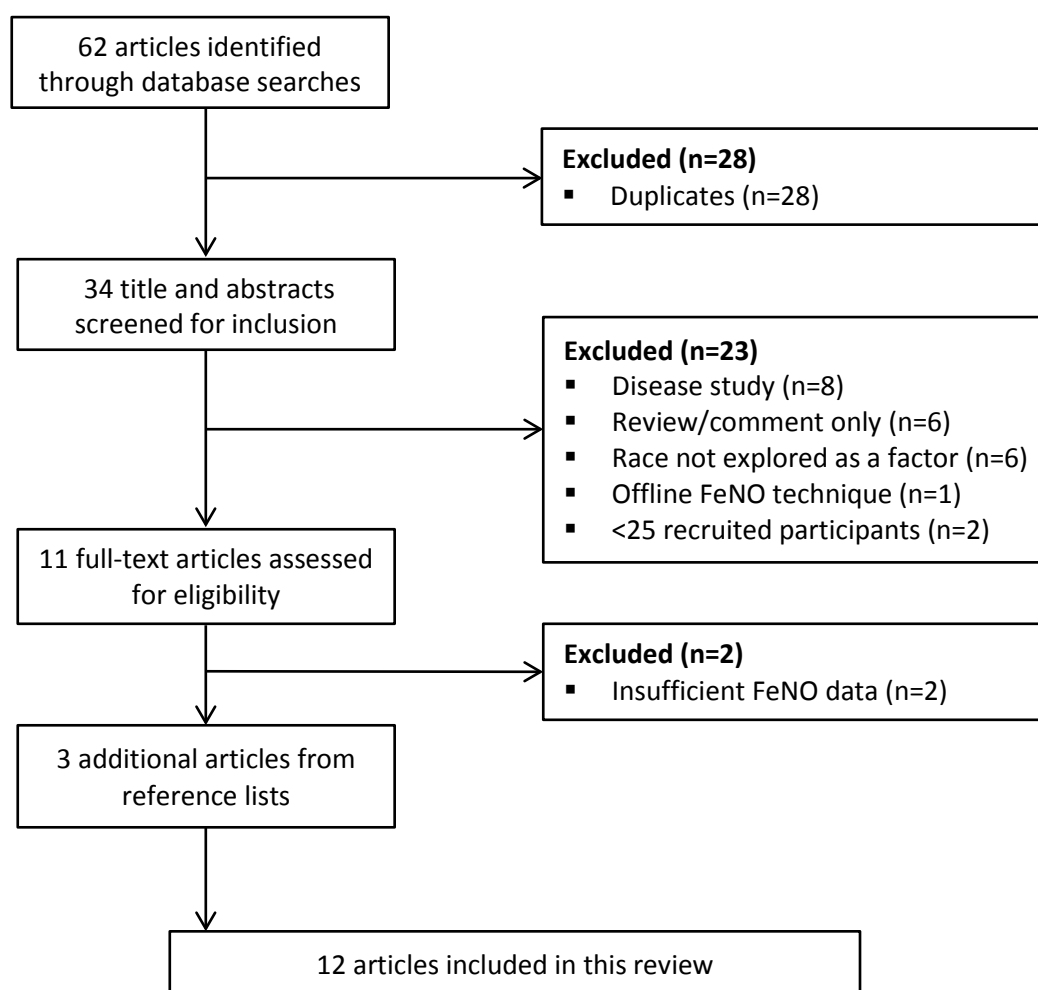


Figure 3.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of included/excluded articles for FeNO systematic review

FeNO: fractional exhaled nitric oxide

3.4.1 Study characteristics

Of the 12 studies, one (8%) study only recruited children (<12 years of age), one (8%) study only recruited adolescents (12-18 years of age), five (42%) studies included children and adolescents (12-18 years of age) as a grouped sample, four (33%) studies focused solely on adults, and one study (8%) included all ages. There were 16 different ethnic populations (children or adults) studied representing 11 ethnicities (Hispanic, African-American, African-Canadian, North-African Arab,

Pacific Islander/Maori, Japanese, Korean, Chinese, Taiwanese, South-Asian [in England], and Asian-Canadian). All participants were selected from schools or the general population.

The studies differed greatly in the type and extent of information obtained. The sample size of the ethnic populations ranged from 31¹⁴⁵ to 1798 participants.¹⁴⁶ Atopy was assessed objectively in seven (58%) studies using skin prick test and/or IgE levels. Three (25%) studies relied on questionnaire data only, whereas two (17%) studies sought no information regarding atopy. Respiratory history and/or current health were assessed by respiratory examination in two (17%) studies, spirometry and clinical examination and/or questionnaire in four (33%) studies and questionnaires alone in three (25%) studies. Smoking status was collected for all of the included studies.

There was a variety of approaches used in the studies to statistically examine potential determinants of FeNO values. Multiple linear regression (MLR) was the predominant analysis method used (n=9, 75%). Exclusion criteria used in the studies varied and included known respiratory disease/illness diagnosis (n=11, 92%); presence of other chronic diseases, asthma and/or atopy (n=6, 50%); premature birth (n=3, 25%); and smoking history (n=2, 17%). The characteristics of the included studies are outlined in Table 3.1.^{107,143,145-154}

Table 3.1 Description of studies included in review

Study/Year	Ethnic group (Location)	Total Sample Size	Age Range, years (No. ^a)	Medical History; Other Data	Analyser Used	Exclusion Criteria	Statistical Model	Factors Influencing ^b FeNO
Baptist <i>et al.</i> 2015 ¹³⁵	African-American (USA)	128	7-18 (72)	Questionnaire (atopy, history); skin prick test, spirometry	NIOX MINO (Aerocrine)	Respiratory disease (other than asthma), cardiac conditions	MLR, logistic regression	Ethnicity, atopy, spirometry results, asthma
Brody <i>et al.</i> 2013 ¹³⁴	African-American (USA) Hispanic (USA)	4718 (combined)	6-11 (216) 12-19 (224) 20-79 (489) 6-11 (446) 12-19 (356) 20-79 (996)	Clinical history, respiratory exam	NIOX MINO (Aerocrine)	Asthma, respiratory symptoms or disease	Univariate and multiple regression (logFeNO)	Ethnicity, age, height, time of testing, ECP
Ko <i>et al.</i> 2013 ¹³⁶	Chinese (China)	1113	18-90 (1093)	IgE, skin prick test	Sievers NOA280i (GE Analytical Instruments)	Respiratory disease	MLR (logFeNO)	Ethnicity, sex, age, height, skin test atopy, IgE, ECP
Rouatbi <i>et al.</i> 2012 ¹³⁷	North African Arab (Tunisia)	354	6-16 (211)	Questionnaire (atopy, history), clinical history	HypAir (Medisoft)	Respiratory disease, atopic conditions, premature birth, other chronic conditions	Univariate and multiple regression	Ethnicity, spirometry results

Yao <i>et al.</i> 2012 ¹³⁸	Taiwanese (Taiwan)	1717	5-18 (693)	IgE, respiratory exam	CLD88sp (EcoMedics)	Respiratory disease, atopic conditions, premature birth, other chronic conditions	Univariate and multivariate analysis (logFeNO)	Ethnicity, age, height, BSA, spirometry results, IgE, ambient NO, atopy, time of testing, drinking water
Sonnappa <i>et al.</i> 2011 ¹³³	South-Asian (England)	68	4-7 (31)	Clinical history, respiratory exam; skin prick test, spirometry	CLD88sp (EcoMedics)	Respiratory disease, atopic conditions, premature birth, other chronic conditions	Univariate, MLR	Ethnicity, skin test atopy
Matsunaga <i>et al.</i> 2010 ¹³⁹	Japanese (Japan)	240	18-74 (197)	Questionnaire (atopy)	NIOX MINO (Aerocrine)	Respiratory disease, atopic conditions, smoking	Regression tree based model (logFeNO)	None
Kim <i>et al.</i> 2010 ¹⁴⁰	Korean (Korea)	263	20-68 (166)	Questionnaire (atopy, history); skin prick test, spirometry	Sievers NOA280i (GE Analytical Instruments)	Smoking, asthma, respiratory illness, recent airway infection	MLR	Ethnicity, sex, atopy,
Levesque <i>et al.</i> 2008 ⁹⁵	African-American (USA)	994	18-40 (895)	Questionnaire (respiratory); IgE, CRP	Sievers NOA280i (GE Analytical Instruments)	Asthma, respiratory symptoms or disease, other chronic conditions	Univariate, MLR (logFeNO)	Ethnicity, sex, current URI symptoms, IgE, ECP

Kovesi <i>et al.</i> 2008 ¹⁴¹	African-Canadian (Canada)	2298 (combined)	9-13 (32)	Questionnaire (ARI); Spirometry	CLD88sp (EcoMedics)	Respiratory illness, asthma, other chronic diseases	Univariate and multivariate analysis (logFeNO)	Ethnicity, age, height
	Asian-Canadian (Canada)		9-13 (70)					
Edwards <i>et al.</i> 2005 ¹⁴²	Pacific Island/Maori (New Zealand)	164	5-17 (76)	Questionnaire (atopy, history); IgE, skin prick test	Model LR 2000 (Logan Research Ltd)	Respiratory disease	Logistic and linear regression	None
Wong <i>et al.</i> 2005 ¹³¹	Chinese (China)	531	12-18 (258)	Questionnaire (atopy)	NIOX MINO (Aerocrine)	Nil	Student t-test, Spearman's rank correlation (logFeNO)	Ethnicity, sex

a: The final size of each ethnic population tested after exclusion criteria was applied to the total sample; **b:** Influencing or having significant association

ARI: acute respiratory infection; **BSA:** body surface area; **CRP:** C-reactive protein; **ECP:** eosinophil cationic protein; **FeNO:** fractional exhaled nitric oxide; **IgE:**

immunoglobulin E; **MLR:** multiple linear regression; **NO:** nitric oxide; **URI:** upper respiratory infection; **USA:** United States of America

3.4.2 Influence of ethnicity on FeNO levels

FeNO results were predominately reported as either the arithmetic (n=6, 50%) or geometric (n=5, 42%) means. One study (8%) reported the median FeNO result. The influence of ethnicity on FeNO reported by the studies was determined by comparing results (1) directly with Caucasian participants recruited at the same time^{143,145,146,153,154} or (2) indirectly using previously published Caucasian studies^{68,77,155} chosen by the study (Table 3.2). Ethnicity was considered a significant determinant of FeNO values in 10 of the 12 studies (83%). Nine (75%) studies found their healthy (non-Caucasian) ethnic groups to have increased FeNO levels when compared to Caucasian results. Only the study of North African Arab children¹⁴⁹ found that measured FeNO values for their group were decreased compared to Caucasian data. The studies conducted by Matsunaga *et al*¹⁵¹ and Edwards *et al*¹⁵⁴ found no difference between their populations (Japanese and New Zealand Pacific Islander/Maori respectively) and comparable to Caucasian results. There was however a large variation in the differences observed (Table 3.2). For example, in the Kovesi *et al*¹⁵³ study, the arithmetic mean FeNO level was 12.7 ppb in Caucasian children, whereas African-Canadian children had higher levels at 17.4 ppb, and Asian-Canadian children had even higher levels at 22.8 ppb. Findings were similar for adults, where Ko *et al*¹⁴⁸ measured geometric mean FeNO levels of 16.6 ppb in Caucasians and 32.6 ppb in Taiwanese adults.

Table 3.2 FeNO result variation of ethnic populations against Caucasian data

Study/Year	Mean FeNO Result of Different Ethnic and Age Groups, ppb		Comparative Study/Year, ppb	Difference Observed, ppb	
Baptist <i>et al.</i> 2015 ¹³⁵	African-American	19.3 ^a	Not specified	N/A	
Brody <i>et al.</i> 2013 ¹³⁴	African-American		Caucasian ^c (n=1748)		
	6-11 yr	10.7 ^b		7.6	3.1
	12-19 yr	14.7 ^b		11.2	3.5
	20-79 yr	13.9 ^b		14.1	-0.2
	Hispanic				
	6-11 yr	8.6 ^b		7.6	1
	12-19 yr	12.1 ^b		11.2	0.9
	20-79 yr	13.6 ^b		14.1	-0.5
Ko <i>et al.</i> 2013 ¹³⁶	Chinese	32.6 ^b	Olin <i>et al.</i> 2006 ⁷⁷	16.6	16
Rouatbi <i>et al.</i> 2012 ¹³⁷	North African Arab	5.0 ^a	Malmberg <i>et al.</i> 2003 ¹⁴³	11.9	-6.9
Yao <i>et al.</i> 2012 ¹³⁸	Taiwanese	13.7 ^b	Malmberg <i>et al.</i> 2003 ¹⁴³	11.9	1.8
Sonnappa <i>et al.</i> 2011 ¹³³	South-Asian	6.3 ^a	Caucasian ^c (n=37)	4.6	1.7
Matsunaga <i>et al.</i> 2010 ¹³⁹	Japanese	15.4 ^b	Travers <i>et al.</i> 2007 ⁶⁸	17.9	-2.5
Kim <i>et al.</i> 2010 ¹⁴⁰	Korean	30.7 ^b	Olin <i>et al.</i> 2006 ⁷⁷	16.6	14.1
Levesque <i>et al.</i> 2008 ⁹⁵	African-American	20.4 ^b	Travers <i>et al.</i> 2007 ⁶⁸	17.9	2.5
Kovesi <i>et al.</i> 2008 ¹⁴¹	African-American	17.4 ^a	Caucasian ^c (n=559)	12.7	4.7
	Asian-Canadian	22.8 ^a			10.1
Edwards <i>et al.</i> 2005 ¹⁴²	Pacific Islander	6.3 ^d	European ^c (n=58)	5.1	1.2
Wong <i>et al.</i> 2005 ¹³¹	Chinese	19.9 ^a	Caucasian ^c (n=33)	12.7	7.2

The comparative studies were either previously published Caucasian studies chosen by the study, or Caucasian participants recruited at the same time as the ethnic group.

N/A: not applicable; **ppb:** parts per billion; **a:** arithmetic mean; **b:** geometric mean; **c:** n value is the number of Caucasian participants recruited; **d:** median

3.4.3 Other factors that significantly influence FeNO levels

Atopic status (as defined by skin prick test) was found to be a significant factor in five (42%) studies, whereas height, age, and sex were significant in four (33%) studies each. Other significant factors identified included spirometry values, IgE, and eosinophil cationic protein levels in three (25%) studies each; time of testing in two studies (17%); body surface area, drinking of water prior to testing, and ambient NO in one (8%) study each.

3.4.4 Clinical implications based on current reference ranges

To better understand potential differences between the ethnic groups, we estimated the 5th and 95th percentiles for all studies involving children (Figure 3.2) and adults (Figure 3.3). As mentioned, five of the paediatric studies included both children (<12 years of age) and adolescents (12-18 years of age) and did not report separate values for these age groupings. Therefore these results could not be readily interpreted according to the current interpretation guidelines⁵⁸ which consider children (<12 years of age) separately to a combined adolescent (>12 years of age) and adult group.

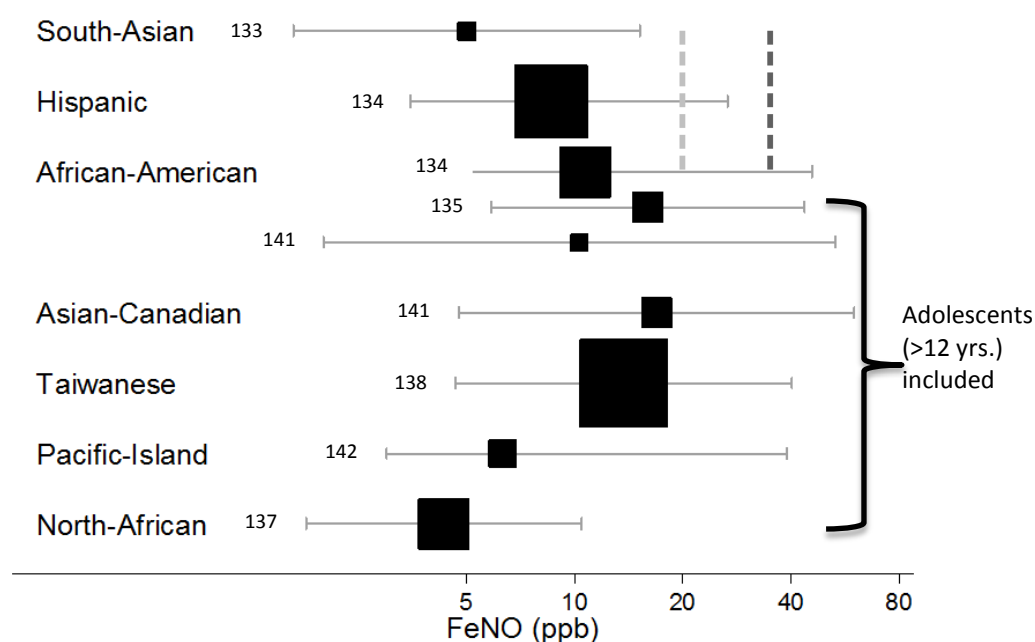


Figure 3.2 Distribution of FeNO (geometric mean and estimated 5th and 95th percentiles) for non-Caucasian samples of children (≤12 years)

Vertical lines (at 20 and 35 ppb) shown for three studies display clinical cut-off points based on the current ATS guidelines⁵⁸ for children (<12 years) where <20 ppb is considered normal, 21-34 ppb is considered intermediate, and >35 ppb is considered inflammation is present. Remaining studies reported combined values for children (< 12 years) and adolescents (12-18 years) and therefore cannot be interpreted using current interpretation guidelines. The size of the marker of the geometric mean (square) is proportional to the sample size. More than 5% of healthy children in two studies had FeNO results above the normal healthy range.

As seen in Figures 3.2 and 3.3, the geometric means of 10 of the non-Caucasian populations (adults and children) were placed within the normal/healthy cut-off range. The geometric mean values for Chinese¹⁴⁸ and Korean¹⁵² adults however fell into the intermediate range. After estimating the 95th percentile of FeNO, we found 5% of recruited participants in three studies (Hispanic children and adults,¹⁴⁶ African-American adults,¹⁴⁶ and Japanese adults¹⁵¹) to have FeNO results in the age-specific intermediate range. Interestingly, we found a further five studies (African-American children,¹⁴⁶ African-American adults,¹⁰⁷ Korean adults¹⁵², and

Chinese adults^{143,148}) where >5% of the population had FeNO results in the age-specific inflammatory range.

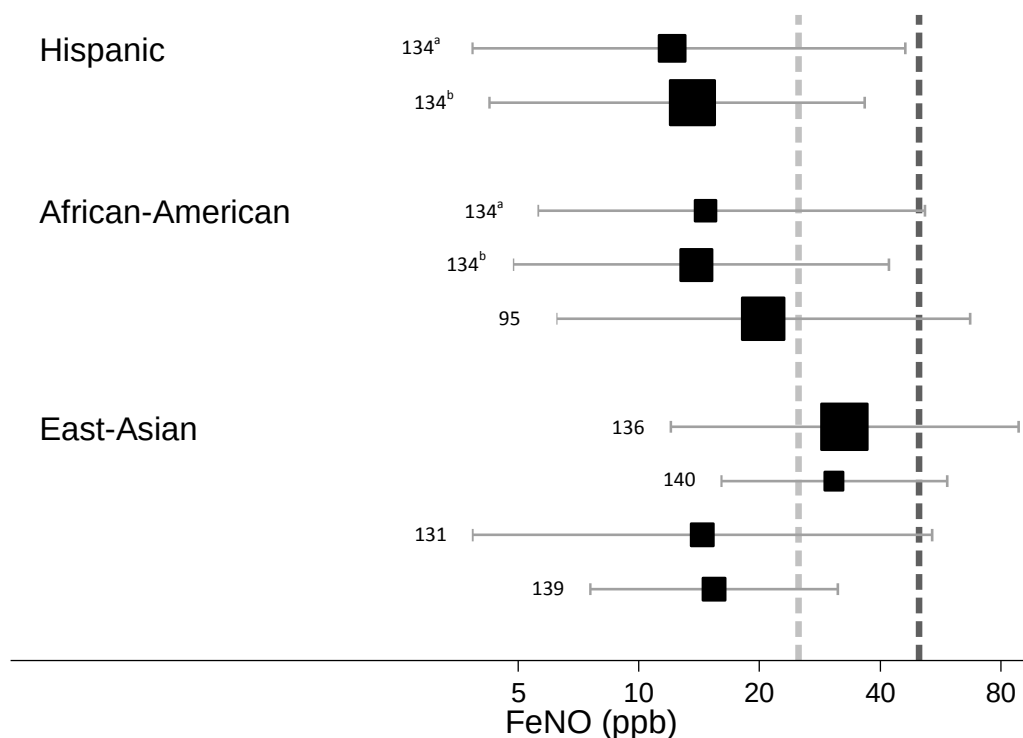


Figure 3.3 Distribution of FeNO (geometric mean and estimated 5th and 95th percentiles) for non-Caucasian samples of adults (>12 years)

Vertical lines (at 25 and 50 ppb) shown for three studies display clinical cut-off points based on the current ATS guidelines⁵⁸ where <25 ppb is considered normal, 26-49 ppb is considered intermediate, and >50 ppb is considered inflammation to be present. The size of the marker of the geometric mean (square) is proportional to the sample size. More than 5% of healthy children in all studies had FeNO results above the normal healthy range. **a:** 12-19 year olds; **b:** >20 year old

3.5 Discussion

Given the growing importance of FeNO as a diagnostic¹⁵⁶ and monitoring tool⁵⁸, we undertook a systematic review to determine the influence (if any) of ethnicity on FeNO results and the consequent impacts on clinical interpretation. We identified 12 relevant studies, of which 10 found ethnicity to influence FeNO levels

in healthy children and/or adults. The studies represented 16 populations from 11 ethnicities. While the geometric means of FeNO for 10 of the non-Caucasian populations were within the normal/healthy FeNO range as recommended by the ATS,⁵⁸ the FeNO means in two populations were outside the normal/healthy range. Furthermore, we found five studies (Figures 3.2 and 3.3) where >5% of the study's sampled population had FeNO levels in the inflammatory range despite these individuals being healthy and free of atopy. In these individuals, their FeNO results indicate the presence of eosinophilic airway inflammation (i.e. abnormal). Therefore, our systematic review's findings may be of clinical significance when interpreting the presence or absence of inflammation during the evaluation of individual patients and in research studies.

This is the first systematic review to focus specifically on the influence of ethnicity on FeNO values. A recent systematic review⁷⁰ that explored FeNO normal/reference values and possible influencing factors (such as age, sex, height, weight, smoking status, race and atopy) only identified three studies where ethnicity influenced FeNO values on non-Caucasian populations. Two of these studies are included in our review, and the third was not included because of recruitment of patients with asthma and allergic conditions. However, this article also reported higher FeNO values for Asian-Canadian and African-Canadian children when compared to Caucasian participants.¹⁵⁷ This review did not comment on the differences observed in FeNO results between the different ethnic groups.

We identified two populations^{148,152} with geometric means of FeNO values in the intermediate range of Caucasian data. Furthermore, by calculating the 95th percentile, we also identified three populations^{146,151} with >5% of values in the intermediate range and five populations^{107,143,146,148,152} with >5% of values in the inflammatory range of current ATS guidelines⁵⁸ which is based predominantly on Caucasian data. Additionally, four^{147,150,153,154} of the five studies (Figure 3.2) that reported combined values from different age groups, had 95th percentiles higher than the normal healthy cut-off ranges⁵⁸ for both children and adults.

Using STATA software, we also estimated the proportion of participants from each study that would be classified as having elevated results (above the inflammatory cut-off values) based off the current ATS⁵⁸ guidelines (Table 3.3). These patients would be classified as having abnormal results and would likely prompt further treatment and/or investigation. Based on these results, we then estimated the number of participants from each study that may be misclassified (either normal or abnormal results) according to current ATS⁵⁸ guidelines. For the studies involving children, the Asian-Canadian¹⁵³ and African-American^{147,153} populations had the highest proportion of participants with results in the inflammatory range. Similarly, for adults, studies involving Chinese,¹⁴⁸ Korean¹⁵² and African-American¹⁰⁷ participants had the highest proportion of participants with results in the inflammatory range.

The proportion of participants possibly misdiagnosed is therefore high in these populations (>10% in some studies^{148,153}), suggesting that current Caucasian cut-off ranges⁵⁸ may be too low for accurate use in some ethnic groups. These observations highlight the need for further studies in non-Caucasian populations to determine if Caucasian-based cut-off reference ranges are clinically applicable for detecting the presence of eosinophilic inflammation.

FeNO values of healthy individuals in a number of ethnic groups appear to be higher than Caucasian values. The mechanism by which ethnicity influences FeNO levels of healthy children and adults are still largely unknown. It is possible that there are differences between ethnic groups in the activity of NO synthase (the enzyme essential for NO production) and in allele frequencies of the NO synthase genes.¹⁰⁴⁻¹⁰⁶ Other contributing factors may include complex interactions between genetic and biological, and/or environmental factors (i.e. diet, second hand smoking, air pollution, and socioeconomic status).^{27,72,107,108} None of these potential factors have been adequately tested in either Caucasian or non-Caucasian populations and preliminary results are inconsistent and require further investigation.

Table 3.3 Clinical implications for interpretation based on current ATS guidelines

	Estimated % of study participants above the ATS defined inflammatory range (>35 ppb for child studies, >50 ppb for adult studies)	Estimated % of study participants that may be misclassified according to current guidelines	Estimated % of study participants greater than the 95 th percentile that may be normal
Child studies			
South-Asian ¹³³	0.2	4.8 ^a	96
Hispanic ¹³⁴	1.3	3.7 ^a	74
African-American ¹³⁴	4.7	0.3 ^a	6
African-American ¹³⁵	10.1	5.1 ^b	0 ^c
African-American ¹⁴¹	11.1	6.1 ^b	0 ^c
Asian-Canadian ¹⁴¹	17.3	12.3 ^b	0 ^c
Taiwanese ¹³⁸	7.7	2.7 ^b	0 ^c
Pacific-Islander ¹⁴²	2	3 ^a	60
North-African ¹³⁷	-	-	-
Adult studies			
Hispanic ^{134d}	2.1	2.9 ^a	58
Hispanic ^{134e}	3.4	1.6 ^a	32
African-American ^{134d}	1.9	3.1 ^a	62
African-American ^{134e}	2.3	2.7 ^a	54
African-American ⁹⁵	10.8	5.8 ^b	0 ^c
East-Asian ¹³⁶	20	15 ^b	0 ^c
East-Asian ¹⁴⁰	10.9	5.9 ^b	0 ^c
East-Asian ¹³¹	6.1	1.1 ^b	0 ^c
East-Asian ¹³⁹	0.3	4.7 ^a	94

All results were estimated using STATA software. For all studies results show (1) proportion of participants above the ATS defined inflammatory range, (2) proportion of participants that may be misclassified according to current guidelines, and (3) proportion of participants with FeNO results greater than the study defined 95th percentile that may be normal.

a: proportion of participants classified as inflammatory but may be normal; **b:** proportion of participants classified as normal but may be inflammatory; **c:** 95th percentiles are already in the respective inflammatory ranges; therefore, participants with FeNO values greater than this are considered abnormal; **d:** adults 12-19 years; **e:** adults >20 years

Current ATS guidelines⁵⁸ only recommend FeNO cut-off ranges to be adjusted for age despite evidence showing other potential factors that may influence results. Clinicians are expected to follow these guidelines when treating patients (Caucasian or non-Caucasian) without consideration of ethnicity, atopy status, diet, geographical location, and other socio-economic factors. The importance of our findings relate to the implications of using the recommended ATS cut-offs⁵⁸ when evaluating patients clinically or in research studies. For example, the United Kingdom-based National Institute for Health and Care Excellence (NICE) recommended that “FeNO testing is used to help diagnose asthma in adults and children when the diagnosis is unclear”.¹⁵⁸ Also, a recent systematic review on the use of FeNO for diagnosing asthma did not consider ethnic factors and suggested that a cut-off of >50 ppb guarantees sufficient positive predictive value for ruling in the presence of asthma.¹⁵⁶ Given that this value is less than the 95th percentile for healthy people in eight populations (Figures 3.2 and 3.3), use of such cut-offs without any ethnic consideration may result in the over treatment of patients with corticosteroids that could result in side-effects without any benefit. We therefore consider that it is appropriate to investigate how applicable the current Caucasian based FeNO cut-off ranges are to other ethnic populations.

Our findings suggest that, in the presented non-Caucasian groups, it may be incorrect to use the current ATS cut-off values to interpret the presence of inflammation and that doing so could lead to inappropriate diagnosis of disease and negatively impact treatment plans. Future studies should also be mindful of the

current age differentiating cut-off points as recommended by the ATS⁵⁸ when analysing and reporting results.

3.5.1 Limitations

This systematic review is limited to 12 studies and only includes 11 ethnic groups. Asian and African ethnicities were the best represented non-Caucasian groups. The differences between the studies in terms of methodology and reporting of results affected our ability to make direct comparisons between the studies. For uniformity, all FeNO results were compared with current ATS guidelines.⁵⁸ Despite our efforts it was not possible to examine the effect on interpretation for five paediatric studies as the data was not reported separately as per ATS guideline⁵⁸ age groupings. Also, our estimated 95th percentile assumes that FeNO data are log-normally distributed. If however the reported data is positively skewed, then our estimate will be an underestimate. Also, there were insufficient studies for us to take into account the possible effect of FeNO analysers used.

3.6 Conclusions

To our knowledge, this is the first systematic review to explore ethnicity as an influencing factor on FeNO. We have shown that ethnicity does influence FeNO levels. The effect of ethnicity was found to be small in some groups with no impact on clinical interpretation. However, in other groups (African- and Asian-Canadian, African-American, Taiwanese, Korean and Chinese), ethnicity may potentially have clinical significance. In these groups, >5% of normal healthy children and adults

without atopy had FeNO values above the 'normal' Caucasian range, thus making it inappropriate to use the current Caucasian ATS cut-off values for clinical interpretation on these ethnic groups. Establishing normal, intermediate and inflammatory ranges for FeNO levels for non-Caucasian ethnicities is crucial to ensuring that the presence of inflammation can be adequately defined. This will ensure that FeNO measurements are clinically beneficial.

3.7 Acknowledgements

We thank the members of the Indigenous Respiratory Outreach Care (IROC) program and the Queensland Statewide Respiratory Clinical Network for their ongoing support. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Chapter 4: Research methodology

4.1 Introduction

This chapter outlines the overall methodology used for this research in order to address the research questions. Included in this chapter are the ethical considerations, research design, population and setting, data collection, analysis and feedback to communities.

4.2 Ethics approval

Due to the nature of this study and current guidelines for performing Indigenous research,¹⁵⁹ multiple ethics applications were submitted to cover the nine communities as well as schools targeted for recruitment. These included:

- Children's Health Queensland (HREC/14/QRCH/111) – Caboolture as well as the Centre for Children's Health Research (CCHR) where the data was stored and analysed
- Far North Queensland (HREC/14/QCH/96-929) – Bamaga, Thursday Island and Horn Island
- Darling Downs (HREC/15/QTDD/27) – Cherbourg, Murgon and Dalby
- Townsville (HREC/15/QTHS/133) – Woorabinda
- Northern Territory/Menzies School of Health Research (HREC-2017-2833) – Darwin

- Education Queensland (550/27/1576) – selected schools at the targeted communities
- Catholic Education – selected schools at the targeted communities
- QUT (Reference number: 1500000354)

Contact with appropriate community leaders (including Elders, local Councils, Health Action Groups, Aboriginal Medical Services, school principals and child care centre directors) at each site was achieved initially through email and phone conversations. If key stakeholders were interested in participating in the study then face to face meetings were organised to discuss the project, and to answer any questions or concerns people may have had. This method was used to ensure respectful communication and cultural appropriateness. Communities and schools were invited to participate but had the option to decline or withdraw their support at a later date with no negative effects to the community. A letter of support for the study was provided from appropriate community Elders/leaders for each site and submitted with each ethics application.

4.3 Research plan

4.3.1 Participants

Our objective was to recruit approximately 600 Aboriginal, 600 Torres Strait Islander and 600 Aboriginal and Torres Strait Islander (Both) children and young adults aged 3-25 years old who fulfilled eligibility criteria (section 4.3.2). We anticipated that some participants would be ineligible for inclusion into the final

‘healthy’ reference data set due to health and environmental factors (e.g. previous respiratory history, smoking status), while others would be eliminated due to an inability to meet acceptable test criteria for spirometry and/or FeNO.

As stated above, study sites were Bamaga, Caboolture, Cherbourg, Dalby, Darwin, Horn Island, Murgon, Thursday Island and Woorabinda (Figure 4.1). The chosen communities are from a mix of city, rural and remote locations¹⁶⁰ and are visited regularly by the IROC program specialist clinics. Within each community we recruited participants from child care centres for 3-5 year olds, school and/or community groups for 5-17 year olds, and community events, sporting groups or health care workplaces for 18-25 year olds.

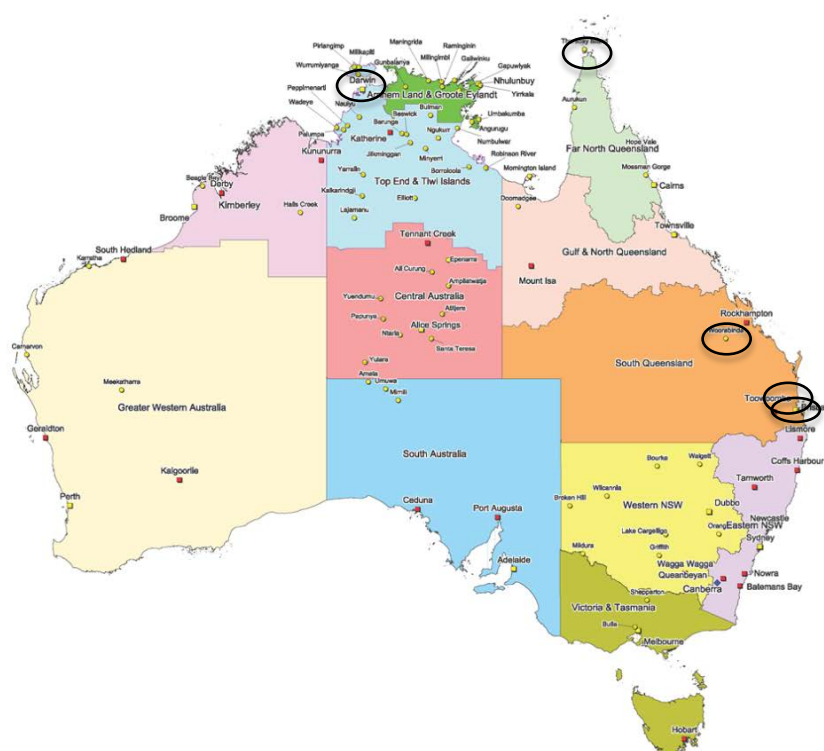


Figure 4.1: Included study sites within Australia
Black circles show approximate location of communities that participated in the study

4.3.2 Inclusion and exclusion criteria

Inclusion:

Individuals (male or female) who identified as Aboriginal or Torres Strait Islander or Both who:

- Was a child/young adult aged 3-25 years
- Had written and informed consent to participate; consent from parent/guardian if < 13 years of age; by parent/guardian and self (assent) if 13-17 years of age and by self if 18-25 years

Exclusion:

Individuals with a known contraindication for performing spirometry and/or FeNO measurement:

- Heart attack, pneumothorax, pulmonary embolus or any surgery to chest, abdomen, brain, eyes, ears, nose or throat in the last 4-6 weeks
- Previously diagnosed with very high blood pressure (200/120mmHg) or an aortic aneurysm

Consent forms included questions regarding the above contraindications to ensure the safety of all participants as well as the integrity of data (Appendix B and C).

4.3.3 Recruitment

Prior to recruitment we were in regular consultation with communities, schools and organisations to discuss what they considered was the most suitable method for distribution of study information sheets, consent forms and health questionnaires. In order to maximise resources and time, we strived to have as many consent forms completed in advance as possible for most of the communities. Due to the nature of this research design we were unable to anticipate ahead of time either the number of participants who would be recruited and tested from each community or the time required to collect the data at each site. This largely depended on the return rate of consent forms and whether or not the consented children were present in the community and attending school at time of testing. Every effort was made to engage with key community leaders and members to recruit as many individuals who fulfilled the inclusion criteria.

Local Indigenous research assistants were employed in Bamaga, Cherbourg, Horn Island, Murgon, Thursday Island and Woorabinda to approach parents/guardians and participants. During this time they introduced the study and discussed any queries/concerns that were raised. If the participant or parent/guardian was happy to participate, the research assistant helped with completion of the consent form and questionnaires. With respect to the questionnaires, research assistants were allowed to explain the questions using the local Indigenous dialect; however they were instructed to not interpret responses but rather to record answers as provided. For Dalby and Caboolture, consent forms and questionnaires were distributed and collected by the local schools. Participants

or parents/guardians were provided with the contact details of research staff in case they had questions or needed assistance with completing the paperwork. In Darwin, members of the research team attended local sporting events to recruit participants and assisted in the completion of paperwork on site.

We expected that a minimum of one to two weeks would be required at most communities to identify potential participants and to collect the required data. The exception was Caboolture, where data collection could be achieved with day trips from Brisbane. Collection of data for the majority of sites occurred during school times which meant that dates and times were coordinated with principals and school staff. When necessary, additional trips were made to communities and schools prior to testing to train employed research assistants, aid in the completion of forms and to engage with the community.

4.4 Data collection

4.4.1 Generic data

Anthropometric data:

Standing and sitting height were measured at the time of testing using a stadiometer (Seca 217, Hamburg, Germany). Standing height was measured while participants stood erect with feet together and no shoes. Sitting height was measured with the participant seated on a metal seat with a mounted stadiometer attached. Both positions required the participants' head to be in the Frankfort plane and the measurement to be taken during a full inhalation breath hold.¹⁶¹ It was a

condition of ethics approval by Education Queensland that no weight measurement was recorded for any school student.

Smokerlyzer results:

The PICO Smokerlyzer (Bedfont, Kent, UK) was used to test for exhaled carbon monoxide (eCO). Results were used as an indicator of recent tobacco smoke exposure and as a way of confirming (or challenging) self-reported smoking history responses. As such, smokerlyzer results were not separately reported on throughout the thesis. The test involves a full inspiration breath hold of approximately 15 seconds and then exhalation into the Smokerlyzer unit through a disposable filter. Exhaled CO results are measured in parts per million (ppm). The measurement was performed by trained respiratory scientists until two results within 3 ppm were achieved.

4.4.2 Questionnaires and medical records

Health questionnaires:

Parents/guardians of participants <18 years were asked to complete two brief questionnaires. The first includes questions regarding the participant's demographics including identified ethnicity, any history of asthma, bronchiectasis, bronchiolitis, pneumonia, cancer or neonatal lung disease, current smoking status, in utero smoke exposure from maternal smoking and gestational age at birth (Appendix D). The second was a modified ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire (Appendix E)¹⁶² which is used to assess the

presence or previous history of asthma, allergic rhinitis and eczema. Participants >18 years completed the questionnaires themselves however they were able to consult with a parent, research assistant or researcher if required.

Medical records:

Participant medical records from relevant health centres and hospitals were examined for any history of respiratory disease (including asthma, pneumonia, bronchiectasis, bronchiolitis and croup), respiratory related hospitalisations, atopic conditions (including allergic rhinitis and eczema), information about gestational age at birth and birthweight. Information was recorded onto a case report form (Appendix F).

4.4.3 Spirometry

Spirometry was performed according to the current ATS/ERS guidelines²⁶ by trained respiratory scientists using Easy on-PC Spirometers (ndd Medizintechnik, Zurich, Switzerland). Participants were seated in the upright position and wore nose clips. When three acceptable and repeatable measurements were achieved, the highest FEV₁ and FVC were reported for data analysis. Acceptable spirometry measurements are those where a maximum inhalation is followed by a rapid forced exhalation until a volume plateau is achieved at >3 second expiratory time in children <10 years and >6 second expiratory time in participants >10 years. Expiratory flows should not be affected by cough, glottic closure or tongue

obstruction.²⁶ If an individual was not able to achieve spirometry testing that met above criteria then their data was not included in final spirometry data analysis.

In the case of young children (3-5 year olds) spirometry data was not immediately deemed unacceptable even if the expiratory time was less than 3 seconds. Expiratory efforts were still recorded as acceptable if they had full inspiration and then a forced expiration without cough, glottic closure or tongue obstruction and there was no evidence of early termination of exhalation as indicated by cessation of flow from >10% of the PEF value.³⁵

4.4.4 Fractional exhaled nitric oxide (FeNO)

FeNO levels of participants were measured by trained respiratory scientists using the NIOX MINO (Aerocrine AB, Solna, Sweden) hand held device. The participant exhaled directly into the device through a connected filter mouthpiece ('online' technique) at a controlled flow rate (50 mL/s with a back pressure of 10-20cm H₂O) until the allocated exhalation time was reached (6 seconds if <10 years and 10 seconds if >10 years).¹⁶³ Results are shown in parts per billion (ppb) and the measurement was performed at least twice to achieve results within 10% of each other as per current guidelines.⁵⁸ The mean value of each participant's acceptable tests was used for data analysis.

4.4.5 Data management

Upon entry into the study each participant was allocated a unique study identification number to be used for all future tests and paperwork. All relevant information was entered into a password protected database and all paper files stored in locked cabinets at the Centre for Children's Health Research, South Brisbane. Database programs and spreadsheets were only accessible to study staff on a secure network. Analysis of data was performed on de-identified information only.

No identifiable data has, or will be made public. Results of the study may be presented at conferences, and to communities and key stakeholders, but no names or details of participants will be disclosed.

4.5 Data analysis

4.5.1 Quality of collected information (research question 3)

Medical history of each participant was collected for the purpose of identifying 'healthy' participants for the final spirometry and FeNO dataset as per current industry guidelines.^{31,36,58} We collected information relating to participants' overall health, birth weight and gestational age, as well as previous and/or current respiratory conditions (further explained in sections 4.5.2 and 4.5.3 respectively). The information sources used were

- self-reported questionnaires (completed either by parents/guardians or participants), and

- medical records (typically completed by doctors, nurses and/or allied health practitioners).

We screened all collected data and for each participant extracted questionnaire responses and medical record information relating only to asthma, bronchiectasis, pneumonia, allergic rhinitis and eczema as these were common between the two information sources. Participants with incomplete data (missing ethnicity, self-reported responses and/or medical record information) were excluded. Self-reported information was only classified as missing if all five topics of interest were recorded as missing. To ensure robustness of the analysis we also excluded participants from city and inner regional locations as we were unable to check all potentially relevant medical records due to multiple primary care and specialist clinics that may have been attended in these locations.

Self-reported asthma was noted if a participant answered 'Yes' on the respiratory health questionnaire and/or a positive ISAAC response was recorded for '*ever had asthma*'. Similarly, self-reported bronchiectasis or pneumonia was noted if a participant answered 'Yes' to these conditions on the respiratory health questionnaire. Positive ISAAC responses to '*ever had hayfever*' and '*ever had a problem with sneezing, or a runny, or blocked nose when not sick*' and/or '*ever had eczema*' indicated self-reported allergic rhinitis and eczema respectively. Positive medical record evidence was noted if a participant had ever been diagnosed by a health professional for any of the five conditions.

Cohen's kappa (κ) analysis was used to assess the level of agreement between self-reported and medical record evidence for each condition. Kappa scores of 0-0.2 were considered poor, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 good and >0.81 very good.¹⁶⁴ All analyses were performed using Stata15 software (StataCorp, TX, USA). Results from this analysis are outlined in Chapter 5.

4.5.2 Spirometry (research questions 4a & 4b)

Validation of existing reference equations requires the recruitment of a large number (preferably >300) of healthy participants who have no chronic respiratory illness or smoking history. Using the online GLI tool,¹⁶⁵ a minimum of 150 healthy males and 150 healthy females from each ethnic group (Aboriginal, Torres Strait Islander and Both) can be used to evaluate the appropriateness of the existing GLI-2012 equations. Questionnaires and medical record information were used to identify 'healthy' participants. Participants were excluded if they had evidence of a current or chronic respiratory condition (such as asthma, bronchiectasis or chronic neonatal lung disease), current or previous smoking history or low birthweight/gestational age (<2.5 kgs/<37 weeks gestation). Furthermore participants were excluded if key data was missing (including ethnicity, health history information) or they failed acceptability/repeatability criteria.

Descriptive analyses were used for participant demographics. The study population was described by participants' identified ethnicity and by total cohort,

and expressed as proportions and/or means/medians of the selected characteristics with the corresponding SD or inter-quartile ranges (IQR), dependent on data distribution. Differences between ethnic groups were assessed using χ^2 tests for proportions, Kruskal-Wallis tests for means (conditional on assumptions of normality) and non-parametric tests for any non-normally distributed data. All analyses were performed using Stata15 software (StataCorp, TX, USA).

To investigate differences between the three Indigenous groups, participants were separated according to their self-identified ethnicity; Aboriginal, Torres Strait Islander or Both. Data was then entered into the GLI2012_DataConversion.exe software and z-scores for each lung function parameter (FEV_1 , FVC and $FEV_1/FVC\%$) were calculated against the 'Caucasian', 'African-American' and 'Other/Mixed' GLI equations to determine which equation best fit the ethnic groups. If the mean z-score=0, SD=1 and approximately 5% of the cohort had z-score values <-1.64 and >1.64 then the selected reference equation (Caucasian, African-American or Other/Mixed) was considered a 'good fit' for the ethnic group. T-tests with Bonferroni correction of 0.016 per test ($0.05/3$) were performed to examine differences in z-scores of all lung function values between the ethnic groups for males and females. One-way ANOVAs were performed to examine differences in z-scores of all lung function parameters between the ethnic groups for males and females.

If the z-score distributions between our cohort and any of the existing GLI reference equations were not close, then the software could also be used to derive an ethnic adjustment factor suitable for Indigenous Australian children and young adults. Results from this analysis are outlined in Chapter 6.

4.5.3 FeNO (research questions 5a & 5b)

Unlike spirometry there is currently no method to validate the appropriateness of the current recommended cut-off values for population and/or disease specific groups. As such, FeNO results and distribution were examined with respect to existing published guidelines; ATS,⁵⁸ NICE,⁷³ BTS/SIGN⁷⁴ and GINA.⁷⁵ Questionnaires and medical record information were used to identify 'healthy' participants. Participants were excluded if they had evidence of a current or chronic respiratory condition (such as bronchiectasis) and a history of current or previous smoking as these are known to reduce FeNO values. Furthermore participants were excluded if key data was missing (including ethnicity, health history information) or they failed acceptability/repeatability criteria.

Descriptive analyses were used for participant demographics. The study population was again described by participants' identified ethnicity and by total cohort, and expressed as proportions and/or means/medians of the selected characteristics with corresponding SD or IQR, depending on data distribution. Differences between ethnic groups were assessed using χ^2 tests for proportions, Kruskal-Wallis tests for means (conditional on assumptions of normality) and non-

parametric tests for any non-normally distributed data. All analyses were performed using Stata15 software (StataCorp, TX, USA).

Analysis of 'healthy' FeNO data was age based; that is participants <12 years and participants >12 years in order to facilitate comparison between the guidelines as they all recommend different age and cut-off values (see Table 1.2, pg. 16). All acceptable data was further separated into three ethnic groups; Aboriginal, Torres Strait Islander or Both. Within each group we describe the distribution of data using histograms and compare results against existing published cut-off ranges. Furthermore, we examined the number of participants (as a percentage) who exceed the various cut-off values recommended by the guidelines. For this analysis, the guideline with the least number of healthy participants in the 'inflammatory zone' was considered the most appropriate for use in this population. The Mann-Whitney test was used to assess the difference in FeNO results between 'healthy' Aboriginal and Torres Strait Islander participants. Similar mean FeNO results and distribution of participants indicate no difference between the ethnic groups. Results from this analysis are outlined in Chapter 7.

4.6 Feedback to communities

Feedback has been provided to participants and their families at appropriate times during the study. In the event that results obtained during the testing phase may prove medically significant (i.e. obstructive spirometry, clearly elevated FeNO

levels), researchers informed the relevant community health workers/medical staff, as well as parents/guardians or participants.

Upon study completion the final results will be relayed back to the school principals, health workers, Elders and other key stakeholders within each community. We envisage this occurring by a formal written report and through a community visit. Prior to publication, the final results of the study will be reported to the Queensland Department of Education and Training, as well as all HRECs.

Chapter 5: How does parent/self-reporting of common respiratory conditions compare with medical records among Aboriginal and Torres Strait Islander (Indigenous) children and young adults (Article 3)

This chapter addresses **research question 3**: “How consistent is the information obtained from self-reported and medical records in this population?” and consists of the following published manuscript:

Blake TL, Chang AB, Chatfield MD, Marchant JM, Petsky HL, McElrea MS. How does parent/self-reporting of common respiratory conditions compare with medical records among Aboriginal and Torres Strait Islander (Indigenous) children and young adults? J Paediatr Child Health. 2019; doi:10.1111/jpc.14490

Estimates of disease prevalence and burden are typically determined through self-reporting and/or data from medical records. There are however limitations to both of these information sources that can substantially impact not only the monitoring of certain diseases, but also research studies’ ability to accurately follow inclusion/exclusion criteria. Few studies have examined discrepancies between self-reported and medical record information for Aboriginal and/or Torres Strait Islander Australians and none have focused solely on respiratory or atopic conditions.

Successfully answer our remaining research questions (questions 4 and 5), requires accurate recruiting and identification of 'healthy' participants. For spirometry, 'healthy' participants should be free of any current (within past 12-months) and/or chronic respiratory condition. For FeNO, 'healthy' participants should be free any respiratory and/or atopic condition.

This article demonstrated varied agreement across the measured conditions for Indigenous children living in rural/remote regions. Agreement between self-reported and medical record diagnoses was moderate for asthma and bronchiectasis, fair for eczema but poor for pneumonia and allergic rhinitis. These results suggest that for some conditions self-reported information may be sufficient to determine an accurate health history, while others may require information to be extracted from medical records. Reasons behind these discrepancies are still largely unknown.

5.1 Abstract

Objective: Self-reporting and/or data from medical records are frequently used in studies to ascertain health history. Data on the discrepancies between these information sources is lacking for Indigenous Australians. This study reports such data for selected respiratory and atopic conditions common amongst Indigenous Australians.

Study design: Data was extracted from the Indigenous Respiratory Reference Value study; a multi-centre cross-sectional study of Indigenous children and young adults (3-25 years) between June 2015 and November 2017. Only those living in rural/remote regions were included.

Setting and participants: Self-reported history was collected from parents (if participants <18 years) or participants. Medical records were manually reviewed. Participants with incomplete data (missing self-reported and/or medical record information) were excluded. Agreement between sources was examined using Cohen's kappa.

Results: Of 1097 participants, 889 (97.1% <18 years) had sufficient self-reported and medical record histories for comparison. Asthma was self-reported by 15.7% of participants, and in medical records for 10.3% ($\kappa=0.53$, 95% CI 0.45-0.61). For bronchiectasis the data were 1.5% and 0.7% ($\kappa=0.52$, 95% CI 0.25-0.80);

pneumonia 1.1% and 5.8% ($\kappa=0.15$, 95% CI 0.02-0.27); allergic rhinitis 6.6% and 0.6% ($\kappa=0.05$, 95% CI -0.03-0.13); eczema 5.8% and 6.2% ($\kappa=0.30$, 95% CI 0.18-0.42).

Conclusions: Within our cohort, agreement was moderate for asthma and bronchiectasis, fair for eczema but poor for pneumonia and allergic rhinitis. These results highlight the challenges associated with how best to obtain accurate health history within Australian Indigenous rural/remote communities. Generalisability of findings and contributions of poor health knowledge and/or poor medical record documentation need further exploration.

5.2 Introduction

Self-reporting and/or data from medical records are frequently used in studies to ascertain health history.^{22,166} There are advantages and disadvantages associated with both data sources. Self-reported data is an inexpensive way to obtain relevant information from a patient and can be administered on a national scale (e.g. health surveys). However, it is dependent on accurate patient recall¹⁰⁹ and understanding of questions and conditions.^{110,111} While medical records may be more robust, they can be influenced by incomplete/inaccurate recording of diagnostic information¹¹² and the complexities of disease coding.^{113,114} Inaccuracies in these data sources not only impact the effective monitoring of conditions and development of interventional strategies, but also pose substantial problems for research studies that use these information sources as a way of checking if participants meet inclusion/exclusion criteria.

In Australia, current estimates of disease prevalence and burden are primarily determined through self-reporting on National Health Surveys (NHS). However, several studies¹⁶⁷⁻¹⁷² have found the agreement between self-reported and medical record data to be better for some conditions (such as diabetes, arthritis and asthma) and worse for others (stroke and heart diseases). These discrepancies have resulted in the under- or over-reporting of some conditions depending on which information source is used.^{113,173-176} No study has investigated the agreement between self-reported and medical record information for these conditions amongst Aboriginal and Torres Strait Islander (here forth referred to as Indigenous) Australians. Several studies however have identified discrepancies in the accuracy

of self-reported information when compared to clinical tests (e.g. biochemical assay and pathology tests). For example, one study found that 17% of pregnant Aboriginal women self-reported no smoking history however cotinine analysis indicated current smoking or exposure to high levels of passive smoking.¹⁷⁷ Similarly, a recent study found that Indigenous Australians were unable to accurately self-report completion of diabetes, cervical cancer and cholesterol screening tests, likely resulting in an under-reporting of disease prevalence.¹⁷⁸ Agreement between self-reported and clinical measurements of physical activity (accelerometer use) has been shown to be relatively high in one study only.¹⁷⁹ Determining the accuracy and agreement between self-reported and/or medical record data is therefore important for this population and for future research studies.

We are conducting a study (Indigenous Respiratory Reference Value [IRRV]) to determine appropriate reference values for two lung function tests (spirometry and fractional exhaled nitric oxide [FeNO]) for Indigenous Australians.^{118,119} The IRRV study requires the recruiting and identification of 'healthy' participants. For spirometry, 'healthy' participants should be free of any current (within past 12-months) and/or chronic respiratory conditions as this is known to reduce lung function.¹¹⁷ For FeNO, 'healthy' participants should be free of any respiratory and/or any atopic condition given the known influence of these factors on FeNO values.⁵⁸ In similar studies, health history is determined solely through participant self-reporting with no medical record involvement.³¹ There are currently no published data on the discrepancies between self-reported and medical record

information for these conditions among Indigenous Australians. Availability of such data will assist in determining how best to identify 'healthy' participants for our IRRV work. In this paper, we determined the agreement between self-reported and medical record diagnoses of asthma, bronchiectasis, pneumonia, allergic rhinitis and eczema of 889 Indigenous participants.

5.3 Materials and methods

5.3.1 Participants

We used data from 1097 participants recruited for our IRRV study (Supplement 1) from eight communities (Queensland n=7; Northern Territory [NT] n=1) between June 2015 and November 2017. The study was a multi-centre, cross-sectional cohort of Indigenous children and young adults (aged 3-25 years old). Ethics approval was given by the Human Research Ethics Committees of Children's Health Queensland, Far North Queensland, Darling Downs and the Menzies School of Health Research/NT Health. Written informed consent was obtained from parents/guardians or participants (if aged ≥ 18 years).

Participants with incomplete data (missing ethnicity, self-reported responses and/or medical record information) were excluded. Self-reported information was only classified as missing if all five topics of interest were recorded as missing. To ensure robustness of the analysis we also excluded participants from city and inner regional locations as we did not have the capacity to check all potentially relevant medical records from multiple primary care and specialist clinics in these locations.

5.3.2 Parent/self-reported diagnoses and questionnaire information

Parent/self-reported (referred to as self-reported) information was collected from parents (if participants <18 years) or from participants (≥18 years) using two questionnaires. The first questionnaire collected information on self-identification of ethnicity (Aboriginal, Torres Strait Islander or both Aboriginal and Torres Strait Islander [Both]) and on respiratory health history; diagnosis ever of asthma/bronchiectasis/pneumonia/lung cancer/neonatal lung disease/other (i.e. croup, whooping cough), current medication use, participant and maternal smoke exposure, and gestational age at birth. An ISAAC¹⁶² (International Study of Asthma and Allergies in Childhood) questionnaire was used to collect information about asthma, allergic rhinitis and eczema history. Local Indigenous research assistants or school liaison staff assisted in contacting parents to optimise communication of the research aims and to assist parents/participants in completing these questionnaires. All research assistants were instructed to deliver plain language explanations of conditions to parents/participants and to record responses only, not interpret.

5.3.3 Medical records information

Paper charts from local hospitals and community primary health centres were checked as appropriate for each community. Electronic medical records (Best Practice, Primary Care Information System) were additionally checked for four communities. We extracted data using a standardised form. All inpatient and outpatient clinic notes, admissions, discharge letter from local or tertiary hospitals, referrals and specialists' clinical letters, and antenatal information were examined. Information was typically completed by the child's treating primary care doctors,

specialists, nurses and allied health professionals. Birth details (gestational age and weight) and diagnosis of asthma, bronchitis, bronchiolitis, bronchiectasis, pneumonia, croup, whooping cough, allergic rhinitis, eczema, scabies, impetigo, otitis media, and tonsillitis were specifically recorded.

5.3.4 Data management

All data (questionnaire responses, medical record information and test results) were entered into a secure database (FileMakerPro 15, CA, USA). Questionnaire responses and medical record information relating only to asthma, bronchiectasis, pneumonia, allergic rhinitis and eczema were extracted from the study database as these were common between the two information sources and the presence of these conditions excluded participants from inclusion into our overarching study. Self-reported asthma was noted if a participant answered 'Yes' on the respiratory health questionnaire and/or a positive ISAAC response was recorded for *'ever had asthma'*. Similarly, self-reported bronchiectasis or pneumonia was noted if a participant answered 'Yes' to these conditions on the respiratory health questionnaire. Positive ISAAC responses to *'ever had hayfever'* and *'ever had a problem with sneezing, or a runny, or blocked nose when not sick'* and/or *'ever had eczema'* indicated self-reported allergic rhinitis and eczema respectively. Positive medical record evidence was noted if a participant had ever been diagnosed by a health professional for any of the five conditions.

5.3.5 Statistical analysis

Cohen's kappa (κ) analysis was used to assess the level of agreement between self-reported and medical record evidence for each condition. Kappa scores of 0-0.2 were considered poor, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 good and >0.81 very good.¹⁶⁴ All analyses were performed using Stata15 software (StataCorp, TX, USA).

5.4 Results

Of the 1097 participants recruited from the IRRV study, 208 (19.0%) were excluded leaving 889 participants for analysis (Table 5.1). The majority of the final cohort (97.1%) were participants <18 years of age. Most of the excluded participants were from the city and inner regional communities, the majority of whom (n=115, 89.1%) were of Aboriginal heritage. Half of the cohort was male and there were fewer Aboriginal participants than Torres Strait Islander or Both.

Table 5.1 Participant demographics

<i>Recruited participants</i>	<i>n=1097</i>
Exclusions	
Missing ethnicity	13 (1.2%)
City/inner regional	129 (11.8%)
Missing Self-Report (SR)	41 (3.7%)
Missing Medical Records (MR)	24 (2.2%)
Missing SR & MR	1 (0.1%)
<i>Included participants</i>	<i>n=889</i>
Age (years) - Median (25 th – 75 th percentile)	10.3 (7.2 – 13.3)
Male	442 (49.7%)
Ethnicity	
Aboriginal	212 (23.8%)
Torres Strait Islander	334 (37.6%)
Aboriginal and Torres Strait Islander (Both)	343 (38.6%)

5.4.1 Agreement between self-reported and medical record diagnoses

The agreement between self-reported and medical record information for the various diagnoses are presented in Table 5.2. Evidence of asthma, bronchiectasis and allergic rhinitis were more commonly self-reported than found in medical records. Conversely, evidence of pneumonia and eczema was more commonly found in medical records than self-reported. The agreement between self-reported and medical record diagnoses was moderate for both asthma ($\kappa=0.53$, 95% CI 0.45-0.61) and bronchiectasis ($\kappa=0.52$, 95% CI 0.25-0.80) whilst that for eczema was fair ($\kappa=0.30$, 95% CI 0.18-0.42), and poor for both allergic rhinitis ($\kappa=0.05$ 95% CI -0.03-0.13) and pneumonia ($\kappa=0.15$, 95%CI 0.02-0.27).

Table 5.2 Agreement between self-reported and medical record diagnoses

	SR n (%)	MR n (%)	Both SR and MR n (%)	κ (95% CI)
Asthma (<i>n</i> =889)	140 (15.7)	92 (10.3)	68 (7.6)	0.53 (0.45-0.61)
Bronchiectasis (<i>n</i> =877)	13 (1.5)	6 (0.7)	5 (0.6)	0.52 (0.25-0.80)
Pneumonia (<i>n</i> =875)	10 (1.1)	51 (5.8)	5 (0.6)	0.15 (0.02-0.27)
Allergic rhinitis (<i>n</i> =882)	58 (6.6)	5 (0.6)	2 (0.2)	0.05 (-0.03-0.13)
Eczema (<i>n</i> =881)	51 (5.8)	55 (6.2)	18 (2.0)	0.30 (0.18-0.42)

SR: self-reported evidence; **MR:** medical records evidence; **Both SR & MR:** evidence is both self-reported and noted in medical records; **κ :** Cohen's kappa; **CI:** confidence interval

5.5 Discussion

To our knowledge this is the first study to examine the agreement between self-reported and medical record information for common respiratory and atopic conditions found among Aboriginal and Torres Strait Islander children and young adults. In our cohort (n=889), pneumonia and eczema were more commonly identified in medical records than self-reported but asthma, bronchiectasis and allergic rhinitis were more commonly self-reported. We found moderate agreement for asthma and bronchiectasis between self-reported and medical record evidence ($\kappa=0.53$ and $\kappa=0.52$ respectively). In contrast, eczema had fair agreement, while pneumonia and allergic rhinitis had poor agreement scores.

We found that within our cohort the frequency percentage for some conditions substantially differed depending on whether self-reported or medical record data was used. Reasons for these discrepancies are likely multifactorial and dependent on the specific condition. Historically, self-reported information is more accurate when the condition is well defined and easily recognised/diagnosed compared to conditions with complex or nonspecific symptoms.^{111,176,180} For example, conditions like allergic rhinitis and eczema are easily recognised by the parent/participant and can be treated with over-the-counter therapies with no documentation in medical charts. This could explain the difference in self-reported and medical record evidence for these conditions in our cohort.

However, this does not explain the discrepancy between self-reported and medical records for asthma. Evidence of asthma in our cohort was more likely to be self-reported (140 out of 232 total cases) and interestingly, only 68 participants had evidence documented in both information sources. Asthma management typically requires routine follow-up with general practitioners or specialists to assess the need for medications, monitor exacerbations and assess asthma control. As such, we expected the agreement between information sources to be higher. Our finding of moderate agreement ($\kappa=0.53$) between information sources for asthma however is similar to previous Caucasian-based studies that have been conducted in Alaska ($\kappa=0.57^{181}$), Canada ($\kappa=0.42^{113}$ and $\kappa=0.55^{176}$) and the Netherlands ($\kappa=0.41^{110}$). It is possible that for our cohort, this may be due to an issue with health literacy (parents/participants confusing asthma with other asthma-like symptoms), language barriers and how the questions were asked (including wording). Health literacy and language barriers are undoubtedly important for all aspects of healthcare and information,¹⁸² including surveys and should be further explored.

This could also explain the discrepancies seen between self-reported and medical record cases for bronchiectasis and pneumonia. Bronchiectasis was more likely to be self-reported (10 out of 16 total cases) than documented in medical records. However, the medical records for all of these participants had documented (at some stage in their life) bronchiolitis and/or bronchitis. Parents and participants answering the questionnaires may have misread or misinterpreted the question as a bronchiolitis/bronchitis query. Conversely, evidence of pneumonia was higher in

medical charts (51 out of 61 total cases) highlighting the possibility of parents/patients not fully understanding this medical condition or that medical professionals did not use the term 'pneumonia' with parents at the time of illness.

These findings may have relevance when considering the accuracy of results published in health surveys or studies on disease prevalence whereby health information is self-reported with no validation process undertaken to confirm yes/no responses. The Australian Bureau of Statistics acknowledges that this may introduce bias as participants' responses may be impacted by the inability to recall disease specific information and a desire to provide responses they feel may be expected.^{22,183} For example, the Aboriginal and Torres Strait Islander Health Survey (ATSISHS)¹⁸³ estimated that approximately 15% of Indigenous Australians in outer regional and very remote areas have asthma. While this was similar to our cohorts' self-reported frequency percentage of 15.7%, when only using medical records data the percentage was lower at 10.3%. This highlights the potential risk to over- or under-report prevalence in this population depending on the information source used.

Despite the known pitfalls of relying solely on self-reported or medical record data there is currently no universally accepted gold standard as to which information source is more appropriate to use when determining disease prevalence and burden, or health history. Due to differences in disease severity, health literacy and access to health services, it is likely that each condition will lend

itself to better recording from one particular source. Furthermore, differences in these influencing factors are also likely to vary between population groups. Future studies that investigate the influence of these factors on the agreement between self-reported and medical record information are needed to determine the impact specific information sources have on accurately determining disease prevalence and burden for certain diseases. As there are only a handful of studies that have examined the agreement between self-reported and medical record diagnosis for Indigenous Australians, further work with a wider disease focus is also needed in this population.

These results suggest that information obtained in this population from self-reported and medical records relating to allergic rhinitis, eczema, asthma, pneumonia and bronchiectasis are not interchangeable. Within the context of our overarching research, our findings suggest that determining the presence (or absence) of conditions which are known to influence lung function results, may be better achieved by also examining medical records rather than relying solely on self-reported information as is current practice.

5.5.1 Limitations

Our study has several limitations. Firstly, our findings are only applicable to Indigenous Australians <25 years of age from outer regional and remote communities throughout Queensland. Secondly, due to our study design and the mobility between communities of many Aboriginal and Torres Strait Islander

individuals we were unable to examine all medical sources for all participants (i.e. general practitioners, interstate records), although we took steps to minimise this. For the respiratory conditions such as asthma and bronchiectasis, the effect of this on agreement between sources may be minimal as diagnosis and treatment of these conditions typically require regular medical review and medications that would be documented in medical records.

There is inherent bias in both self-reported and medical record sources. Our questionnaires may be impacted by recall bias and literacy (particularly where English was not the first language) although assistance from local Indigenous research assistants or school staff were sought to minimise this effect. Our cohort consisted predominantly of children and as such, parents completed questionnaires. Parent-obtained medical history can be influenced by the parents' emotions and lack of exposure to the child's daily symptoms,¹⁸⁴ as well as issues with recall and health literacy. Also, the variation between research assistants may have introduced some bias. However, as it was necessary to adhere to Indigenous local needs and cultural sensitivities, several Indigenous research assistants across the communities were employed rather than just a single person. Regardless, responses to these questionnaires are reflective of our participants' understanding of conditions. For medical record data, the quality and accuracy of information we extracted for comparison is dependent on the quality, accuracy and completeness of information recorded. The medical chart recordings are likely to have a bias to presenting symptoms rather than comprehensive health history. Variations in

information recorded by medical staff, and their individual preferences/opinions relating to specific conditions may impact our results however; we are unable to overcome this in our analysis as it was not our aim to assess the accuracy of doctor diagnoses.

5.6 Conclusion

This is the first study to report on the agreement between self-reported and medical record information for common respiratory and atopic conditions impacting Indigenous Australians. We found that identifying an existing history of some conditions may be better achieved by examining medical records rather than relying solely on self-reporting. These results highlight the challenges associated with how best to determine disease prevalence within Australian Indigenous rural/remote communities. Future studies are needed to better understand how the use of self-reported and medical record information can be best utilised in this population.

5.7 Acknowledgements

The Indigenous Respiratory Outreach Care Program received funding under the Queensland Aboriginal and Torres Strait Islander Health Investment Strategy for this work, through the Aboriginal and Torres Strait Islander Health Unit of Queensland Health. Tamara Blake is supported by a National Health and Medical Research (NHMRC) Postgraduate Scholarship (1133059) and was supported by a scholarship from the NHMRC CRE in Indigenous Lung Health (1040830). Anne Chang

is supported by a NHMRC Practitioner Fellowship (1058213). The authors would like to thank the IROC Project Officers, Mr Allan Takken and Mr Brian Peacock and local Indigenous research assistants for their guidance and help with recruitment.

Chapter 6: Global Lung Function Initiative (GLI)-2012 ‘Other/Mixed’ spirometry reference equation provides the best overall fit for Australian Aboriginal and/or Torres Strait Islander children and young adults (Article 4)

This chapter addresses **research question 4a & 4b**: “Is there a difference in spirometry values between participants who identify as Aboriginal, Torres Strait Islander or Both?” and “Which (if any) of the GLI-2012 reference equations are most suitable for Australian Indigenous children and young adults?” This manuscript has been accepted for publication with *Respirology*.

Blake TL, Chang AB, Chatfield MD, Marchant JM, McElrea MS. Global Lung Function Initiative (GLI)-2012 ‘Other/Mixed’ spirometry reference equation provides the best overall fit for Australian Aboriginal and/or Torres Strait Islander children and young adults.

Ethnic specific reference equations are recommended when performing spirometry however the Global Lung Function Initiative (GLI)-2012 all age, multi-ethnic reference equations have still not been validated for use by many ethnic groups, including Aboriginal and/or Torres Strait Islander (Indigenous) Australians. There are currently no Indigenous Australian reference equations that have met

current international guidelines for the selection of 'healthy' participants. As such, existing data does not likely reflect a true healthy population.

We performed spirometry on 930 'healthy' Indigenous Australians children and young adults (aged 3-25 years) and found that the GLI-2012 'Other/Mixed' reference equation is the best fit for this population. Furthermore, we found no difference in spirometry results between the ethnic groups. Our results are also the first to report data on the lung function of Torres Strait Islander participants. Continued work is needed however to confirm results in other communities around Australia and also in an adult population.

6.1 Abstract

Background: Ethnic specific reference equations are recommended when performing spirometry. In the absence of any appropriate reference equations for Australian Aboriginal and/or Torres Strait Islanders (Indigenous), we determined whether any of the existing Global Lung Function Initiative (GLI)-2012 equations were suitable for use in Indigenous children/young adults.

Methods: We performed spirometry on 1278 participants (3-25 years) who identified as Aboriginal, Torres Strait Islander or Both. Questionnaires and medical records were used to identify 'healthy' participants. GLI2012_DataConversion software was used to apply the 'Caucasian', 'African-American' and 'Other/Mixed' equations.

Results: We included 930 healthy participants. Mean z-scores for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were lower than the 'Caucasian' predicted values (range -0.53, -0.60), higher than 'African-American' (range 0.70, 0.78) but similar to 'Other/Mixed' (range 0.00, 0.08). The distribution of healthy participants around the upper and lower limits of normal (~5%) fit well for the 'Other/Mixed' equation compared to the 'Caucasian' and 'African-American' equations.

Conclusion: Of the available GLI-2012 reference equations, the 'Other/Mixed' reference equation provides the best overall fit for Indigenous Australian children

and young adults (3-25 years). Healthy data from additional communities and adults around Australia will be required to confirm generalisability of findings.

6.2 Introduction

Differences in body habitus, socioeconomic and educational status, nutrition and genetic ancestry^{40,43,46,92,94,95,102,185} between ethnic groups are known to influence lung function results. Current recommendations are to use ethnic specific reference equations or a race correction factor for non-Caucasian individuals.³¹ The Global Lung Function Initiative (GLI)-2012³¹ recently developed all-age, multi-ethnic reference equations. These reference equations span the 3-95 year age range and cover four major ethnic groups; Caucasian, African-American, North- and South-East Asian, as well as providing values for a Mixed/Other ethnicity group³¹ and have been validated for several population groups¹⁸⁶⁻¹⁸⁹ including Caucasian Australians.¹⁹⁰

Several studies have found these reference equations to be unsuitable for some Caucasian and non-Caucasian populations.¹⁹¹⁻¹⁹⁶ For this reason, appropriateness of the GLI-2012 equations should be confirmed prior to their use for ethnic groups not currently covered by the equations. This includes Indigenous Australians who identify as Aboriginal, Torres Strait Islander or both Aboriginal and Torres Strait Islander ('Both'). This is particularly important in the context of the high burden of respiratory diseases (such as asthma, bronchiectasis and chronic obstructive pulmonary disease) experienced by Australian Indigenous people.

Previous studies^{115,124-126,129} have reported Australian Aboriginals to have forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) values

up to 25% and 30% lower respectively than healthy Caucasians. However, our systematic review¹¹⁸ found that in these studies, spirometry was not performed to current American Thoracic Society (ATS), European Respiratory Society (ERS) or GLI guidelines.^{26,31,118,197} Therefore, results obtained from these studies are unlikely to reflect a true 'healthy' population.

In the absence of any current appropriate spirometry reference values for Aboriginal and/or Torres Strait Islanders, we used the GLI software to evaluate if any of the equations could be applied to this population. The software requires a minimum of 300 healthy participants^{31,165} that have completed spirometry to current guidelines.²⁶ Our study's specific aims were to determine if (i) any of the existing GLI-2012 equations are suitable for children and young adults who identify as Aboriginal, Torres Strait Islander or 'Both' and (ii) there are any differences in healthy spirometry values between the three Indigenous Australian ethnic groups.

6.3 Materials and methods

6.3.1 Study participants and design

Participants aged 3-25 years were recruited from child care centres, schools and community events from nine communities in Queensland and the Northern Territory (Australia). Written informed consent was obtained from parents/guardians or participants (if >18 years). Ethics approval for the study was given by the Human Research Ethics Committees of Children's Health Queensland,

Far North Queensland, Darling Downs, Townsville, Menzies School of Health Research/Northern Territory Health and Education Queensland.

6.3.2 Anthropometric and spirometry data

Standing height was measured using a stadiometer (Seca 217, Hamburg, Germany) at the time of testing. Weight was not measured at schools or child care centres as Education Queensland did not give permission to do so. Spirometry was performed according to current ATS/ERS guidelines for preschool³⁵ and school²⁶ children using portable Easy on-PC Spirometers (nidd Medizintechnik, Zurich, Switzerland) by trained respiratory scientists. A minimum of three acceptable tests were required and they were considered repeatable if the two largest FEV₁ and FVC values were each within 0.15 L of each other.²⁶

6.3.3 Questionnaires and medical record information

Two questionnaires were used to ascertain current health and medical history. The first collected information relating to the participant's self-identification of ethnicity (Aboriginal, Torres Strait Islander or 'Both'), respiratory related history (including asthma, bronchiectasis, bronchitis and pneumonia), smoking status and exposure, and gestational age at birth. The second, a modified ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire,¹⁶² was used to determine participant history of asthma, allergic rhinitis and/or eczema. Questionnaires were self-administered by parents/guardians or

participants (if >18 years) and if required, with the help of local Indigenous research assistants.

Paper and electronic medical records (inpatient and outpatient) from relevant health centres and hospitals were examined and information relating to respiratory disease diagnosis and hospitalisation (including asthma, bronchitis, bronchiolitis, pneumonia, bronchiectasis, chronic neonatal lung disease and croup) was documented. Information regarding allergic rhinitis, eczema, scabies, impetigo, otitis media, tonsillitis, gestational age and birth weight were collected when available.

6.3.4 Final dataset, data management and statistical analysis

Asthma or bronchiectasis history was considered present if there was documented evidence in medical records, or (for asthma) a positive response was recorded on the ISAAC questionnaire for *'ever had asthma'*. Medical record evidence overrode negative questionnaire responses. Smoking history was considered present if parents or participants answered yes to *'does your child/do you currently smoke'* on the health questionnaire.

Participants were excluded from the final 'healthy' data set if any of the following were present: (i) failed acceptability/repeatability criteria as described above (n=113), (ii) self-reported and/or medical record evidence of current (within last 12 months) or chronic respiratory condition including asthma, bronchiectasis,

chronic neonatal lung disease (n=81), (iii) self-reported smoking history (n=80), (iv) low birthweight/gestational age (<2.5kgs or <37 weeks gestational age) (n=44) or (v) missing data (e.g. ethnicity, health history information) (n=30). See Figure 6.1. In the interests of developing a more inclusive reference set, we did not exclude participants who reported mild, common cold-like symptoms (n=90) at the time of testing or within the last three months.^{37,198}

Data analysis was performed using the GLI2012_DataConversion software¹⁶⁵ and Stata15 (StataCorp, TX, USA). One-way ANOVAs were performed to examine differences in z-scores of all lung function values between the ethnic groups for males and females. The Bonferroni correction was used for pairwise-comparisons. We examined the appropriateness of the 'Caucasian', 'African-American' and 'Other/Mixed' GLI reference equations for our cohort. As outlined by the GLI^{31,165} a mean z-score of 0 (maximum difference ± 0.5), SD of 1, and roughly 5% of participants with z-scores <-1.64 and >1.64, suggests that the sample agrees with the selected GLI predicted equation.

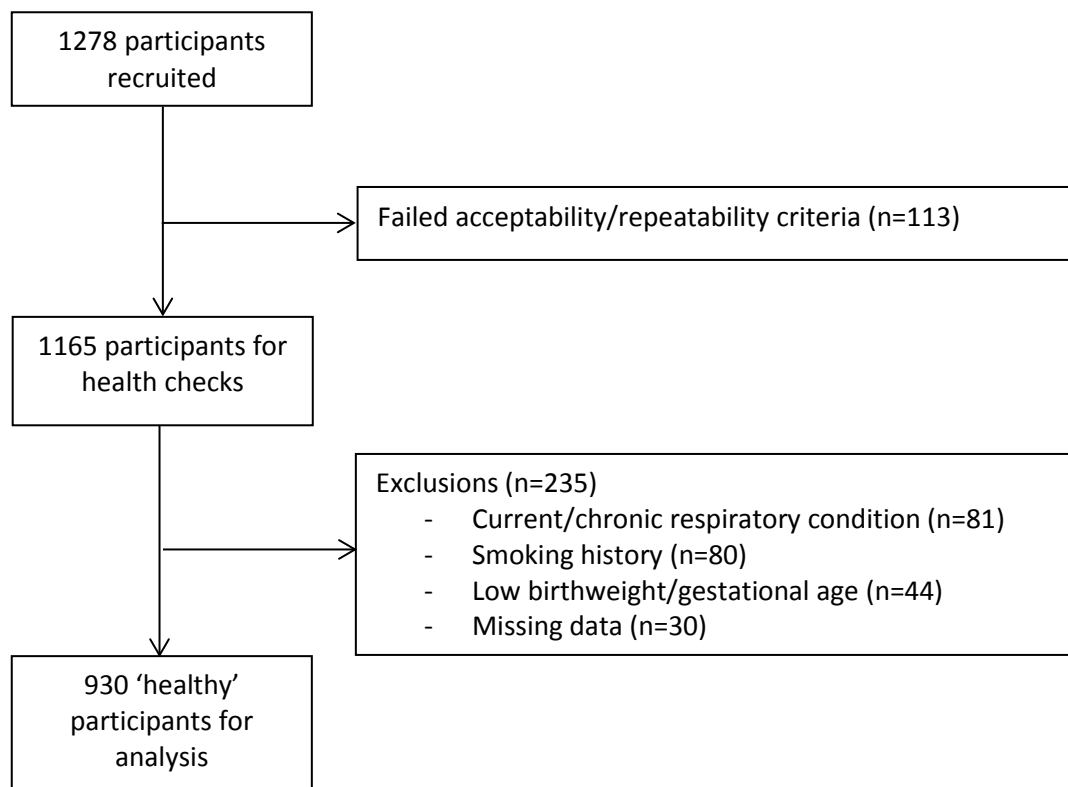


Figure 6.1 Exclusion criteria to identify 'healthy' Indigenous Australian spirometry data

6.4 Results

Between June 2015 and October 2017, 1278 participants completed spirometry measurements. After exclusions, a total of 930 healthy participants (72.8%) were included in the final dataset. Cohort demographics of included participants, according to Indigenous ethnicity, are shown in Table 6.1.

Table 6.1 Cohort demographics

	Aboriginal	Torres Strait Islander	Aboriginal & Torres Strait Islander ('Both')
N	302	321	307
Male	150 (49.7%)	153 (47.7%)	152 (49.5%)
Female	152 (50.3%)	168 (52.3%)	155 (50.5%)
Age (years)	10.2 (7.8-13.1)	11.5 (8.3-14.0)	9.8 (7.1-13.0)
Height (cm)	140.9 (127.9-158.6)	148.7 (130.7-162.4)	138.9 (122.8-157.9)
Height-for-age (z-score)	0.23 (-0.40, 0.94)	0.18 (-0.36, 0.95)	0.31 (-0.41, 0.93)

All variables reported as median (IQR)

We applied three of the GLI-2012 equations ('Caucasian', 'African-American' and 'Other/Mixed') to our cohort of healthy Indigenous Australians and examined results according to ethnicity (Table 6.2). Overall, mean z-scores for FEV₁, FVC and the FEV₁/FVC ratio for males and females were lower than the Caucasian predicted values (range 0.15 to -0.68). Use of this equation identified between 2-16% of males and 1-13% of females to have z-scores below the lower limit of normal (LLN, <-1.64). In comparison, the mean z-scores of our cohort were typically higher than the 'African-American' predicted values (range -0.36 to 0.91) and resulted in between 3-20% of males and 1-16% of females with z-scores above the upper limit of normal (ULN, >1.64). Use of the 'Other/Mixed' equation resulted in mean z-scores for FEV₁, FVC and FEV₁/FVC% that were typically closer to zero (range -0.46 to 0.26). Between 3-7% of males and 1-8% of females had z-scores below the LLN and between 1-8% of males and females had z-scores above the ULN.

Examination of the distribution of z-scores for FEV₁, FVC and FEV₁/FVC% (Figure 6.2) showed a shift to the right (towards lower percentiles) for FEV₁/FVC% only in both males and females. There was no statistically significant difference in the mean z-scores of FEV₁ or FVC values between the three ethnic groups for males or females. There was a statistically significant difference between the ethnic groups for FEV₁/FVC% for males (one-way ANOVA p=0.046) with Torres Strait Islanders higher than 'Both' by 0.28 (95% CI 0.06, 0.51, Bonferroni-corrected p=0.041). No statistically significant difference between the ethnic groups was seen for females.

We found the same trend in results when data from the three Indigenous ethnicities was combined and separated by gender (Table 6.3). For both males and females, mean z-scores were lower than the 'Caucasian' predicted values with 8-12% of participants having z-scores below the LLN. Mean z-scores were again higher than the 'African-American' predicted values and 15-18% of participants had z-scores above the ULN. The GLI 'Other/Mixed' equation however had very little mean z-score difference to our cohort for FEV₁, FVC and FEV₁/FVC%. The percent of healthy males below the LLN and above the ULN were 3.1% and 3.6% for FEV₁, 4.7% and 6.1% for FVC and 5.0% and 1.9% for FEV₁/FVC% respectively. Results were similar for females; 3.9% and 3.7% for FEV₁, 2.3% and 6.9% for FVC and 4.9% and 0.3% for FEV₁/FVC%. The distribution of z-scores for FEV₁, FVC and FEV₁/FVC% as a combined cohort (Figure 6.3) showed a shift to the right (towards lower percentiles) for FEV₁/FVC% for females only.

There was a statistically significant weak correlation between age and height and the z-score values for FEV₁, FVC and FEV₁/FVC% for males and females (Supplementary Figures S1-S2 [Appendix F]). There was no age or height related bias seen with respect to the number of participants observed below the LLN or above the ULN when using the GLI 'Other/Mixed' equation.

Table 6.2 Suitability of GLI equations for Australian Indigenous males and females (according to ethnicity)

		FEV ₁			FVC			FEV ₁ /FVC			
		Aboriginal	Torres Strait Islander	‘Both’	Aboriginal	Torres Strait Islander	‘Both’	Aboriginal	Torres Strait Islander	‘Both’	
Males	Caucasian	z-score	-0.61	-0.57	-0.53	-0.68	-0.65	-0.47	-0.01	0.15	-0.12
		SD	0.81	0.91	0.85	0.85	0.92	0.80	0.97	0.85	0.75
		%z<-1.64	10.1	9.4	6.7	13.9	15.6	5	5.2	2.3	1.7
		%z>1.64	0	1.3	1.3	1.7	0.8	0.8	4.4	5.5	0.8
	African	z-score	0.66	0.71	0.73	0.70	0.74	0.91	-0.13	0.32	-0.24
		SD	0.86	0.97	0.90	0.91	0.98	0.86	0.98	0.86	0.76
		%z<-1.64	0.7	0.7	0	0	0	0	6.1	3.9	3.3
		%z>1.64	12.8	18.1	16.0	14.8	20.3	17.5	2.6	3.1	0
	Other	z-score	-0.04	0.01	0.04	-0.00	0.03	0.22	-0.17	-0.01	-0.29
		SD	0.86	0.97	0.90	0.96	1.04	0.91	1.02	0.90	0.79
		%z<-1.64	3.4	3.4	2.7	7.8	4.7	2.5	6.1	4.7	4.2
		%z>1.64	1.4	4.7	4.7	3.5	7.8	6.7	2.6	3.1	0
Females	Caucasian	z-score	-0.60	-0.52	-0.62	-0.43	-0.48	-0.64	-0.26	-0.19	-0.08
		SD	0.90	0.83	0.86	0.88	0.76	0.92	0.78	0.68	0.77
		%z<-1.64	13.4	8.3	9.5	6.2	5.7	11.7	5.5	0.7	2.5
		%z>1.64	0.7	0.6	0.7	1.5	0	0.8	0	0.7	0.8
	African	z-score	0.59	0.67	0.56	0.61	0.75	0.58	-0.36	-0.29	-0.17
		SD	0.97	0.89	0.91	0.92	0.80	0.96	0.79	0.69	0.77
		%z<-1.64	0	0.6	0.7	0.4	0.7	0.8	7.0	2.1	4.2
		%z>1.64	14.8	16.1	12.9	14.7	12.1	14.2	0	0.7	0
	Other	z-score	-0.03	0.05	-0.05	0.26	0.20	0.17	-0.46	-0.39	-0.27
		SD	0.86	0.89	0.92	0.99	0.86	1.03	0.81	0.72	0.80
		%z<-1.64	5.4	3.0	3.4	2.3	1.4	3.3	8.6	2.1	5
		%z>1.64	4.0	4.2	2.7	7.0	6.4	7.5	0	0.6	0

'Both': Aboriginal and Torres Strait Islander; **FEV₁:** forced expiratory volume in 1 second; **FVC:** forced vital capacity; **SD:** standard deviation; **%z<-1.64:** percent of participants with z-score <-1.64; **%z>1.64:** percent of participants with z-score >1.64; **African:** GLI African-American; **Other:** GLI Other/Mixed

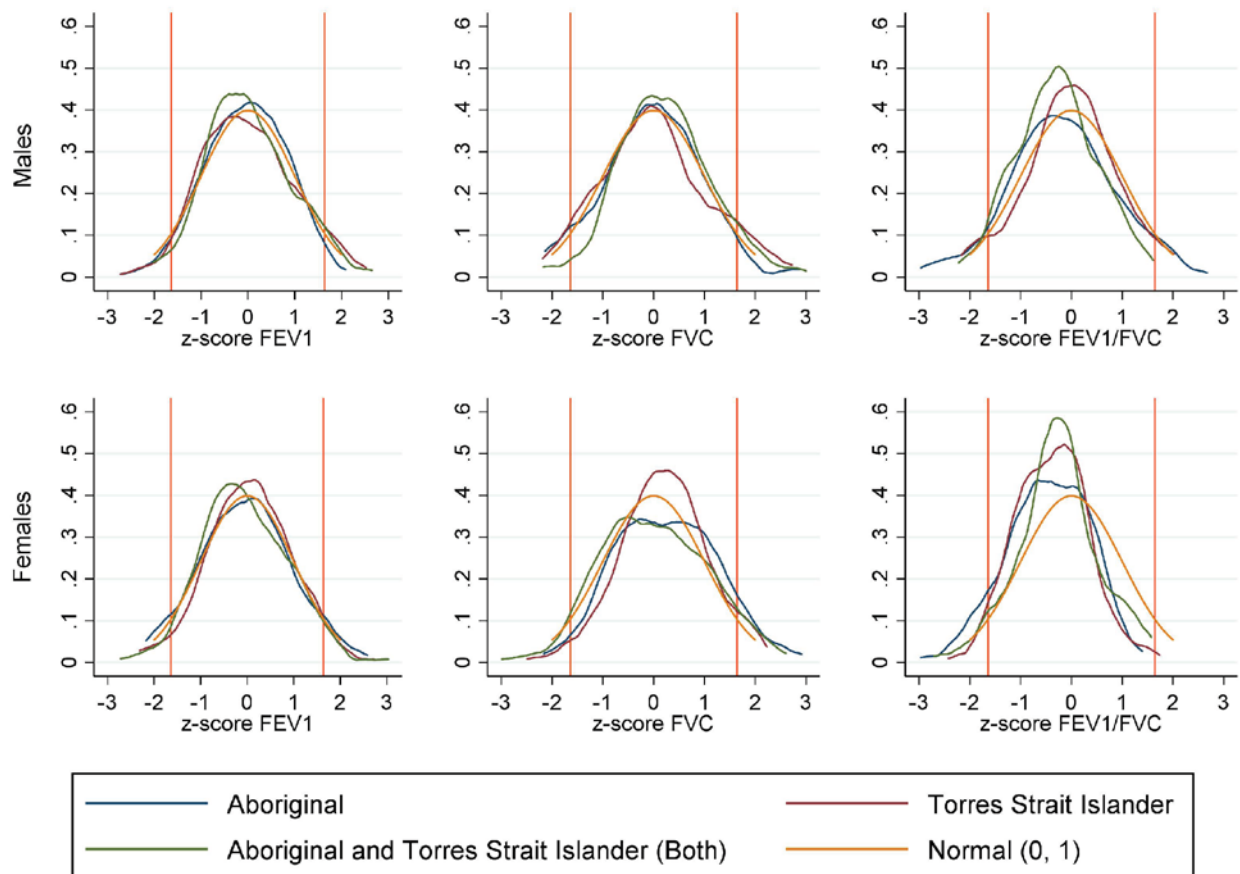


Figure 6.2 Distribution of z-scores for Australian Indigenous males and females separated according to ethnicity, using Global Lung function Initiative ‘Other/Mixed’ equation

No difference was seen between ethnic groups for distribution of $zFEV_1$ or $zFVC$ (males or females). There was a statistically significant difference between Torres Strait Islander and ‘Both’ males (Bonferroni-corrected $p=0.041$) for distribution of $zFEV_1/FVC$. No difference was seen for females.

Table 6.3 Suitability of GLI equations for Australian Indigenous males and females
(combined cohort)

			FEV ₁	FVC	FEV ₁ /FVC
Males	Caucasian	z-score	-0.57	-0.60	0.01
		SD	0.86	0.86	0.86
		%z<-1.64	8.7	11.6	3.0
		%z>1.64	0.7	1.1	3.6
	African	z-score	0.70	0.78	-0.10
		SD	0.91	0.92	0.88
		%z<-1.64	0.4	0.0	4.4
		%z>1.64	15.7	17.6	1.9
	Other	z-score (95% CI)	0.00 (-0.08, 0.08)	0.08 (-0.02, 0.18)	-0.15 (-0.24, -0.06)
		SD (95% CI)	0.91 (0.85, 0.97)	0.97 (0.90, 1.0)	0.91 (0.85, 0.98)
		%z<-1.64 (95% CI)	3.1 (1.7, 5.2)	4.7 (2.9, 7.7)	5.0 (3.0, 7.7)
		%z>1.64 (95% CI)	3.6 (2.1, 5.7)	6.1 (3.8, 9.0)	1.9 (0.7, 3.9)
Females	Caucasian	z-score	-0.58	-0.51	-0.18
		SD	0.86	0.86	0.75
		%z<-1.64	10.3	7.5	2.8
		%z>1.64	0.6	0.8	3.6
	African	z-score	0.70	0.71	-0.28
		SD	0.91	0.89	0.75
		%z<-1.64	0.4	0.5	4.4
		%z>1.64	15.7	15.2	1.9
	Other	z-score (95% CI)	-0.01 (-0.09, 0.07)	0.16 (0.06, 0.26)	-0.37 (-0.45, -0.29)
		SD (95% CI)	0.92 (0.86, 0.98)	0.96 (0.90, 1.0)	0.77 (0.72, 0.83)
		%z<-1.64 (95% CI)	3.9 (2.3, 6.0)	2.3 (1.0, 4.3)	4.9 (3.1, 7.8)
		%z>1.64 (95% CI)	3.7 (2.1, 5.8)	6.9 (4.6, 9.9)	0.3 (0.0, 1.4)

'Both': Aboriginal and Torres Strait Islander; **FEV₁**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **SD**: standard deviation; **%z<-1.64**: percent of participants with z-score <-1.64; **%z>1.64**: percent of participants with z-score >1.64; **African**: GLI African-American; **Other**: GLI Other/Mixed

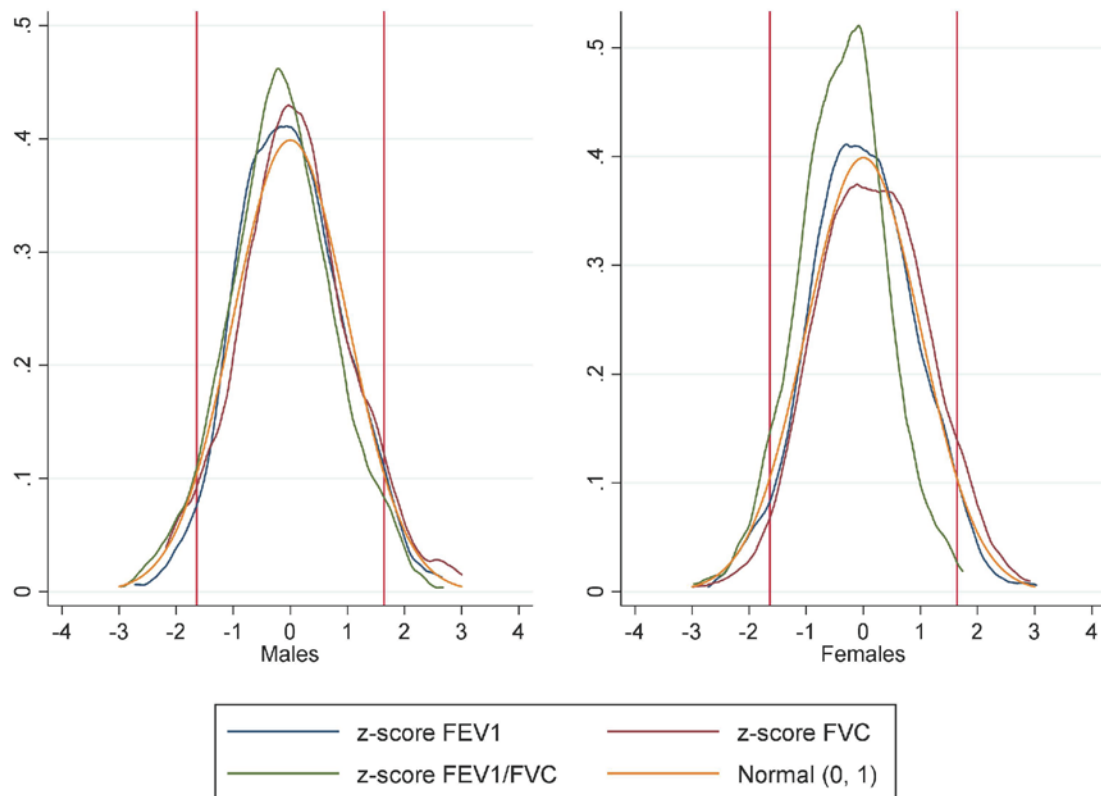


Figure 6.3 Distribution of z-scores for males and females as a combined cohort, using Global Lung Function Initiative ‘Other/Mixed’ equation

6.5 Discussion

Our study is the first to provide spirometry data of ‘healthy’ Aboriginal, Torres Strait Islander and ‘Both’ Aboriginal and Torres Strait Islander Australian children and young adults. Unlike previous studies,¹¹⁸ our cohort consisted of >300 participants (per ethnic group) who were free of both current/chronic respiratory illnesses and smoking history. In assessing the suitability of the GLI-2012 reference equations for use by Indigenous Australians, we found that the GLI-2012 ‘Other/Mixed’ equations gave the best overall fit for all lung function parameters compared to ‘Caucasian’ and ‘African-American’. We found no difference in mean FEV₁ or FVC z-scores between the three Indigenous ethnic

groups for males or females. There was a statistically significant difference between Torres Strait Islander and 'Both' males for FEV₁/FVC% (Bonferroni-corrected p=0.041), but no difference was seen for females.

In assessing the appropriateness of the GLI equations for use among Indigenous Australian children and young adults (as a cohort), we considered the GLI-2012 'Caucasian' equation to be unsuitable as it resulted in 8-12% of our healthy participants to be considered below the LLN (<-1.64). This would likely result in an over-reporting and/or misclassification of obstruction and possible restriction. The GLI-2012 'African-American' equations are 14-16% lower than Caucasian values. Therefore, if previously conducted studies^{115,124-126} on Indigenous Australian reference values were accurate (FEV₁ and FVC values up to 25% lower than Caucasians), then the 'African-American' equation may be more appropriate. However, we found spirometry values for all Australian Indigenous ethnicities to be higher than the 'African-American' values; with 15-18% of participants having z-scores above the ULN (>1.64). Thus, using the 'African-American' equation is inappropriate and could lead to under-reporting and/or misclassification of obstruction and possible restriction in Indigenous Australians.

For ethnic groups not covered by the GLI equations, use of the 'Other/Mixed' equation is recommended by GLI but continued care is required for interpretation as it is an average of the four main ethnic group equations.³¹ Using the 'Other/Mixed' equation resulted in mean z-scores for all parameters that were closer to zero for our combined cohort and a better distribution of healthy participants around the upper and lower limits

of normal. For FEV₁ and FEV₁/FVC%, less than 5% of healthy male and female participants had z-scores below the LLN and above the ULN. For FVC, less than 5% of healthy males and females had z-scores below the LLN, and 6.1% of males and 6.9% of females had z-scores above the ULN. The GLI2012_DataConversion software also has the ability to derive adjustment coefficients for new ethnic groups. When performed on our combined cohort the FEV₁, FVC and FEV₁/FVC% adjustment coefficients (from Caucasian values) were -7.7%, -7.3% and 1.1% respectively. Interestingly, these closely match the adjustment coefficients of the existing 'Other/Mixed' equation (-6.8%, -7.9% and 1.1%) further highlighting the appropriateness of this equation for use by Australian Indigenous children and young adults in comparison to other available equations.

As identified in our systematic review,¹¹⁸ there were several limitations in previously developed spirometry reference equations for Indigenous Australians that impeded their use in the clinical setting. These studies reported only Aboriginal lung function and no Torres Strait Islander or 'Both' data and the difference in values compared to Caucasian data were greater than those typically observed in other non-Caucasian ethnic groups.⁹⁸⁻

¹⁰¹ Close examination of these studies revealed that none had excluded participants with a chronic respiratory illness or smoking history. These factors are well known to influence lung development and early disease progression thereby resulting in lower lung function results.^{13,117,199} Given that we excluded any participant with chronic respiratory illnesses, hospitalisations for bronchiolitis or pneumonia and smoking history from our final dataset, it is not surprising that our cohort of healthy young Indigenous Australians achieved spirometry values higher than those achieved in earlier studies. As seen in

previous studies,^{37,198} there was no significant difference in the mean z-score results when participants who were mildly symptomatic were excluded from the final cohort (mean z-score (SD) for FEV1: 0.03 (0.91) and 0.02 (0.93); FVC: 0.08 (0.98) and 0.17 (0.97); FEV₁/FVC: -0.18 (0.91) and -0.37 (0.78) for males and females respectively). Inclusion of these participants has allowed us to develop a more inclusive reference set and provides important data on what 'healthy' spirometry values are for this population.

6.5.1 Limitations

Although this is the first study that fulfils ATS/ERS and GLI criteria for validating existing reference equations for Indigenous Australians, our study does have limitations. We were unable to explore the influence of weight on lung function results as we were not allowed to obtain children's weights within schools. We acknowledge that this may impact FVC results in individuals who were obese. While one of our study's strengths is the extent we took to exclude unhealthy participants from our final dataset (through both self-reporting and assessing medical records),²⁰⁰ there is a possibility that some included participants may have had a history of respiratory illness or were preterm/low birthweight. Due to our study design we were unable to examine all medical sources for all participants (i.e. general practitioners, interstate records) and therefore information on early childhood factors for some individuals was missing. In these situations we relied solely on parent self-reporting to determine eligibility however, this is common practice in similar population studies that have measured lung function.^{31,186,196} We acknowledge the challenges in using self-reported data. Questionnaires are frequently impacted by recall bias and poor understanding of the questions may have affected answers

particularly where English was not the first language spoken. We sought to minimise this effect with the employment of local Indigenous research assistants.

Due to differences in socioeconomic and health status between rural/remote and urban communities, the generalisability of our findings may not apply to all Indigenous children and young adults throughout Australia as our participants were predominantly recruited from rural and remote Queensland communities. In the context that socio-economic disadvantage is a risk factor for reduced lung function,⁹² data from urban-based Indigenous Australians without socio-economic disadvantage is also required as the majority of our cohort were enrolled from regional-remote regions with lower socioeconomic indices. Further, as our dataset is limited to participants <25 years, quality adult data is required to add to our paediatric and young adult data set to fully characterise the spirometry values of Indigenous Australians across all ages.

6.6 Conclusion

This is the first study to report ‘healthy’ lung function data for children and young adults (3-25 years) who identify as Aboriginal, Torres Strait Islander and ‘Both’. We found no difference in FEV₁ and FVC between participants from the three Indigenous ethnicities. Of the available GLI-2012 reference equations, the ‘Other/Mixed’ reference equation is likely the most appropriate to use for Indigenous Australian children and young adults. Additional data in Indigenous adults from urban centres and other communities around Australia will be required to ensure generalisability of findings. Importantly, these results

suggest that healthy Australian Indigenous spirometry data may not be as low as previously reported in earlier studies.

6.7 Acknowledgements

The authors would like to acknowledge Mr Brian Peacock and Mr Allan Takken (Indigenous Project Officers, IROC Program) and numerous local Indigenous research assistants for their invaluable community knowledge and guidance in completing this study. We also thank the many respiratory scientists who helped in collecting this data. We especially thank the study participants, families, community elders and leaders, schools and Indigenous health staff for their willing participation and support.

This study was facilitated by the Indigenous Respiratory Outreach Care (IROC) Program, funded by the Aboriginal and Torres Strait Islander Health Unit (Queensland Health) and supported by a National Health and Medical Research (NHMRC) Centre for Research Excellence (CRE) grant for Indigenous Children (grant 1040830) and The Prince Charles Hospital Foundation New Investigator grant (NI2017-34). Tamara Blake is supported by a NHMRC Postgraduate Scholarship (1133059) and a CRE top up scholarship (grant 1040830). Anne Chang is supported by a NHMRC Practitioner Fellowship (1058213). Julie Marchant is supported by a Children's Hospital Foundation Fellowship (0772019).

Chapter 7: Fractional exhaled nitric oxide (FeNO) values in Indigenous Australians aged 3-16 years (Article 5)

This chapter addresses **research question 5a & 5b**: “Is there a difference in FeNO results between participants who identify as Aboriginal, Torres Strait Islander or Both?” and “Based on the distribution of FeNO values found, can current Caucasian-based FeNO cut-off values be applied to Indigenous children and young adults?” This manuscript has been accepted by *CHEST*.

Blake TL, Chang AB, Chatfield MD, Marchant JM, Petsky HL, McElrea MS. Fractional exhaled nitric oxide (FeNO) values in Aboriginal and Torres Strait Islander (Indigenous) Australians aged 3-16 years. CHEST. 2019; doi:10.1016/j.chest.2019.02.401

This is the first study to have performed FeNO testing in Indigenous Australian children. We identified a subgroup of ‘healthy’ children who were non-smokers, and free of any current or chronic history of asthma or atopy. Knowing that ethnicity has the potential to influence FeNO results we examined the difference in median FeNO values and distribution between participants who identified as Aboriginal, Torres Strait Islander or Both.

We also assessed how well our cohort of healthy Indigenous children fit within current recommended guidelines with respect to interpretation. Results from this study

continue to highlight the influence ethnicity may have on FeNO results for some ethnic groups. Furthermore, these findings clearly show the challenge with choosing clinically meaningful cut-points for FeNO and the impact this has on interpretation, diagnosis and management.

7.1 Abstract

Background: Fractional exhaled nitric oxide (FeNO) levels can identify eosinophilic asthma phenotypes. We aimed to determine FeNO values of 'healthy' Aboriginal and/or Torres Strait Islander (Indigenous) Australians, differences between these Indigenous ethnic groups and appropriateness of published cut-off values.

Methods: We measured FeNO in 1036 Indigenous Australians (3-16 years). Participants were classified into 'healthy' (i.e. no asthma or atopy history) or asthmatic and/or atopic groups.

Results: Median FeNO values and distribution did not differ between Indigenous ethnicities. For healthy participants <12 years (n=390), 7.2% of our cohort fell into the 'inflammatory' zone of the American Thoracic Society (ATS), National Institute for Health and Care Excellence (NICE) and British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines (cut-off 35 ppb) but only 3.8% when using the Global Initiative for Asthma (GINA) guidelines (50 ppb). Similarly, when using the NICE and BTS/SIGN guidelines (40 ppb) for 12-16 years (n=213), more healthy participants fell into the 'inflammatory' zone compared to the ATS and GINA guidelines (50 ppb) (9.9% vs. 4.7%).

Conclusion: FeNO values for healthy Indigenous Australians children (aged 3-16 years) are likely higher than published Caucasians-based values. The GINA recommended

cut-off value (>50 ppb) appears the most appropriate for identifying healthy Indigenous children but requires confirmation from a larger study.

7.2 Introduction

Fractional exhaled nitric oxide (FeNO) is increasingly used to assist in the diagnosis and monitoring of asthma, predicting exacerbations and identifying possible corticosteroid responsive individuals.^{58,73-75} Current published guidelines for clinical interpretation of FeNO recommend the use of cut-off values which are dependent only on age.^{58,73-75} The use of age-based cut-off values remain controversial in clinical practice due to the known influence of other factors such as atopy, smoking status and respiratory infections^{66,138,141} on FeNO values. Furthermore, FeNO cut-off values are predominantly based on Caucasian data despite findings from several studies that show ethnicity can also influence FeNO values.¹⁴⁶⁻¹⁴⁸ Our systematic review¹¹⁹ found that current cut-off values recommended by the American Thoracic Society (ATS)⁵⁸ may not be suitable for use in some non-Caucasian populations, given that >5% of healthy non-Caucasian children and adults tested had FeNO values above the age-dependent inflammatory cut-off value which could lead to potentially unnecessary treatment interventions. Thus, understanding the range of healthy FeNO values in ethnic groups with a high burden of respiratory diseases including asthma is clinically important.

Incorporating FeNO into routine clinical practice is further complicated by variations in current published guidelines²⁰¹ (Table 7.1) with respect to different definitions of child vs. adult, the age defined cut-off value that would suggest the presence of inflammation, and how a positive test should be interpreted. Depending on which guideline is followed these differences can not only influence whether a patient is diagnosed as having asthma, but also the treatment pathway.

There are currently no studies that have examined FeNO in healthy Aboriginal and Torres Strait Islander (hence forth referred to as Indigenous) Australians. Among Indigenous Australians, asthma is the most common self-reported respiratory illness² with a higher burden (exacerbations and hospitalisations) compared to their non-Indigenous counterparts.^{2,3,6,183} Therefore, there is a need to determine FeNO values in healthy Indigenous Australians. Our overall aim was to describe the distribution of FeNO values in 'healthy' (i.e. no asthma or atopy history) participants (3-16 years) who identify as Aboriginal, Torres Strait Islander or Both (Aboriginal and Torres Strait Islander). We also further aimed to (i) identify if there is any difference in FeNO between these three Indigenous ethnic groups, (ii) report the percentage with FeNO results above current recommended cut-off values described in Table 7.1 and (iii) report on preliminary FeNO results for Indigenous participants who have asthma and/or atopy history.

Table 7.1 Current FeNO guidelines

	Age	FeNO value suggestive of inflammation	Interpretation
ATS	Child <12 yrs. or Adult	>35 ppb >50 ppb	Suggest inflammation, consider history
NICE	Child <17 yrs. or Adult	≥35 ppb ≥40 ppb	Diagnose & treat
BTS/SIGN	Child <17 yrs. or Adult	≥35 ppb ≥40 ppb	Suggest inflammation, consider history
GINA	All ages	>50 ppb	Suggest inflammation, consider history

ATS: American Thoracic Society; **BTS/SIGN:** British Thoracic Society/Scottish Intercollegiate Guidelines Network; **GINA:** Global Initiative for Asthma; **NICE:** National Institute for Health and Care Excellence; **ppb:** parts per billion

7.3 Materials and methods

7.3.1 Study participants and design

We recruited 1036 participants aged between 3-16 years who identified as Aboriginal, Torres Strait Islander or Both from eight communities in Queensland, Australia. In the Australian context an Aboriginal or Torres Strait Islander is a person who identifies (self-reports) as such and is accepted by the community in which he (or she) lives. Participants were recruited from local child care centres, schools and community events. Ethics approval was given by the Human Research Ethics Committees of Children's Health Queensland (HREC/14/QRCH/111), Far North Queensland (HREC/14/QCH/96-929), Darling Downs (HREC/15/QTDD/27) and the Menzies School of Health Research/Northern Territory Health (HREC-2017-2833). Written informed consent was obtained from parents/guardians at the time of recruitment.

FeNO measurement

The NIOX MINO (Aerocrine AB, Solna, Sweden) hand held device was used to measure FeNO levels in parts per billion (ppb). As per current recommended guidelines,²⁷ the participant exhaled directly into the device through a filter mouthpiece ('online' technique) at a controlled flow rate (50 mL/s with an exhalation pressure between 10-20cm H₂O) until the allocated exhalation time was reached (6 seconds if <10 years and 10 seconds if >10 years).¹⁶³ The measurement was performed at least twice to achieve results within 10% of each other as per current guidelines²⁷ and the mean value was recorded for analysis.

Questionnaires and medical record information

Two brief questionnaires completed by parents/guardians were used for this study. The first questionnaire collected information relating to the participant's self-identification of ethnicity (Aboriginal, Torres Strait Islander or Both), current health and medical history, smoking status and exposure, and gestational age at birth. The second, a modified ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire,¹⁶² was used to determine the history of asthma, allergic rhinitis and/or eczema for each participant. Questionnaires were self-administered with the help of local Indigenous research assistants if required.

Paper and electronic medical records (inpatient and outpatient) from relevant health centres and hospitals were examined. We documented information relating to any respiratory disease (with or without hospitalisation) including asthma, bronchitis,

bronchiolitis, pneumonia, bronchiectasis and croup. Evidence of allergic rhinitis, eczema, scabies, impetigo, otitis media and tonsillitis was also noted. Gestational age and birth weight data were collected when available.

Data management and clinical groups

All participant data (questionnaire responses, medical record information and test results) were entered into a secure database (FileMaker Pro 15, CA, USA). Exclusion criteria for the final dataset (Figure 7.1) were inability to meet FeNO acceptability/repeatability criteria (n=136), chronic respiratory disease (e.g. bronchiectasis) that would impact FeNO results (n=3), and current smokers (n=41) incomplete medical history (n=11).

Participants were separated into two age groups; participants <12 years or participants 12-16 years to facilitate comparison with the guidelines.^{58,73-75} Participants were then classified into one of four groups according to their respiratory and atopic history; (i) healthy i.e. no asthma or atopy, (ii) no asthma but with atopy, (iii) with asthma but no atopy or (iv) with both asthma and atopy (Figure 7.1). Asthma history was considered present if there was documented evidence in medical records, or a positive response was recorded on the ISAAC questionnaire for *'ever had asthma'*. Atopy history was considered present if there was any medical record evidence of allergic rhinitis or eczema or, positive responses to ISAAC questions for *'ever had hayfever'* and *'ever had a problem with sneezing, or a runny, or blocked nose when not sick'* and/or *'ever had*

eczema were recorded. When there was a discrepancy between information sources, medical record evidence overrode negative questionnaire responses.

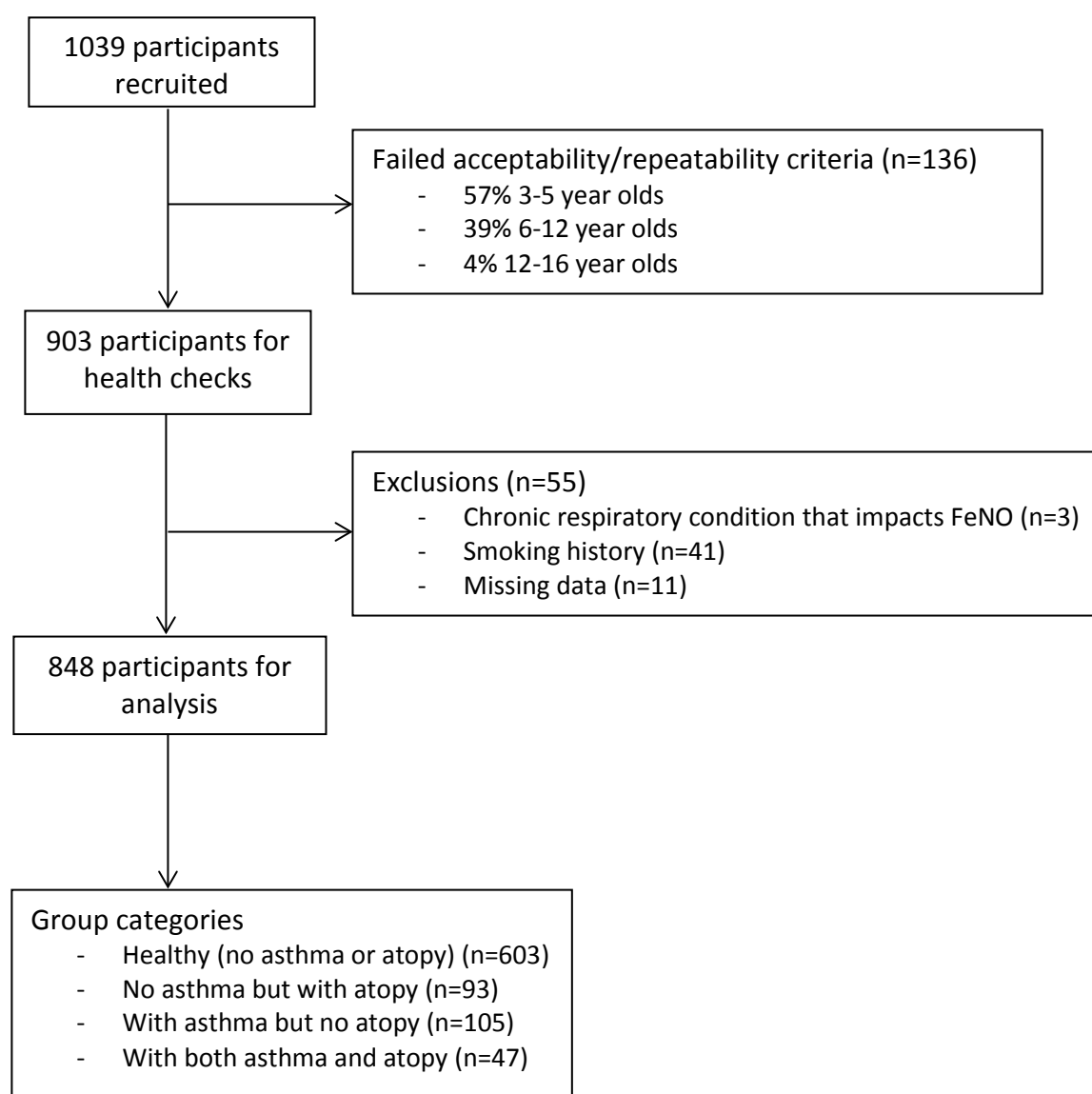


Figure 7.1 Flow diagram depicting exclusion criteria used to identify participants for analysis and separation of according to asthma and/or atopy history

Statistical analyses

FeNO results are reported as medians since data were not normally distributed even after log-transformation. The Mann-Whitney test was used to assess the difference in FeNO results between healthy Aboriginal and Torres Strait Islander participants. We then calculated the percentage of our healthy cohort with FeNO values suggestive of eosinophilic inflammation as recommended by the various guidelines (see Table 7.1). All analyses were performed using Stata15 software (StataCorp, TX, USA).

7.4 Results

Between June 2015 and October 2017, 1039 participants attempted FeNO measurements. After exclusions, a total of 848 participants (81.7%) were included in the final analysis. Cohort demographics and health categories are described in Table 7.2. The cohort spanned an age range of 3.2 to 16.9 years and consisted predominantly of participants <12 years of age (63.0%). In both age groups the majority of participants had no asthma or atopy (<12 years 73.0% and 12-16 years 67.8%). Participants with both asthma and atopy were the least recruited for both age groups (5.4% and 5.7% respectively).

Table 7.2 Cohort demographics

	Participants <12 years n=534	Participants 12-16 years n=314	Total (n=848)
Male <i>n</i> (%)	259 (48.5)	155 (49.4)	414 (48.8)
Age years (<i>median, IQR</i>)	8.6 (7.1-10.4)	14.0 (13.0-15.3)	10.5 (8.0-13.3)
Height <i>cm</i> (<i>median, IQR</i>)	132.1 (122.4-142.9)	162.5 (157.3-169.0)	143.5 (128.5-159.3)
Indigenous ethnicity <i>n</i> (%)			
Aboriginal	170 (31.8)	95 (30.3)	265 (31.3)
Torres Strait Islander	159 (29.8)	130 (41.4)	289 (34.1)
Aboriginal and Torres Strait Islander (Both)	205 (38.4)	89 (28.3)	294 (34.6)
Group categories & FeNO results (ppb)			
No asthma	No atopy ('healthy') <i>n</i> (%)	390 (73.0)	603 (71.1)
		Median (IQR)	11 (7-19)
	With atopy [#] <i>n</i> (%)	50 (9.4)	93 (11.0)
		Median (IQR)	23 (11-46)
With asthma ^{##}	No atopy <i>n</i> (%)	65 (12.2)	105 (12.4)
		Median (IQR)	19 (10-34)
	With atopy [#] <i>n</i> (%)	29 (5.4)	47 (5.5)
		Median (IQR)	24 (9-54)

ppb: parts per billion; **#:** any evidence of allergic rhinitis or eczema from medical records or questionnaires;

##: any evidence of asthma history from medical records or questionnaires

7.4.1 FeNO distribution in healthy participants with no asthma or atopy

The distribution of FeNO results for healthy Aboriginal, Torres Strait Islander and Both participants is shown in Figures 7.2 and 7.3. For participants <12 years (Figure 7.2), there was little difference in the median FeNO values between the three ethnic groups (Aboriginal=11 ppb, Torres Strait Islander=10 ppb, Both=9 ppb). There was no statistically significant difference in FeNO distributions between Aboriginal and Torres Strait Islander participants ($p=0.73$). For participants 12-16 years (Figure 7.3), again no difference was seen between the ethnic groups with respect to median FeNO values (Aboriginal=9 ppb,

Torres Strait Islander=12 ppb, Both=11 ppb) and there was no statistically significant difference in distributions between Aboriginal and Torres Strait Islander participants ($p=0.17$). Results did not differ when data was analysed with the definition of ‘asthma in the last 12 months’ (Supplement file [Appendix I]).

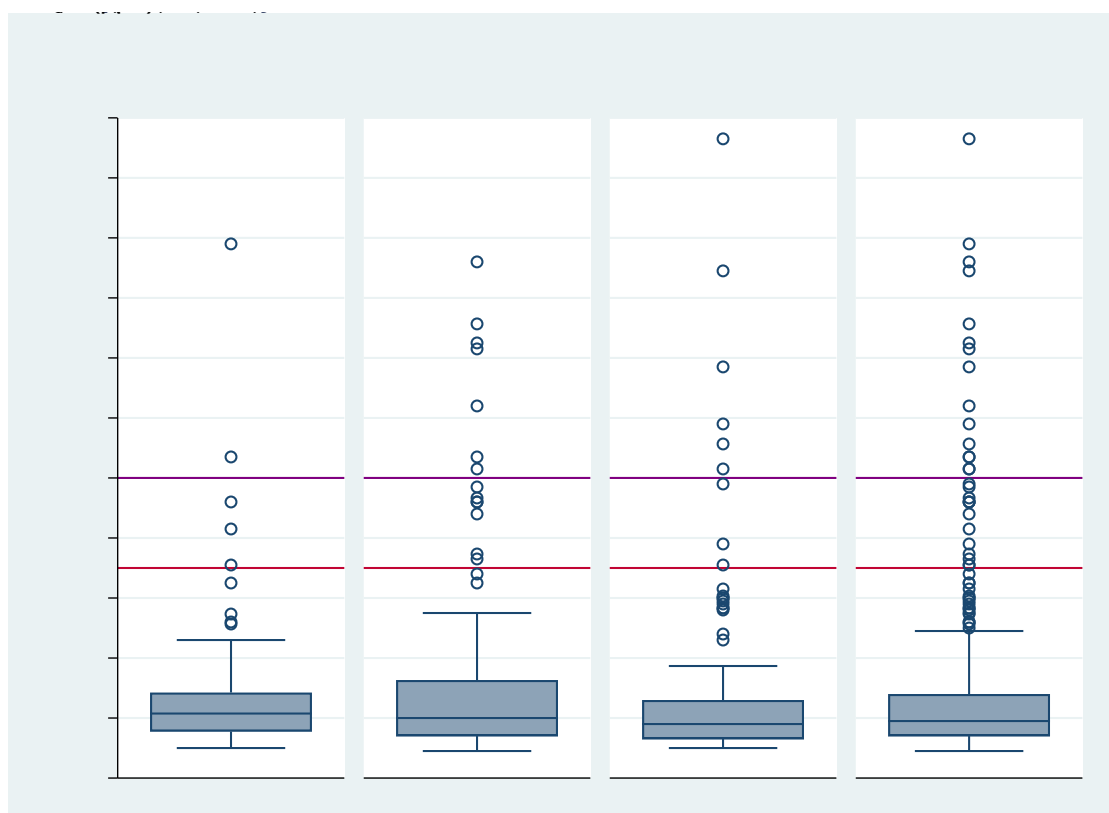


Figure 7.2 Box and whisker plots of FeNO for ‘healthy’ (no asthma or atopy) Australian Indigenous participants <12 years (n=390) separated according to ethnicity

Red horizontal line denotes the ATS/NICE/BTS/SIGN recommended cut-off value of 35 ppb. Purple horizontal line denotes the GINA recommended cut-off value of 50 ppb. **Both:** Aboriginal and Torres Strait Islander; **ppb:** parts per billion

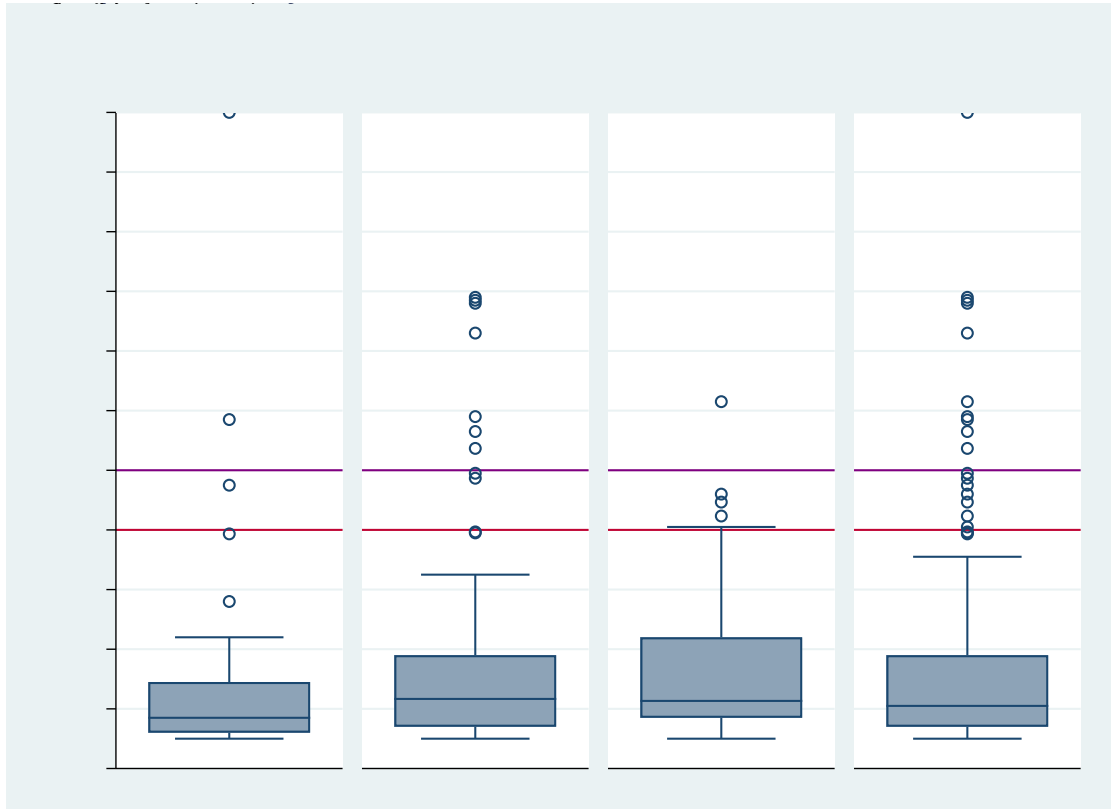


Figure 7.3 Box and whisker plots of FeNO for 'healthy' (no asthma or atopy) Australian Indigenous participants 12-16 years (n=213) separated according to ethnicity

Red horizontal line denotes the NICE/BTS/SIGN recommended cut-off value of 40 ppb. Purple horizontal line denotes the ATS/GINA recommended cut-off value of 50 ppb. **Both:** Aboriginal and Torres Strait Islander; **ppb:** parts per billion

7.4.1 Interpretation according to current guidelines based on age

As there was no difference in FeNO results between the ethnic groups, we combined all data and examined the percent of the healthy participants (with no asthma or atopy) that would be considered positive for inflammation according to the current guidelines. When using ATS, NICE or BTS/SIGN guidelines for participants <12 years of age (all use the same cut-off value of 35 ppb), 7.2% of healthy participants (n=28) in our cohort would be considered in the 'inflammatory' zone (Figure 7.2). In comparison, the

GINA guidelines with a higher cut-off value (>50 ppb), identified only 3.8% of healthy participants <12 years (n=15) in the 'inflammatory' zone. For healthy participants aged between 12-16 years, the NICE and BTS/SIGN guidelines again identified more participants (n= 21, 9.9%) to be positive for inflammation compared to the ATS and GINA (n= 10, 4.7%) guidelines due to the differing cut-off values recommended (35 ppb vs. >50 ppb) (Figure 7.3).

7.4.2 FeNO values in participants with asthma and/or atopy history

For both age groups, FeNO values were higher for those with asthma and/or atopy history compared to those without. Participants aged <12 years (Figure 7.4) with both asthma and atopy had the highest median FeNO values (19 ppb), followed by participants with asthma but no atopy and no asthma but with atopy (both 11 ppb). For participants between 12-16 years (Figure 7.5) median FeNO values were highest in participants with both asthma and atopy (24 ppb), followed by participants with no asthma but with atopy (23 ppb) and with asthma but no atopy (19 ppb).

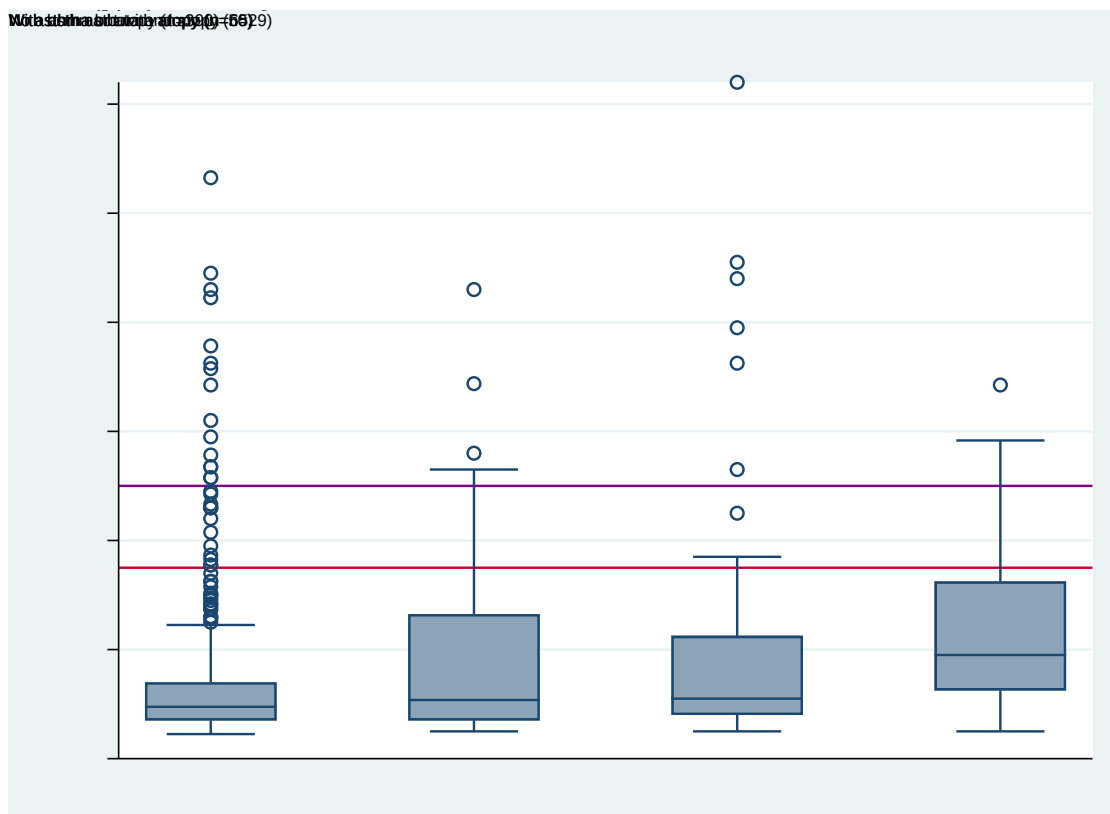


Figure 7.4 Box and whisker plots of FeNO for Australian Indigenous participants <12 years (n=534) separated according to asthma and/or atopy history

Red and purple horizontal lines as per Figure 7.2. **ppb**: parts per billion

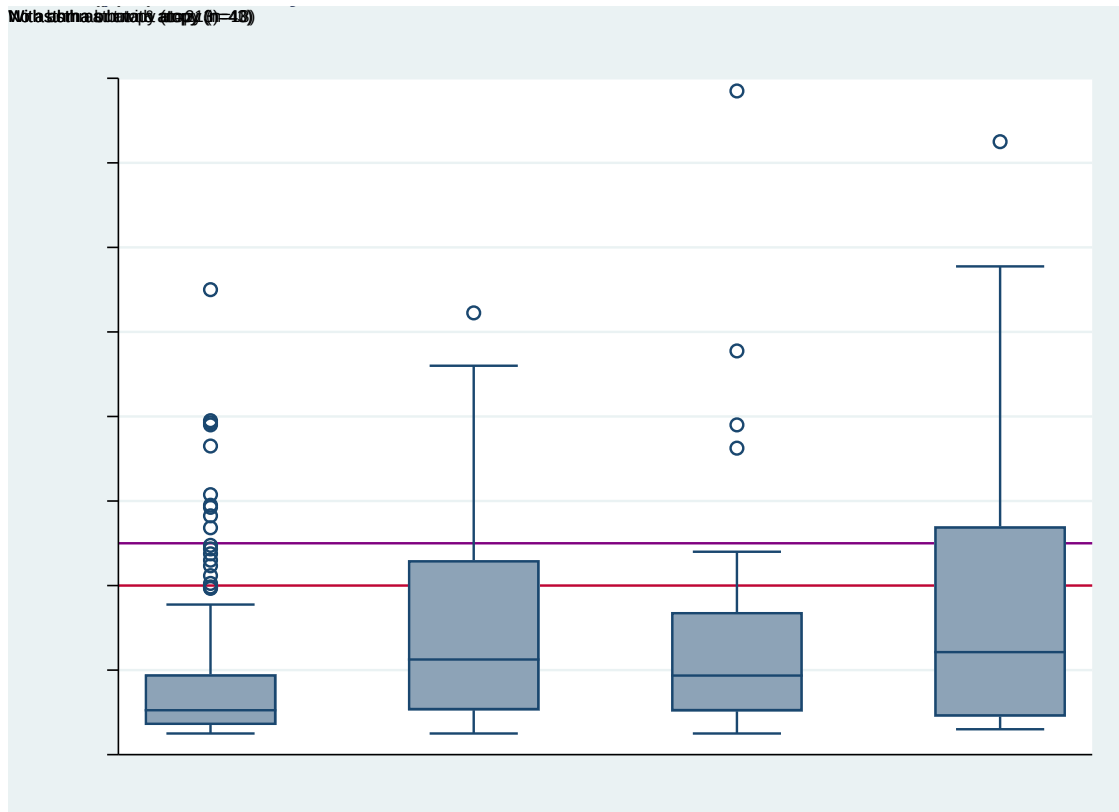


Figure 7.5 Box and whisker plots of FeNO for Australian Indigenous participants 12-16 years (n=314) separated according to asthma and/or atopy history

Red and purple horizontal lines as per Figure 7.3. **ppb**: parts per billion

7.5 Discussion

To our knowledge this is the first study to report FeNO values for Aboriginal and Torres Strait Islander Australians aged between 3-16 years. We found no difference in the distribution of FeNO results of healthy participants (i.e. those with no asthma or atopy) who were <12 years or 12-16 years when separated according to their Australian Indigenous ethnicity. For those <12 years, 7.2% of our healthy participants had FeNO values in the 'inflammatory' zone when using the ATS, NICE or BTS/SIGN cut-off value

(>35 ppb), however only 3.8% when using the GINA guidelines (cut-off value >50 ppb). Respective values for those aged 12-16 years, were 9.9% when using the NICE or BTS/SIGN cut-off value and (4.7%) when using the ATS or GINA cut-off value (>35 ppb vs. >50 ppb)

Our data is important in the context of the high asthma burden among Indigenous Australians,² and our recent systematic review¹¹⁹ that identified the healthy FeNO levels in several ethnic groups (e.g. African-American, Chinese, Korean) were not well characterised within the ATS cut-off values. In these groups, between 5 and 11% of healthy participants had FeNO values in the ATS defined 'inflammatory' zone.¹¹⁹ Using the ATS,⁵⁸ NICE⁷³ and BTS/SIGN⁷⁴ recommended cut-off value (35 ppb), 7.2% of our healthy Australian Indigenous participants <12 years had results in the inflammatory zone. In comparison, the GINA⁷⁵ guidelines (cut-off value >50 ppb) only identified 3.8% of healthy participants. Similarly for participants 12-16 years, the NICE⁷³ and BTS/SIGN⁷⁴ recommended cut-off value (≥ 35 ppb) identified 9.9% of healthy participants in the inflammatory zone with a smaller proportion (4.7%) identified when using the ATS⁵⁸ and GINA⁷⁵ recommended cut-off value (>50 ppb). Thus, care is still needed when selecting which guidelines and cut-off values to apply when interpreting FeNO values among Australian Indigenous children as inappropriate cut-off values have the potential to over diagnose asthma and result in unnecessary treatment interventions.

Two studies have reported FeNO values in healthy Australian children^{202,203} but to our knowledge, neither contained data collected from Indigenous Australians.¹¹⁹ The

geometric mean in one study²⁰² was lower than the median FeNO value in our study (7.2 vs. 9-12 ppb) but the second study²⁰³ had a similar geometric mean (11 ppb). We reported medians as even with log transformation, our data did not have a normal distribution. The FeNO testing methods in both these studies^{202,203} differed from ours in that both used higher expiratory flows and mouth pressures than our study. The higher expiratory flows may result in lower FeNO values compared to when using the current ATS standard pressure and flow parameters.^{202,204,205} Furthermore, we are unable to comment on differences in upper limits of normal (95th percentile) as neither study reported them.

There is still uncertainty regarding the use and definition of clinically meaningful cut-off values for interpreting FeNO values. This is due to the influence of confounding factors (such as diet, exercise and atopy) and the overlap in results between certain disease profiles. Individuals can have high FeNO values despite no asthma or atopy history^{206,207} and conversely, well controlled asthmatic individuals can have FeNO results within the normal range.⁷⁷ Several studies have found an association between atopy^{69,208-210} or the number of positive skin prick tests^{203,211,212} with high FeNO results suggesting that the relationship between asthma and FeNO may in fact be largely influenced by atopy itself.²¹³ For both age groups in our cohort, we noted median FeNO results were highest for participants who had a history of both asthma and atopy, followed by participants with no asthma but with atopy and participants with asthma but no atopy (participants <12 years; 19 vs 11 vs 11 ppb and participants 12-16 years; 24 vs 23 vs 19

ppb). However as seen in Figures 7.4 and 7.5, there is considerable overlap in the distribution of FeNO between the asthma and/or atopy groups for both age groups.

Current international guidelines are based predominantly on data collected from Caucasian populations. The reason FeNO levels of healthy children and adults differ between different ethnic groups is still largely unknown. Differences in the activity of NO synthase (the enzyme essential for NO production) and in allele frequencies of the NO synthase genes has been shown between some ethnic groups.¹⁰⁴⁻¹⁰⁶ Ethnicity refers to a group of people who identify with each other based on common ancestral, social, cultural, or national experiences¹⁰² and as such, complex interactions between genetic and biological, and/or environmental factors i.e. diet, second hand smoking, air pollution, and socioeconomic status are likely to result in differences in FeNO readings between ethnic groups.^{72,107,108}

Taking into consideration evidence that shows FeNO to be a sensitive tool for monitoring adherence to asthma medications and predicting exacerbations following withdrawal of inhaled corticosteroid therapy,^{58,59} it is possible that until cut-off values (or reference equations) are inclusive of the known influencing factors on FeNO, the clinical utility of FeNO may lie more in the monitoring of asthma in an individual rather than as a diagnostic tool. Nevertheless, future studies in this population should examine the distribution of FeNO results in individuals with asthma and atopy phenotypes preferably with skin prick testing and direct sputum eosinophil counts to determine how sensitive

current cut-off values are in accurately identifying eosinophilic inflammation and asthma in Indigenous Australians.

7.5.1 Limitations

There are some important limitations to our study. The primary limitation is that we were unable to perform any direct measurements of atopy (skin prick test) or sputum eosinophil counts to positively identify participants with eosinophilic inflammation. Rather, we relied solely on self-reported and medical record information to identify participants with a history of these conditions. We acknowledge that some participants who were classified as having asthma historically would not have had current eosinophilic asthma. As we were unable to verify asthma phenotype or medication use we grouped any evidence of asthma together to ensure robustness of the healthy group. There is a possibility that some participants may have been atopic at the time of testing but relevant information was missing or incorrectly reported on questionnaires and in medical charts. We attempted to minimise this risk by using medical chart history to augment self-reported (questionnaire) responses.

During data collection, we were also unable to account for other known influencing factors which increase FeNO values such as nitrate intake and strenuous exercise, and we acknowledge that this may influence some of our results. Further, our results are only applicable for Aboriginal and Torres Strait Islanders up to the age of 17 living in Queensland. Continued work is needed in adults and in other communities around Australia. With respect to FeNO results from individuals with asthma and/or atopy

history, continued studies that specifically target these groups are needed to better understand how to incorporate FeNO effectively into asthma management pathways for Aboriginal and Torres Strait Islander Australians.

7.6 Conclusion

This is the first study to report FeNO values of Aboriginal and Torres Strait Islander Australians. We found no difference in the distribution or median FeNO results between healthy Aboriginal and/or Torres Strait Islander participants. For our healthy cohort of Indigenous Australians between 3 and 16 years of age, the GINA recommended cut-off value of 50 ppb appears to be the most appropriate for identifying healthy individuals and considering abnormality. Continued work is still needed to confirm the most robust and clinically meaningful cut-off value to identify eosinophilic inflammation and to determine how best to incorporate FeNO testing into asthma management pathways for Indigenous Australians.

7.7 Acknowledgments

The authors would like to acknowledge Brian Peacock and Allan Takken (Indigenous Project Officers, IROC Program) for their invaluable community knowledge and guidance in completing this study. We also thank the many respiratory scientists who helped in collecting this data. Special thanks to the study participants, families, community elders and leaders, schools and Indigenous health practitioners for their willing participation.

TB had full access to the data and takes responsibility for the integrity of data and accuracy of analysis. TB, AC and MM contributed to study design and data collection. TB performed statistical analysis with guidance provided by MC. All authors were involved in interpretation of results. TB contributed to preparation of the manuscript as well as the design of figures and tables. AC, MC, HP, JM and MM edited manuscript. All authors agreed on the final version before submission. The project was supported as part of the Indigenous Respiratory Outreach Care (IROC) Program, funded by the Aboriginal and Torres Strait Islander Health Unit (Queensland Health) and supported by a National Health and Medical Research (NHMRC) Centre for Research Excellence (CRE) grant for Indigenous Children (grant 1040830) and The Prince Charles Hospital Foundation New Investigator grant (NI2017-34). Tamara Blake is supported by a NHMRC Postgraduate Scholarship (1133059) and a CRE top up scholarship (grant 1040830). Anne Chang is supported by a NHMRC Practitioner Fellowship (1058213). Julie Marchant is supported by a Children's Hospital Foundation Fellowship (0772019).

Chapter 8: Conclusion

8.1 Introduction

Aboriginal and/or Torres Strait Islander (Indigenous) Australians continue to have a higher burden of respiratory diseases compared to non-Indigenous Australians.^{2,3} Lung function tests (such as spirometry and FeNO) are important tools used to aid in the diagnosis and treatment of respiratory illnesses. Interpretation of these tests relies on comparing the results achieved by an individual with reference values that are appropriate for the age, height, gender and ethnicity of the patient. Prior to my PhD studies, it was not known which, if any, of the available reference values were most appropriate for us by Australian Indigenous children and young adults for either spirometry or FeNO.^{118,119} This information is crucial to improving the accuracy of test interpretation and subsequent disease diagnosis, as well as effectively monitoring disease progression and treatment regimes.

This chapter summarises important research findings of this thesis, discusses its strengths and limitations, and addresses the wider clinical implications and recommendations that have arisen from the results.

8.2 Summary of findings

The overall aim of my PhD was to determine the suitability of currently available spirometry and FeNO reference values for Indigenous Australians. To achieve this, five

research questions were formulated. These questions, as well as a summary of findings are described below.

Research question 1: (Chapter 2) Do any of the published spirometry reference value studies for Aboriginal and/or Torres Strait Islander Australians meet current ATS/ERS guidelines?

A systematic review of all available published and grey literature was performed to identify studies that had reported spirometry data for Australian Aboriginal and/or Torres Strait Islander peoples.¹¹⁸ Particular attention was paid to studies that had reported development of reference equations/values from their data. There were nine articles^{14,115,123-129} included in the review and all reported spirometry data of Aboriginal participants only (no study included Torres Strait Islander peoples). All of the included studies reported lower spirometry values (as much as 30% lower) for Aboriginal people compared with non-Indigenous people. Five studies developed spirometry reference values for Indigenous Australians however, none of the studies adhered to all criteria recommended by the ATS/ERS or GLI for adequate sample size or for defining 'healthy' participants. These guidelines state that a representative sample should consist of a minimum of 300 individuals (150 male/ 150 female) who are free of any current or chronic respiratory illness and have no smoking history.^{31,36,165}

Furthermore, examination of these reference equations in a hypothetical scenario highlighted the ease with which misinterpretation and subsequent misdiagnosis of respiratory disease in this population could occur when inappropriate reference

equations are used. For example, predicted FEV₁ values differed by up to 500mLs between studies. In this way, an individual's spirometry results could be interpreted as either normal or suggestive of the presence of disease, depending on which predicted values were used. We therefore concluded that application of any of these reported Aboriginal reference equations in a clinical setting was inappropriate, and further studies were required to examine the suitability of existing GLI reference sets for Indigenous Australians.

Research question 2: (Chapter 3) Does ethnicity impact FeNO values and what are the potential implications?

Whilst several factors such as age, smoking status, diet and atopy status,^{66,138,141} are known to influence individuals' FeNO levels, the potential influence of 'ethnicity' on FeNO values has not been systematically evaluated. Thus, a systematic review of published literature was conducted to explore ethnicity as a potential factor on FeNO results in healthy non-Caucasian children and adults.¹¹⁹ There were 12 studies^{107,143,145-154} included in the review with a total of 11 different ethnic groups recruited. Notably, no study had been conducted with Australian Indigenous participants. The review found that ethnicity influenced FeNO values in 10 of the included studies and for some of these groups, this influence impacted clinical interpretation according to current guidelines.

By estimating the proportion of participants from each study that had FeNO results above the inflammatory cut-off values, we identified between 5-11% of healthy participants from some ethnic groups that would be classified as having abnormal results.

These participants may go on to receive further investigations or commence treatment therapies. This highlights the need for further studies in non-Caucasian populations to determine if Caucasian-based cut-off ranges are clinically applicable for detecting the presence of eosinophilic inflammation. We expect that less than 5% of healthy Caucasians might be expected to have FeNO results above the inflammatory cut-off values. This review further emphasises the challenge of using a single cut-off value for interpretation. The influence of contributing factors on FeNO values, particularly ethnicity, requires further investigation so as to fully optimise its use in a clinical setting.

Research question 3: (Chapter 5) How consistent is the information obtained from self-reported and medical records in this population?

Success of research questions 4 and 5 was ultimately dependent on our ability to accurately identify 'healthy' participants. For spirometry, healthy participants should have no smoking history, and be free of any current (within past 12-months) and/or chronic respiratory conditions. For FeNO, healthy participants should in addition to this, be free of any atopic condition. Identification of these conditions was achieved through parent/participant self-reporting and through medical record checks. However, there are currently no published data on the discrepancies between self-reported and medical record information for these conditions among Indigenous Australians.

We found pneumonia and eczema were more commonly identified in medical records than self-reported but asthma, bronchiectasis and allergic rhinitis were more commonly self-reported. There was moderate agreement for asthma and bronchiectasis

between self-reported and medical record evidence ($\kappa=0.53$, 95% CI 0.45-0.61 and $\kappa=0.52$, 95% CI 0.25-0.80 respectively). In contrast, agreement for eczema was fair, while agreement for pneumonia and allergic rhinitis was poor. Self-reported information is typically more accurate when the condition is well defined and easily recognised/diagnosed compared to conditions with complex or nonspecific symptoms, however this was not the case for some of the well-defined conditions (asthma, bronchiectasis and pneumonia) that were measured. These findings i) suggest that accurate health history of some conditions may be better achieved by examining medical records rather than relying solely on self-reporting and ii) highlight the challenges associated with how best to determine disease prevalence within Australian Indigenous rural/remote communities. Based on these findings we chose to collate information from both data sources (self-reported and medical records) in order to identify 'healthy' participants for research questions 4 and 5.

Research question 4: (Chapter 6)

a) Is there a difference in spirometry values between participants who identify as Aboriginal, Torres Strait Islander or Both?

b) Which (if any) of the GLI-2012 reference equations are most suitable for Australian Indigenous children and young adults?

In 930 healthy participants, mean FEV₁ and FVC z-scores did not statistically differ between the three Indigenous ethnic groups (Aboriginal, Torres Strait Islander and Both) for males or females. However, there was a statistically significant difference between FEV₁/FVC% z-scores for Torres Strait Islander and Both males.

In comparison to the GLL-2012³¹ 'Caucasian' and 'African-American' equations, the 'Other/Mixed' equation had the best overall fit for all lung function parameters for males and females for all Indigenous ethnicities. Using the 'Other/Mixed' equation resulted in mean z-scores for all parameters that were close to 0, SD close to 1 and a better distribution of healthy participants around the upper and lower limits of normal. For FEV₁ and FEV₁/FVC%, less than 5% of healthy male and female participants had z-scores below the LLN and above the ULN. For FVC, less than 5% of healthy males and females had z-scores below the LLN, and 6.1% of males and 6.9% of females had z-scores above the ULN. Further studies in Indigenous adults from urban centres and other communities around Australia will be required to ensure generalisability of findings. Importantly, these results suggest that healthy Australian Indigenous spirometry data may not be as low as previously reported in earlier studies.

Research question 5: (Chapter 7)

a) Is there a difference in FeNO values between participants who identify as Aboriginal, Torres Strait Islander or Both?

b) Based on the distribution of FeNO values found, can current Caucasian-based FeNO cut-off values be applied to Indigenous children and young adults?

In 603 healthy participants (n=390 <12 years and n=213 12-16 years), the distribution of FeNO values did not statistically differ between the Indigenous ethnic groups (Aboriginal, Torres Strait Islander or Both) for either age group.

In determining the applicability of current suggested FeNO cut-off values for identifying abnormality (i.e. the 'inflammatory' zone), 7.2% of healthy participants <12 years had FeNO values in the 'inflammatory' zone when using the ATS,⁵⁸ NICE⁷³ or BTS/SIGN⁷⁴ cut-off value (>35 ppb), however only 3.8% were in the 'inflammatory' zone when using the GINA⁷⁵ guidelines (cut-off value >50 ppb). Respective values for those aged 12-16 years, were 9.9% when using the NICE or BTS/SIGN cut-off value and (4.7%) when using the ATS or GINA cut-off value (>35 ppb vs. >50 ppb). Therefore, we concluded that the GINA recommended cut-off value of 50 ppb is the most appropriate for identifying healthy individuals and considering abnormality in this population. However, confirmation from a larger study with a wider age range is required.

8.3 Strengths and limitations

The findings presented in my thesis help to fill a considerable gap in current literature and improve the clinical utility of lung function tests for healthy Aboriginal and Torres Strait Islander children and young adults. Availability of this data will lead to improved accuracy of test interpretation which will aid in better diagnosis and management of respiratory conditions amongst Indigenous Australian children and young adults. My PhD is the first to quantify a number of 'healthy' lung function parameters in this population across multiple Queensland sites. Furthermore, it is the first to report any data on the lung function of healthy Torres Strait Islander participants.

8.3.1 Strengths

Importantly, all testing was performed by trained respiratory scientists to current international standards (ATS/ERS) thereby ensuring high quality results and the ability for data to be safely incorporated into future national and/or international studies if required. In addition, we applied a strict systematic process for identifying healthy participants who were free of known influencing factors on lung function (including current and/or chronic respiratory illness, low birthweight and/or gestational age, smoking history, atopic history [for FeNO only]).

This research followed current Australian research guidelines¹⁵⁹ by employing Indigenous project officers and local research assistants to assist with document preparation and recruitment. Their involvement was crucial to the success of this research and adds significant value and strength to our data. Indigenous project officers were involved in the development of the information sheets, consent forms and medical questionnaires to ensure that language used was appropriate for the different communities. They provided introductions into communities and assisted with recruitment where appropriate. Local research assistants assisted primarily in the completion and return of consent forms and questionnaires. Community members were often more comfortable discussing the study and completing paperwork with local research assistants, particularly where the usual language spoken was an Indigenous language. Without local research assistants' crucial contributions of language and community knowledge it is likely that our recruitment rate within some communities would have been much lower.

8.3.2 Limitations

The limitations inherent to each research question are outlined within each chapter and associated manuscript. However, there are several limitations that are common to the overall research of my PhD and are outlined below.

Firstly, there is limited data from participants over the age of 18 years which may impact the generalisability of findings for Indigenous individuals in the 18-25 year age range. In addition to this, the majority of data were obtained from Queensland and as such, the findings of this research may not be applicable to Indigenous Australian children and young adults located in other Australian states. Across the country there are likely to be differences in individual and community demographics that may impact the generalisability of our findings to all Indigenous Australians. This may be due to a combination of factors including geographical (urban vs. remote vs. rural), education, socio-economic status, as well as access to health services and baseline health characteristics. Secondly, due to the study design and mobility of Indigenous Australians between communities we were unable to check all potentially relevant medical charts. This limitation may potentially impact the accuracy of some of our data as information relating to health factors of interest for our studies (particularly exclusion criteria) may have been available at other locations, for example GP offices, private clinics or interstate, which we were unable to access. For this reason, using both self-reported and medical record information to assess health history was appropriate to try and minimise further bias and to reduce the loss of potentially relevant data.

Although we fulfilled the GLI criteria^{31,165} for the minimum number required to assess appropriateness of existing reference equations, the number of participants recruited were lower than expected. A number of factors contributed to this. The first was allowing sufficient time to engage with communities in the early stages of the study. There were a number of reasons (i.e. “sorry business” within a community, conflicting schedules, weather, staff availability and multiple ethics approval requirements) that impacted the number and timing of visits required to each community in order to gain approval and to discuss logistics of recruitment. This caused delays in the commencement of our recruitment phase in some communities resulting in less on-site time. The bulk of data collection occurred during school times; however recruitment of participants ranged between 15-80% of the school’s estimated Indigenous student cohort depending on the community. As such, a large group of potentially suitable individuals were not recruited into the study. The complexity of the study paperwork (information sheets, consent forms and questionnaires) may have impacted the recruitment rate and responses to questions. Feedback from community members indicated that despite our attempts to make the paperwork as friendly as possible, the volume of paperwork was sometimes off-putting to parents and difficult to understand. The employment of local research assistants helped to an extent with this; however they were not always able to oversee the completion of all documentation. Additionally, changes in family living situations (i.e. mobility between community, kinship carers, family disruption and change in contact details) sometimes made identification of appropriate parent/guardian to approach for consent challenging.

Finally, our study was not designed to assess the potential influence of contributing factors to lung health and development within this population. While some information was adequately collected (i.e. birthweight, gestational age, frequency of hospitalisations, smoking), we did not collect information relating to other known socioeconomic or household factors (i.e. income, education levels, access to health services, living standards) and therefore any attempt to investigate this would likely not be a robust reflection of these contributing factors for this population.

8.4 Implications and recommendations

The findings of this research, once implemented, ultimately will contribute to better diagnosis and monitoring of respiratory conditions amongst Indigenous Australian children and young adults, thereby improving clinical outcomes. Several implications and recommendations for clinical practice and areas for future research can be drawn from this study. These will be discussed in the context of each results chapter; that is medical history information, spirometry and FeNO.

8.4.1 Clinical practice

Medical history information

Obtaining accurate health history is challenging for all areas of epidemiology-based research. Our results suggest that within our cohort of Australian Indigenous children and young adults, information obtained from self-reporting and medical records with respect to conditions such as allergic rhinitis, eczema, asthma, pneumonia and bronchiectasis are not interchangeable. This may be due to several reasons. Differences in disease

severity/overlapping symptoms, health literacy and access to health services is likely to impact to accuracy of self-reported information regarding these conditions between patients. Clinicians treating our Indigenous population should be mindful of this and where possible, check available medical records. However, the transient nature of Indigenous Australians is also likely to impact the availability of medical records particularly in regional and remote areas. As such, improving the accuracy of self-reported information through increased health education in Indigenous communities both at an individual and community level is crucial.

These findings are also relevant when considering the accuracy of results published in health surveys or studies on disease prevalence whereby health information is solely self-reported with no validation process undertaken to confirm yes/no responses. The Australian Bureau of Statistics acknowledges that this may introduce bias as participants' responses may be impacted by the inability to recall disease specific information and a desire to provide responses they feel may be expected.^{22,183} This further highlights the potential risk to over- or under-report prevalence of conditions in this population depending on the information source used. Surveys and future studies should be mindful of this and consider the possible inaccuracies in results when choosing which data source to use. Additionally, future studies would benefit from conducting a wider search of medical records so as to be more inclusive of potentially relevant information.

Spirometry

This thesis has shown that the GLI-2012 'Other/Mixed' equations are currently the most appropriate to use when performing and interpreting spirometry for Indigenous Australian children and young adults. These results are directly translational and will aid doctors, nurses, respiratory scientists and other allied health practitioners who perform and interpret these tests on Australian Indigenous children and young adults. Many spirometry software programs already have the GLI-2012 equations pre-loaded and therefore, use of 'Other/Mixed' equation for Indigenous Australian children and young adults in Queensland can be introduced immediately for clinical use. The 'Other/Mixed' equation could be used for Indigenous adults and/or those living outside of Queensland; however careful interpretation will still be needed until further studies have validated the use of these equations for these other populations.

These results are clinically relevant given that poor lung function in early adulthood is an independent risk factor associated with increased future risk of early all-cause mortality, cardiovascular morbidity and respiratory outcomes.²¹⁴⁻²¹⁹ In addition, several (but not all) longitudinal studies have reported that asthma, bronchiectasis, pneumonia, bronchiolitis and/or bronchitis in childhood are associated with future lung function deficits.²²⁰⁻²²⁴ Given also that Indigenous Australians continue to suffer from a number of early life risk factors (including low birthweight, overcrowding, tobacco smoke exposure) that are known to influence respiratory illnesses,²²⁵ the use of appropriate reference values amongst the Indigenous Australian population is necessary not only to aid in the diagnosis and management of respiratory disease, but also to better understand the projected respiratory disease burden.

Finally, our findings have shown that the lung function of healthy Indigenous Australian children and young adults is not as low as suggested in earlier studies. This is likely to be reflective of our recruitment of a true 'healthy' cohort as previous studies did not exclude participants with chronic respiratory illness and/or smoking history. Hence, our findings have implications for clinicians who have made a blanket ethnic adjustment of 15-20% in their spirometry software for Indigenous patients. The software of many spirometers enables previous lung function results to be adjusted for GLI equations; however clinicians should be aware that this may cause a dramatic shift in results and trend reports.

FeNO

This thesis has shown that using the cut-off values recommended by the GINA guidelines (50 ppb) appears the most appropriate for identifying healthy Indigenous children (3-16 years) within Queensland. These guidelines could be followed for Indigenous adults and/or patients in other states however results will require careful interpretation until future studies in this cohort can be performed. Prior to this work, no studies had examined FeNO in healthy Indigenous Australians. The use of FeNO in assisting in the diagnosis and monitoring of asthma, predicting exacerbations and identifying possible corticosteroid responsive individuals^{58,73-75} has been well documented. Considering the high burden (exacerbations and hospitalisations)^{2,3,6,183} of asthma amongst Indigenous Australians, understanding how best to interpret FeNO values in this population is crucial.

Researchers and clinicians still need to be mindful of the complex interactions between FeNO and confounding factors (such as atopy, diet, exercise) when interpreting results and therefore, as recommended by current guidelines, this test should always be interpreted in conjunction with current symptoms and clinical history. Nevertheless, increased effort should be made to incorporate FeNO testing into asthma management pathways for Indigenous Australians considering evidence that shows FeNO to be a sensitive tool for monitoring adherence to asthma medications and predicting exacerbations following withdrawal of inhaled corticosteroid therapy,^{58,59} issues which are known to be prevalent in this population.⁶

8.4.2 Future research

Medical history information

It would be useful to compare medical record history with self-reported history in an adult population as well as in other communities around Australia to examine how generalisable our findings are. In addition to this, there are only a handful of studies that have examined the agreement between self-reported and medical record information for non-respiratory diagnoses for Indigenous Australians and so, further studies with a wider disease focus are needed for this population. Investigations into the impact of potential factors such as poor health knowledge/literacy, information recall, access to health services, disease severity and community demographics are also needed to better understand how best to use these data sources in clinical practice and in research. Results from this would also identify areas for increased health education in Indigenous communities both at an individual and community level.

Spirometry

Despite the GLI equations consisting of the largest pooled data source to date (>160 000 spirometry results from 33 countries), there have been several studies that have been unable to validate the use of the GLI equations within their respective populations. The majority of these validation studies have been conducted using the 'Caucasian' equations^{191-193,196} compared to the 'African-American',¹⁹⁴ and 'North-/South-East Asian',¹⁹⁵ equations however; nearly all have been conducted in adult populations of varying age ranges. In several of these studies, it is hypothesised that the poor fit of the GLI equations may be due to differences between the GLI sample and the studied population. For example, data from several ethnic groups from different geographical locations were combined to make the GLI equations and as such may not be reflective of all anthropometric, environmental and/or socioeconomic variant possibilities.^{191,193} Furthermore, data from some countries were not included in the GLI sample and therefore uncertainty remains as to how well the equations will fit these populations.^{192,193,226} Therefore, it is crucial to continue our study in a full age range of adults (18-95 years) and also in other communities around Australia to confirm whether the GLI-2012 'Other/Mixed' equations are appropriate for use by all Indigenous Australians or if a new adjustment factor is required.

As identified in Chapter 6, there were several limitations to the generalisability of our findings to all Indigenous Australians. These included our inability to measure weight, the minimal collection of socioeconomic data, nutritional status and adverse environmental factors (air quality, biomass fuels), all of which are known to impact spirometry results.^{40,43,46} Better understanding of the relevant influence these factors

have on lung function results within this population would be an important step in further assessing the appropriateness of potential reference equations. This could be achieved through a larger validation study that measures and assesses these factors. Additionally, a validation study performed within a group of Indigenous patients with diagnosed asthma, COPD and emphysema would also be appropriate so as to assess the impact of using the 'Other/Mixed' equation on monitoring disease severity and progression.

Following on from the spirometry reference equations, the GLI taskforce has now developed reference equations for the diffusing capacity of the lung for carbon monoxide (DLCO) and is currently working on finalising reference equations for lung volumes. Since accurate diagnosis and monitoring of respiratory disease progression often requires results from more than one lung function test, it is important that these new reference equations also be validated for use amongst Indigenous Australians to improve the accuracy and quality of clinical care that is provided to current and future patients.

FeNO

Performing this research in adults and in additional communities around Australia is needed to assess the broad applicability of our findings, and to confirm the most robust and clinically meaningful cut-off value to identify eosinophilic inflammation in this population. Future studies should also examine the distribution of FeNO results in individuals with asthma and atopy phenotypes, preferably identified through the use of skin prick testing and direct sputum eosinophil counts. This will help to determine the sensitivity of current cut-off values in patients with confirmed eosinophilic inflammation

and provide a better understanding of how to incorporate FeNO testing effectively into asthma management pathway for Indigenous Australians.

8.5 Impact of research to date

Results from the spirometry component of this research have had a significant impact on clinical interpretation at several sites to date. The use of the GLI-‘Other/Mixed’ equation has been adopted by the IROC program when performing spirometry during outreach clinics and is currently used for all Aboriginal and Torres Strait Islander children presenting to the Department of Respiratory and Sleep Medicine at the Queensland Children’s Hospital, South Brisbane. Upon presentation of findings at both national and international conferences, several other respiratory departments in Australia have expressed their interest in the final published paper so as to implement changes to their own standard operating procedures. A number of collaborative discussions have occurred with other researchers around Australia with the aim of increasing the generalisability of results.

Throughout the recruitment and testing phases, basic respiratory education by the research team was provided to participants, parents, health workers and the general community when required. This gave the research team the opportunity to not only increase the awareness of respiratory diseases within the targeted communities, but also the chance to promote visiting respiratory specialist teams and services that can assist with disease diagnosis and management. Furthermore, this study allowed for the identification of individuals who may require more thorough follow up with a specialist

respiratory service. In some communities the Elders specifically requested that we respond in this manner to abnormal test results and/or questionable symptoms. As a result, 60 participants were referred to local community health groups and/or the IROC program for potential follow up. This was well received and appreciated in all the communities we recruited from.

Finally, preliminary results and study findings have allowed us to secure initial funding to continue this study by recruiting adults from several Indigenous communities within Queensland.

Bibliography

1. Australian Government. Closing the Gap: Prime Minister's Report. 2014. [cited 2016 Apr 26]. Available from: https://www.dpmc.gov.au/sites/default/files/publications/closing_the_gap_2014.pdf.
2. Australian Health Ministers' Advisory Council, 2017. Aboriginal and Torres Strait Islander Health Performance Framework 2017 Report. AHMAC, Canberra.
3. Australian Institute of Health and Welfare 2015. Australian Burden of Disease Study: fatal burden of disease in Aboriginal and Torres Strait Islander people 2010. Australian Burden of Disease Study series no. 2. Cat. no. BOD 2. Canberra: AIHW.
4. O'Grady KA, Taylor-Thomson DM, Chang AB, Torzillo PJ, Morris PS, Mackenzie GA, et al. Rates of radiologically confirmed pneumonia as defined by the World Health Organization in Northern Territory Indigenous children. *Med J Aust*. 2010;192(10):592-595.
5. Chang AB, Grimwood K, Mulholland K, Torzillo PJ. Bronchiectasis in Indigenous children in remote Australian communities. *Med J Aust*. 2002;177:200-204.
6. Chang AB, Shannon C, O'Neil MC, Tiemann AM, Valery PC, Craig D, et al. Asthma management in indigenous children of a remote community using an indigenous health model. *J Paediatr Child Health*. 2000;36(3):249-251.
7. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med*. 2012;185(11):1183-1189.
8. Chang AB, Masel JP, Boyce NC, Wheaton G, Torzillo PJ. Non-CF bronchiectasis: clinical and HRCT evaluation. *Pediatr Pulmonol*. 2003;35(6):477-483.
9. World Health Organization. Pneumonia. 2016. [cited 2016 Oct 18]. Available from: <http://www.who.int/mediacentre/factsheets/fs331/en/#>.
10. Redding G, Singleton R, Lewis T, Martinez P, Butler J, Stamey D, et al. Early radiographic and clinical features associated with bronchiectasis in children. *Pediatr Pulmonol*. 2004;37(4):297-304.
11. Grimwood K, Chang AB. Long-term effects on pneumonia in young children. *Pneumonia*. 2015;27(6):101-114.
12. Stafler P, Carr SB. Non-cystic fibrosis bronchiectasis: its diagnosis and management. *Arch Dis Child Educ Pract Ed*. 2010;95(3):73-82.
13. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *Lancet Respir Med*. 2013;1(9):728-742.
14. Bucens IK, Reid A, Sayers SM. Risk factors for reduced lung function in Australian Aboriginal children. *J Paediatr Child Health*. 2006;42(7-8):452-457.
15. Valery PC, Torzillo PJ, Mulholland K, Boyce NC, Purdie DM, Chang AB. Hospital-Based Case-Control Study of Bronchiectasis in Indigenous Children in Central Australia. *The Pediatric Infectious Disease Journal*. 2004;23(10):902-908.
16. Turner SW, Young S, Landau LI, Le Souef PN. Reduced lung function both before bronchiolitis and at 11 years. *Arch Dis Child*. 2002;87:417-420.
17. Steinfort DP, Brady S, Weisinger HS, Einsiedel L. Bronchiectasis in Central Australia: a young face to an old disease. *Respir Med*. 2008;102(4):574-578.
18. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.

2016. [cited 2016 Jan 19]. Available from: <https://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/>.
19. Vos T, Barker B, Begg S, Stanley L, Lopez AD. Burden of disease and injury in Aboriginal and Torres Strait Islander Peoples: the Indigenous health gap. *Int J Epidemiol*. 2009;38(2):470-477.
20. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ*. 1991;303(6804):671-675.
21. Zhao Y, Wright J, Begg S, Guthridge S. Decomposing Indigenous life expectancy gap by risk factors: a life table analysis. *Popul Health Metr*. 2013;11(1):1.
22. Australian Bureau of Statistics. National Health Survey: First Results 2014-15. [cited 2017 Nov 14]. Available from: <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4364.0.55.0012014-15?OpenDocument>.
23. Australian Institute of Health and Welfare 2014. Coronary heart disease and chronic obstructive pulmonary disease in Indigenous Australians. Cat. no. IHW 126. Canberra: AIHW.
24. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *Eur Respir J*. 2005;26(1):153-161.
25. Enright PL, Johnson LR, Connett JE, Voelker H, Buist AS. Spirometry in the Lung Health Study. 1. Methods and quality control. *Am Rev Respir Dis*. 1991;143(6):1215-1223.
26. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
27. American Thoracic S, European Respiratory S. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171(8):912-930.
28. Eigen H, Bieler H, Grant D, Christop K, Terrill D, Heilman DK, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med*. 2001;163:619-623.
29. Zapletal A, Chalupova J. Forced expiratory parameters in healthy preschool children (3-6 years of age). *Pediatr Pulmonol*. 2003;35(3):200-207.
30. Quanjer PH, Stanojevic S, Stocks J, Hall GL, Prasad KV, Cole TJ, et al. Changes in the FEV(1)/FVC ratio during childhood and adolescence: an intercontinental study. *Eur Respir J*. 2010;36(6):1391-1399.
31. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.
32. Kozłowska WJ, Aurora P. Spirometry in the pre-school age group. *Paediatr Respir Rev*. 2005;6(4):267-272.
33. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948-968.
34. Crapo RO. Pulmonary-function testing. *N Engl J Med*. 1994;331(1):25-30.
35. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med*. 2007;175(12):1304-1345.

36. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis.* 1991;144(5):1202-1218.
37. Lum S, Bountziouka V, Sonnappa S, Cole TJ, Bonner R, Stocks J. How "healthy" should children be when selecting reference samples for spirometry? *Eur Respir J.* 2015.
38. European Respiratory Society. Interpretation of results: "Lower Limit of Normal". [cited 2016 Oct 10]. Available from: <https://spirxpert.ers-education.org/en/global-lung-function-initiative/interpretation-of-results-lower-limit-of-normal/>.
39. Hibbert ME, Lannigan A, Landau LI, Phelan PD. Lung function values from a longitudinal study of healthy children and adolescents. *Pediatr Pulmonol.* 1989;7(2):101-109.
40. Whitrow MJ, Harding S. Ethnic differences in adolescent lung function: anthropometric, socioeconomic, and psychosocial factors. *Am J Respir Crit Care Med.* 2008;177(11):1262-1267.
41. Rossiter CE, Weill H. Ethnic Differences in Lung Function: evidence for proportional differences. *Int J Epidemiol.* 1974;3(1):55-61.
42. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging.* 2006;1(3):253-260.
43. Harik-Khan RI, Fleg JL, Muller DC. The effect of anthropometric and socioeconomic factors on the racial difference in lung function. *Am J Respir Crit Care Med.* 2001;164:1647-1654.
44. Johnston I, Bland J, Anderson H. Ethnic variation in respiratory morbidity and lung function in children. *Thorax.* 1987;42:542-548.
45. Patrick K, Patel A. Ethnic differences in the growth of lung function in children: a cross sectional in inner-city Nottingham. *Ann Hum Biol J.* 1986;13:307-315.
46. Harik-Khan RI, Muller DC, Wise RA. Racial difference in lung function in African-American and White children: effect of anthropometric, socioeconomic, nutritional, and environmental factors. *Am J Epidemiol.* 2004;160(9):893-900.
47. Van Sickle D, Magzamen S, Mullahy J. Understanding socioeconomic and racial differences in adult lung function. *Am J Respir Crit Care Med.* 2011;184(5):521-527.
48. Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, et al. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. *Am J Respir Crit Care Med.* 2009;180(6):547-552.
49. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999;159(1):179-187.
50. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med.* 2008;177(3):253-260.
51. Bougrida M, Bourahli MK, Aissaoui A, Rouatbi S, Mehdioui H, Ben Saad H. Spirometric reference values for children living in Constantine (Eastern region of Algeria). *Tunis Med.* 2012;90(1):51-61.
52. Arnall DA, Kanuho V, Interpreter C, Nelson AG, Coast JR, Eisenmann JC, et al. Spirometry reference values for Navajo children ages 6-14 years. *Pediatr Pulmonol.* 2009;44(5):489-496.
53. Leung TF, Liu TC, Mak KK, Su X, Sy HY, Li AM, et al. Reference standards for forced expiratory indices in Chinese preschool children. *Pediatr Pulmonol.* 2013;48(11):1119-1126.

54. Memon MA, Sandila MP, Ahmed ST. Spirometric reference values in healthy, non-smoking, urban Pakistani population. *J Pak Med Assoc.* 2007;57(4):193-195.
55. Barnes PJ, Belvisi MG. Nitric oxide and lung disease. *Thorax.* 1993;48:1034-1043.
56. Gibson P. Using fractional exhaled nitric oxide to guide asthma therapy: design and methodological issues for ASThma Treatment Algorithm studies. *Clin Exp Allergy.* 2009;39(4):478-490.
57. Grob NM, Laskowski D, Dweik RA. A technical report on exhaled nitric oxide measurement: asthma monitoring in athletes. *J Breath Res.* 2008;2(3):37027.
58. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications. *Am J Respir Crit Care Med.* 2011;184:602-615.
59. Pijnenburg MW, De Jongste JC. Exhaled nitric oxide in childhood asthma: a review. *Clin Exp Allergy.* 2008;38(2):246-259.
60. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* 2014;43(2):343-373.
61. Petsky HL, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax.* 2012;67(3):199-208.
62. Gaston BM, Drazen JM, Chee CBE, Wohl MED, Stamier JS. *In* Biology of nitric oxide: Clinical and Physiological Implications. 1994. Portlad Press, London. 497-500.
63. Alving K, Janson C, Nordvall L. Performance of a new hand-held device for exhaled nitric oxide measurement in adults and children. *Respir Res.* 2006;7:67.
64. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. *J Allergy Clin Immunol.* 2005;115(6):1130-1136.
65. Ozkan M, Dweik RA. Ozkan M, Dweik RA. Nitric oxide and airway reactivity. *Clin Pulm Med.* 2001;8:199-206.
66. Hahn YS. Measurements of fractional exhaled nitric oxide in pediatric asthma. *Korean J Pediatr.* 2013;56(10):424-430.
67. Ricciardolo FL. Revisiting the role of exhaled nitric oxide in asthma. *Curr Opin Pulm Med.* 2014;20:53-59.
68. Travers J, Marsh S, Aldington S, Williams M, Shirtcliffe P, Pritchard A, et al. Reference ranges for exhaled nitric oxide derived from a random community survey of adults. *Am J Respir Crit Care Med.* 2007;176(3):238-242.
69. Scott M, Raza A, Karmaus W, Mitchell F, Grundy J, Kurukulaarachy RJ, et al. Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. *Thorax.* 2010;65(3):258-262.
70. Jacinto T, Alving K, Correia R, Costa-Pereira A, Fonseca J. Setting reference values for exhaled nitric oxide: a systematic review. *Clin Respir J.* 2012;7(2):113-120.
71. Dressel H, de la Motte D, Reichert J, Ochmann U, Petru R, Angerer P, et al. Exhaled nitric oxide: independent effects of atopy, smoking, respiratory tract infection, gender and height. *Respir Med.* 2008;102(7):962-969.
72. Lund MB, Kongerud J, Nystad W, Boe J, Harris JR. Genetic and environmental effects on exhaled nitric oxide and airway responsiveness in a population-based sample of twins. *Eur Respir J.* 2007;29(2):292-298.

73. National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. 2017. [cited 2017 Dec 08]. Available from: www.nice.org.uk/guidance/ng80.
74. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma : a national clinical guideline. 2016. [cited 2018 Feb 12]. Available from: <https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/>.
75. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2018. [cited 2018 Mar 19]. Available from: <https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf>.
76. Grob NM, Dweik RA. Exhaled nitric oxide in asthma: progress since the introduction of standardized methodology. *J Breath Res*. 2008;2(3):37002.
77. Olin AC, Rosengren A, Thelle DS, Lissner L, Bake B, Toren K. Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. *Chest*. 2006;130(5):1319-1325.
78. Bjermer L, Alving K, Diamant Z, Magnussen H, Pavord I, Piacentini G, et al. Current evidence and future research needs for FeNO measurement in respiratory diseases. *Respir Med*. 2014;108(6):830-841.
79. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med*. 2005;172(4):453-459.
80. Hahn PY, Morgenthaler TY, Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. *Mayo Clin Proc*. 2007;82(11):1350-1355.
81. Szeffler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol*. 2005;115(2):233-242.
82. Zietkowski Z, Kucharewicz I, Bodzenta-Lukaszyk A. The influence of inhaled corticosteroids on exhaled nitric oxide in stable chronic obstructive pulmonary disease. *Respir Med*. 2005;99(7):816-824.
83. Antus B. [Role of exhaled nitric oxide in predicting steroid response in chronic obstructive pulmonary disease]. *Orv Hetil*. 2010;151(51):2083-2088.
84. Nolte H, Pavord I, Backer V, Spector S, Shekar T, Gates D, et al. Dose-dependent anti-inflammatory effect of inhaled mometasone furoate/formoterol in subjects with asthma. *Respir Med*. 2013;107(5):656-664.
85. Koster ES, Raaijmakers JA, Vijverberg SJ, Maitland-van der Zee AH. Inhaled corticosteroid adherence in paediatric patients: the PACMAN cohort study. *Pharmacoepidemiol Drug Saf*. 2011;20(10):1064-1072.
86. McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *Am J Respir Crit Care Med*. 2012;186(11):1102-1108.
87. Zeiger RS, Schatz M, Zhang F, Crawford WW, Kaplan MS, Roth RM, et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. *J Allergy Clin Immunol*. 2011;128(2):412-414.
88. Gelb AF, Flynn Taylor C, Shinar CM, Gutierrez C, Zamel N. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. *Chest*. 2006;129(6):1492-1499.

89. Jones SL, Kittelson J, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med*. 2001;164(5):738-743.
90. van Veen IH, Ten Brinke A, Sterk PJ, Sont JK, Gauw SA, Rabe KF, et al. Exhaled nitric oxide predicts lung function decline in difficult-to-treat asthma. *Eur Respir J*. 2008;32(2):344-349.
91. Lawlor DA. Association between self-reported childhood socioeconomic position and adult lung function: findings from the British Women's Heart and Health Study. *Thorax*. 2004;59(3):199-203.
92. Hegewald MJ, Crapo RO. Socioeconomic status and lung function. *Chest*. 2007;132(5):1608-1614.
93. Burchfiel CM, Marcus EB, Sharp DS, Enright P, Rodriguez BI, Masaki KH, et al. Characteristics associated with rapid decline in forced expiratory volume. *Ann Epidemiol*. 1996;6:217-227.
94. Tabak C, Spijkerman AM, Verschuren WM, Smit HA. Does educational level influence lung function decline (Doetinchem Cohort Study)? *Eur Respir J*. 2009;34(4):940-947.
95. Kumar R, Seibold MA, Aldrich MC, et al. Genetic ancestry in lung-function predictions. *N Engl J Med*. 2010;363(4):321-330.
96. Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, Zhivotovsky LA, et al. Genetic structure of human populations. *Science*. 2002;298(5602):2381-2385.
97. Kaplan JB, Bennett T. Use of race and ethnicity in biomedical publication. *JAMA*. 2003;289:2709-2716.
98. Whittaker AL, Sutton AJ, Beardsmore CS. Are ethnic differences in lung function explained by chest size? *Arch Dis Child Fetal Neonatal Ed*. 2005;90(5):F423-428.
99. Kiefer EM, Hankinson JL, Barr RG. Similar relation of age and height to lung function among Whites, African Americans, and Hispanics. *Am J Epidemiol*. 2011;173(4):376-387.
100. Chinn SR, R. Height and age adjustments for cross sectional studies of lung function in children aged 6-11 years. *Thorax*. 1992;47:707-714.
101. Yang TS, Peat JK, Keena VK, Donnelly PM, Unger W, Woolcock AJ. A review of the racial differences in the lung function of normal Caucasian, Chinese and Indian subjects. *Eur Respir J*. 1991;4:872-880.
102. Braun L, Wolfgang M, Dickersin K. Defining race/ethnicity and explaining difference in research studies on lung function. *Eur Respir J*. 2013;41(6):1362-1370.
103. Donnelly PM, Yang TS, Peak JK, Woolcock AJ. What factors explain racial differences in lung volumes? *Eur Respir J*. 1991;4:829-838.
104. Grasemann H, Storm van's Gravesande K, Buscher R, Drazen JM, Ratjen F. Effects of sex and of gene variants in constitutive nitric oxide synthases on exhaled nitric oxide. *Am J Respir Crit Care Med*. 2003;167(8):1113-1116.
105. Storm van's Gravesande K, Wechsler ME, Grasemann H, Silverman ES, Le L, Palmer LJ, et al. Association of a missense mutation in the NOS3 gene with exhaled nitric oxide levels. *Am J Respir Crit Care Med*. 2003;168(2):228-231.
106. Salam MT, Bastain TM, Rappaport EB, Islam T, Berhane K, Gauderman WJ, et al. Genetic variations in nitric oxide synthase and arginase influence exhaled nitric oxide levels in children. *Allergy*. 2011;66(3):412-419.

107. Levesque MC, Hauswirth DW, Mervin-Blake S, Fernandez CA, Patch KB, Alexander KM, et al. Determinants of exhaled nitric oxide levels in healthy, nonsmoking African American adults. *J Allergy Clin Immunol*. 2008;121(2):396-402 e393.
108. Spanier AJ, Kahn RS, Hornung RW, Wang N, Sun G, Lierl MB, et al. Environmental exposures, nitric oxide synthase genes, and exhaled nitric oxide in asthmatic children. *Pediatr Pulmonol*. 2009;44(8):812-819.
109. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol*. 1995;142(10):1103-1112.
110. Mohangoo AD, van der Linden MW, Schellevis FG, Raat H. Prevalence estimates of asthma or COPD from a health interview survey and from general practitioner registration: what's the difference? *Eur J Public Health*. 2006;16(1):101-105.
111. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49(12):1407-1417.
112. Draper GK, Somerford PJ, Pilkington AS, Thompson SC. What is the impact of missing Indigenous status on mortality estimates? An assessment using record linkage in Western Australia. *Aust N Z J Public Health*. 2009;33(4):325-331.
113. Fortin M, Haggerty J, Sanche S, Almirall J. Self-reported versus health administrative data: implications for assessing chronic illness burden in populations. A cross-sectional study. *CMAJ Open*. 2017;5(3):E729-E733.
114. Lix LM, Yogendran MS, Shaw SY, Targownik LE, Jones J, Bataineh O. Comparing administrative and survey data for ascertaining cases of irritable bowel syndrome: a population-based investigation. *BMC Health Serv Res*. 2010;10:31.
115. Bremner PR, De Klerk NH, Ryan GF, James AL, Musk M, Murray C, et al. Respiratory Symptoms and Lung Function in Aborigines from Tropical Western Australia. *Am J Respir Crit Care Med*. 1998;158(6):1724-1729.
116. Chang AB, Marsh RL, Upham JW, Hoffman LR, Smith-Vaughan H, Holt D, et al. Toward making inroads in reducing the disparity of lung health in Australian indigenous and new zealand maori children. *Front Pediatr*. 2015;3:9.
117. Tennant PW, Gibson GJ, Parker L, Pearce MS. Childhood respiratory illness and lung function at ages 14 and 50 years: childhood respiratory illness and lung function. *Chest*. 2010;137(1):146-155.
118. Blake TL, Chang AB, Petsky HL, Rodwell LT, Brown MG, Hill DC, et al. Spirometry reference values in Indigenous Australians: a systematic review. *Med J Aust*. 2016;205(1):35-40.
119. Blake TL, Chang AB, Chatfield MD, Petsky HL, Rodwell LT, Brown MG, et al. Does Ethnicity Influence Fractional Exhaled Nitric Oxide in Healthy Individuals?: A Systematic Review. *Chest*. 2017;152(1):40-50.
120. Queensland Health, Health Statistics Centre. Experimental Life Tables by Remoteness, Queensland, 2002-04 and 2005-07: Closing the gap between Indigenous and non-Indigenous Life Expectancy. 2012. [cited 2016 Apr 26]. Available from: <https://www.health.qld.gov.au/hsu/pdf/other/explifetab0512.pdf>.
121. Australian Centre for Asthma Monitoring 2011. Asthma in Australia 2011. AIHW Asthma Series no. 4. Cat. no. ACM 22. Canberra: AIHW.

122. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. *European Respiratory Journal*. 1995;8(3):492-506.
123. Musk AW, James AL, Palmer LJ, Ryan GF, Lake F, Golledge CL, et al. Respiratory infections and lung function in an Australian Aboriginal community. *Respirology*. 2008;13(2):257-262.
124. Verheijden MW, Ton A, James AL, Wood M, Musk AW. Respiratory morbidity and lung function in two Aboriginal communities in Western Australia. *Respirology*. 2002;7(3):247-253.
125. Veale AJ, Peat JK, Salome CM, Woolcock AJ, Thompson JE. 'Normal' lung function in rural Australian Aborigines. *Aust N Z J Med*. 1997;27(5):543-549.
126. Thompson JE, Sleigh AC, Passey ME, Barnes A, Streatfield RW. Ventilatory standards for clinically well Aboriginal adults. *Med J Aust*. 1992;156:566-569.
127. Watson DS, Watson RM, Siskind V. Respiratory function in aboriginal children. *Med J Aust*. 1986;144:S11-13.
128. Chandler D, Dugdale AE. Respiratory function tests in Aboriginal children on Mornington Island. *Med J Aust*. 1980;1(10).
129. Chandler D, Dugdale AE. Respiratory function in Aboriginal school children. *Med J Aust*. 1979;24(1):10-12.
130. James AL, Knuiman MW, Divitini ML, Musk AW, Ryan G, Bartholomew HC. Associations between white blood cell count, lung function, respiratory illness and mortality: the Busselton Health Study. *Eur Respir J*. 1999;13(5):1115-1119.
131. Gore CJ, Crockett AJ, Pederson DG, Booth ML, Bauman A, Owen N. Spirometric standards for healthy adult lifetime nonsmokers in Australia. *Eur Respir J*. 1995;8(5):773-782.
132. Gibson J, Gallagher H, Johansen A, Webster I. Lung function in an Australian population: 1. Spirometric standards for non-smoking adults. *Med J Aust*. 1979;1(7):292-295.
133. Polgar G, Promadhat V. Pulmonary Function Testing in Children: Techniques and Standards. 1971. Saunders: Philadelphia.
134. Valery PC, Masters IB, Taylor B, Laifoo Y, O'Rourke PK, Chang AB. An education intervention for childhood asthma by Aboriginal and Torres Strait Islander health workers: a randomised controlled trial. *Med J Aust*. 2010;192(10):574-579.
135. Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. *Lancet Respir Med*. 2013;1(8):610-620.
136. Ludviksdottir D, Diamant Z, Alving K, Bjermer L, Malinovschi A. Clinical aspects of using exhaled NO in asthma diagnosis and management. *Clin Respir J*. 2012;6(4):193-207.
137. Warke TJ, Fitch PS, Brown V, Taylor R, Lyons JD, Ennis M, et al. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax*. 2002;57(5):383-387.
138. Petsky HL, Li AM, Au CT, Kynaston JA, Turner C, Chang AB. Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: A dual centre randomized controlled trial. *Pediatr Pulmonol*. 2015;50(6):535-543.
139. Fleming L, Tsartsali L, Wilson N, Regamey N, Bush A. Longitudinal relationship between sputum eosinophils and exhaled nitric oxide in children with asthma. *Am J Respir Crit Care Med*. 2013;188(3):400-402.

140. Singer F, Luchsinger I, Inci D, Knauer N, Latzin P, Wildhaber JH, et al. Exhaled nitric oxide in symptomatic children at preschool age predicts later asthma. *Allergy*. 2013;68(4):531-538.
141. Gill R, Krishnan S, Dozor AJ. Low-level environmental tobacco smoke exposure and inflammatory biomarkers in children with asthma. *J Asthma*. 2014;51(4):355-359.
142. Sandrini A, Taylor DR, Thomas PS, Yates DH. Fractional exhaled nitric oxide in asthma: an update. *Respirology*. 2010;15(1):57-70.
143. Wong GW, Liu EK, Leung TF, Yung E, Ko FW, Hui DS, et al. High levels and gender difference of exhaled nitric oxide in Chinese schoolchildren. *Clin Exp Allergy*. 2005;35(7):889-893.
144. People J, Bailey G. *Humanity: An Introduction to Cultural Anthropology*. 2010. Wadsworth Cengage. 389.
145. Sonnappa S, Bastardo CM, Stafler P, Bush A, Aurora P, Stocks J. Ethnic differences in fraction of exhaled nitric oxide and lung function in healthy young children. *Chest*. 2011;140(5):1325-1331.
146. Brody DJ, Zhang X, Kit BK, Dillon CF. Reference values and factors associated with exhaled nitric oxide: U.S. youth and adults. *Respir Med*. 2013;107(11):1682-1691.
147. Baptist AP, Li L, Dichiaro CA. The importance of atopy on exhaled nitric oxide levels in African American children. *Ann Allergy Asthma Immunol*. 2015;114(5):399-403.
148. Ko FW, Leung TF, Wong GW, Chu JH, Sy HY, Hui DS. Determinants of, and reference equation for, exhaled nitric oxide in the Chinese population. *Eur Respir J*. 2013;42(3):767-775.
149. Rouatbi S, Alqodwa A, Ben Mdella S, Ben Saad H. Fraction of exhaled nitric oxide (FeNO) norms in healthy North African children 5-16 years old. *Pediatr Pulmonol*. 2013;48(10):981-995.
150. Yao TC, Lee WI, Ou LS, Chen LC, Yeh KW, Huang JL, et al. Reference values of exhaled nitric oxide in healthy Asian children aged 5 to 18 years. *Eur Respir J*. 2012;39(2):378-384.
151. Matsunaga K, Hirano T, Kawayama T, Tsuburai T, Nagase H, Aizawa H, et al. Reference ranges for exhaled nitric oxide fraction in healthy Japanese adult population. *Allergology International*. 2010;59(4):363-367.
152. Kim SH, Kim TH, Sohn JW, Yoon HJ, Shin DH, Park SS. Reference values and determinants of exhaled nitric oxide in healthy Korean adults. *J Asthma*. 2010;47(5):563-567.
153. Kovesi T, Kulka R, Dales R. Exhaled nitric oxide concentration is affected by age, height, and race in healthy 9- to 12-year-old children. *Chest*. 2008;133(1):169-175.
154. Edwards EA, Douglas C, Broome S, Kolbe J, Jensen CG, Dewar A, et al. Nitric oxide levels and ciliary beat frequency in indigenous New Zealand children. *Pediatr Pulmonol*. 2005;39(3):238-246.
155. Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. *Thorax*. 2003;58(6):494-499.
156. Karrasch S, Linde K, Rucker G, Sommer H, Karsch-Volk M, Kleijnen J, et al. Accuracy of FENO for diagnosing asthma: a systematic review. *Thorax*. 2016;72(2):109-116.
157. Kovesi T, Dales R. Exhaled nitric oxide and respiratory symptoms in a community sample of school aged children. *Pediatr Pulmonol*. 2008;43(12):1198-1205.

158. National Institute for Health and Care Excellence. Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath. 2014. [cited 2016 Jul 22]. Available from: <https://www.nice.org.uk/guidance/DG12/chapter/About-this-guidance>.
159. Australian Institute of Aboriginal and Torres Strait Islander Studies. Guidelines for ethical research in Australian Indigenous studies (Rev. 2nd ed). 2012. Australian Institute of Aboriginal and Torres Strait Islander Studies. Canberra. .
160. Australian Bureau of Statistics. Australian Statistical Geography Standard (ASGS): Volume 2 - Indigenous Structure. 2011. [cited 2018 Mar 16]. Available from: <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1270.0.55.002July%202011?OpenDocument>.
161. Quanjer PH, Hall GL, Stanojevic S, Cole TJ, Stocks J, Global Lungs I. Age- and height-based prediction bias in spirometry reference equations. *Eur Respir J*. 2012;40(1):190-197.
162. Asher I. The International Study of Asthma and Allergies in Childhood (ISAAC). *N Z Med J*. 2008;121(1279):117-118.
163. Circassia AB. NIOX MINO: User Manual version 9; 2017. Sweeden.
164. Altman DG. Practical Statistics for Medical Research. 1991. Chapman & Hall: London.
165. Global Lung Function Initiative. Implementing GLI-2012 regression equations. 2016. [cited 2016 Oct 24]. Available from: <http://www.ers-education.org/home/browse-all-content.aspx?idParent=138979>.
166. Adams PF, Dey AN, Vickerie JL. Summary health statistics for the U.S. population: National Health Interview Survey, 2005. *Vital Health Stat 10*. 2007(233):1-104.
167. Navin Cristina TJ, Stewart Williams JA, Parkinson L, Sibbritt DW, Byles JE. Identification of diabetes, heart disease, hypertension and stroke in mid- and older-aged women: Comparing self-report and administrative hospital data records. *Geriatr Gerontol Int*. 2016;16(1):95-102.
168. Comino EJ, Tran DT, Haas M, Flack J, Jalaludin B, Jorm L, et al. Validating self-report of diabetes use by participants in the 45 and Up Study: a record linkage study. *BMC Health Serv Res*. 2013;13:481.
169. Peeters GM, Alshurafa M, Schaap L, de Vet HC. Diagnostic accuracy of self-reported arthritis in the general adult population is acceptable. *J Clin Epidemiol*. 2015;68(4):452-459.
170. Knox SA, Harrison CM, Britt HC, Henderson JV. Estimating prevalence of common chronic morbidities in Australia. *Med J Aust*. 2008;189(2):66-70.
171. Gresham E, Forder P, Chojenta CL, Byles JE, Loxton DJ, AJ H. Agreement between self-reported perinatal outcomes and administrative data in New South Wales, Australia. *BMC Pregnancy and Childbirth*. 2015;15:161.
172. Barr EL, Tonkin AM, Welborn TA, Shaw JE. Validity of self-reported cardiovascular disease events in comparison to medical record adjudication and a statewide hospital morbidity database: the AusDiab study. *Intern Med J*. 2009;39(1):49-53.
173. Kehoe R, Wu SY, Leske MC, Chylack LT, Jr. Comparing self-reported and physician-reported medical history. *Am J Epidemiol*. 1994;139(8):813-818.
174. Lujic S, Watson DE, Randall DA, Simpson JM, Jorm LR. Variation in the recording of common health conditions in routine hospital data: study using linked survey and administrative data in New South Wales, Australia. *BMJ Open*. 2014;4(9):e005768.

175. Jiang L, Zhang B, Smith ML, Lorden AL, Radcliff TA, Lorig K, et al. Concordance between Self-Reports and Medicare Claims among Participants in a National Study of Chronic Disease Self-Management Program. *Front Public Health*. 2015;3:222.
176. Muggah E, Graves E, Bennett C, Manuel DG. Ascertainment of chronic diseases using population health data: a comparison of health administrative data and patient self-report. *BMC Public Health*. 2013;13:16.
177. Gilligan C, Sanson-Fisher R, Eades S, Wenitong M, Panaretto K, D'Este C. Assessing the accuracy of self-reported smoking status and impact of passive smoke exposure among pregnant Aboriginal and Torres Strait Islander women using cotinine biochemical validation. *Drug Alcohol Rev*. 2010;29(1):35-40.
178. Stewart J, Sanson-Fisher R, Eades S. Aboriginal and Torres Strait Islander health: accuracy of patient self-report of screening for diabetes, high cholesterol and cervical cancer. *Aust N Z J Public Health*. 2016;40 Suppl 1:S3-6.
179. Gwynn JD, Hardy LL, Wiggers JH, Smith WT, D'Este CA, Turner N, et al. The validation of a self-report measure and physical activity of Australian Aboriginal and Torres Strait Islander and non-Indigenous rural children. *Aust N Z J Public Health*. 2010;34 Suppl 1:S57-65.
180. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol*. 2004;57(10):1096-1103.
181. Koller KR, Wilson AS, Asay ED, Metzger JS, Neal DE. Agreement Between Self-Report and Medical Record Prevalence of 16 Chronic Conditions in the Alaska EARTH Study. *J Prim Care Community Health*. 2014;5(3):160-165.
182. Perales F, Baffour B, Mitrou F. Ethnic Differences in the Quality of the Interview Process and Implications for Survey Analysis: The Case of Indigenous Australians. *PLoS One*. 2015;10(6):e0130994.
183. Australian Bureau of Statistics. Australian Aboriginal and Torres Strait Islander Health Survey: First Results 2012-13. [cited 2018 Mar 13]. Available from: <http://www.abs.gov.au/ausstats/abs@.nsf/mf/4727.0.55.001>.
184. Brand PLP, van Dulmen S. Can we trust what parents tell us? A systematic review. *Paediatr Respir Rev*. 2017;24:65-71.
185. Mukhopadhyay S, Macleod KA, Ong TJ, Ogston SA. "Ethnic" variation in childhood lung function may relate to preventable nutritional deficiency. *Acta Paediatr*. 2001;90(11):1299-1303.
186. Ketfi A, Gharnaout M, Bougrida M, Ben Saad H. The multi-ethnic global lung initiative 2012 (GLI-2012) norms reflect contemporary adult's Algerian spirometry. *PLoS One*. 2018;13(9):e0203023.
187. Hulo S, de Broucker V, Giovannelli J, Cherot-Kornobis N, Neve V, Sobaszek A, et al. Global Lung Function Initiative reference equations better describe a middle-aged, healthy French population than the European Community for Steel and Coal values. *Eur Respir J*. 2016;48(6):1779-1781.
188. Huls A, Kramer U, Stolz S, Hennig F, Hoffmann B, Ickstadt K, et al. Applicability of the Global Lung Initiative 2012 Reference Values for Spirometry for Longitudinal Data of Elderly Women. *PLoS One*. 2016;11(6):e0157569.

189. Langhammer A, Johannessen A, Holmen TL, Melbye H, Stanojevic S, Lund MB, et al. Global Lung Function Initiative 2012 reference equations for spirometry in the Norwegian population. *Eur Respir J*. 2016;48(6):1602-1611.
190. Hall GL, Thompson BR, Stanojevic S, Abramson MJ, Beasley R, Coates A, et al. The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. *Respirology*. 2012;17(7):1150-1151.
191. Backman H, Lindberg A, Sovijarvi A, Larsson K, Lundback B, Ronmark E. Evaluation of the global lung function initiative 2012 reference values for spirometry in a Swedish population sample. *BMC Pulm Med*. 2015;15:26.
192. Kainu A, Timonen KL, Toikka J, Qaiser B, Pitkaniemi J, Kotaniemi JT, et al. Reference values of spirometry for Finnish adults. *Clin Physiol Funct Imaging*. 2016;36(5):346-358.
193. Pereira CA, Duarte AA, Gimenez A, Soares MR. Comparison between reference values for FVC, FEV1, and FEV1/FVC ratio in White adults in Brazil and those suggested by the Global Lung Function Initiative 2012. *J Bras Pneumol*. 2014;40(4):397-402.
194. Rebacz-Maroon E. The multi-ethnic global lung initiative 2012 and Third National Health and Nutrition Examination Survey reference values do not reflect spirometric measurements in Black boys and men from Tanzania. *Clin Physiol Funct Imaging*. 2018;38(1):76-86.
195. Zhang J, Hu X, Shan G. Spirometry reference values for population aged 7-80 years in China. *Respirology*. 2017;22(8):1630-1636.
196. Ben Saad H, El Attar MN, Hadj Mabrouk K, Ben Abdelaziz A, Abdelghani A, Bousarsar M, et al. The recent multi-ethnic global lung initiative 2012 (GLI2012) reference values don't reflect contemporary adult's North African spirometry. *Respir Med*. 2013;107(12):2000-2008.
197. Lung function testing: Selection of reference values and interpretative strategies. 1991. [cited (2014)] Available from: <https://www.thoracic.org/statements/resources/archive/lft-1991.pdf>.
198. Shackleton C, Czovek D, Grimwood K, Ware RS, Radics B, Hantos Z, et al. Defining 'healthy' in preschool-aged children for forced oscillation technique reference equations. *Respirology*. 2018;23(4):406-413.
199. Samet JM, Lange P. Longitudinal studies of active and passive smoking. *Am J Respir Crit Care Med*. 1996;154(6 Pt 2):S257-265.
200. Blake TL, Chang AB, Chatfield MD, Marchant JM, Petsky HL, McElrea MS. How does parent/self-reporting of common respiratory conditions compare with medical records among Aboriginal and Torres Strait Islander (Indigenous) children and young adults? *J Paediatr Child Health*. 2019;DOI: 10.1111/jpc.14490.
201. Shaw DE. FeNO monitoring to adjust treatment in asthma: has it come of age? *Thorax*. 2018;73(12):1095-1096.
202. Franklin PJ, Taplin R, Stick SM. A community study of exhaled nitric oxide in healthy children. *Am J Respir Crit Care Med*. 1999;159(1):69-73.
203. Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax*. 2003;58(12):1048-1052.
204. Byrnes CA, Dinarevic S, Busst CA, Shinebourne EA, Bush A. Effect of measurement conditions on measured levels of peak exhaled nitric oxide. *Thorax*. 1997;52(8):697-701.

205. Silkoff PE, McClean PA, Slutsky AS, Furlott HG, Hoffstein E, Wakita S, et al. Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. *Am J Respir Crit Care Med*. 1997;155(1):260-267.
206. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med*. 2007;176(3):231-237.
207. Olin AC, Bake B, Toren K. Fraction of exhaled nitric oxide at 50 mL/s: reference values for adult lifelong never-smokers. *Chest*. 2007;131(6):1852-1856.
208. Welsh L, Lercher P, Horak E. Exhaled nitric oxide: interactions between asthma, hayfever, and atopic dermatitis in school children. *Pediatr Pulmonol*. 2007;42(8):693-698.
209. Cibella F, Cuttitta G, La Grutta S, Passalacqua G, Viegi G. Factors that influence exhaled nitric oxide in Italian schoolchildren. *Ann Allergy Asthma Immunol*. 2008;101(4):407-412.
210. van Asch CJ, Balemans WA, Rovers MM, Schilder AG, van der Ent CK. Atopic disease and exhaled nitric oxide in an unselected population of young adults. *Ann Allergy Asthma Immunol*. 2008;100(1):59-65.
211. Leung TF, Liu EK, Tang NL, Ko FW, Li CY, Lam CW, et al. Nitric oxide synthase polymorphisms and asthma phenotypes in Chinese children. *Clin Exp Allergy*. 2005;35(10):1288-1294.
212. Cardinale F, de Benedictis FM, Muggeo V, Giordano P, Loffredo MS, Iacoviello G, et al. Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. *Pediatr Allergy Immunol*. 2005;16(3):236-242.
213. Jouaville LF, Annesi-Maesano I, Nguyen LT, Bocage AS, Bedu M, Caillaud D. Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. *Clin Exp Allergy*. 2003;33(11):1506-1511.
214. Agusti A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med*. 2017;5(12):935-945.
215. Vasquez MM, Zhou M, Hu C, Martinez FD, Guerra S. Low Lung Function in Young Adult Life Is Associated with Early Mortality. *Am J Respir Crit Care Med*. 2017;195(10):1399-1401.
216. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ*. 1996;313(7059):711-715; discussion 715-716.
217. Friedman GD, Klatsky AL, Siegelau AB. Lung function and risk of myocardial infarction and sudden cardiac death. *N Engl J Med*. 1976;294(20):1071-1075.
218. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Spirometric findings and mortality in never-smokers. *J Clin Epidemiol*. 1990;43(9):867-873.
219. Duong M, Islam S, Rangarajan S, Leong D, Kurmi O, Teo K, et al. Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV1 (PURE): an international, community-based cohort study. *Lancet Glob Health*. 2019;7(5):e613-e623.
220. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med*. 2019;7(4):358-364.
221. Dratva J, Zemp E, Dharmage SC, Accordini S, Burdet L, Gislason T, et al. Early Life Origins of Lung Ageing: Early Life Exposures and Lung Function Decline in Adulthood in Two European Cohorts Aged 28-73 Years. *PLoS One*. 2016;11(1):e0145127.

222. Dharmage SC, Erbas B, Jarvis D, Wjst M, Raheison C, Norback D, et al. Do childhood respiratory infections continue to influence adult respiratory morbidity? *Eur Respir J*. 2009;33(2):237-244.
223. Shaheen SO, Barker DJ, Shiell AW, Crocker FJ, Wield GA, Holgate ST. The relationship between pneumonia in early childhood and impaired lung function in late adult life. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):616-619.
224. Shaheen SO, Sterne JA, Tucker JS, Florey CD. Birth weight, childhood lower respiratory tract infection, and adult lung function. *Thorax*. 1998;53(7):549-553.
225. Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health*. 2013;3(1):010401.
226. Ratomaharo J, Linares Perdomo O, Collingridge DS, Andriamihaja R, Hegewald M, Jensen RL, et al. Spirometric reference values for Malagasy adults aged 18-73 years. *Eur Respir J*. 2015;45(4):1046-1054.

Appendices

Appendix A

Article 1 Supplement file: Search strategy for systematic review

((("spirometry"[MeSH Terms] OR "spirometry"[All Fields]) OR ("forced expiratory volume"[MeSH Terms] OR ("forced"[All Fields] AND "expiratory"[All Fields] AND "volume"[All Fields]) OR "forced expiratory volume"[All Fields])) AND (indigenous[All Fields] OR native[All Fields] OR Aboriginal[All Fields] OR (Torres[All Fields] AND Strait[All Fields] AND Islander[All Fields])) AND (("respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields]) OR respiratory[All Fields] OR ("lung"[MeSH Terms] OR "lung"[All Fields] OR "pulmonary"[All Fields]))

Appendix B

Indigenous Respiratory Reference Value (IRRV) Study Information Sheet



**PARENT/GUARDIAN INFORMATION SHEET (for 3-17 year olds) FOR PARTICIPATION IN THE STUDY –
THURSDAY ISLAND:
Improving lung function results in Aboriginal and Torres Strait Islander children and young adults**

Principal Investigator: Margaret McElrea

Contact Person: Tamara Blake
Centre for Children's Health Research (CCHR)
South Brisbane, 4101
Phone : (07) 3069 7275
Email: Tamara.Blake@health.qld.gov.au

Thank you for considering participating in this study, a combined project between the IROC (Indigenous Respiratory Outreach Care) program and the Respiratory Department at the Lady Cilento Children's Hospital, Brisbane. This study has been approved by the Human Research Ethics Committee of Far North Queensland, in accordance with the National Health and Medical Research Council's guidelines.

Why are we doing this study?

The Indigenous Respiratory Outreach Care team is planning a study to measure two types of lung function in healthy Aboriginal and Torres Strait Islander children and young adults. The two tests are spirometry and exhaled nitric oxide which are both standard tests used in Australia and around the world. Results from these tests are used to help diagnose and manage treatment of lung problems such as asthma. International studies have shown that the results can vary in different ethnic groups. Therefore for these tests to be of maximum benefit for Aboriginal and Torres Strait Islander children and young adults we need to know what their healthy ranges are. Once we know the healthy ranges, the tests will be more reliable in detecting what is abnormal. This will benefit the many Indigenous children and young adults who are affected by chronic respiratory problems such as asthma.

Who can be in this study?

Aboriginal or Torres Strait Islander children or young adults (teenagers), aged 3 to 25 years.

What is involved?

If you agree to participate in this study, participation will involve:

- 1) A short questionnaire - regarding your child's (or teenager's) current health, past medical history and family history. The researcher may also need to check your child's (or teenager's) medical records.
- 2) Your child (or teenager) performing 2 lung function tests - this would involve your child (or teenager) seeing the respiratory scientists (either at school or in the community) and doing the tests.



What are the benefits for my child and for other people in the future?

Participation in this study may not be of direct benefit to your child. Through being in the study, you may learn more about your child's respiratory condition. The results of this study will also help doctors to interpret lung function in Indigenous children and young adults.

What are the possible risks, side effects and/or discomforts?

Short history

These questions may make you feel uncomfortable. The research assistant or study nurse conducting these questionnaires with you will record only your answers and this information will not be used for any purpose other than for the research project.

Lung function testing

Neither of these tests will cause your child (or teenager) serious discomfort. The tests are easily done and will not take very long. However they should not be performed if in the last 4-6 weeks your child (or teenager) has had surgery (on chest, abdomen, brain, eyes, ears, nose or throat), a collapsed lung, a blood clot in the lung or a heart attack. Nor should they be performed if your doctor has told you that your child (or teenager) has high blood pressure or an aortic aneurysm.

What will happen with my and my child's information?

The information gathered in this process will remain confidential unless legally required to be disclosed. All data will be kept stored in a locked cabinet and password protected database at the Lady Cilento Children's Hospital, for 15 years, which only the investigators can access. The results of the study will be published in medical journals and talked about at meetings and conferences but no patients' names or details will be made public.

What are my child's alternatives to taking part?

Participation in this study is voluntary, and your child does not have to take part in this study. If you decide that you do not want your child to take part, they will continue to receive their routine medical care from the doctors at your local Health Centre, the IROC team and the Children's Health Services in Brisbane (Lady Cilento Children's Hospital).

Withdrawing from the study

If you agree for your child to be part of the study but later change your mind, you have the right to do so. You can withdraw your child from the study at any time and they will continue to receive the usual medical treatment from all doctors, Health Centres and the IROC team.

Who do I talk to if I have questions or concerns about this study?

Any queries regarding this study are welcome at any time by contacting either Margaret McElrea or Tamara Blake on (07) 3068 4067 or (07) 3069 7275. If you have any complaints or concerns about the conduct of the research, and you do not feel comfortable contacting the research staff, you may contact the Ethics Committee of Far North Queensland on (07) 4226 5513.

Thank you very much for assisting us in this project which aims to improve the respiratory care of Indigenous children and young adults.

Appendix C

Indigenous Respiratory Reference Value (IRRV) Study Consent Form



PARENT/GUARDIAN RESEARCH CONSENT FORM (for 3-17 year olds) –THURSDAY ISLAND

HREC Study Number:	HREC/14/QCH/96-929	
Research Study Title:	Improving lung function results in Aboriginal and Torres Strait Islander children and young adults	
Child's Name:		Date of Birth:
I have read and understood the Information Statement about this study. I understand that my child's participation in this study is voluntary, and that I may say NO. I understand that I can withdraw my child from the study at any time, and this will not affect his/her access to the best treatment available Yes ☐		
- This research involves completing questionnaires with personal information regarding my child's health and family history - This research also involves doing lung function testing, specifically exhaled nitric oxide and spirometry - I give permission for the researcher to check my child's medical records Yes ☐		
I understand that this project has been approved by the Far North Queensland Human Research Ethics Committee. If I have any problems or queries about the way in which the study is or was conducted, and I do not feel comfortable contacting the research staff, I am aware I may contact the Ethics Committee on (07) 4226 5513 Yes ☐		
I have had an opportunity to ask questions and I am satisfied with the answers Yes ☐		
I understand I will receive a copy of the Information Statement and Consent Form to keep Yes ☐		
Has your child had any of these: - Surgery (chest, abdomen, brain, eyes, ears, nose or throat) in the last 4-6 weeks, a collapsed lung, a blood clot in the lung, high blood pressure or an aortic aneurysm - If Yes please give details _____ Yes ☐ No ☐		
Parent/Guardian Name	Parent/Guardian Signature	Date
Parent/Guardian Address		Phone Number
Witness Name	Witness Signature	Date

Appendix D

Respiratory and health questionnaire



PARENT/GUARDIAN QUESTIONNAIRE FOR STUDY:
Improving lung function results in Aboriginal and Torres Strait Islander children and young adults

Please complete this questionnaire about your child. If you require assistance please ask one of the research assistants.

Participant details:

Child's name				
Date of Birth				
Is your child Aboriginal, Torres Strait Islander or both?	☐ Aboriginal ☐ Torres Strait Islander ☐ Both			
Is your child Aboriginal or Torres Strait Islander from your mother's side (1 or 2 grandparents) or father's side (1 or 2 grandparents)?	Mother's side Grandparent 1 ☐ Aboriginal ☐ Torres Strait Islander ☐ Both ☐ Don't know	Grandparent 2 ☐ Aboriginal ☐ Torres Strait Islander ☐ Both ☐ Don't know	Father's side Grandparent 1 ☐ Aboriginal ☐ Torres Strait Islander ☐ Both ☐ Don't know	Grandparent 2 ☐ Aboriginal ☐ Torres Strait Islander ☐ Both ☐ Don't know

Previous history:

1. Have you ever been told that your child has any of the following respiratory illnesses?

	No	Not sure	Yes	Doctor/medical centre/hospital where receiving treatment
Asthma (short wind)	☐	☐	☐	_____
Bronchiectasis	☐	☐	☐	_____
Pneumonia	☐	☐	☐	_____
Lung cancer	☐	☐	☐	_____
Neonatal lung disease	☐	☐	☐	_____
Other _____			☐	_____

2. Does your child usually have a cough that brings up mucus (bagur)?

☐ No
 ☐ Yes, how long for _____

3. Does your child currently have a chest infection?

- ☐ No ☐ Yes but not being treated ☐ Yes and is being treated. Please list medications your child is taking

4. Is your child currently on any medication?

- ☐ No ☐ Yes, please list _____

5. Does your child smoke?

- ☐ No ☐ Yes, how many per day _____

What age did they start smoking _____

6. Does anybody at your child's house usually smoke inside?

- ☐ No ☐ Yes, how many people _____

7. Did the child's mother smoke while pregnant with the child?

- ☐ No ☐ Yes, how many cigarettes a day _____

8. At how many weeks of pregnancy was your child born?

- ☐ <30 weeks ☐ 30-34 weeks ☐ 34-36 weeks ☐ >36 weeks ☐ Not sure

Thank you for your time in completing this questionnaire. When completed please return to the research assistant.

Appendix E

ISAAC questionnaire

8.2 Core questionnaire for asthma

1. Is there a family history of asthma (ie. Immediate: father, mother or siblings of child)?

No	Yes	Father	Mother	Siblings
☐	☐	☐	☐	☐

2. Has your child ever had wheezing or whistling in the chest at anytime in the past?

No	Yes	
☐	☐	If "No" please skip to question 7

3. Has your child had wheezing or whistling in the chest in the past 12 months?

No	Yes	
☐	☐	If "No" please skip to question 7

4. How many attacks of wheezing has your child had in the past 12 months?

None	1 - 3	4 - 12	More than 12
☐	☐	☐	☐

5. In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

Never woken with wheezing	Less than 1 night/week	More than 1 night/week
☐	☐	☐

6. In the past 12 months, has wheezing ever been severe enough to limit your child's speech to only 1 or 2 words at a time between breaths?

No	Yes
☐	☐

-
7. Has your child ever had asthma?

No	Yes
☐	☐

8. In the past 12 months, has your child's chest sounded wheezy during or after exercise?

No	Yes
☐	☐

9. In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?

No	Yes
☐	☐

8.3 Core questionnaire for rhinitis

1. Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?

No	Yes	
☐	☐	If "No" please skip to question 6

2. In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?

No	Yes	
☐	☐	If "No" please skip to question 6

3. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

No	Yes
☐	☐

4. In which of the past 12 months did this nose problem occur? (Tick all which apply)

January		May		September	
February		June		October	
March		July		November	
April		August		December	

5. In the past 12 months, how much did this nose problem interfere with your child's daily activities?

Not at all	A little	A moderate amount	A lot
☐	☐	☐	☐

6. Has your child ever had hayfever?

No	Yes
☐	☐

8.4 Core questionnaire for eczema

1. Is there a family history of eczema (ie. Immediate: father, mother or siblings of child)?

No	Yes	Father	Mother	Siblings
☐	☐	☐	☐	☐

2. Has your child ever had an itchy rash which was coming and going for at least six months?

No	Yes	
☐	☐	If "No" please skip to question 8

3. Has your child had this itchy rash at any time in the past 12 months?

No	Yes	
☐	☐	If "No" please skip to question 8

4. Has this itchy rash at any time affected any of the following places:

The folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

No	Yes
☐	☐

5. At what age did this itchy rash first occur?

Under 2 years	Aged 2 – 4 years	Aged 5 or more
☐	☐	☐

6. Has this rash cleared completely at any time during the past 12 months?

No	Yes
☐	☐

7. In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?

Never in the past 12 months	Less than 1 night/week	More than 1 night/week
☐	☐	☐

8. Has your child ever had eczema?

No	Yes
☐	☐

Appendix F

Medical chart form

IRRV Study number IRRV _____

Medical Chart Review of Participants: Indigenous Respiratory Reference Values Study

Child's name		
Date of Birth		
Patient ID		
Location of Chart		
Community		Location other charts?

1. Diagnoses: Is there evidence / diagnosis of

	No	Yes	Evidence / Dates (1 st 3 episodes plus any in last 5y)	Hospitalised	
Asthma					
Bronchiectasis					
Pneumonia					
Bronchiolitis Wheeze creps incr RR <18mths					
Bronchitis Wet productive cough treated with AB					
Neonatal Lung Disease					
Other lung disease					
Any other illness? Eg Impetigo Otitis Media Scabies Eczema					

2. How many weeks gestation was the participant at birth?

- ☐ <30 weeks ☐ 30-34 weeks ☐ 34-36 weeks
☐ >37 weeks ☐ Not sure

3. Birth weight? _____ (kg)

4. Smoke exposure?

In-utero	No / Yes	
Current	No / Yes	Who?

5. Other information relevant to respiratory function?

Appendix G

Article 3 Supplement file: Study protocol

The IRRV study is a cross-sectional study that aims to establish 'normal' reference values in spirometry and fractional exhaled nitric oxide (FeNO) for Aboriginal and Torres Strait Islander children and young adults (according to current guidelines). Between June 2015 and November 2017 we recruited 1097 Aboriginal and/or Torres Strait Islander children and young adults aged between 3 and 25 years, from seven urban and remote communities across Queensland and one from the Northern Territory. Study sites included Thursday Island, Horn Island, Bamaga, Cherbourg, Murgon, Dalby, Caboolture and Darwin. This age bracket was targeted as a first phase of IRRV study with future plans in place for the adult phase.

This study was done in collaboration with the Indigenous Respiratory Outreach Care (IROC) program. IROC is a Queensland Health funded program that delivers specialist respiratory clinical care and education to Indigenous communities throughout Queensland. The selected communities all had visiting respiratory paediatric clinics 1-2 times per year. This study was conducted in consultation with, and with approval from, local Aboriginal and Torres Strait Islander Elders and key community members from each community.

Community information

Community	Geographical classification	Population*	Distance to tertiary facility (Brisbane)	Local medical facilities	Health system organisation of checked medical charts
Bamaga, QLD	Very remote	<2000	2657kms	Primary health care and local hospital	Queensland Health
Caboolture, QLD	Major city	<68000	55kms	Primary health care and local hospital	Community controlled
Cherbourg, QLD	Outer regional	<1300	266kms	Primary health care and local hospital	Queensland Health
Dalby, QLD	Inner regional	<13000	207kms	Primary health care and local hospital	Community controlled
Darwin, NT	Outer regional	<137000	3423kms	Primary health care and local hospital	Northern Territory Health
Horn Island, QLD	Very remote	<400	2184kms	Primary health care and local hospital	Queensland Health
Murgon, QLD	Outer regional	<2400	261kms	Primary health care and local hospital	Queensland Health
Thursday Island, QLD	Very remote	<3000	2190kms	Primary health care and local hospital	Queensland Health

* Approximate population according to 2016 census

Participant recruitment

We recruited eligible participants by approaching:

- Child care centres for 3-5 year olds
- Schools and/or community groups for 5-17 year olds
- Community events and groups and sporting groups for 18-25 year olds

Every effort was made to recruit all available individuals who fulfilled inclusion criteria. Once individuals were identified, study packs (include information sheets, consent forms and questionnaires) were distributed. Assistance in completing the forms was provided by local community members who were either trained research assistants or school staff. Consent forms also included permission for the participants' medical charts to be checked by the researchers.

Inclusion and exclusion criteria

Inclusion:

- Male or female child/young adult who identified as Aboriginal, Torres Strait Islander or Aboriginal and Torres Strait Islander aged 3-25 years who:
- Had written and informed consent to participate; consent from parent/guardian if <18 years of age or by self if 18-25 years

An Aboriginal or Torres Strait Islander is a person who identifies as an Aboriginal or Torres Strait Islander and is accepted as such by the community in which he (or she) lives.

Exclusion:

- Individuals with a known contraindication for performing spirometry and/or FeNO measurement:

- Heart attack, pneumothorax, pulmonary embolus or any surgery to chest, abdomen, brain, eyes, ears, nose or throat in the last 4-6 weeks
- Previously diagnosed with very high blood pressure (200/120mmHg) or an aortic aneurysm

To ensure the safety of all participants as well as the integrity of results, consent forms included questions regarding the above contraindications.

Data collection

Questionnaires:

Two questionnaires were used. The first included questions regarding the participant's demographics, current health and medical history (Supplement 2) while the second was a modified ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire.

Anthropometric data:

Standing height was measured using a stadiometer (Seca 217, Hamburg, Germany) at the time of testing. Standing height was measured by standing erect with no shoes and sitting height was measured by having the participant seated on a hard surface with a mounted stadiometer attached.

Smokerlyzer test:

The PICO Smokerlyzer (Bedfont, Kent, UK) was used to test for exhaled carbon monoxide (eCO) as an indicator of recent tobacco smoke exposure. The measurement was repeated until two results were within 3 parts per million.

Spirometry and FeNO tests:

Spirometry was performed according to the current ATS/ERS guidelines using Easy on-PC Spirometers (ndd Medizintechnik, Zurich, Switzerland). A minimum of three acceptable and repeatable measurements were achieved. The NIOX MINO (Aerocrine AB, Solna, Sweden) hand held device was used to measure participant's FeNO levels. Results are shown in parts per billion (ppb) and the measurement was performed at least twice to achieve results within 10% of each other as per current guidelines.

Health history from medical records:

Participant medical records from relevant health centres and hospitals were examined for any history of respiratory disease, respiratory related hospitalisations and information about gestational age and weight at birth. All information was recorded onto a case report form.

Appendix H

Article 4 Supplement file: Z-score scatterplots

Figure S1: Scatterplots of spirometry parameters as z-scores vs. age for males and females

Distribution of z-scores for FEV₁, FVC and FEV₁/FVC vs. age based off the GLI-2012 'Other/Mixed' equation. Y-lines at 1.64 and -1.64 denote the 5th and 95th percentiles of 'Other/Mixed' equation.

Figure S2: Scatterplots of spirometry parameters as z-scores vs. height for males and females

Distribution of z-scores for FEV₁, FVC and FEV₁/FVC vs. height based off the GLI-2012 'Other/Mixed' equation. Y-lines at 1.64 and -1.64 denote the 5th and 95th percentiles of 'Other/Mixed' equation.

Figure S1

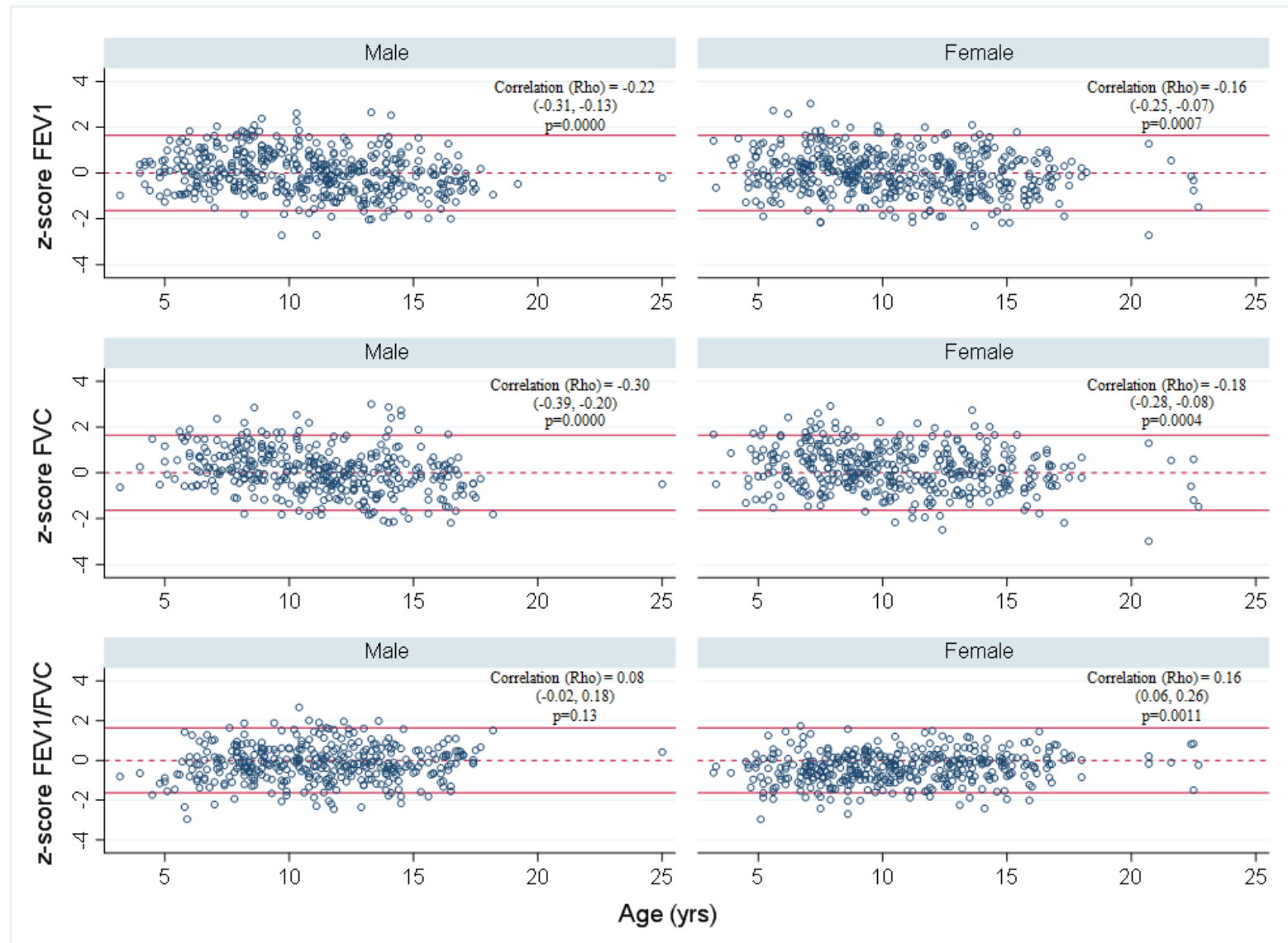
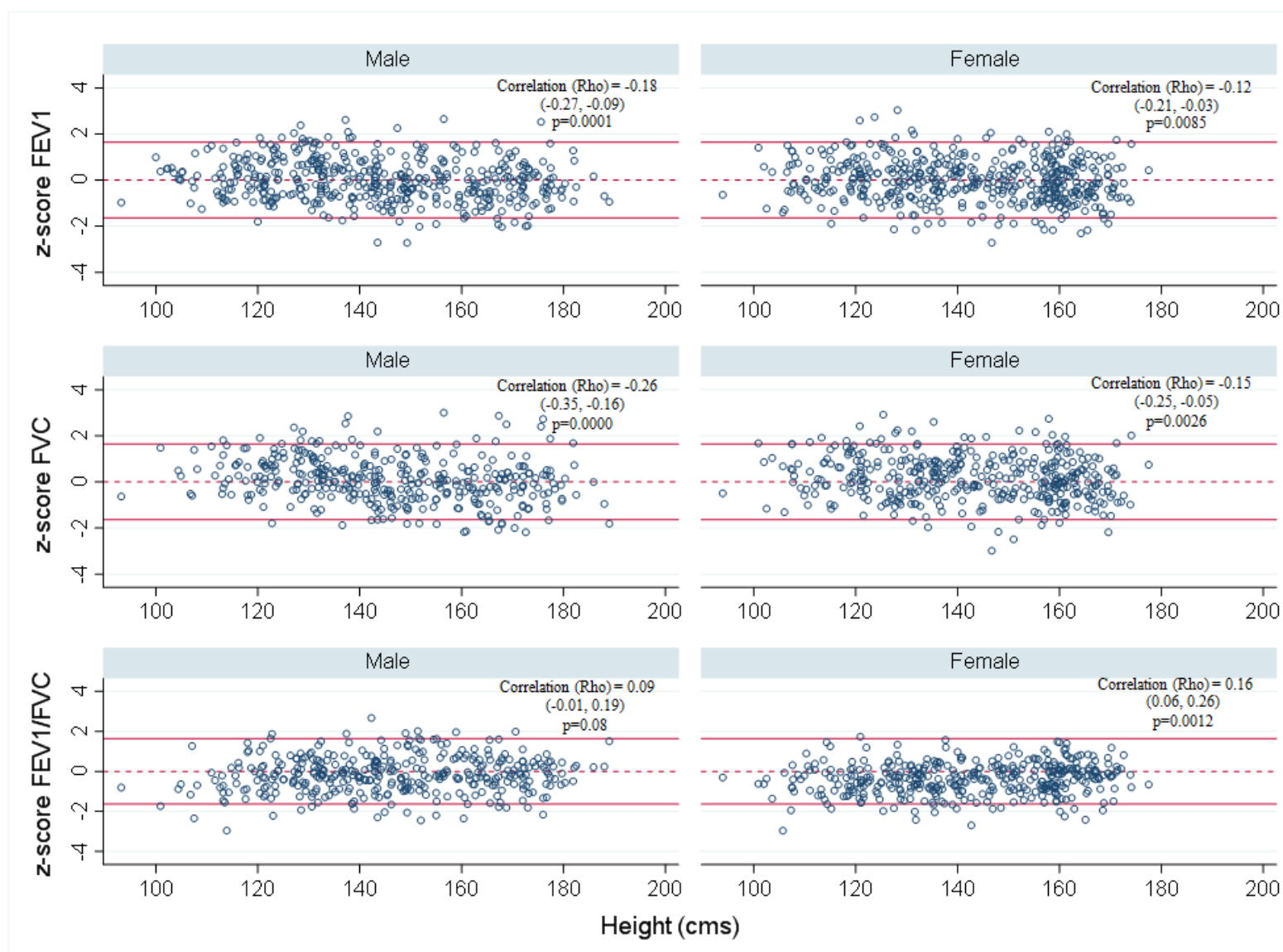


Figure S2



Appendix I

Article 5 Supplement file: Asthma within 12 months

We reanalysed data with the definition of 'asthma in the last 12 months' (c.f. definition of 'ever asthma' in the main text). Using the aforementioned definition, an additional 55 participants from our cohort were included into the 'healthy' groups. However, no difference was seen in the median FeNO values for the two age groups (participants <12 years = 10 ppb or 12-16 years = 11 ppb) with the inclusion of these participants (Table S1). An additional four participants <12 years and three participants 12-16 years were identified by the guidelines as being positive for eosinophilic inflammation. This also made little difference to overall results; 7.6% identified using ATS/NICE/BTS/SIGN (originally 7.2%) vs. 4.5% using GINA (originally 3.8%) for participants <12 years and 10.2% identified using NICE/BTS/SIGN (originally 9.9%) vs. 4.2% using ATS/GINA (originally 4.7%) for participants 12-16 years.

Table S1: FeNO results for healthy Indigenous Australian participants

	FeNO levels (ppb)	n (%) of cohort above recommended cut-off values	
	Median (IQR)		
Participants <12 years (n=422)	10 (7-15)	ATS/NICE/BTS/SIGN 32 (7.6)	GINA 19 (4.5)
Participants 12-16 years (n=236)	11 (8-19)	NICE/BTS/SIGN 24 (10.2)	ATS/GINA 10 (4.2)

GSD: geometric standard deviation; **ppb:** parts per billion

For participants <12 years: ATS/NICE/BTS/SIGN recommended cut-off value of 35 ppb. GINA recommended cut-off value of 50 ppb. **For participants 12-16 years:** NICE/BTS/SIGN recommended cut-off value of 40 ppb. ATS/GINA recommended cut-off value of 50 ppb.

Appendix J

Co-author contribution statements for manuscripts

Statement of Contribution of Co-Authors for Thesis by Published Paper

The authors listed below have certified that:

1. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. They agree to the use of the publication in the student's thesis and its publication on the QUT's ePrints site consistent with any limitations set by publisher requirements.

In the case of this chapter:

Spirometry reference values in Indigenous Australians: a systematic review; Medical Journal of Australia; July 2016

<i>Contributor</i>	<i>Statement of contribution</i>
Tamara L Blake 05/02/19	Experimental design, identifying and reviewing of articles for inclusion, data interpretation and analysis, preparation of manuscript, development of figures and tables
Anne B Chang 21/2/19	Experimental design, reviewing of articles If agreement could not be reached, data interpretation, editing of manuscript

Contributor	Statement of contribution
Helen I. Petsky	Experimental design, editing of manuscript
25/02/19 Leanne T Rotwell	Editing of manuscript
21/2/2019 Michael G Brown	Editing of manuscript
Email acknowledged	
Debra C Hill	Editing of manuscript
Email acknowledged	
Bruce Thompson	Editing of manuscript
Email acknowledged	
Margaret S McElrea	Experimental design, identifying and reviewing of articles for inclusion, data interpretation, editing of manuscript
21. Feb 2019	

Principal Supervisor Confirmation

I have sighted email or other correspondence from all Co-authors confirming their certifying authorship.

Margaret McElrea

Name

Signature

27. 2 2019

Date

Statement of Contribution of Co-Authors for Thesis by Published Paper

The authors listed below have certified that:

1. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. They agree to the use of the publication in the student's thesis and its publication on the QUT's ePrints site consistent with any limitations set by publisher requirements.

In the case of this chapter:

Does ethnicity influence fractional exhaled nitric oxide in healthy individuals? a systematic review; CHEST; July 2017

<i>Contributor</i>	<i>Statement of contribution</i>
Tamara L Blake 05/02/19	Experimental design, identifying and reviewing of articles for inclusion, data interpretation and analysis, preparation of manuscript, development of figures, graphs and tables
Anne B Chang 21/4/19	Experimental design, reviewing of articles if agreement could not be reached, data interpretation, editing of manuscript

Contributor	Statement of contribution
Mark D Chatfield 5 Feb 2019	Performed all statistical analysis, aided in designing of graphs, editing of manuscript
Helen L Petsky 25/02/19	Experimental design, editing of manuscript
Leanne T Rodwell 21/2/2019.	Editing of manuscript
Michael G Brown Email acknowledged	Editing of manuscript
Debra C Hill Email acknowledged	Editing of manuscript
Margaret S McElrea 21/2/2019	Experimental design, identifying and reviewing of articles for inclusion, data interpretation, editing of manuscript

Principal Supervisor Confirmation

I have sighted email or other correspondence from all Co-authors confirming their certifying authorship.

Margaret McElrea

Name

Signature

27. 2. 2019

Date

Statement of Contribution of Co-Authors for Thesis by Published Paper

The authors listed below have certified that:

1. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. They agree to the use of the publication in the student's thesis and its publication on the QUT's ePrints site consistent with any limitations set by publisher requirements.

In the case of this chapter:

How does parent/self-reporting of common respiratory conditions compare with medical records among Aboriginal and Torres Strait Islander (Indigenous) children and young adults; Journal of Paediatrics and Child Health; 2019

<i>Contributor</i>	<i>Statement of contribution</i>
Tamara L Blake 05/02/19	Experimental design, data collection, data entry and cleaning, data analysis and interpretation, preparation of manuscript, development of figures, graphs and tables
Anne B Chang 21/2/19	Experimental design, data collection, data interpretation, editing of manuscript

Contributor	Statement of contribution
Mark D Chatfield 5 Feb 2019	Assisted with statistical analysis, data interpretation, editing of manuscript
Helen L Petsky 25/02/19	Data interpretation, editing of manuscript
Julie M Marchant 27 Feb 2019	Data interpretation, editing of manuscript
Margaret S McElrea 21 Feb 2019	Experimental design, data collection, data interpretation, editing of manuscript

Principal Supervisor Confirmation

I have sighted email or other correspondence from all Co-authors confirming their certifying authorship.

Margaret McElrea

27. 2. 2019

Name

Signature

Date

Statement of Contribution of Co-Authors for Thesis by Published Paper

The authors listed below have certified that:

1. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. They agree to the use of the publication in the student's thesis and its publication on the QUT's ePrints site consistent with any limitations set by publisher requirements.

In the case of this chapter:

Are any of the Global Lung Function Initiative (GLI)-2012 reference equations appropriate for Australian Aboriginal and/or Torres Strait Islander children and young adults?; Respiriology; 2019

<i>Contributor</i>	<i>Statement of contribution</i>
Tamara L Blake 05/02/19	Experimental design, data collection, data entry and cleaning, data analysis and interpretation, preparation of manuscript, development of figures, graphs and tables
Anne B Chang 2/4/19	Experimental design, data collection, data interpretation, editing of manuscript

<i>Contributor</i>	<i>Statement of contribution</i>
Mark D Chatfield 5 Feb 2019	Assisted with statistical analysis and graphical presentation, data interpretation, editing of manuscript
Julie M Marchant 27 Feb 2019	Data interpretation, editing of manuscript
Margaret S McElrea 21 Feb 2019	Experimental design, data collection, data interpretation, editing of manuscript

Principal Supervisor Confirmation

I have sighted email or other correspondence from all Co-authors confirming their certifying authorship.

Margaret McElrea

27. 2. 2019

Name

Signature

Date

Statement of Contribution of Co-Authors for Thesis by Published Paper

The authors listed below have certified that:

1. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit, and
5. They agree to the use of the publication in the student's thesis and its publication on the QUT's ePrints site consistent with any limitations set by publisher requirements.

In the case of this chapter:

Fractional exhaled nitric oxide (FeNO) values in Indigenous Australians aged 3-16 years; CHEST; 2019

Contributor	Statement of contribution
Tamara L Blake 05/02/19	Experimental design, data collection, data entry and cleaning, data analysis and interpretation, preparation of manuscript, development of figures, graphs and tables
Anne B Chang 21/2/19	Experimental design, data collection, data interpretation, editing of manuscript

Contributor	Statement of contribution
Mark D Chatfield 5 Feb 2019	Assisted with statistical analysis and graphical presentation, data interpretation, editing of manuscript
Helen L Petsky 25/02/19	Data interpretation, editing of manuscript
Julie M Marchant 27 Feb 2019	Data interpretation, editing of manuscript
Margaret S McElrea 21 Feb 2019	Experimental design, data collection, data interpretation, editing of manuscript

Principal Supervisor Confirmation

I have sighted email or other correspondence from all Co-authors confirming their certifying authorship.

Margaret McElrea

Name

Signature

27. 2. 2019

Date