

ABORIGINAL AND TORRES STRAIT ISLANDER LUNG FUNCTION: DETERMINANTS, OUTCOMES, AND REFERENCE VALUES

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Abstract

Background

Lung function testing and interpretation is essential in clinical practice for the diagnosis and monitoring of lung diseases. There is substantial evidence to suggest that reduced lung function in childhood predicts reduced lung function in adulthood. Further, associations between impaired respiratory function and respiratory and cardiovascular disease morbidity, and all-cause mortality in adulthood are now established across a broad range of socioeconomic and environmental settings. Several novel lung function trajectories suggest that (1) catch-up growth is possible in young children provided there is early intervention and appropriate management, and (2) reduced lung function may be further aggravated in adulthood by factors such as smoking of tobacco cigarettes, and sub-optimal management of chronic respiratory diseases. These findings are of particular significance to Aboriginal and Torres Strait Islander (First Nations) Australians whose burden of chronic respiratory and cardiovascular diseases are substantially higher than non-First Nations Australians. For example, Australian First Nations children have among the highest pneumonia rates reported in the world and chronic obstructive pulmonary disease in First Nations adults exceeds their non-First Nations counterparts.

To improve lung health within Queensland, the Indigenous Respiratory Outreach Care (IROC), a culturally appropriate outreach service, delivers specialist respiratory care directly to children and adults in communities with large First Nations populations. However, prior to my PhD work, there were: (1) a lack of appropriate reference values resulting in difficulty in the interpretation of lung function tests; (2) sparse data relating to the determinants of reduced lung function, and (3) poor understanding of how reduced lung function is related to clinical outcomes in First Nations Australians. The PhD work addresses these gaps.

Aims and Objectives

The overall aims of my PhD program were to improve interpretation of lung function testing, to understand determinants of lung function, and to relate lung function to clinical outcomes in First Nations Australian children and adults. To achieve these aims, five objectives formed the basis of 10 peer-reviewed papers/manuscripts completed during my PhD. These five objectives were to: (1) determine the impact of early childhood pneumonia on the lung function of First Nations Australian children, and on children and adults more generally, (2) evaluate changes in spirometry values of paediatric patients treated through IROC and compare these changes to those

seen in tertiary paediatric facilities, (3) evaluate determinants and changes in lung function and associations between reduced lung function, cardiovascular morbidity and all-cause mortality in adults treated through IROC, (4) develop reference values for spirometry and fractional exhaled nitric oxide (FeNO) lung function tests, for use in First Nations Australian children and adults, and (5) investigate the influence of anthropometric differences between First Nations children and their non-First Nations counterparts, and how this accounts for known differences in lung function between healthy children of both ethnicities.

Methods

My PhD thesis is comprised of published (n=8), submitted (n=1), and drafted (n=1) papers/manuscripts in peer-reviewed journals, each forming a chapter of my thesis. Objective 1 was completed through a (i) cohort study that utilised the Indigenous Respiratory Reference Values (IRRV) database developed by my supervisory team and, (ii) systematic review and meta-analysis of the literature. Objective 2 was completed through two cohort studies utilising data from the paediatric IROC clinics and a paediatric tertiary hospital. Objective 3 was completed through three cohort studies, including two survival analyses, using a database developed during my PhD using data collected at adult IROC clinics.

For Objective 4, participants were recruited prospectively within Queensland, Northern Territory and Western Australia. Their demographic, medical, anthropometric, spirometry, and FeNO data were collected. Generalised additive modelling for location, scale, and shape (GAMLSS) were used to develop height-for-age FeNO predicted and upper limit of normal (ULN) values, and a calculator was developed for clinician use. Spirometry values of First Nations Australians were compared to existing Global Lung Function Initiative 2012 (GLI-2012) reference equations to determine which is appropriate for use in this population. In Objective 5, I used anthropometric and spirometry data from the IRRV study database and publicly available Third National Health and Nutrition Examination Survey data in a two-arm cohort study.

Results

For Objective 1, I found that early childhood pneumonia (occurring when ≤ 5 years) impacted the forced expiratory volume in the first second (FEV₁) and forced vital capacity (FVC) Z-scores of 909 First Nations Australian children and young adults (FEV₁ $\beta=-0.49$, [95%CI -0.79, -0.18]; FVC $\beta=-0.55$, [95%CI -0.86, -0.24]), compared to those who never had pneumonia. My meta-analysis of 21,996 participants from 14 studies found that early childhood pneumonia significantly reduces the FEV₁ of both children ($\beta=-55$ [ml], 95%CI -104, -6, I²=41%, $\tau=33$) and adults ($\beta=-$

61 [ml], 95%CI -81, -41, $I^2=0\%$, $\tau=0$), while FVC values were reduced for adults ($\beta= -63$ [ml], 95%CI -90, -36, $I^2=36\%$, $\tau=19$), but not for children ($\beta= -51$ [ml], 95%CI -133, 31, $I^2=42\%$, $\tau=48$).

Evaluation of changes in spirometry values of 252 children managed at IROC clinics (Objective 2) showed significant improvements in FEV₁ ($\Delta zFEV_1=0.35$, 95%CI 0.22, 0.48) and FVC ($\Delta zFVC=0.36$, 95%CI 0.23, 0.50) values from baseline to recent follow-up visit. These improvements were comparable to improvements observed in 2,249 children managed at tertiary paediatric hospitals ($\Delta zFEV_1=0.22$, 95%CI 0.17, 0.27; $\Delta zFVC=0.23$, 95%CI 0.18, 0.28), for both FEV₁ ($p=0.10$) and FVC ($p=0.08$). These findings held after adjusting for differences in the age of children at baseline, and differences in the overall duration of their care.

Evaluation of changes in spirometry and diffusing capacity values of 701/1734 adults seen at follow-up at IROC (Objective 3) showed significant improvements in FEV₁ ($\Delta Z=0.15$, 95%CI 0.10, 0.20) and FVC ($\Delta Z=0.25$, 95%CI 0.20, 0.31), significant decreases in FEV₁/FVC ($\Delta Z=-0.10$, 95%CI -0.07 to -0.03), and no change in the diffusing capacity of the lung for carbon monoxide (D_{LCO}) ($\Delta Z=0.08$, 95%CI -0.05, 0.21) Z-scores. Adults with FEV₁ and FVC Z-scores <-1 were at significantly elevated mortality risk (hazard ratio [HR]=3.2, 95%CI 1.4, 7.4; HR=2.6, 95%CI 1.3-5.1 respectively), and cardiovascular disease prevalence (odds ratio [OR]=1.5, 95%CI 1.2, 2.2; OR=1.6, 95%CI 1.2, 2.3), compared to patients with Z-scores ≥ -1 . In 1165 adults, D_{LCO} , transfer coefficient of the lung for carbon monoxide (K_{CO}), and alveolar volume (V_A) values below the lower limit of normal (<-1.64 Z-scores) were associated with significantly elevated mortality risk (HR=2.99, 95%CI 1.83, 4.90; HR=2.14, 95%CI 1.38, 3.32; HR=2.75, 95%CI 1.18, 2.58), and cardiovascular disease prevalence (OR=1.83, 95%CI 1.31, 2.55; OR=1.56, 95%CI 1.08, 2.25; OR=2.20, 95%CI 1.60, 3.01).

Height-for-age FeNO predicted and ULN values for First Nations Australians were developed as per Objective 4. In healthy children aged <18 years, ULN values ranged between 25-60 parts per billion (ppb), while for healthy adults, ULN values ranged between 39-88ppb. Importantly, neither current FeNO interpretation guidelines nor the currently recommended cut-off of 50ppb for First Nations children ≤ 16 years were appropriate in this population. Analysis of spirometry data of 1444 healthy children and adults suggested the GLI-2012 'Other/mixed' reference equation was most suitable, and that First Nations Australian spirometry values are 9% lower than Caucasian predicted values. The FEV₁ ($\beta= -0.44$, 95%CI -0.57, -0.31) and FVC ($\beta= -0.55$, 95%CI -0.69, -0.40) Z-scores of rural participants were lower than urban participants, and that this difference increased with age for FEV₁ (β per 10 years= -0.13, 95%CI -0.21, -0.04) and FVC (β per 10 years= -0.14, 95%CI -0.23, -0.05) Z-scores.

Analysis of spirometry values and the Cormic Index (ratio of sitting-height to standing-height) (Objective 5) found that, compared to Caucasians, FEV₁ and FVC Z-scores of First Nations children were 8% lower for children aged 8–11.9 years and 9%–10% lower for children aged 12–16 years. Cormic Index was lower among First Nations Australians, accounting for 14% (95%CI 7% to 21%) of FEV₁ and 15% (95%CI 8% to 21%) of FVC differences in the younger group, and 26% (95%CI 16% to 37%) of FEV₁ and 31% (95%CI 19% to 42%) of FVC differences in the older group after adjusting for age, sex, and standing height.

Conclusion

My thesis has provided several novel findings including insight into some of the major determinants of lung function in First Nations Australians, beginning in early life where pneumonia significantly reduces the spirometry values of First Nations children and young adults. Lung function data from IROC clinics show how access to specialist respiratory care that is culturally appropriate and tailored to the needs of communities may slow, halt, or reverse lung function decline in First Nations Australian children and adults who suffer from chronic respiratory disease.

My thesis described for the first time how reduced spirometry and the D_{LCO} values related to increased cardiopulmonary morbidity and all-cause mortality risk in First Nations Australians. In a population with a high burden of chronic respiratory and cardiovascular diseases, and lower overall life expectancy, these findings highlight the importance of accurate test interpretation from knowledge of the normal distribution of values in the healthy population, and through understanding determinants of low lung function.

Development of FeNO reference values for First Nations Australians using advanced statistical techniques enables accurate interpretation of FeNO values, and the model used could be considered for other ethnicities. This PhD also confirms the GLI-2012 ‘Other/mixed’ spirometry reference equation are appropriate for use in First Nations Australians across the full lifespan. The 9% gap found between Caucasian and First Nations spirometry values is important in the context of previous studies that have reported First Nations spirometry values to be as much as 20-30% lower. Finally, the difference in spirometry values between First Nations Australians and Caucasian individuals is due in part to inherent differences in body proportions.

This PhD addresses knowledge gaps on efficacy of culturally appropriate outreach services, lung function determinants and associations with future outcomes, FeNO reference values, and guidance on reference equation selection for spirometry in First Nations Australians.

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List of Abbreviations

ATS	American Thoracic Society
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
ERS	European Respiratory Society
FeNO	Fractional exhaled nitric oxide
FEV ₁	Forced expiratory volume in the first second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
HRCT	High-resolution computed tomography
IROC	Indigenous Respiratory Outreach Care
K_{CO}	Transfer coefficient of the lung for carbon monoxide
L	litres
LLN	Lower limit of normal
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care
PURE	Prospective Urban Rural Epidemiology study
sec	second
ULN	Upper limit of normal
V_{A}	Alveolar volume

List of Presentations

1. Thoracic Society of Australia and New Zealand Annual Scientific Meeting – March 2019
(A review of Children's Health Queensland patients having respiratory function tests in regional and remote clinics)
2. Centre for Children's Health Research Research Seminar – February 2020 *(Paediatric patients of outreach specialist Queensland clinics have lung function improvement comparable to that of tertiary paediatric patients)*
3. European Respiratory Society International Congress – August 2020 *(Spirometry improvement is similar for Australian children treated at outreach clinics and tertiary hospitals)*
4. Centre for Children's Health Research HDR Student Symposium – October 2020
(Paediatric patients of outreach specialist Queensland clinics have lung function improvement comparable to that of tertiary paediatric patients)
5. Thoracic Society of Australia and New Zealand Annual Scientific Meeting – April 2021
(Adults referred to specialist respiratory outreach clinics in regional and remote Queensland)
6. AusBREATHE Bronchiectasis Centre for Research Excellence – October 2021
(Evidence for improving the lung function of First Nations Australians)
7. Children's Health Queensland Allied Health Symposium – October 2021 *(Paediatric patients of outreach specialist Queensland clinics have lung function improvement comparable to that of tertiary paediatric patients)*
8. Queensland Children's Hospital Grand Rounds – April 2022 *(Walking the Talk for First Nations Health)*
9. AusBREATHE Bronchiectasis Centre for Research Excellence – July 2022
(Associations of spirometry with early childhood pneumonia and adult outcomes)

List of Publications

1. Collaro AJ, Chang AB, Marchant JM, Masters IB, Rodwell LT, Takken AJ, McElrea MS. Culturally Appropriate Outreach Specialist Respiratory Medical Care Improves the Lung Function of Children in Regional and Remote Queensland. *Lung*. 2020;198(2):361-9.

Published, available in Chapter 5.

2. Collaro AJ, Chang AB, Marchant JM, Rodwell LT, Masters IB, Chatfield MD, McElrea MS. Pediatric Patients of Outreach Specialist Queensland Clinics Have Lung Function Improvement Comparable to That of Tertiary Pediatric Patients. *Chest*. 2020;158(4):1566-75.

Published, available in Chapter 6.

3. Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Dent A, Blake T, Mawn P, Fong K, McElrea MS. Determinants and Follow-up of Lung Function Data from a Predominantly First Nations Cohort of Adults Referred to Specialist Respiratory Outreach Clinics in Regional and Remote Queensland. *Lung*. 2021;199(4):417-25.

Published, available in Chapter 7.

4. Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Dent A, Blake T, Mawn P, Fong K, McElrea MS. Associations between lung function and future cardiovascular morbidity and overall mortality in a predominantly First Nations population: a cohort study. *Lancet Reg Health West Pac*. 2021;13:100188.

Published, available in Chapter 8.

5. Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Blake TL, McElrea MS. How do Cormic Index profiles contribute to differences in spirometry values between White and First Nations Australian children? *Pediatr Pulmonol*. 2021;56(12):3966-74.

Published, available in Chapter 12.

6. Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Vicendese D, Blake TL, McElrea MS, Dharmage SC. Early Childhood Pneumonia Is Associated with Reduced Lung Function and Asthma in First Nations Australian Children and Young Adults. *J Clin Med*. 2021;10(24).

Published, available in Chapter 3.

7. Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Dent A, Fong KM, McElrea MS. Association of Gas Diffusing Capacity of the Lung for Carbon Monoxide with Cardiovascular Morbidity and Survival in a Disadvantaged Clinical Population. *Lung*. 2022;200(6):783-92.

Published, available in Chapter 9.

8. Collaro AJ, Chang AB, Marchant JM, Vicendese D, Chatfield MD, Cole JF, Blake TL, McElrea MS. Developing Fractional Exhaled Nitric Oxide Predicted and Upper Limit of Normal Values for a Disadvantaged Population. *Chest*. 2022; In Press.

Accepted and In-Press. Available in Chapter 10.

9. Collaro AJ, McElrea MS, Marchant JM, Chatfield MD, Sondergeld P, Perret JL, Vicendese D, Anuntaseree W, Dharmage SC, Chang AB. A systematic review of the effect of early childhood respiratory infections and pneumonia on lung function throughout the lifespan. *Lancet Child Adolesc Health*. 2023; In Press.

Accepted and In-Press. Available in Chapter 4.

10. Collaro AJ, Foong RE, Chang AB, Marchant JM, Blake TL, Cole JF, Pearson G, Hii RM, Brown H, Chatfield MD, Hall GL, McElrea MS. Spirometry reference values in First Nations Australian children and adults. *TBD*.

Currently being prepared for submission. Available in Chapter 11.

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Chapter 1: Introduction

1.1 DEFINITION OF TERMS

First Nations Australian: an individual who self-identifies as either Aboriginal, Torres Strait Islander, or both Aboriginal and Torres Strait Islander.

1.2 LUNG FUNCTION TESTING AND RESPIRATORY HEALTH

Globally, it is estimated that at least 450 million people are affected by chronic, non-transmissible respiratory disease.¹ In Australia, such disease makes up an estimated 8% of total disease burden.² For First Nations Australians, the burden of chronic respiratory disease is 2.5 times higher than for non-First Nations Australians, despite a gradual decline in respiratory-related mortality since 1998.^{3,4} Lung function tests provide objective data for the diagnosis and monitoring of lung and airways diseases supported by clinical history and other tools such as radiological imaging.

1.2.1 Respiratory function testing in assessment and monitoring of acute and chronic respiratory disease

Lung function testing enables non-invasive diagnosis and monitoring of respiratory disease. The advantages of tests such as spirometry and fractional exhaled nitric oxide (FeNO) include their (relatively) low cost of equipment and consumables, and the portability of equipment enabling their use in outreach and office-based settings. Complex lung function tests such as diffusion capacity of the lung for carbon monoxide (D_{LCO}) require more elaborate and expensive equipment, with higher cost of consumables. More advanced technician training is also required, though considerably less so than for other monitoring modalities e.g., radiology equipment.^{5,6} The utilisation of lung function testing, together with the overall clinical picture, enables appropriate clinical care.

Raw lung function measurements are compared to predicted values derived from reference equations, and are presented to physicians as both a percentage of the predicted value, and as a Z-score that indicates the number of standard deviations away from the predicted value.^{7,8} Abnormality in lung function values may be defined in several ways. Some parameters such as spirometric measurements are one-tailed, where abnormality defined by the lower 5th centile (or -1.64 Z-scores) of healthy individuals, while others are two-tailed as in the case of static lung volume measurements, where abnormality is defined as the 2.5th centile and 97.5th percentile (-

1.96 and 1.96 Z-scores, respectively) of healthy individuals.⁹ Despite the importance of appropriate lung function values, reference equations describing the normal range of values spanning childhood into adulthood were lacking for First Nations Australians. Objective 4 of my PhD addresses this important clinical gap, and the results are contained in Chapters 10 and 11 of my thesis.

1.2.1.1 Spirometry

Spirometry is the most common test of lung function and is highly standardised in both the testing and interpretation aspects.^{8,10} Spirometry values provide a measure of airway calibre via the flow rate of expired air (reported as the forced expiratory volume in one second or FEV₁), and lung size by via the maximal expired lung volume (reported as the forced vital capacity or FVC) during a forced maximal exhalation lasting ≥ 6 seconds and/or until volume plateau is reached (defined as $<25\text{mL}$ change over 1 second).¹⁰ Undertaking spirometry is recommended in almost all respiratory-based clinical practice guidelines for diagnosing and monitoring respiratory disease.^{11,12} It is used in variety of settings, including screening, primary care, tertiary laboratories, and in regional and remote clinics.^{7,8} Spirometry is the gold standard for the diagnosis of obstructive lung disease, in which FEV₁ as a proportion of FVC (FEV₁/FVC) falls below the lower limit of normal (LLN). It provides supportive evidence in the diagnosis of restrictive lung disease where a fall in the FVC below the LLN occurs usually in the absence of a fall in the FEV₁/FVC% below the LLN.⁷ The flow-volume loop, a visual representation of flow in litres per second plotted against the volume of expired air in litres, and volume-time curve, a plot of the volume of expired air against time in seconds, may assist clinicians in further characterising the nature of lung and airway disease.⁷

Interpretation may be affected, or may not be possible, when test data are not acceptable and/or repeatable as set out by current standards,^{8,10} as there may be uncertainty as to whether measurements are representative of the subjects lung function. Technician comments relating to the quality of the test are thus relied upon by the interpreting physician.⁷ There are minimum requirements for resolution of air flow sensor in the spirometer (12-bit or 4096 possible measurements) and sampling rate ($\geq 100\text{Hz}$), as well as accuracy ($\pm 3\%$) and linearity over the range of biologically plausible flows and volumes,⁸ and the performance of the sensor should be regularly evaluated using a 3L calibration syringe.⁸ Acceptability and repeatability criteria, and routine evaluation of air flow sensor performance ensure confidence in interpretation in spirometry testing.

Spirometry values are influenced by several factors, including a person's age, sex, height and ethnicity.¹³⁻¹⁶ Non-Caucasian populations such as African-Americans have been shown to have spirometry values a full standard deviation less than Caucasian populations.¹⁷ Much of these ethnic-related differences appear attributable to anthropometric factors (differences in body proportions).^{15,17} Therefore, appropriate reference values are developed by testing significant numbers of healthy individuals across of both biological sexes across the entire age spectrum from individual ethnic groups.

In 2012, the Global Lung Function Initiative (GLI) published multi-ethnic reference equations for spirometry for persons aged 3-95 years using data submitted for approximately 76,000 participants from around the world.⁹ While these reference equations capture more ethnic populations across a wider age range than previous reference sets, Aboriginal and Torres Strait Islander Australians are not represented due to insufficient data. A 2016 systematic review found no existing reference set had been appropriately validated for use in these populations.¹⁸ Respiratory function tests in First Nations Australian populations therefore require careful interpretation, as predicted values generated for use in these populations may not be truly representative of normal lung function, and misdiagnosis of lung disease can impact clinical management. Although published literature on First Nations Australian lung function is sparse, the need for normative reference values in the adult population is now being recognised.¹⁹ A 2019 publication found the 'Other/Mixed' category of the GLI-2012 reference values was most appropriate for use in Aboriginal and Torres Strait Islander children through the testing of healthy participants across urban, regional and remote communities in Queensland and the Northern Territory.²⁰

A 2016 systematic review¹⁸ identified nine studies that included spirometry in healthy First Nations adults. Common to all were issues with non-adherence to ATS/ERS and GLI criteria for the development of reference values were identified in each, including the absence of participant smoking history, respiratory history, inadequate sample sizes.¹⁸ While validation of the existing GLI-2012 'Other/mixed' category has occurred for First Nations children, no such validation had occurred for First Nations adults prior to my PhD. Reference values used for these individuals are often inconsistently applied at different sites due to the lack of First Nations-specific values coupled with a lack of objective data to inform practice. This was problematic as these values may differ by as much as 30% depending on which reference set is used. Both under- or over-diagnosis of respiratory disease is likely to occur and may preclude the provision of quality care that is culturally appropriate. Collection of adult data to combine with previously collected paediatric

data in order to validate GLI-2012 reference sets against an all-age First Nations Australian dataset is presented in Chapter 11, for the completion of Objective 4 set out in Section 1.4.

1.2.1.2 Fractional exhaled nitric oxide (FeNO)

FeNO is a non-invasive tool used increasingly as a biomarker to identify and monitor asthma²¹ and eosinophilic airway inflammation²² that is often associated with type 2 inflammation.²³ FeNO is a measure of nitric oxide (NO) produced continuously within airway epithelial cells, mast cells, and neutrophils through cumulative nitric oxide synthase activity,^{23,24} and is often elevated above the upper limit of normal (ULN) or ‘cut-off’ in subjects with eosinophilic asthma and/or atopy.^{21,25-27} Airway inflammation contributes to airway reactivity and obstruction, and serial FeNO measurements are often used to monitor inhaled corticosteroid (ICS) responsiveness and continued adherence.²³ FeNO, reported in parts-per-billion (ppb), is measured in exhaled air collected from a 10 second (6 seconds in children <12 years of age) exhalation at a controlled flow rate (50mL/s). The controlled flow rate reduces the confounding effects of lower or higher flow rates and initial inspiration through a NO scrubber eliminates ambient NO from the exhaled sampling.²⁸ NO analysers may use a range of techniques, including chemiluminescence and electrochemical sensors, but should have a sensitivity (smallest change detectable) of 1ppb.²⁸ Several subject-specific factors may temporarily confound FeNO testing, including smoking,²⁹⁻³¹ dietary caffeine³² and nitrates³³, and alcohol consumption.³⁴ The susceptibility of FeNO to these factors should be considered in the clinical interpretation of results.

Unlike other respiratory function tests in which normative ranges are influenced by age, ethnicity, sex and height, current interpretive guidelines for FeNO use all-age, or age-based (paediatric and adult) cut-off values.^{21,25-27} Age and height have been shown to be independently associated with FeNO values,^{35,36} and there is now evidence to suggest that ethnic differences also modify FeNO results.³⁷ Males may have higher FeNO values than females,³⁸ though this not a consistent finding.³⁵ Despite the apparent strength of some of these associations, current guidelines propose either age-based cut-off values^{21,25,26} or a single cut-off value for use in all individuals.²⁷ Results above the values are considered suggestive of eosinophilic inflammation. These cut-off values are based mostly on data from Caucasian populations³⁷ and have been shown to be unsuitable for use in some ethnic groups whose FeNO distributions are generally higher than White populations,¹⁸ increasing the likelihood of unnecessary investigations and treatment interventions.

Values for both children and adults were recommended in guidelines approved by the ATS in 2011,²¹ where FeNO values ≥ 35 ppb in children (<12years) and ≥ 50 ppb in adults (≥ 12 years) are suggestive of eosinophilic asthma, and intermediate FeNO values between 20-35ppb (children) or

25-50ppb (adults) should be interpreted with caution. Other organisations such as the National Institute for Health and Care (NICE), British Thoracic Society (BTS), suggest similar paediatric cut-off values (≥ 35 ppb) but adult cut-off values vary between ≥ 40 to ≥ 50 ppb.³⁹ FeNO cut-offs values were validated within an adult population referred to specialists for assessment of asthma, which found the intermediate cut-off of ≥ 25 ppb proposed by the ATS to be sensitive for eosinophilic asthma, with significant reduction in sensitivity for the ≥ 50 ppb cut-off used by other organisations (37%).⁴⁰

Blake et al evaluated FeNO measurements from 1036 healthy First Nations Australian children aged 3-16 years to determine the suitability of published FeNO cut-offs within this population.³⁹ Blake found a cut-off of ≥ 50 ppb, as recommended by the Global Initiative for Asthma (GINA), was the most appropriate.³⁹ However, arguably, this cut-off and all currently published cut-offs available in interpretive guidelines for FeNO, are not fit for purpose. They fail to account for factors that modify FeNO values such as age and height. Biologically, it is plausible that airway epithelium surface area is related to the length and diameter of the airways, which is related to both age and height.²⁴ Development of reference values using more sophisticated statistical techniques was completed in Chapter 10, to meet Objective 4 set out in Section 1.4.

1.2.1.3 Diffusing capacity of the lung for carbon monoxide (D_{LCO})

D_{LCO} is a measure of carbon monoxide uptake in the lung, and represents the capacity for gas exchange to occur at the alveolar-capillary interface within the lung.⁴¹ An acceptable single-breath manoeuvre involves a rapid, maximal inhalation, followed by a 10 second breath hold (± 2 seconds⁴¹), then full exhalation. The D_{LCO} is the product of two constituent measurements; the first, K_{CO} , is the rate of carbon monoxide (CO) removal from alveolar gas during the breath hold,⁴² and is the change in log concentration of CO in the inspired gas volume (V_I) divided by the breath hold time. The second, V_A , is an estimate of the volume of gas accessible to surfaces of gas exchange (the respiratory membrane that forms the alveolar wall) and equates to V_I minus the volume of gas remaining in the large and small airways that does not participate in gas exchange.⁴² The product of the K_{CO} and V_A is then adjusted for pressure to give the D_{LCO} . The K_{CO} and V_A provide complementary information to the D_{LCO} and afford insight into the root cause of D_{LCO} abnormality, and both should be reported alongside the D_{LCO} according to the current standard.⁴¹

A number of factors may confound D_{LCO} results. Firstly, haemoglobin (Hb) availability will affect the uptake of inhaled CO and will vary between individuals, particularly between males and females.⁴³ Exposure to carbon monoxide (CO), either through the environment (smoke and other pollution) or through previous D_{LCO} test attempts, may reduce D_{LCO} due to acute binding of inhaled

CO to Hb to form COHb within the blood, thereby reducing CO uptake by the capillary blood as it moves past the alveoli.^{41,44} For this reason, D_{LCO} testing should be limited to five attempts, to avoid both gradual reductions in D_{LCO} , and the anaemia-like effects that occur due to COHb accumulation.⁴¹ Changes in pulmonary blood flow as a result of positional changes (seated versus supine), and exercise may also confound measurements, with the supine position and exercise being associated with significant increases to the D_{LCO} .^{41,45}

The additional complexity of D_{LCO} testing necessitates more complex hardware than spirometry. Air flow sensor requirements are similar to those for spirometric testing such as requirements for sensor accuracy and linearity over biologically plausible flows and volumes, including when used with commonly used gas mixtures.⁴¹ Also required are gas analysers with rapid response times capable of both precise sampling and rapid analog-to-digital conversion (at $\geq 100\text{Hz}$) to record rapid changes in gas concentrations, particularly during the inspiratory and expiratory phases.⁴¹ Despite added hardware and its relative complexity, relatively portable equipment has been developed, and D_{LCO} testing is performed routinely in specialist respiratory outreach clinics in regional and remote Queensland.^{46,47}

As with spirometry, D_{LCO} is influenced by age, height, and biological sex, and these are accounted for in the GLI-2017 reference equations used to generate predicted values and Z-scores for children and adults aged 5-85 years.⁴³ The majority of data (85%) submitted to the GLI for the development these reference equations was Caucasian test data and no adjustment of reference values for other ethnicities is currently available in the GLI-2017 reference set. There is some evidence that D_{LCO} may be influenced by ethnicity^{48,49} as with other lung function tests, including in a study First Nations Australian adults.⁵⁰ These data may not be representative, however, as sample sizes included only 129 First Nations adults who formed part of a clinical population, with only chest radiography used to determine respiratory health.⁵⁰

1.2.2 Lung function trajectories

The importance of childhood lung function and its trajectories to adulthood have received increasing attention.⁵¹⁻⁵⁶ Normal lung function trajectories have three distinct phases: growth (from childhood to young adulthood at approximately 18 years), plateau (18-25 years), followed by gradual decline into advanced age.⁵⁵ A range of variant trajectories have been proposed and are now well-supported.⁵⁵ Trajectories beginning with below average (but still within normal range) or abnormally low FEV_1 in childhood/young adulthood, with or without accelerated FEV_1 decline, have been associated with increased cardiopulmonary and all-cause mortality.⁵¹⁻⁵⁵ Increased chronic obstructive pulmonary disease (COPD) prevalence in adulthood is now also associated

with these trajectories, an association that is further strengthened when followed by accelerated decline occurring as a result of aggravation in adulthood (i.e. smoking or environmental stimuli).^{51,54} Associations with COPD diagnosis in adulthood are particularly relevant in the First Nations Australian population, who are 2.9 times more likely to smoke⁵⁷ and disproportionately affected by COPD, with incidence rates 2.5 times higher than non-First Nations Australians.⁵⁸

There is some evidence that catch-up growth may occur,^{55,56,59} and so early identification and management of chronic respiratory illness in childhood/young adulthood may improve the trajectories of children treated. Lung function optimisation in childhood, or lack thereof, may have lasting impacts throughout the lifespan. An important step in eliminating cardiopulmonary health disparities between First Nations and non-First Nations Australians is addressing the disproportionate burden of acute and chronic respiratory disease in First Nations Australian children. As part of Objective 2 (Section 1.4), my thesis assesses the impact of a culturally appropriate respiratory outreach service on the lung function of First Nations Australian children seen and treated (Chapters 5 and 6).

1.3 BURDEN OF RESPIRATORY DISEASE IN FIRST NATIONS AUSTRALIANS

1.3.1 First Nations Australian children

Unlike most other forms of illness which emerge in adolescence or adulthood, respiratory disease affects between 4% and 13% of the First Nations Australian population across all age groups from birth.⁶⁰ Contributing to these poor outcomes are high self-discharge rates (19 times greater than non-First Nations Australians), delayed diagnosis and treatment due to poor service access, and complexities surrounding medication adherence.^{58,61} Early childhood pneumonia is a significant public health issue worldwide, and it remains the leading cause of morbidity and mortality in children under age five years.^{62,63} For First Nations Australian children, it is the leading cause of preventable death and hospitalisation.⁶⁴ The impact on lung function as a result of this burden has yet to be explored within the First Nations Australian population. Pneumonia disproportionately affects not only First Nations Australians, but disadvantaged populations within developing nations.⁶³ Despite this, there appears to be little to no published data on the impacts on lung function within these populations. Reports from affluent countries suggest obstructive deficits are the typical finding in children.⁶⁵⁻⁷⁰ Reductions in lung function persist into adulthood, where restrictive deficits are most frequently reported.^{65,68,71-73} Given the disproportionate impact to First Nations Australians, measurement of the impact of pneumonia on lung function in First Nations children formed one of my PhD objectives to address this knowledge gap. Thus Objective 1

(Section 1.4) was to assess the impact of early childhood pneumonia on lung function through the full lifespan. The results are presented in Chapters 3 and 4 of my thesis.

O’Grady et al evaluated the provision of programs, resources and services to First Nations people with chronic lung disease in Queensland and found that equitable distribution was unlikely due to assumed homogeneity of morbidity and mortality across Queensland communities, and issues with identification of First Nations Australians.⁷⁴ Services directed at the management of chronic lung disease are scant and under-resourced. In addition, First Nations health workers, who have been shown to significantly improve outcomes in asthma education programs, are underutilised.^{74,75} Significant barriers to accessing specialist care exist for the 43% of First Nations Australians living in outer regional and remote areas.⁵⁷ Such barriers include logistics, distance and cost of travel.⁴ Outreach services that deliver specialist care directly to isolated communities is one such solution shown to have significant potential. Ideally these outreach services should be correctly modelled to the needs of the target community (culturally appropriate services for First Nations communities), be linked with local primary care and utilise and provide resources for First Nations health workers.⁷⁶⁻⁷⁸ Reducing obstacles to accessing specialist care may encourage health-seeking behaviours and improve outcomes.

Public funding for outreach services has been made available in Australia since 2000 through the Medical Specialist Outreach Assistance Program (MSOAP). The IROC service officially launched in 2011, following a previously established paediatric outreach program that launched in 1998 (funded from various sources) and operated through to the launch of IROC.^{79,80} IROC provides specialist respiratory care to rural and remote communities in Queensland. The program is funded by the Queensland Government as part of the National First Nations Health Partnership Agreement to Close the Gap.⁸¹ Community engagement occurred through consultation with Elders and other key stakeholders such as local council.⁸¹ Capacity building is an important element that involves education of patients, First Nations health workers and clinical staff, development of governance structure and encouragement of community ownership of IROC and utilisation of First Nations artwork to promote IROC.⁸¹ A forum held in 2012 heard positive community feedback, however it has been recognised that local staff in some communities are under-resourced.⁸¹

The most common respiratory illnesses seen on paediatric IROC clinics are asthma and bronchiectasis. Asthma at clinical review, from a lung function perspective, may show normal spirometry values or airway obstruction with bronchodilator reversibility⁸², and normal or high FeNO.⁸³ In severe or uncontrolled asthma, fixed airway obstruction (characterised by post-bronchodilator airway obstruction) is more prevalent⁸⁴ in asthma compared with healthy

individuals and is caused by airway remodelling involving epithelial inflammation and smooth muscle thickening.⁸⁵ Lung function monitoring is important in children with asthma. A recent study from combined randomised controlled trials found that a 10% reduction in FEV₁ between clinic visits increased the odds for asthma exacerbation by 28% within 3 months, combined with increased chance of having poor asthma control 6 months after baseline.⁸⁶ Infiltration of eosinophils into the airways is the most common cause of the atopic asthma phenotype, and FeNO measurement and percentage eosinophils in bronchoalveolar lavage fluid have been shown to be well correlated.⁸⁷ As with spirometry, serial FeNO measurements are useful in the continued monitoring of asthmatic children, however there is less certainty surrounding the ability of increased FeNO to predict future outcomes.⁸⁶

Among First Nations children, morbidity and mortality related to asthma is higher than in non-First Nations children.^{79,88} Further, incidence rates are higher for First Nations children <15 years (15%) than for non-First Nations children (9%).⁸⁹ Chang et al evaluated First Nations children with asthma on Thursday Island, and found 30% of children referred to respiratory specialist care for the management of asthma had more severe, persistent asthma, compared to the national average of 5-13%.⁷⁹ Research in the Northern Territory did not find any difference in asthma severity during asthma-related hospital admissions between First Nations and non-First Nations children, however both studies found deficiencies in asthma education and self-management among First Nations patients.^{79,90} Knowledge of the purpose of prescribed medications was poor, and delivery technique was suboptimal in two-thirds of children. Upon discharge from hospital, First Nations children with asthma received an asthma action plan less frequently than non-First Nations children. Improved management of First Nations children with asthma around medication and discharge planning is needed to improve outcomes.⁹¹

Bronchiectasis also has high prevalence among First Nations children, affecting 1 in 68 First Nations children aged <15 years.⁹² Limited access to health services, inadequate follow-up, in addition to issues with medication adherence were again cited as likely reasons contributing to high incidence. Bronchiectasis is diagnosed by high resolution computed tomography (HRCT) which identifies areas of abnormally dilated airways. Whilst it is considered irreversible in adults, there is mounting evidence that early bronchiectasis may be reversible in children.⁹³ Appropriate medical management and physiotherapy can reduce the incidence of recurrent respiratory exacerbations. Given the serious impact of bronchiectasis on paediatric First Nations populations, and the knowledge that early intervention could prevent or reverse disease in childhood, there is a need for specialist care of children with bronchiectasis in these First Nations communities.

The paediatric IROC service was modelled on a previous culturally-informed respiratory outreach service to the Torres Straits region that had been operational since the late 1990s.⁷⁹ The outreach team consists of paediatric-trained clinicians based at the Queensland Children's Hospital (QCH), and includes paediatric-trained respiratory medical specialists, nurses, scientists, physiotherapists and Indigenous project officers. Following each clinic, each child's clinical care plan is reviewed with local treating teams (variably community doctor, nurse, and Indigenous health worker) who implement the suggested clinical approach. There are few objective Australian studies that have evaluated the impact of any model of care for chronic diseases. Indeed, there are no such published respiratory or lung function data that extends beyond a single region. Availability of such data informs evaluation of health services and potentially guides future strategies and policies that address the high burden of chronic respiratory diseases. The paediatric IROC service was formally evaluated, using the lung function of children diagnosed with asthma and bronchiectasis as an outcome measure in Chapter 5. As yet, no respiratory outreach service has been evaluated against a complementary tertiary hospital service with respect to lung function. Identifying this important gap in evaluation of health services, I evaluated the paediatric IROC service against the paediatric tertiary respiratory service offered at QCH in Chapter 6. Together, these chapters complete Objective 2 outlined in Section 1.4.

1.2.2 First Nations Australian adults

The two largest reported contributors to lung disease in First Nations adults are chronic obstructive pulmonary disease (COPD)⁵⁷ and asthma (3 and 1.9 times more common in First Nations compared with non-First Nations Australians⁴ respectively).⁹⁴ These data were obtained from epidemiological studies which may be inaccurate as both conditions have high disease misclassification (as high as 31% for COPD).⁹⁵ Published First Nations Australian lung function data from regional and remote communities are sparse. From 1990 onward, there have been six publications, two of which have been published within the last fifteen years.^{88,96-100} The first, published in 2008, examined the spirometry of First Nations Australians from the Kimberley region in Western Australia.⁹⁹ Most recently in early 2019, Schubert et al published the first lung function data for adult patients seen at specialist clinics in the Northern Territory.¹⁰⁰ Spirometry data from communities in Queensland were published in 1992 and 1997, one of which included paediatric data, however these studies included only clinically well First Nations Australians.^{88,96} Accurate diagnostic data from a large cohort of adults would contribute to the current sparsity of First Nations specific data. The little data that does exist suggests that significant lung function derangement is common among First Nations adults as young as 18-40 years¹⁰⁰ particularly in the

presence of bronchiectasis and COPD where severe airflow limitation is present in the majority of patients seen at respiratory clinics.^{101,102}

From a lung function perspective, COPD is characterised by airway obstruction (reduced FEV₁ relative to FVC).¹⁰³ Differentiating COPD from other causes of airway obstruction such as asthma are i) poor reversibility of airway obstruction (i.e. fixed obstruction) and ii) changes to lung parenchyma (emphysema) that result in reductions to gas exchange across the alveolar membrane (reduced D_{LCO}) and the development of lung hyperinflation.¹⁰³ COPD diagnosis and tracking of progression often requires gas diffusing capacity and static lung volume testing.^{41,104} Destruction of alveolar walls within an emphysematous lung have been shown to correlate well with tissue volume loss on computed tomography imaging,^{105,106} while changes to volumes at different phases of the respiratory cycle reflect the loss of elastic recoil and greater expiratory flow limitation within the lung.^{107,108}

Schubert et al reported that nearly 60% of First Nations adults seen at outreach clinics within the Northern Territory had a diagnosis of asthma, COPD or bronchiectasis.¹⁰⁰ Further, 37% of patients demonstrated post-bronchodilator airflow limitation, with 67% of these patients classified as having severe obstruction.¹⁰⁰ Heraganahally et al reported that 49% of First Nations adults seen within regional and remote Northern Territory communities had a diagnosis of COPD, with 49.8% of these patients classified as having co-morbid bronchiectasis.¹⁰² First Nations adults with bronchiectasis have lung function within the severe disease range,⁷ and a median age of respiratory-related death 20 years earlier than for non-First Nations adults (48.8 years vs. 69.6 years).

Similar to paediatric IROC, a parallel IROC service for adults operates within Queensland, targeting regional and remote communities with high First Nations populations. The service, based at The Prince Charles Hospital, is staffed by First Nations project officers and respiratory physicians, nurses, physiotherapists, and respiratory scientists. Adult IROC teams engage with community Elders groups and works closely with local primary care teams (community doctor, nurse, and First Nations health workers). The adult IROC service is formally evaluated in Chapter 7 using lung function as an outcome measure, as part of Objective 3 outlined in Section 1.4.

The importance of spirometric lung function in adult populations has been consolidated in several studies,¹⁰⁹⁻¹¹³ including in the recent Prospective Urban Rural Epidemiology (PURE) study, involving 126,359 participants aged 35-70 years.¹¹⁴ The PURE study found FEV₁ is an independent predictor of future all-cause mortality, and cardiovascular and respiratory morbidity

within a mean follow-up period of 7.8 years.¹¹⁴ There is a comparatively smaller body of evidence to suggest that clinically abnormal D_{LCO} may also be associated with elevated mortality risk, with an effect size greater than for spirometry.^{115,116} As yet, no studies have reported on associations between D_{LCO} and overall cardiovascular morbidity. Furthermore, other key parameters of the diffusing capacity test, i.e., the K_{CO} and V_A , remain entirely unexplored for their association with either overall cardiovascular morbidity or all-cause mortality.

These associations are particularly relevant for First Nations Australians, who not only have increased exposure to traditional risk factors such as smoking,⁵⁷ but are already at increased risk of cardiovascular disease,⁶¹ respiratory hospitalisation,² and mortality.³ As yet, associations between reduced spirometry and gas diffusing capacity values, and all-cause mortality risk and cardiovascular disease incidence, have yet to be described in First Nations Australians. Associations between spirometry and all-cause mortality risk, and cardiovascular disease incidence in First Nations Australians are described in Chapter 8, while associations with gas diffusing capacity values are described in Chapter 9. Together with Chapter 6, these chapters fulfil Objective 3 outlined in Section 1.4.

1.4 RESEARCH AIM AND OBJECTIVES

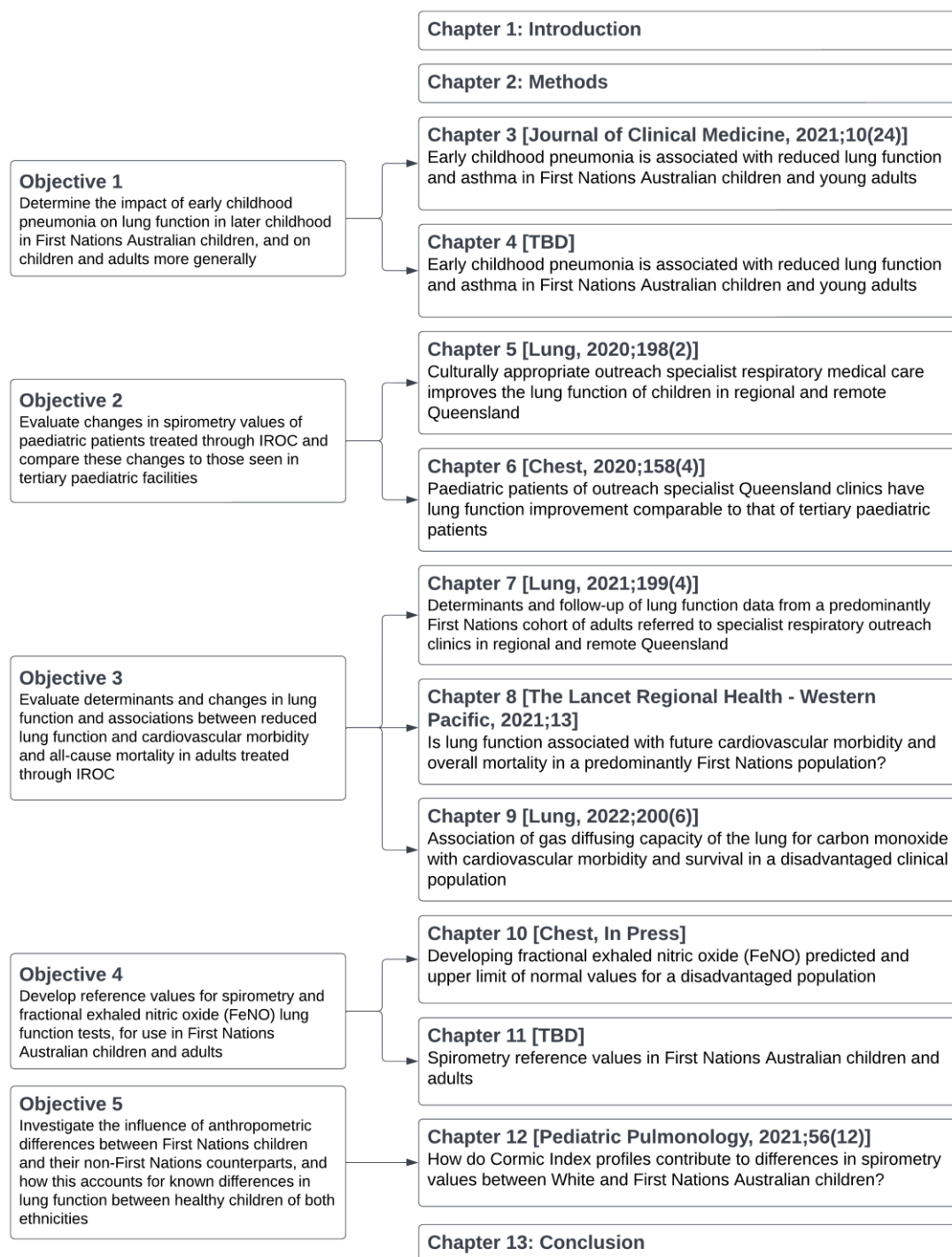
My PhD program overall aims are to improve interpretation of lung function testing, to understand determinants of lung function, and to relate lung function to clinical outcomes in First Nations Australian children and adults. To achieve these aims, the following objectives form the basis of several studies that form the body of this PhD thesis:

1. Determine the impact of early childhood pneumonia on lung function in later childhood in First Nations Australian children, and on children and adults more generally;
2. Evaluate changes in spirometry values of paediatric patients treated through IROC and compare these changes to those seen in tertiary paediatric facilities;
3. Evaluate determinants and changes in lung function and associations between reduced lung function and cardiovascular morbidity and all-cause mortality in adults treated through IROC;
4. Develop reference values for spirometry and fractional exhaled nitric oxide (FeNO) lung function tests, for use in First Nations Australian children and adults; and
5. Investigate the influence of anthropometric differences between First Nations children and their non-First Nations counterparts, and how this accounts for known differences in lung function between healthy children of both ethnicities.

1.5 THESIS OUTLINE AND RESEARCH DESIGN

To achieve the research objectives set out in Section 1.4, I have undertaken ten studies in total and, to date, have published (n=8), submitted (n=1), and will submit (n=1) all to peer-reviewed journals, with each publication forming a chapter within the body of this thesis. Figure 1 summarises the five research objectives and their related studies.

Figure 1. Titles of each of my thesis chapters, encompassing ten chapters/publications addressing my five research objectives. Studies that have been published are referenced at the beginning of each chapter.



1.6 COMMUNITY CONSULTATION

For each community in which recruitment of First Nations Australians was to take place, First Nations community Elders and leaders (as appropriate) were consulted during the planning phase of this research. These discussions took place within communities during face-to-face meetings that usually included my principal supervisor (Dr Margaret McElrea), a First Nations Project Officer (Mr Allan Takken), and myself. The objectives of these meetings were to provide Elders and community leaders and their communities the opportunity to:

1. Learn about his research and the potential benefits to their communities and First Nations Australians more generally; and
2. Offer feedback on study questionnaires and recruitment strategies.

For my supervisory team and me, these meetings were an opportunity to hear the Elders perspectives on:

1. The respiratory health of First Nations Australians within their communities;
2. The quantity and conduct of research in First Nations Australian communities;
3. Healthcare delivery in their communities (local hospitals, medical centres, and specialist outreach clinics).

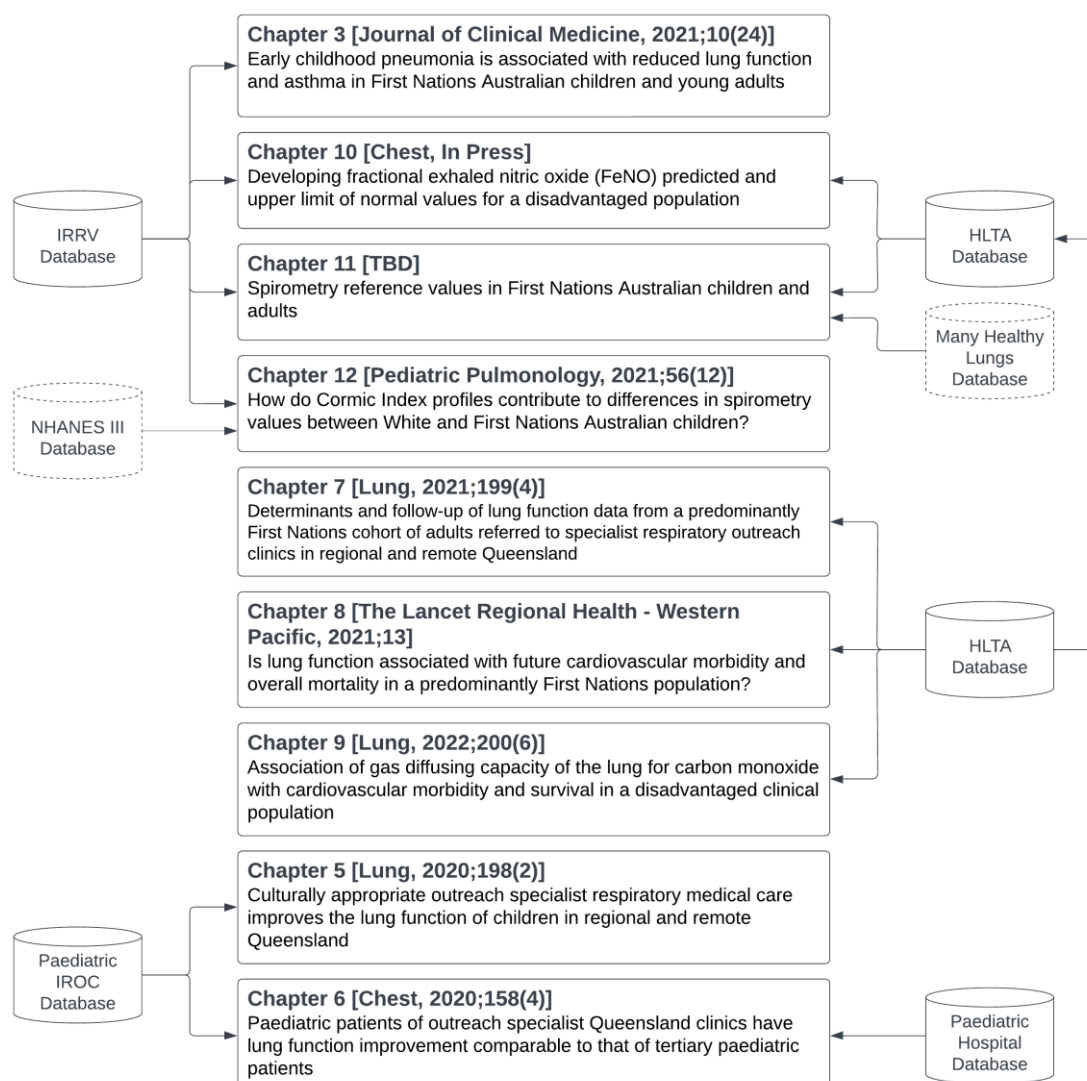
On the advice of Elders groups, we made several changes to study documentation including participant questionnaires and adjusted our recruitment strategies.

Chapter 2: Methods

2.1 OVERVIEW

For the completion of the work contained within this thesis, I utilised patient or participant data from five databases, most of which contained data collected by my supervisory team, which I cleaned and collated. Two additional externally developed databases were used; the Third National Health and Nutrition Examination Survey (NHANES III) was used in Chapter 12, and the Many Healthy Lungs database was used in Chapter 11. This methods chapter discusses the five databases developed for this thesis, and the two external databases used in peer-reviewed articles/chapters within my thesis (Figure 2). How these databases were used in each publication are discussed in each of the relevant chapters.

Figure 2. Six databases used in nine peer-reviewed original articles (chapters).



Externally developed databases marked with dashed lines. IRRV = Indigenous Respiratory Reference Values. IROC = Indigenous Respiratory Reference Values. HILTA = Healthy Indigenous Lung Function Testing in Adults. NHANES III = The Third National Health and Nutrition Examination Survey.

2.2 INDIGENOUS RESPIRATORY REFERENCE VALUES DATABASE

IRRV was a study of 1276 First Nations Australian children and young adults aged 3-25 recruited from childcare centres and schools in Queensland and Northern Territory communities, with recruitment completed by my supervisory team in October 2017. Data collected included demographic and medical histories using a participant and modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires. Also collected were anthropometric, spirometry, and FeNO data. These data were stored in a password protected FileMaker (Clariss, CA, US) database.

IRRV study data were used in three analyses in my thesis. To prepare this data for use, I converted data exported from FileMaker into a Microsoft Excel (Microsoft, WA, US) spreadsheet. Predicted values and Z-scores were calculated for all participants in this database using the GLI-2012 ‘Other/mixed’ reference equations. Three copies of these data were created for use in (1) the early childhood pneumonia analysis in Chapter 3, (2) analysis of normative FeNO and spirometry data in Chapters 10 and 11, and (3) the analysis of anthropometric data in conjunction with the NHANES III dataset in Chapter 12.

For Chapter 3, I used electronic medical records to re-verify reported histories of pneumonia, including the number of pneumonia occurrences and their dates. These data were used to establish the age of children or young adults at each pneumonia occurrence. For Chapters 10 and 11, data were re-structured to facilitate import into a larger REDCap (Vanderbilt University, TN, US) database for future analysis of combined databases. Finally, data were re-structured and merged with publicly available interview, anthropometric, and spirometry data from NHANES III.

2.3 PAEDIATRIC INDIGENOUS RESPIRATORY OUTREACH CARE (IROC) DATABASE

Demographic and spirometry data, originally contained in physical IROC spirometry reports, were previously transcribed into a password protected Microsoft Excel spreadsheet by a Vacation Research Experience Scheme student. I then verified that demographic and spirometry data were entered correctly, firstly using automated methods including data validation tools and hand-written macros in Microsoft Excel to screen for common data entry errors. I then did a manual check for any remaining data entry errors.

I verified demographic and respiratory diagnoses using a combination of electronic medical records, clinic databases maintained by IROC clinic nurses and doctors, and clinic letters. I used GLI-2012⁹ reference equations to derive Z-score and percentage-predicted values for each child. The Caucasian reference equation was used for non-First Nations children, and ‘Other/mixed’ reference equation for First Nations children.

Data to the end of 2017 were used in the analysis for Chapter 5. For the paediatric tertiary hospital comparison in Chapter 6, I transcribed spirometry data from physical reports into the same password-protected database. Verification of demographic and respiratory diagnoses data were repeated, as were the generation of predicted values and Z-scores.

2.4 PAEDIATRIC HOSPITAL DATABASE

I extracted spirometry data from tertiary hospital clinics from SentrySuite (Vyair Medical, Mettawa, IL) database using Sentry Data Cube, into a password-protected Microsoft Excel database. I verified demographic and diagnostic data against electronic medical records, clinic letters, and respiratory nurse records. GLI-2012⁹ reference values were used to derive predicted values and Z-scores for each child. Caucasian reference values were used for non-First Nations children and ‘Other/mixed’ for First Nations children. I then merged this database with the paediatric IROC database described in Section 2.2.

Due to the large number of spirometry tests (>40,000), I developed macros to automate tasks such as data cleaning, categorisation of spirometry values by Prospective Urban Rural Epidemiology study criteria,¹¹⁴ categorisation of patients into groups by diagnosis, and to sort through tests for individuals patients to determine their baseline spirometry and best follow-up spirometry values in the years following their first clinic visit. Macros were developed iteratively through testing on copies of the original database until no issues remained and data were cleaned and sorted correctly.

2.5 ADULT INDIGENOUS RESPIRATORY OUTREACH CARE DATABASE

Patient demographics, lung function data, respiratory diagnosis as confirmed by a respiratory physician, comorbidities, smoking behaviours, and secondary smoke exposure were collected at each clinic visit and stored as both paper charts, and electronically within a FileMaker database. This information was manually transcribed into a separate password protected Microsoft Excel spreadsheet, and missing information was filled where possible using electronic medical records, physical paper charts, and completed patient questionnaires housed within the IROC offices at The Prince Charles Hospital in Brisbane.

Spirometry and D_{LCO} data were exported with the assistance of local respiratory scientists from EasyOne Connect (nidd, Zurich, Switzerland) installations on clinical testing machines based at The Prince Charles Hospital and regional hospitals of Queensland. I merged these data into a centralised EasyOne Connect installation and then exported this database into XML format. I imported this database XML into a password protected Microsoft Excel database and re-structured the data for use in Chapters 7, 8, and 9. Predicted and Z-score values were generated using GLI-2012⁹ reference equations for spirometry, and GLI-2017⁴³ reference equations for D_{LCO} .

Macros I developed for sorting spirometry tests into baseline and best follow-up visits within each year for the paediatric IROC database (Section 2.3) were re-purposed and used to sort adult

IROC spirometry tests. For Chapters 8 and 9, I used electronic medical records to access death certificates and discharge summaries to determine whether patients seen were diagnosed with new or additional respiratory and cardiovascular disease, and been hospitalised, or were deceased.

2.6 HEALTHY INDIGENOUS LUNG FUNCTION TESTING IN ADULTS DATABASE

Demographic and ancestry data were collected using a participant questionnaire (Appendix B). Medical and smoking histories for all participants were obtained from medical charts using the medical chart review form by study investigators and modified International Study of Asthma and Allergies in Childhood (ISAAC) (Appendix D) questionnaires (parent-completed for participants <18 years). FeNO and anthropometric data (standing height, sitting height, and weight), originally transcribed to a per-participant results run sheet.

I developed a REDCap database to securely host demographic, ancestry, medical history, anthropometric, and lung function test data. Following individual participant recruitment, or on completion of a recruitment trip, I transcribed data collected on physical forms and reports into this database, which was then exported into a password protected Microsoft Excel spreadsheet following the cessation of recruitment for data analysis. I exported spirometry data from EasyOne Connect on study laptops, into a centralised EasyOne Connect database for review of lung function tests (review and selection of acceptable and repeatable trials). Spirometry data were exported from SentrySuite using Sentry Data Cube for participants tested within the Queensland Children's Hospital respiratory laboratory and entered into REDCap.

Spirometry tests were independently reviewed against current ATS/ERS criteria for acceptability and repeatability⁸ by myself and one of my supervisory team. Tests were then jointly discussed and tests that did not meet criteria were flagged for later exclusion. I generated predicted values and Z-scores for spirometry were generated using GLI-2012⁹ reference equations.

2.7 MANY HEALTHY LUNGS DATABASE

I provided a database template to the research team at the Telethon Kid's Institute, Perth to facilitate the sharing of relevant collected data. Demographic, medical history, and spirometry data of First Nations Australians collected in Perth, Broome, and the Kimberley in Western Australia were sent in this format, and these data were merged with the HILTA database discussed in Section 2.6.

Chapter 3: Early childhood pneumonia is associated with reduced lung function and asthma in First Nations Australian children and young adults

This chapter addresses the first part Objective 1, outlined in Section 1.4, to “determine the impact of early childhood pneumonia on lung function in later childhood in First Nations Australian children...”. This was published as:

Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Vicendese D, Blake TL, McElrea MS, Dharmage SC. Early Childhood Pneumonia Is Associated with Reduced Lung Function and Asthma in First Nations Australian Children and Young Adults. *J Clin Med*. 2021;10(24).

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
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Don Vicendese	Reviewed draft manuscript, assisted with data analysis
Tamara Blake	Led data collection, input into study design
Margaret McElrea	Reviewed draft manuscript, data collection, input into study design
Shyamali Dharmage	Reviewed draft manuscript, led study design

3.1 ABSTRACT

3.1.1 Background

Some but not all previous studies report that pneumonia in children aged less than five years is associated with lower lung function and elevated risk of respiratory disease. To date, none have explored these associations in at-risk populations such as First Nations Australians whose incidence of early childhood pneumonia is among the highest reported in the world.

3.1.2 Methods

This cross-sectional study included 1,276 First Nations Australian children/young adults aged 5-25 years recruited from regional/remote Queensland and Northern Territory communities and schools. Associations between pneumonia and both spirometry values and asthma were investigated using linear and logistic regression.

3.1.3 Results

Early childhood pneumonia was associated with lower FEV1 and FVC Z-scores, but not FEV1/FVC% Z-scores, when occurring before age three (FEV1 β =-0.42, [95%CI -0.79, -0.04]; FVC β =-0.62, [95%CI -1.14, -0.09]), and between three and five years (β =-0.50, [95%CI -0.88, -0.12]; β =-0.63, [95%CI -1.17, -0.10]), compared to those who never had pneumonia. Similarly, pneumonia occurring when aged before age three years (OR=3.68, 95%CI 1.96-6.93) and three-to-five years (OR=4.81, 95%CI 1.46-15.8) were associated with increased risk of asthma in later childhood.

3.1.4 Conclusion

Early childhood pneumonia is associated with lung function deficits and increased asthma risk in later childhood/early adulthood in First Nations Australians. The disproportionate impact of pneumonia on at-risk children must be addressed as a priority

3.2 INTRODUCTION

Pneumonia is an important global public health issue as it remains the leading cause of morbidity and mortality in children aged under five years,^{62,63} with an estimated 156 million cases⁶³ and nearly one million deaths annually.¹¹⁷ It disproportionately affects Indigenous children worldwide, including Aboriginal and Torres Strait Islander Australian (henceforth respectfully referred to as First Nations Australian) children, for whom it is the leading cause of preventable death and hospitalisation in those aged less than five years.⁶⁴ The potential adverse consequences of this high burden have not yet been investigated in these populations despite increasing, although still inconsistent, evidence of the impact of childhood pneumonia on subsequent lung function and respiratory morbidity.

Childhood pneumonia has been associated with reduced lung function (defined by reduced forced expiratory volume in one second [FEV₁] and forced vital capacity [FVC] as measured by spirometry) both in later childhood,⁶⁵⁻⁷⁰ where primarily obstructive deficits are seen, and adulthood where restrictive deficits are most common.^{65,68,71-73} These adverse consequences are greater when pneumonia occurs before five years of age.^{65,70} These observations are plausible given continued airway growth and rapid proliferation of alveoli occur up to three to four years post-natally, and infection in these early years may impair overall lung growth.¹¹⁸ Low childhood lung function predicts low adulthood lung function^{52,54-56} which is associated with future cardiopulmonary and all-cause morbidity and mortality,¹¹⁴ including for the First Nations Australians.⁴⁷

Despite the increasing evidence on adverse lung function outcomes of childhood pneumonia, there is no such data in populations with reported high-risk of severe chronic respiratory disease such as First Nations Australians. The incidence of early childhood respiratory infections in First Nations Australians is among the highest reported in the world.⁶⁴ To address these knowledge gaps, we utilised Indigenous Respiratory Reference Values (IRRV) study²⁰ data to evaluate the effects of documented childhood pneumonia occurring at or before five years of age on lung function in later childhood/early adulthood in 909 First Nations Australian children. We hypothesised early childhood pneumonia is associated with poorer lung function and asthma, and that the age of pneumonia first occurring modifies these associations, with decreasing age of pneumonia having greater impact.

3.3 MATERIALS AND METHODS

3.3.1 Study design, setting, and participants

We used cross-sectional data of First Nations Australian children and young adults aged 5-25 years from the Indigenous Respiratory Reference Values (IRRV) study.²⁰ Participants were recruited opportunistically from childcare centres, schools, and community events from nine Queensland and Northern Territory communities in Australia between June 2015 and October 2017. Written participant or parent/guardian consent (where participants were aged <18 years) was obtained in all cases, and ethical approval was obtained from the Children's Health Queensland Human Research Ethics Committee (HREC/14/QRCH/111).

3.3.2 Data collection

Participants (aged ≥ 18 years), or parents/guardians (for participants <18 years) completed two study questionnaires. Information collected included demographic data, respiratory history (including smoking status and household exposure), gestational age at birth, and detailed histories of asthma and atopy. For all participants, paper and electronic medical records from local hospitals and medical centres were used to verify questionnaire data and collect data on hospitalisations. Where there was disagreement between information collected through participant questionnaires and medical records, information obtained from medical records was used.

3.3.3 Definitions

Ever-pneumonia status was considered verifiable and thus assigned when it was recorded in the participant's medical records and the illness was consistent with pneumonia (fever, cough, and respiratory signs or chest radiograph changes). Medical records were also used to assign diagnoses of asthma. Eczema, hay fever, rash, and wheeze were assigned where recorded on study questionnaires.

3.3.4 Spirometry

Spirometry measurements were performed according to meet American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines^{8,119} in the seated position with a nose clip, using Easy on-PC spirometers (nidd Medizintechnik, Switzerland).²⁰ Z-scores and % predicted values for spirometric measurements were re-calculated using 'Other/mixed' values from the GLI 2012 reference equations, as these were found be most appropriate for use in First Nations Australians.²⁰

3.3.5 Participant selection for the current analysis

Children whose spirometry did not meet ATS/ERS criteria were excluded during a previous analysis of this dataset.²⁰ For our analysis, we excluded those with parent-reported pneumonia only (i.e., no verifiable evidence), and children with neonatal pneumonia as we are unable to distinguish between pneumonia and residual pulmonary fluid in foetal lung tissue when reviewing charts retrospectively.

3.3.6 Statistical analyses

Generalised additive models (GAMs) in R (R Core Team) were used to fit FEV₁ and FVC Z-scores against age of first pneumonia to test for non-linear associations. Non-linearity was checked using the ‘mgcv’ package with the R software (references provided in supplement). As no compelling evidence for non-linear fits was found, we used univariable linear regression to model FEV₁ and FVC Z-scores against history of pneumonia (model A) and age of first pneumonia (model B). For the second model, we stratified children into two early childhood groups (less than three years, and between three and five years of age) to explore the effects of pneumonia occurring in different windows within this critical development period, and a third group representing pneumonia not occurring in early childhood (greater than five years). Potential confounders (sex, household smoking, gestational age, eczema, hay fever, rash, and wheeze) were adjusted for in a multivariable linear regression model. Variables with $p < 0.2$ for any level were included in the final models.

Odds ratios (ORs) for asthma occurring later in development were calculated using multivariable logistic regression modelling (adjusted for age, sex, household smoking, gestational age, and wheeze) for children with ever-pneumonia status (model A), and for age of first pneumonia (model B). Stata 16.1 (StataCorp LLC) was used for all other statistical analyses; two-tailed p -values < 0.05 were considered significant.

Table 1. Summary of demographics and lung function at the time of lung function testing, for 909 First Nations subjects, including 48 subjects with ever-pneumonia status during critical development windows

		All subjects (n=909)	Nev. er-pneumonia (n=861)	Ever-pneumonia (n=48)		Pneumonia occurred when <3 years of age (n=26)	Pneumonia occurred when 3–5 years of age (n=13)	First pneumonia when >5 years of age (n=9)
		Median (IQR) or n (%)						
Age when lung function undertaken		11.0 (8.2, 13.8)	11.0 (8.2, 13.8)	10.1 (8.1, 14.1)		9.1 (8.0, 14.1)	9.1 (7.4, 11.9)	13.4 (11.6, 16.7)
Female		464 (51%)	442 (51%)	22 (46%)		9 (35%)	7 (54%)	6 (67%)
Household smoking		130 (14%)	126 (15%)	4 (8%)		2 (8%)	1 (8%)	1 (11%)
Gestation age (weeks)	>36	464 (51%)	438 (51%)	26 (54%)		15 (58%)	7 (54%)	4 (44%)
	34-36	45 (5%)	42 (5%)	3 (8%)		1 (4%)	1 (8%)	1 (11%)
	30-33	10 (1%)	10 (1%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)
	<30	6 (1%)	6 (1%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)
	Unknown	385 (42%)	365 (42%)	20 (42%)		10 (38%)	5 (38%)	4 (44%)
Eczema		48 (5%)	45 (5%)	3 (6%)		2 (8%)	0 (0%)	1 (11%)
Hayfever		59 (6%)	53 (6%)	6 (12%)		4 (15%)	0 (0%)	0 (0%)
Rash		44 (5%)	43 (5%)	1 (2%)		0 (0%)	0 (0%)	1 (11%)
Wheeze		115 (13%)	104 (12%)	11 (23%)		6 (23%)	1 (8%)	2 (22%)
FEV ₁	Litres (L)	2.02 (1.51, 2.77)	2.03 (1.52, 2.77)	1.97 (1.38, 2.75)		1.77 (1.32, 2.76)	1.74 (1.35, 2.12)	2.73 (2.13, 2.99)
	Z-score	-0.13 (-0.71, 0.54)	-0.11 (-0.70, 0.58)	-0.42 (-1.01, 0.12)		-0.51 (-1.07, -0.04)	-0.44 (-1.17, -0.24)	0.01 (-0.43, 0.42)
	% Predicted	98.5 (91.5, 106.4)	98.7 (91.6, 106.8)	94.9 (87.0, 100.2)		94.0 (86.0, 99.6)	94.7 (85.8, 97.2)	100.1 (95.1, 104.9)
FVC	Litres (L)	2.33 (1.74, 3.18)	2.34 (1.75, 3.18)	2.26 (1.60, 3.22)		1.99 (1.54, 3.39)	1.99 (1.55, 2.38)	3.03 (2.61, 3.44)
	Z-score	0.04 (-0.58, 0.72)	0.06 (-0.58, 0.73)	-0.30 (-1.00, 0.21)		-0.28 (-1.14, 0.14)	-0.47 (-1.03, -0.31)	0.05 (-0.34, 0.81)
	% Predicted	100.4 (93.3, 108.3)	100.6 (93.3, 108.6)	96.6 (88.2, 102.5)		97.0 (87.6, 101.6)	94.7 (88.8, 96.5)	100.5 (96.0, 109.2)

Table 2. Univariable and multivariable regression modelling of FEV₁ Z-scores in 909 First Nations subjects.

		Univariable (n=909)		Multivariable (n=909)			
				Model A		Model B	
		β (95%CI)	p	β (95%CI)	p	β (95%CI)	p
Age when lung function undertaken (per 1 year increase)		-0.03 (-0.05, -0.01)	<0.01	-0.03 (-0.04, -0.01)	<0.01	-0.03 (-0.05, -0.01)	<0.01
Sex (Female) (n=465)		0.01 (-0.12, 0.13)	0.93				
Household smoking (n=130)		-0.19 (-0.37, -0.01)	0.04	-0.19 (-0.37, -0.01)	0.04	-0.19 (-0.37, -0.01)	0.03
Gestational age (weeks)	>36 (n=464)	Reference	-	Reference	-	Reference	-
	34-36 (n=45)	-0.01 (-0.30, 0.29)	0.97	-0.00 (-0.29, 0.29)	1.00	-0.01 (-0.30, 0.29)	0.96
	30-34 (n=10)	-0.46 (-1.07, 0.14)	0.13	-0.40 (-1.01, 0.20)	0.19	-0.40 (-1.00, 0.21)	0.20
	<30 (n=6)	-1.06 (-1.84, -0.27)	<0.01	-0.95 (-1.73, -0.17)	0.02	-0.95 (-1.72, -0.17)	0.02
	Unknown (n=385)	-0.14 (-0.27, -0.01)	0.03	-0.15 (-0.28, -0.02)	0.03	-0.15 (-0.28, -0.01)	0.03
Eczema (n=48)		-0.16 (-0.45, 0.12)	0.26				
Hay fever (n=59)		-0.18 (-0.43, 0.08)	0.18	-0.07 (-0.34, 0.19)	0.58	-0.06 (-0.33, 0.20)	0.64
Rash (n=44)		-0.15 (-0.45, 0.15)	0.32				
Wheeze (n=115)		-0.29 (-0.48, -0.09)	<0.01	-0.22 (-0.42, -0.02)	0.03	-0.23 (-0.43, -0.03)	0.02
Ever-pneumonia (n=49)		-0.34 (-0.62, -0.06)	0.02	-0.35 (-0.63, -0.07)	0.01		
Age (years) of first pneumonia	Never (n=464)	Reference	-			Reference	-
	0-2 (n=27)	-0.40 (-0.78, -0.02)	0.04			-0.42 (-0.79, -0.04)	0.03
	3-5 (n=13)	-0.54 (-1.07, -0.00)	0.05			-0.62 (-1.14, -0.09)	0.02
	>5 (n=9)	0.13 (-0.51, 0.77)	0.70			0.23 (-0.40, 0.86)	0.48

Table 3. Univariable and multivariable regression modelling of FVC Z-scores in 909 First Nations subjects.

		Univariable (n=909)		Multivariable (n=909)			
				Model A		Model B	
		β (95%CI)	p	β (95%CI)	p	β (95%CI)	p
Age when lung function undertaken (per 1 year increase)		-0.04 (-0.06, -0.03)	<0.01	-0.04 (-0.06, -0.03)	<0.01	-0.04 (-0.06, -0.03)	<0.01
Sex (Female) (n=465)		0.06 (-0.07, 0.19)	0.33				
Household smoking (n=130)		-0.15 (-0.33, 0.04)	0.12	-0.16 (-0.34, 0.03)	0.09	-0.16 (-0.34, 0.02)	0.09
Gestational age (weeks)	>36 (n=464)	Reference	-	Reference	-	Reference	-
	34-36 (n=45)	0.07 (-0.23, 0.37)	0.66	0.07 (-0.22, 0.37)	0.63	0.06 (-0.23, 0.36)	0.66
	30-34 (n=10)	-0.33 (-0.95, 0.30)	0.30	-0.32 (-0.93, 0.29)	0.30	-0.32 (-0.93, 0.29)	0.30
	<30 (n=6)	-1.23 (-2.03, -0.43)	<0.01	-1.23 (-2.01, -0.44)	<0.01	-1.23 (-2.01, -0.45)	<0.01
	Unknown (n=385)	-0.14 (-0.27, -0.00)	0.05	-0.11 (-0.24, 0.03)	0.12	-0.10 (-0.23, 0.03)	0.14
Eczema		-0.11 (-0.40, 0.18)	0.47				
Hay fever		0.02 (-0.24, 0.28)	0.88				
Rash		-0.13 (-0.43, 0.18)	0.41				
Ever-wheeze (n=115)		-0.04 (-0.24, 0.15)	0.67				
Ever-pneumonia (n=49)		-0.37 (-0.66, -0.09)	0.01	-0.40 (-0.68, -0.12)	<0.01		
Age (years) of first pneumonia	Never (n=464)	Reference	-			Reference	-
	0-2 (n=27)	-0.45 (-0.83, -0.06)	0.02			-0.50 (-0.88, -0.12)	0.01
	3-5 (n=13)	-0.56 (-1.10, -0.01)	0.05			-0.63 (-1.17, -0.10)	0.02
	>5 (n=9)	0.10 (-0.56, 0.75)	0.77			0.22 (-0.42, 0.87)	0.49

3.4 RESULTS

3.4.1 Study population

Of 1,276 study participants, 355 (28%) were excluded as spirometry did not meet acceptability and/or repeatability criteria⁸ or were not undertaken. Eleven participants with parent-recorded but unverifiable pneumonia (where there was no evidence in hospital/clinic charts) were excluded, and one participant with neonatal pneumonia was excluded, leaving 909 participants in our analysis. Their demographic data and spirometry values are summarised in Table 1.

Forty-eight subjects had verifiable pneumonia, with 27 subjects first having pneumonia before three years, 13 between three and five years, and nine after five years of age. Hay fever and wheeze occurred more frequently in subjects with ever-pneumonia status, but household smoking and premature birth appear unrelated to pneumonia status. Participants without spirometry results or whose spirometry did not meet criteria were younger than included participants (median age=8.1 years, IQR 5.8, 13.0), but other demographic factors were otherwise similar.

3.4.2 Spirometry

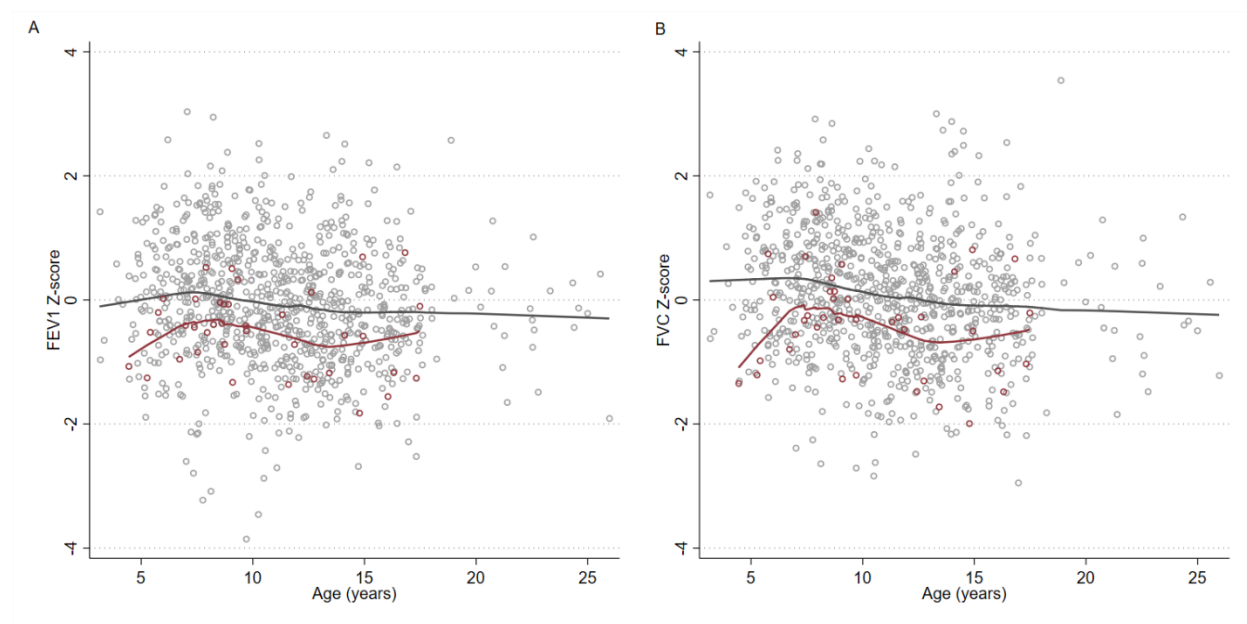
Non-linear fitting of FEV₁ and FVC Z-scores against age of first pneumonia (Figure 4 and Figure 5) were not statistically significant in either case ($p=0.74$; $p=0.05$ respectively). Univariable and multivariable linear regression modelling of FEV₁ and FVC Z-scores against exposure of interest was used to explore linear relationships while adjusting for potential confounders and are presented in Table 2 and Table 3, while FEV₁/FVC% modelling is presented in Table 4.

Pneumonia was significantly associated with lower FEV₁ (reduced by 0.35 Z-scores) and FVC (reduced by 0.40 Z-scores). When stratified by age, those whose pneumonia occurred at before three years of age, FEV₁ was reduced by 0.42 Z-scores and FVC was reduced by 0.50 Z-scores. When pneumonia occurred at 3-5 years of age, FEV₁ was reduced by 0.62 Z-scores and FVC was reduced by 0.63 Z-scores. Subjects whose pneumonia occurred age at or before five years were combined and plotted against other subjects (Figure 3), including those whose pneumonia occurred age after five years and those with never-pneumonia status.

There was no significant association between pneumonia status and FEV₁/FVC% Z-scores including when stratified by age of first pneumonia, and this is evident when subjects whose first pneumonia occurred while aged five years or less were plotted against other subjects (Figure 6).

Figure 3. Scatter plots with lowess smoothing comparing FEV₁ (A) and FVC (B) Z-scores of First Nations subjects whose pneumonia occurred age ≤ 5 years versus other subjects. Locally weighted

smoothing of participants shows the reduction in lung function occurring post-early childhood pneumonia.



Gray hollow circle marks participants with no history of pneumonia, or pneumonia occurring after age five years. Gray line is locally weighted smoothing of participants marked with gray hollow circles. Maroon hollow circle marks participants with a history of pneumonia occurring at or before age five years. Maroon line is locally weighted smoothing of participants marked with maroon hollow circles. Age as marked on the horizontal axis indicates the age of the participant when lung function was performed.

3.4.3 Associations with subsequent diagnosis of asthma

Multivariable linear regression modelling showed ever-pneumonia status was associated with increased risk of developing childhood asthma (OR=3.10, 95%CI 1.49-6.45). When modelling was repeated with age of first pneumonia as the exposure, we found that pneumonia first occurring before three (OR=2.67, 95%CI 1.04-6.85) and between three and five years (OR=8.23, 95%CI 2.73-24.8) of age were associated with an increased risk of childhood asthma. In contrast, pneumonia occurring after five years of age was not associated with increased asthma risk (OR=2.88, 95%CI 0.38-21.9) but the wide confidence interval suggests a lack of power.

3.5 DISCUSSION

In this study of 909 First Nations Australian children including 48 children with medical record documented pneumonia, we found that pneumonia in early childhood (at or before five years of age) is associated with lower lung function as measured by spirometry in later childhood. There was a reduction in Z-score of >0.4 Z-score across both FEV₁ and FVC, 95%CI ranging from -1.14 to -0.04 compared to those who never had pneumonia. Pneumonia first occurring after five

years of age was not significantly associated with reduced lung function, but this analysis was limited by a small sample size. Overall, associations between age of first pneumonia and spirometry Z-scores appeared to be linear in nature. In addition to pneumonia, other independent predictors of FEV₁ Z-scores were household smoke exposure, age when spirometry was undertaken, wheeze, and gestational age <30 weeks, with only the last factor having a larger effect size than pneumonia. Other factors impacting on FVC Z-scores were only gestational age <30 weeks and age when spirometry was undertaken. Finally, we have demonstrated pneumonia first occurring between birth and five years of age was also associated with increased risk of childhood asthma, independent of wheeze and other factors.

Our study is novel for several reasons. This is the first investigation of the impact of early childhood pneumonia on subsequent child/young adult lung function years later, in a population at high-risk of pneumonia and chronic lung disease.^{47,64} We have demonstrated a significant association between early childhood pneumonia and reduced FEV₁ and FVC values in later childhood/early adulthood in the First Nations Australian population, independent of age at spirometry testing, household smoking, gestational age, and wheeze. Several studies have found significant reductions in FEV₁ values in later childhood,^{65,66,68,70} however only one other study found a reduction in FVC (-0.25 [95%CI -0.40, -0.10]).⁶⁶ Our data suggest FVC is significantly affected, with an estimated effect size one-half and one-third that of very preterm birth (<30 weeks) in children less than three and between three and five years of age respectively. We were unable to demonstrate that pneumonia has any impact on FEV₁/FVC%, and so the impact to lung function in this cohort of children appears to be restrictive in nature. Previous reports have found obstructive or mixed deficits in children following early childhood pneumonia, with restrictive deficits found in adult populations.^{65,68,71-73} Secondly, our study's findings also suggest an association between early childhood pneumonia and development of asthma in later childhood in the First Nations Australian population. It has been demonstrated in other populations that pneumonia less than three years increases the likelihood of physician-diagnosed asthma.^{69,70} In the context of the known impact of low lung function in young adulthood on future health^{47,114} and the very high morbidity and premature mortality from cardio-respiratory illness in First Nations Australians, we believe that our study's findings are important.

Our study is exploratory in nature and limited by a small number of children with a history of pneumonia, especially in children aged five years or less. Despite the small sample size and imprecision of our measurements, our effect size estimates are comparatively large compared to previous studies of paediatric populations. Early childhood pneumonia has been previously

estimated to reduce childhood FEV₁ Z-scores by 0.25 (95%CI 0.04, 0.50)⁶⁵ and 0.34 (95%CI 0.18, 0.50)⁶⁶ respectively, while the only study to find a reduction in FVC estimated the effect to be 0.25 Z-scores (95%CI 0.10-0.40).⁶⁵ When compared to our modelling of pneumonia occurring between birth to age five, we estimate the effects of childhood pneumonia on the lung function of First Nations children to be one to three times larger (based on confidence intervals) than that of other populations studied. These findings suggest that at-risk populations whose incidence of pneumonia is disproportionately high may also experience disproportionate impacts to lung function, and thus related morbidity and mortality. Why this is so can only be speculated, but may include differences in organisms, intrinsic factors such as differential immuno-inflammatory responses to infections, environmental differences, or interactions of multiple factors (e.g., gene-infection, infection-environment, or infection-impaired intrinsic factors). For example, humoral immune responses to vaccines are known to be reduced in Australian First Nation People compared to other Australians, shown for hepatitis B¹²⁰ and pneumococcal vaccines.¹²¹ While we lack evidence for this speculation, it has been shown ‘small lungs’ measured at birth do not predispose infants to acute lower respiratory tract infections (ALRIs)/pneumonia, but does have a multiplicative effect.⁶⁷ The Drakenstein child health study prospective cohort study where the infants had their lung function measured at six weeks of age (using multiple breath washout [MBW] and forced oscillation technique) showed conclusively that ALRI impaired lung function when remeasured when aged one year, independent of baseline lung function.⁶⁷

The clinical significance of reduced lung function is not limited to respiratory disease. Recent studies have shown that reduced lung function, even when still within the clinically normal range, is associated with increased risk of cardiovascular disease, and all-cause mortality.¹¹⁴ These associations have now also been demonstrated in First Nations Australians.⁴⁷ In a recent study of 351,874 adults, preserved ratio impaired spirometry, a pattern we observed in participants with a history of early childhood pneumonia, had significantly higher risk of breathlessness, multimorbidity, cardio-vascular disease and increased risk of death, that were unrelated with smoking, obesity, or existing lung disease.¹²² These associations are of heightened significance in the First Nations Australians, for whom cardiovascular disease is the leading cause of morbidity and mortality (1.2 and 1.6 times higher than other Australians, respectively).⁴ Attaining normal lung function in adulthood is thus important, and the foundations are established in early childhood. There is now evidence that catch-up lung function trajectory improvement is possible in childhood,^{54,55} and so timely and appropriate management of respiratory disease and infections is critical. We had previously shown that lung function among First Nations Australians can be

improved with appropriate clinical management.⁴⁶ To achieve this, understanding factors that modify childhood lung function, especially during critical windows of lung development is important.

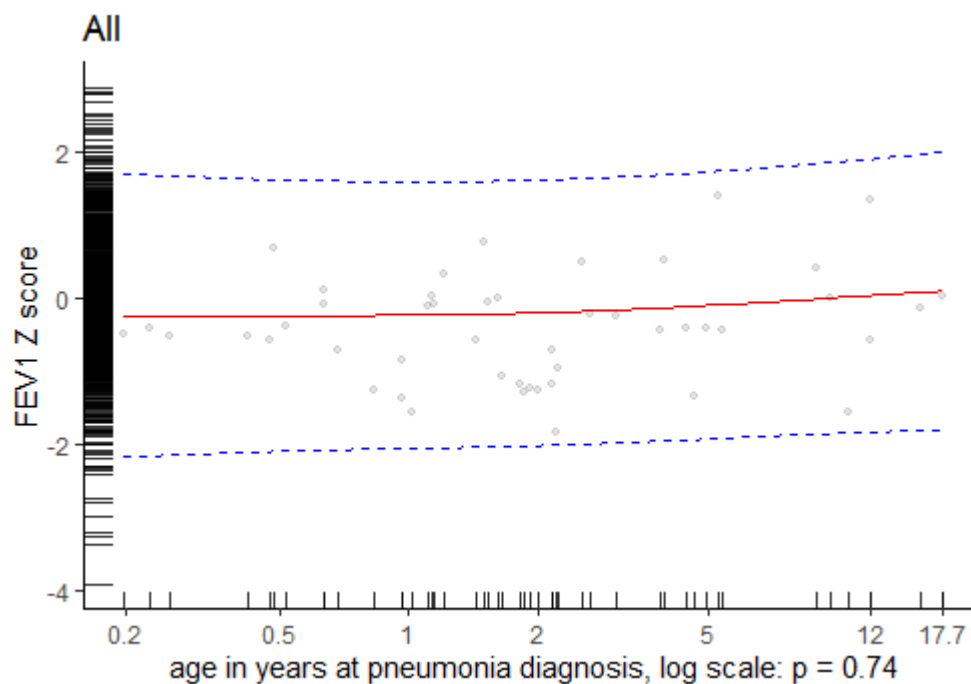
Our study has several limitations. Our sample size is small, and we lack the power to explore other associations (e.g., with other respiratory disease). Despite this, our findings are consistent with current literature regarding lung function impairment post-pneumonia in early childhood. Secondly, our data is based only from First Nations children in Queensland and the Northern Territory and so may limit the generalizability of our findings to the wider First Nations population across Australia. Thirdly, we cannot dismiss the possibility of reverse causation whereby low lung function predisposes children to infection. However, this is an unlikely limitation, as low lung function at six weeks of age (as measured using MBW) was not associated with increased lower respiratory tract infections (LRTI) within the first year of life, but LRTIs were associated with lower lung function measured at 12 months.⁶⁷ Finally, 28% of participants either did not have spirometry testing, or their results did not meet acceptability or repeatability criteria. Overall, these children had similar demographic characteristics to those who were included in the analysis except for age, which was included in our modelling as an effect modifier and so is unlikely to affect our findings.

In conclusion, our findings suggest that early childhood pneumonia is associated with lung function deficits in the form of reduced FEV₁ and FVC values, and development of asthma in later childhood. Given the extremely high prevalence of pneumonia in children, particularly in developing countries and disadvantaged Indigenous populations of affluent countries, it is important to understand its impact on lung development. Indeed, pneumonia incidence among young First Nations Australian children is among the highest reported in the world. In the context of growing evidence of childhood lung function tracking well into adulthood, a better understanding of the impact of pneumonia may inform future research and investment in populations severely affected to improve outcomes through childhood and into adulthood.

3.6 SUPPLEMENTARY MATERIALS

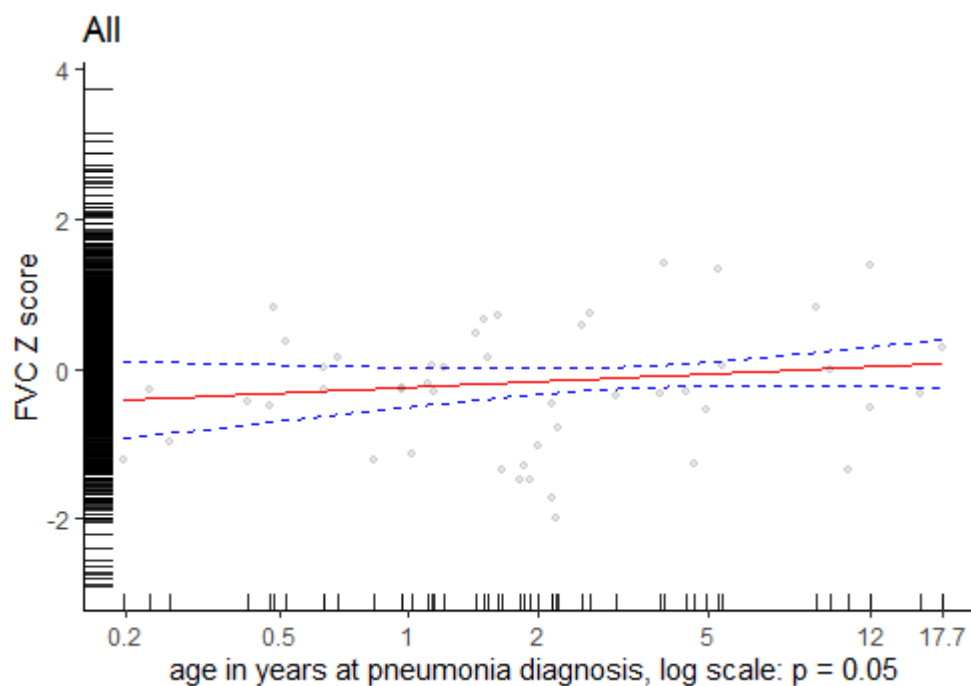
Generalised additive modelling using the mgcv¹²³ package with freeware R.¹²⁴

Figure 4. Generalised additive modelling of FEV1 Z-scores against age of first pneumonia diagnosis.



Modelled adjusted for age when lung function undertaken and household smoking.

Figure 5. Generalised additive modelling of FVC Z-scores against age of first pneumonia diagnosis.

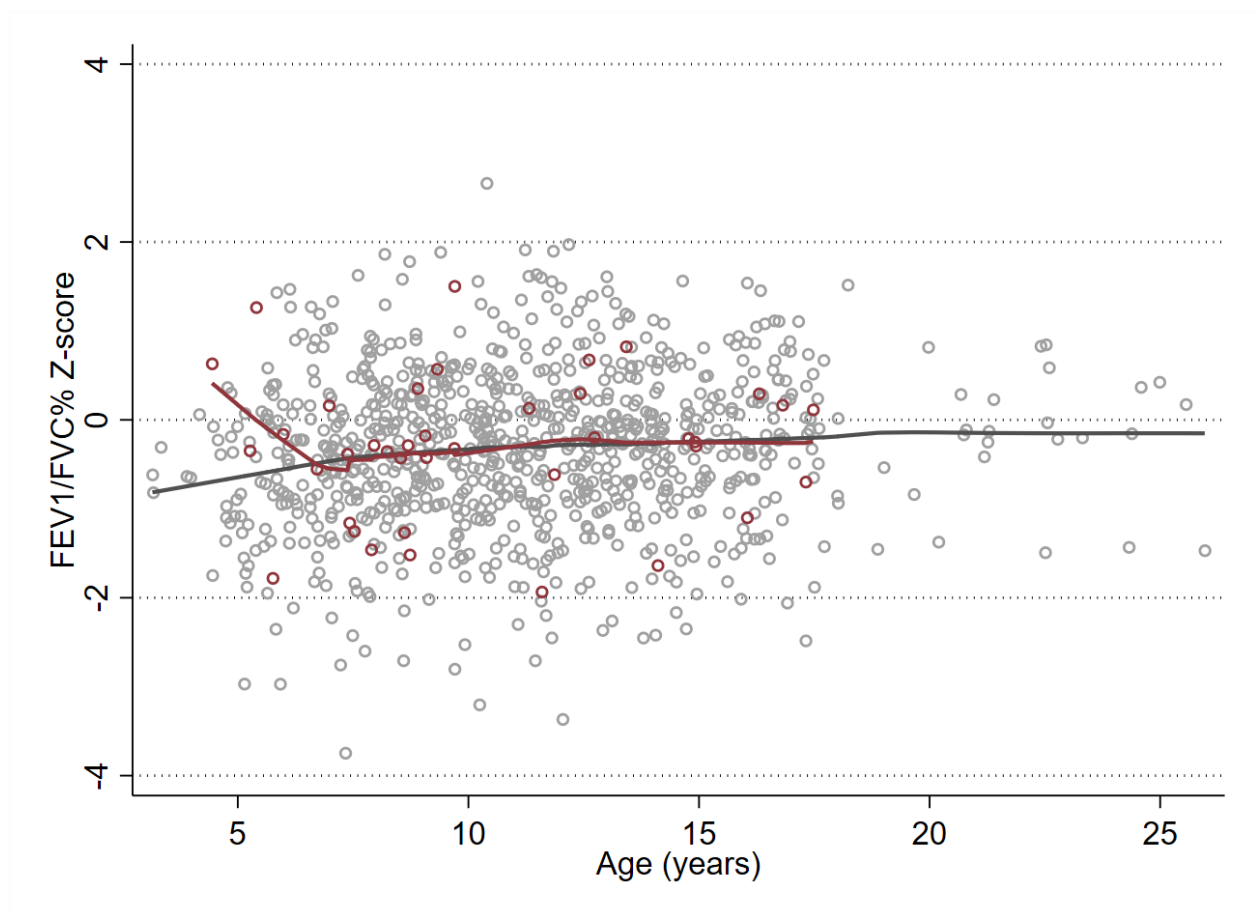


Modelled adjusted for age when lung function undertaken and household smoking.

Table 4. Univariable and multivariable regression modelling of FEV1/FVC Z-scores in 909 First Nations subjects.

		Univariable (n=909)		Multivariable (n=909)			
				Model 1		Model 2	
		β (95%CI)	p	β (95%CI)	p	β (95%CI)	p
Age when lung function undertaken (per 1 year increase)		0.02 (0.01, 0.04)	<0.01	0.02 (0.01, 0.04)	<0.01	0.02 (0.01, 0.04)	<0.01
Sex (Female) (n=465)		-0.16 (-0.27, -0.04)	<0.01	-0.17 (-0.28, -0.06)	<0.01	-0.16 (-0.28, -0.05)	<0.01
Household smoking (n=130)		-0.09 (-0.26, 0.07)	0.27				
Gestational age (weeks)	>36 (n=464)	Reference	-				
	34-36 (n=45)	-0.15 (-0.42, 0.12)	0.27				
	30-34 (n=10)	-0.31 (-0.87, 0.24)	0.27				
	<30 (n=6)	0.16 (-0.55, 0.87)	0.66				
	Unknown (n=385)	-0.03 (-0.15, 0.09)	0.58				
Eczema		-0.12 (-0.38, 0.14)	0.36				
Hayfever		-0.33 (-0.56, -0.09)	<0.01	-0.22 (-0.46, 0.01)	0.07	-0.23 (-0.47, 0.01)	0.06
Rash		-0.08 (-0.35, 0.19)	0.55				
Ever-wheeze (n=115)		-0.43 (-0.61, -0.26)	<0.01	-0.42 (-0.59, -0.24)	<0.01	-0.42 (-0.59, -0.24)	<0.01
Ever-pneumonia (n=49)		0.02 (-0.24, 0.27)	0.90	0.04 (-0.21, 0.29)	0.76		
Age (years) of first pneumonia	Never (n=464)	Reference	-			Reference	-
	0-2 (n=27)	0.08 (-0.27, 0.42)	0.66			0.13 (-0.21, 0.47)	0.45
	3-5 (n=13)	-0.09 (-0.58, 0.39)	0.71			-0.09 (-0.57, 0.38)	0.70
	>5 (n=9)	-0.00 (-0.59, 0.58)	0.99			-0.03 (-0.61, 0.54)	0.91

Figure 6. Scatter plots with lowess smoothing comparing FEV1/FVC% Z-scores of First Nations subjects whose pneumonia occurred age ≤ 5 years versus other subjects. Gray hollow circle marks participants with no history of pneumonia, or pneumonia occurring after age five years. Gray line is locally weighted smoothing of participants marked with gray hollow circles. Maroon hollow circle marks participants with a history of pneumonia occurring at or before age five years. Maroon line is locally weighted smoothing of participants marked with maroon hollow circles. Age as marked on the horizontal axis indicates the age of the participant when lung function was performed.



Chapter 4: A systematic review of the effect of early childhood respiratory infections and pneumonia on lung function throughout the lifespan

This chapter addresses the second part of Objective 1 outlined in Section 1.4, “Determine the impact of early childhood pneumonia on lung function in later childhood in ... children and adults more generally”. This chapter was accepted for publication in *The Lancet Child and Adolescent Health* on 1st February 2023. It is in-press and presented below are uncorrected proofs, and so may differ from the published version:

Collaro AJ, McElrea MS, Marchant JM, Chatfield MD, Sondergeld P, Perret JL, Vicendese D, Anuntaseree W, Dharmage SC, Chang AB. A systematic review of the effect of early childhood respiratory infections and pneumonia on lung function throughout the lifespan. *Lancet Child Adolesc Health*. 2023; In Press.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
Andrew Collaro	Drafting of manuscript, led data analysis, led study screening, input into study design

Margaret McElrea	Reviewed draft manuscript, contribution to study screening, input into study design
Julie Marchant	Reviewed draft manuscript, input into study design
Mark Chatfield	Reviewed draft manuscript, assisted with data analysis
Peter Sondergeld	Reviewed draft manuscript, led database search
Jennifer Perret	Reviewed draft manuscript, input into study design
Don Vicendese	Reviewed draft manuscript, assisted with data analysis
Wanaporn Anuntaseree	Reviewed draft manuscript, contributed revised data
Shyamali Dharmage	Reviewed draft manuscript, assisted with data analysis, led study design
Anne Chang	Reviewed draft manuscript, assisted with data analysis, led study screening, led study design

4.1 KEY MESSAGES

- Our systematic review of the effects of early childhood respiratory infections and pneumonia on future lung function included 14 articles (21,996 participants including 9969 children and 13307 adults)
- Eight of 14 included articles reported significant reductions in FEV₁, and six of 12 included studies reported reductions in FVC values in children with a history of early childhood respiratory infections or pneumonia, compared to unexposed controls.
- Most studies reported similar reduction in FEV₁ and FVC values, suggesting respiratory infection in early life may be associated with future restrictive spirometry pattern
- The negative impacts of early childhood respiratory infection on lung function were observed in both child and adult spirometry values, consistent with published data on lung function trajectory which suggests childhood lung function predicts adulthood lung function
- Despite the disproportionate higher burden of early childhood respiratory infections in populations of developing nations and disadvantaged populations of affluent nations,

only two of 14 studies reported data from these populations and is thus an identified major gap.

4.2 SEARCH STRATEGY AND SELECTION CRITERIA PANEL

References for this Systematic Review were identified through searches of PubMed, Web of Science, and Embase using the search strategy outlined in Appendix A. Searches included English articles published between database inception to May 2022 and were performed under the guidance of a health librarian. The final reference list consisted of papers (1) included in the narrative synthesis of the systematic review, (2) relevant to the subject matter but did not meet all inclusion/exclusion criteria, or (3) are useful background reading.

4.3 SUMMARY

Early childhood infections, including pneumonia, are an important global public health issue, with over 150 million cases annually resulting in approximately one million deaths. A growing number of published studies have examined the effects of early childhood respiratory infection or pneumonia on lung function, particularly as part of larger early life exposure studies, but to date, there is no published systematic review of these data. We undertook a systematic review of currently available evidence of the effects of early childhood pneumonia and lower respiratory tract infections on spirometry values in later childhood and adulthood. We discuss impacts on low lung function in the context of recent evidence relating reduced spirometry values to future all-cause mortality and cardiopulmonary morbidity. Finally, we highlight the need for further data from developing nations and disadvantaged populations, whose early childhood respiratory infection burden is disproportionately high.

4.4 INTRODUCTION

Pneumonia is the leading cause of morbidity and mortality in children aged <5 years,^{62,63} with an estimated 156 million cases⁶³ and one million deaths annually.¹¹⁷ Each year, an estimated 11-20 million children with pneumonia require hospitalisation.¹²⁵ The overwhelming majority of burden occurs in developing nations,⁶³ and among the Indigenous children of affluent countries such as First Nations Australian children, where pneumonia incidence is as high as 57·5 per 1000 infants aged 1-11 months in the Northern Territory, Australia.¹²⁶ While there is disproportionate risk of pneumonia in these populations, childhood pneumonia also remains common in high-income countries, with a high burden of hospitalisations and health-care visits.¹²⁷ Thus, the

consequences of childhood respiratory infections and pneumonias are universally important in low-middle and high-income countries.

Interest in determinants of lower lung function including early childhood pneumonia is growing in the published literature. Childhood lung function, now known to predict adulthood lung function,⁵¹⁻⁵⁶ has been shown to be significantly associated with future cardiopulmonary disease burden, and all-cause mortality risk when it is low, irrespective of whether it is outside the clinically low range.^{47,114} As there is now also evidence that catch-up lung growth and improvement in airway calibre is possible in childhood,^{55,56,59} pulmonary optimisation strategies in children are critically important.

Given the substantial worldwide burden of respiratory infections and pneumonias in early childhood, understanding its impacts on lung development and function is a priority. Particularly so, given the established importance of childhood lung function on adulthood lung function and future cardio-respiratory outcomes.^{47,114} Improved understanding of the impact of pneumonia may be useful in informing future research and investment into reducing childhood pneumonia, especially in severely affected populations. In the absence of a systematic review of the current evidence on the impact of childhood pneumonia on lung function, we undertook this systematic review. Our objective was to systematically examine the effect of pneumonia occurring ≤ 5 years of age on forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) values in children >5 years of age, and adults.

4.5 MATERIALS AND METHODS

4.5.1 Search strategy and selection criteria

The review protocol was registered in August 2021 on the International Prospective Register of Systematic Reviews [PROSPERO Registration no. CRD42021265295]. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods and checklist.¹²⁸ PubMed, Embase, and Web of Science online databases were searched from database inception to October 2021, using search strategies (Appendix A). Only papers published in English were reviewed. These searches were updated in May 2022 using the same strategies, under the guidance of a health librarian.

4.5.2 Eligibility criteria

Case control, cohort, and cross-sectional studies were included if the study documented pneumonia status during early childhood (age ≤ 5 years) and participants had spirometry testing

reported as FEV₁ and/or FVC values after age 5 years. Pneumonia is difficult to objectively define in population-based studies, especially in retrospective studies that base identification of pneumonia only on participant questionnaires and interviews. Therefore, we included all exposures under the umbrella of lower respiratory tract infections (LRTIs), including infection involving organisms with the potential of causing pneumonia including tuberculosis and measles. Infection described as serious respiratory or lung infections, with no other information, were classified as pneumonia within this review. Children without any LRTIs were considered the unexposed group. We excluded studies that focused on respiratory syncytial virus (RSV) or bronchiolitis if they did not separate these conditions from other early childhood pneumonia. We also excluded studies where no adjustment was made for concurrent illnesses that could impact spirometry values (e.g., cardiac illness, primary immunodeficiency, and neuromuscular disorders).

4.5.3 Study selection

Two authors (AJC and ABC) independently reviewed search results using Rayyan.¹²⁹ Potentially relevant articles were retrieved for full-text review. A third author (MSM) was available to adjudicate disagreements but there were no disagreements. Full-text versions of articles were reviewed by two authors (AJC and MSM) with a third author (ABC) available to adjudicate disagreements. Bibliographies of full-text articles were reviewed to identify additional studies. Where minor methodological issues prevented study inclusion in this systematic review, study authors were contacted with a request for further data.

4.5.4 Quality of evidence

The Newcastle-Ottawa Scale¹³⁰ for observational studies were used to evaluate the quality of each study. Cohort selection, comparability, and assessment of outcomes were evaluated and given a star-grade (out of four, two, and three stars, respectively) to give an overall scale of 0-9 (Figure 12). Studies scoring overall 0-3, 4-6, and 7-9 were considered low, moderate, and high quality, respectively.

4.5.5 Data extraction

We used data extraction techniques set out in the Cochrane Handbook for Systematic Reviews of Interventions.¹³¹ Where possible, adjusted regression coefficients in millilitres and 95% confidence intervals (95% CIs) were obtained. Mean differences with 95% CIs were calculated for studies that reported mean FEV₁ and/or FVC data for exposed and unexposed groups using Cochrane RevMan 5.4. (London, UK). Where studies presented data from multiple exposed subgroups, both pooled (within the single study) and non-pooled results are presented in this

systematic review. Stata 17.0 (StataCorp LLC, College Station, TX) was used for visualisation of data.

4.6 RESULTS

Findings of the searches and included papers are summarised in Figure 7. Database searches in October 2021 identified 2950 potential articles. After removal of duplicate articles (n=466) and unsuitable articles during title and abstract screening (n=2370), 115 studies were retrieved for full-text screening. Authors of 13 studies were contacted for further information and we received additional information for two studies. One study that used the same dataset⁷² as previously published work¹³² was identified and excluded. After exclusion of 102 studies, 13 were eligible for inclusion. Repeated database searches in May 2022 yielded an additional 120 articles, of which 8 studies were retrieved for full-text screening. One additional study¹³³ was assessed eligible, and we requested revised data from another. The corresponding author was unable to provide revised data and so the second study was not included. A total of 14 studies were therefore included in this systematic review (Table 5).

Figure 7. Study selection process using the PRISMA 2020¹²⁸ flow diagram.

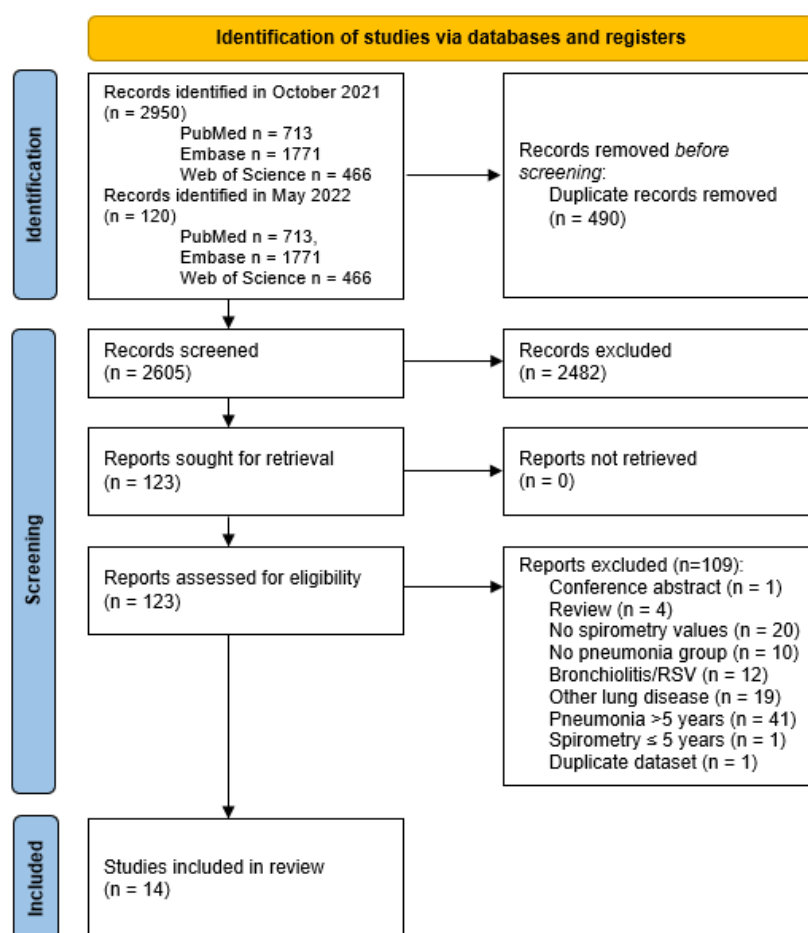


Table 5. Summary of the characteristics of the 14 included studies.

Author, Year	Dataset or location	Dataset type, year	Sample with spirometry data	Inclusion and exclusion criteria	Pneumonia age-range	Pneumonia assessment	Spirometer; criteria/protocol used
Allinson et al ¹³⁴ (2017)	National Survey of Health and Development (NSHD) [UK]	Birth cohort (1946)	n=2172 adults (FEV ₁) and n=1960 adults (FVC) aged 43 years	Inclusion: complete early-life and pack-year data	≤2 years	Interviewer-recorded questionnaire	Micro Medical Plus (Micro Medical Ltd., Rochester, Kent, UK); published methodology ¹³⁵
Anuntaseree et al ¹³⁶ (2020)	Prospective Cohort Study of Thai Children (PCTC) [Thailand]	Birth cohort (2000-2001)	n=892 children aged 8.5 years	Inclusion: subjects recruited in one of five sites Exclusion: twin-births	<1 year	Hospital admission records	KoKo Spirometer (nSpire Health, CO, USA); 2005 ATS/ERS standards ¹⁰
Barker et al ¹³⁷ (1991)	Hertfordshire, England	Birth cohort (1911-1930)	n=825 adults aged 59-70 years	Inclusion: agreed to participate in follow-up, complete data	<5 years	Researcher-recorded	Micro Medical Spirometer (Micro Medical Ltd., Rochester, Kent, UK); published methodology ^{138,139}
Collaro et al ¹³³ (2021)	Indigenous Respiratory Reference Values [Australia]	Cross-sectional study (2015-2017)	n=887 children and young adults aged 5-25 years	Inclusion: physician-confirmed pneumonia on medical records Exclusion: neonatal pneumonia, parent-reported but unverifiable pneumonia	≤5 years	Medical records	Easy on-PC (ndd, Zurich, Switzerland); 2005 ATS/ERS standards ¹⁰
Dharmage et al ¹³² (2009)	European Community Respiratory Health Survey (ECRHS) I and II	Cohort study (1991-2001)	n=9175 adults aged 20-44 years	Inclusion: participation in both ECRHS I and II	<5 years	Questionnaire (self and interviewer-recorded)	Biomedin spirometer (Biomedin srl, Padova, Italy); published methodology ¹⁴⁰
Haland et al ¹⁴¹ (2009)	Environmental and Childhood Asthma (ECA) [Norway]	Birth cohort (1992)	n=585 children aged 10 years	Inclusion: lower respiratory tract infection information from the first two years of life; agreed to participate in follow-up	≤2 years	Parent-recorded questionnaire	V _{max} 20c (SensorMedics, Yorba Linda, CA, USA); 1993 ERS standards ¹⁴²

Krantz et al ¹⁴³ (1990)	Gotenborg [Sweden]	Birth cohorts (1972, 1977, 1978, 1980)	n=63 children aged 6-13 years	Inclusion: whooping cough during first year of life ($\pm$ positive <i>B. pertussis</i> culture), or no whooping cough (controls)	≤ 1 year	Parent recall and/or medical and welfare records	Jaeger Pneumoscreen (Erich Jaeger, Friedberg, Hesse, Germany); not stated
Lopez Bernal et al ⁷¹ (2013)	Barry Caerphilly Growth Study [UK]	Birth cohort (1972-1974)	n=475 adults (FEV ₁), n=449 adults (FVC) aged 25 years	Inclusion: agreed to participate in follow-up	≤ 5 years	Interviewer-recorded questionnaire	Fleisch pneumotachograph (Vitalograph Ltd., Buckingham, UK); 1994 ATS standards ¹⁴⁴
Luzak et al ¹⁴⁵ (2017)	GINIplus and LISApus [Germany]	Birth cohorts (1995-1998, 1997-1999)	n=1326 children aged 15 years	Inclusion: complete data for investigated factors	≤ 3 years	Parent-recorded questionnaire	EasyOne Worldspirometer (nidd, Zurich, Switzerland); 2005 ATS/ERS standards ¹⁰
MacBean et al ¹⁴⁶ (2018)	King's College Hospital cohort [UK]	Cohort study (2008-?)	n=41 children aged 5-7 years	Inclusion: within travelling distance of King's College Hospital, agreed to participate in follow-up	Infancy	Nasopharyngeal aspirate following parent-report	Jaeger Masterscreen (Erich Jaeger, Friedberg, Hesse, Germany); 2005 ATS/ERS standards ¹⁰
Shaheen et al ¹⁴⁷ (1998)	St Andrew's, Scotland [UK]	Birth cohort (1921-1935)	n=239 adults (mean age 58 years)	Not stated	< 2 years	Interviewer-recorded questionnaire	Turbine spirometer, and Vitalograph spirometer (Vitalograph Ltd., Buckingham, UK); 1994 ATS standards ¹⁴⁴
Tennant et al ¹⁴⁸ (2008)	Newcastle Thousand Families Study [UK]	Birth cohort (1947)	n=392 adults aged 49-51 years	Inclusion: Remained in Newcastle upon Tyne, agreed to participate in follow-up, complete health and lifestyle data	< 5 years	Parent-recorded questionnaire	Vitalograph Compact II (Vitalograph Ltd., Buckingham, UK); not stated
Tennant et al ¹⁴⁹ (2010)	Newcastle Thousand Families Study [UK]	Birth cohort (1947)	n=252 children aged 14 years; n=122 followed-up as adults 49-51 years	Inclusion: Agreed to participate in follow-up	< 5 years	Parent-recorded questionnaire	Vitalograph Compact II (Vitalograph Ltd., Buckingham, UK); not stated

van Meel et al ⁶⁶ (2018)	Generation R Study [Netherlands]	Birth cohort (2002- 2006)	n=4672 children aged 10 years	Not stated	≤3 years	Parent-recorded questionnaire	Jaeger Masterscreen (Erich Jaeger, Friedberg, Hesse, Germany); 2005 ATS/ERS standards ¹⁰
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ATS = American Thoracic Society, ERS = European Respiratory Society, GINIplus = German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development, LISApplus = Life-style related factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics.

Table 6. Summary of results for 14 included studies.

Author, Year	Exposure(s)	Number in exposed group(s)	Statistical method	Explanatory variables	Effect
Allinson et al ¹³⁴ (2017)	LRTI ≤ 2 years (yes vs. no) [non-smokers]	Not stated	Multivariable linear regression	Biological sex, height, weight, birth weight, father's occupational class at 4-years old (manual vs. non-manual), home overcrowding at age 2-years, high pollution exposure at age 0-2 years, pack-years at age 20-43 years, smoking at age 43-64 years)	LRTI at ≤ 2 years lowers FEV ₁ and FVC values in adulthood.
Anuntaseree et al ¹³⁶ (2020)	LRTI <1-year (yes vs. no)	44/892 (5%)	Multivariable linear regression	Biological sex, weight, and height	LRTI at <1-year lowers may low FEV ₁ and FVC values in childhood (<95% confidence).
Barker et al ¹³⁷ (1991)	Bronchitis/pneumonia, whooping cough, or measles at <1 or 1-4 years (yes vs. no)	Bronchitis/pneumonia at <1-year 59/825 (7%) and 1-4 years 63/825 (8%) Whooping cough at <1-year 31/825 (4%) and 1-4 years 124/825 (15%) Measles at <1-year 20/825 (2%) and 1-4 years 134/825 (16%)	Multivariable linear regression	Age, height, sex, maternal smoking, maternal asthma, social class, and random effects for centre	Pneumonia/bronchitis or whooping cough at <1-year lowers FEV ₁ and FVC values. Pneumonia/bronchitis, whooping cough, or measles at 1-4 years may lower FEV ₁ and FVC values (<95% confidence). Measles at <1-year may increase FEV ₁ and FVC values (<95% confidence).
Collaro et al ¹³³ (2021)	Pneumonia ≤ 5 years (yes vs. no)	47/887 (5%)	Multivariable linear regression	Age, gestational age, biological sex, height, wheeze	Early childhood pneumonia may lower FEV ₁ and FVC values (<95% confidence)
Dharmage et al ¹³² (2009)	Serious respiratory infection <5 years (yes vs. no)	884/9175 (10%)	Multivariable linear regression	Age, biological sex, height, maternal smoking, maternal asthma, social class, and random effects for centre	Early childhood pneumonia lower FEV ₁ values and may lower FVC values (<95% confidence)
Haland et al ¹⁴¹ (2009)	Pneumonia ≤ 2 years (yes vs. no)	47/585 (8%)	Two-sample student T-test	N/A	Early childhood pneumonia increases FVC values, and may increase FEV ₁ values (<95% confidence)
Krantz et al ¹⁴³ (1990)	Whooping cough ≤ 2 years (yes vs. no)	31/63 (49%)	Two-sample student T-test	N/A	Whooping cough in infancy may lower FEV ₁ and FVC values (<95% confidence)

Lopez Bernal et al ⁷¹ (2013)	LRTI at <1-year, 1-2 years, 2-5 years (yes vs. no)	Not stated	Multivariable linear regression	Age, biological sex, height, biological sex#height, maternal smoking in pregnancy, age and sex adjusted birth weight, father's social class, gestational age at birth, breastfeeding, family history of asthma, BMI, smoking status, pack-years smoked, current social class, asthma.	LRTIs at <1 years lowers FEV ₁ values and may lower FVC values (<95% confidence). LRTIs at 1-2 years may increase FEV ₁ and FVC values (<95% confidence). LRTIs at 2-5 years may lower FEV ₁ and FVC values.
Luzak et al ¹⁴⁵ (2017)	Pneumonia ≤3 years (yes vs. no)	414/1326 (31%)	Multivariable linear regression	Age, biological sex, height, indoor second-hand smoke, serum vitamin D, BMI, asthma, study, and study centre	Pneumonia at ≤3 years of age lowers FEV ₁ values.
MacBean et al ¹⁴⁶ (2018)	LRTI (rhinovirus and other) <1-year (yes vs. no)	21/41 (51%)	Mann-Whitney U-Test	N/A	Rhinovirus and other viral LRTI at <1-year lowers FEV ₁ and FVC values.
Shaheen et al ¹⁴⁷ (1998)	Pneumonia, measles, whooping cough, or influenza at <2 years (yes vs. no)	133/239 (56%)	Multivariable linear regression	Age, height, smoking, asthma	Pneumonia <2 years lowers FEV ₁ and FVC values. Measles at <2 years may lower FEV ₁ and FVC values (<95% confidence). Whooping cough at <2 years may increase FEV ₁ and FVC values (<95% confidence). Influenza at <2 years may lower FEV ₁ and FVC values (<95% confidence).
Tennant et al ¹⁴⁸ (2008)	LRTIs at 6 months, 1-year, 2 years, 3 years, and 4 years (yes vs. no)	Not stated	Multivariable linear regression	Biological sex, height, height ² (difference from mean), birth weight, breast fed for <4 weeks, smoking status, body fat percentage, asthma	LRTIs at 6 months may lower FEV ₁ values and may lower FVC values (<95% confidence). LRTIs at 1-year lowers FEV ₁ and FVC values. LRTIs at 2 years may lower FEV ₁ and increase FVC values (<95% confidence). LRTIs at 3 years lowers FEV ₁ and may lower FVC values (<95% confidence).

					LRTIs at 4 years may lower FEV ₁ and FVC values (<95% confidence).
Tennant et al ¹⁴⁹ (2010)	Tuberculosis between ages 0 and 5 (yes vs. no)	18/252 (7%)	Multivariable linear regression	Biological sex, case-control status, social class at birth, duration of breast feeding, BMI at age 14-years, height at age 14-years, asthma	Early childhood pneumonia lowers FEV ₁ values.
van Meel et al ⁶⁶ (2018)	Lower respiratory tract infections up to age 3 years	3828/4672 (82%)	Multivariable linear regression	Gestational age, biological sex, BMI, birth weight corrected for gestational age, mode of delivery, breastfeeding, day care attendance, maternal education, smoking during pregnancy, psychiatric symptoms during pregnancy, pet keeping, asthma or atopy	LRTIs at 6 months may lower FEV ₁ and FVC values (<95% confidence). LRTIs at 1-year lowers FEV ₁ values and may lower FVC values (<95% confidence). LRTIs at 2 years lowers FEV ₁ values and may lower FVC values (<95% confidence) LRTIs at 3 years lowers FEV ₁ values and may lower FVC values (<95% confidence) No associations with LRTIs at 1-4 years.

ATS = American Thoracic Society, ERS = European Respiratory Society.

4.6.1 Study characteristics

The 14 included studies were published between 1990-2021. Their sample sizes ranged from 41¹⁴⁶ to 9175¹³² (Table 5) providing a total of 21,996 participants, including 9969 children and 13307 adults. Thirteen of 14 studies were cohort studies, including 11 birth cohorts, and the remaining study was cross-sectional.¹³³ Included studies utilised datasets from the United Kingdom,^{71,134,137,146-149} Europe,^{66,132,141,143,145} North America,¹³² India,¹³² Thailand,¹³⁶ Australia,^{132,133} and New Zealand (Figure 8).¹³² Two studies reported data primarily from either a disadvantaged population¹³³ or a developing nation.¹³⁶ Eight studies reported childhood spirometry data, which were generally more contemporary than the six studies that reported adulthood spirometry data. Spirometry data were reported as raw values (11/14), Z-scores (2/14),^{66,146} or percentages of predicted values (1/14).¹⁴¹ In five studies, spirometry data of respiratory infection or pneumonia-exposed participants were stratified by disease profile/causative agent,^{137,146,147} or age of exposure,^{66,71} or a combination of both.¹³⁷ FEV₁ and FVC data for these stratified groups (subgroups with a history of early childhood respiratory infection or pneumonia) are henceforth reported as subgroups within this systematic review.

Questionnaire data, either self or interviewer-recorded (9/14), were the most frequently used method for collecting history of early childhood pneumonia, followed by medical record assessment (3/14),^{133,136,143} nasopharyngeal aspirate samples (1/14),¹⁴⁶ and researcher/clinician assessment (1/14).¹⁴⁶

Figure 8. Map of countries from which data is sourced for this systematic review.

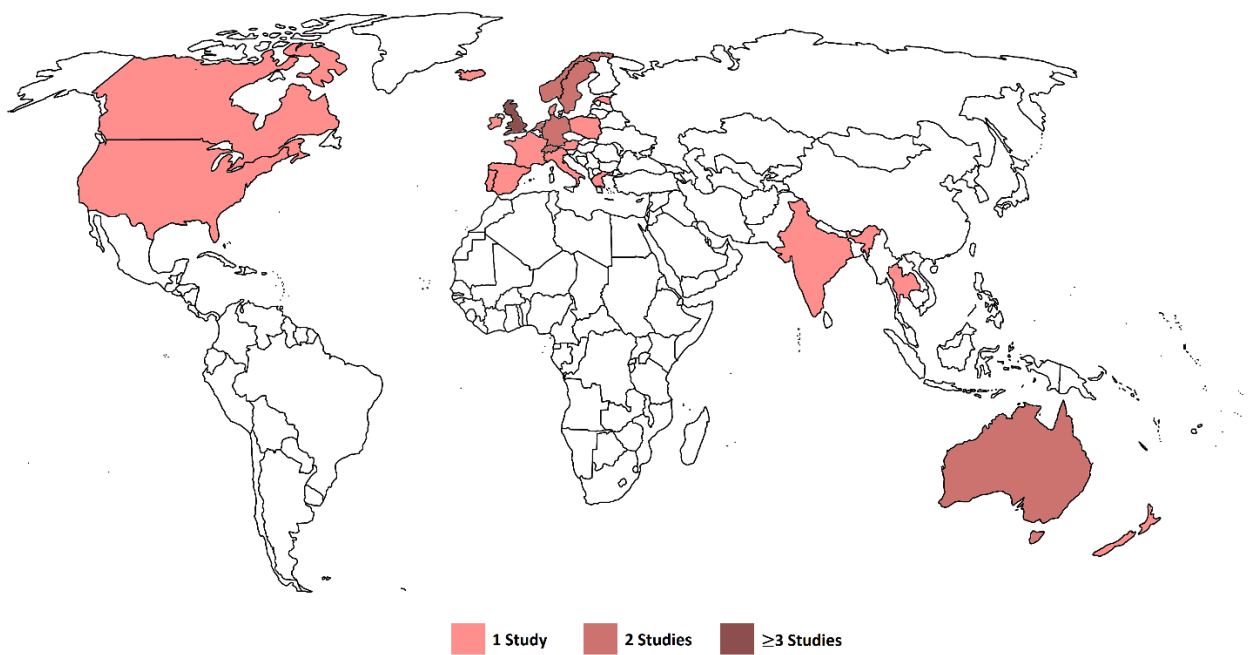
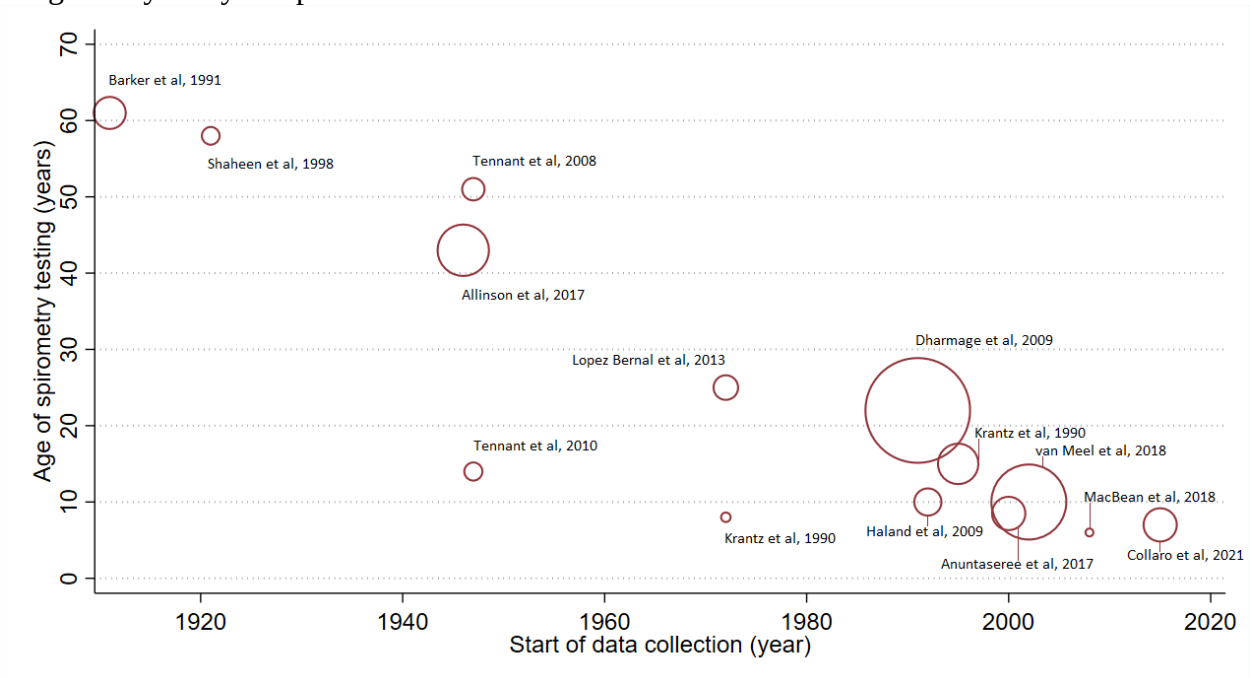


Figure 9. Age at which spirometry testing occurred against year that data collection commenced, weighted by study sample size.



Spirometer devices and standards used for spirometry testing varied due to the large temporal gap between the earliest and most recent studies. The 1993 European Respiratory Society (ERS)¹⁴² standard, the 1994 American Thoracic Society (ATS)¹⁴⁴ standard, and the joint 2005 ATS/ERS¹⁰ standard and 2019 update⁸ were utilised by most of the included studies. Three of the included

studies^{132,134,137} used other methodology. For two of the three studies, the published methodology includes routine spirometer maintenance with daily calibration, and performance of the test with a nose clip using a forced manoeuvre lasting at least 6 seconds following a maximal inhalation, with the best FEV₁ and FVC of at least three tests reported.^{132,134} The remaining study¹³⁷ referenced the methodology used in two separate original studies^{138,139} where the best FEV₁ and FVC of three tests were reported.

Quality of evidence graded using the Newcastle-Ottawa Scale is summarised in Table 7. Ten studies were considered high quality evidence, while 4 were considered moderate quality.

The follow-up periods varied greatly between studies. The variation in age at which spirometry testing occurred, plotted against the first year of data collection for each study and weighted by total sample size, is depicted in Figure 9. There was marked heterogeneity in the spirometer devices and standards used for spirometry testing (Table 5).

). This variation is likely related to large temporal gaps between the studies when data collection occurred. The 1993 European Respiratory Society (ERS)¹⁴² standard, the 1994 American Thoracic Society (ATS)¹⁴⁴ standard, and the joint 2005 ATS/ERS¹⁰ standard and 2019 update⁸ were used by most of the included studies. Three of the included studies^{132,134,137} used other methodology. For two of these three studies, the published methodology includes routine spirometer maintenance with daily calibration, and performance of the test with a nose clip using a forced manoeuvre lasting at least 6 seconds following a maximal inhalation, with the best FEV₁ and FVC of at least three tests reported.^{132,134} The remaining study¹³⁷ referenced the methodology used in two separate original studies^{138,139} where the best FEV₁ and FVC of three tests were reported. When we formally evaluated the quality of evidence presented in each study, ten studies were considered high quality evidence, and four considered moderate quality (Table 7).

4.6.2 Overall impact of early childhood respiratory infections on FEV₁ values

Comparison of spirometry values between groups with and without early childhood respiratory infections or pneumonia for each study are summarised in Table 6.

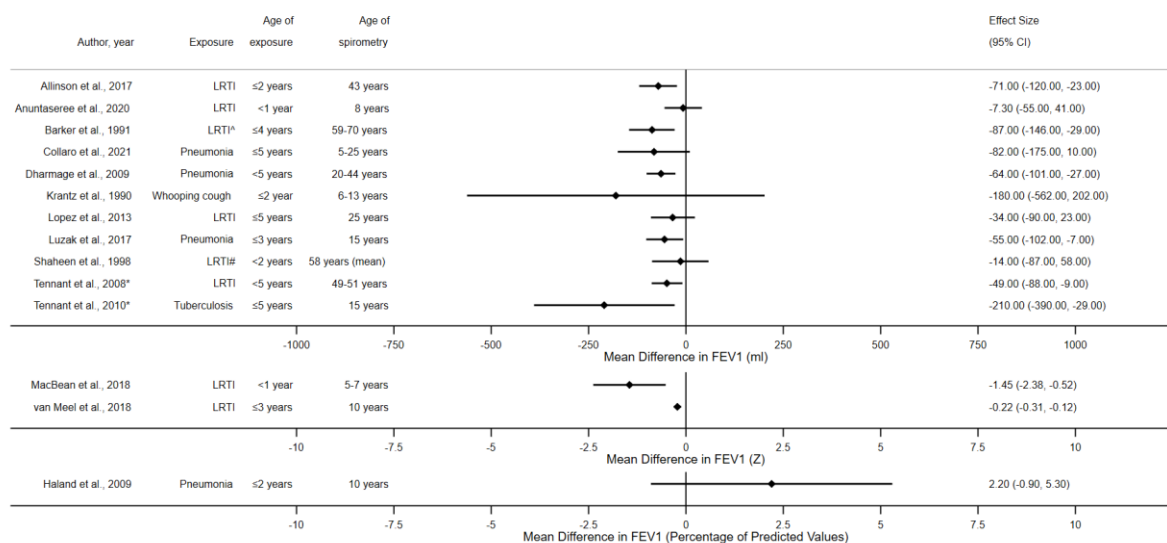
Of the 14 included studies, eight reported that the FEV₁ values for the exposed group were significantly lower than unexposed controls (Figure 10), ranging between -49 (95%CI -88, -9)¹⁴⁸ to -210 (95%CI -390, -129) millilitres for studies that reported raw values, and -0.22 (95%CI -0.31, -0.12)⁶⁶ to -1.45 (95%CI -2.38, -0.52) Z-scores.¹⁴⁶ Five studies reported non-significant reductions in FEV₁ values ranging from -180 (95%CI -562, 202) to -7 (95%CI -55, 41) millilitres, and one reported FEV₁ values that trended in the opposite direction.¹⁴¹ The one study reporting

divergent data was from a birth cohort, and was one of four to be graded as moderate quality evidence due to <80% rate of follow-up, and univariable rather than multivariable modelling to produce adjusted estimates that account for factors that may otherwise influence spirometry results.

Data from studies that reported subgroup FEV₁ values are summarised in Figure 13. Of the 14 included studies, nine studies that presented FEV₁ data for multiple exposed groups reported significantly lower FEV₁ values for at least one exposed subgroup. Mean differences ranged between -49ml (95%CI -88, -9)¹⁴⁸ to -390ml (95%CI -670, -110)¹⁴⁹, and from -0.29 (95%CI -0.55, -0.03)⁶⁶ to -1.8 (95%CI -3.4, -0.2) Z-scores.¹⁴⁶ Seven studies reported non-significant reductions in FEV₁ values for at least one exposed subgroup. Four studies reported FEV₁ differences that trended in the opposite direction¹⁴¹, ranging from 36ml (95%CI -50, 122)⁷¹ to 170ml (95%CI -90, 420),¹³⁷ and 2.2% predicted (95%CI -0.90, 5.3) for the only study to report percentage of predicted values.¹⁴¹ Delving into possible reasons for the 4 studies reporting divergent data, we found no commonality ARI exposure type as these studies included pneumonia,¹⁴¹ measles,¹³⁷ LRTIs,⁷¹ bronchitis,¹⁴⁷ and whooping cough.¹⁴⁷ However, a common element of these studies was relatively small sample sizes of either the exposed groups (or subgroups) for which improvements to FEV₁ values were reported (n=20¹³⁷ and n=47)¹⁴¹ or the overall study sample size where the sizes of individual subgroups were not reported (n=475 spread across 3 sets of exposed and unexposed groups,⁷¹ and n=239 spread across 8 sets of exposed and unexposed groups).¹⁴⁷ Thus, over-stratification of small numbers of participants may have contributed to the divergent trend. Another possible factor of the divergent data from these studies is that three of four studies were from birth cohorts ranging from 1911-30,¹³⁷ 1921-35,¹⁴⁷ and 1972-74,⁷¹ with two studies relying on participant recall of early life exposures, which may have been affected by recall bias.^{71,147} However, recall bias is a limitation of two other studies that did not have the divergent data.^{132,134}

Overall, data supporting significant reductions in FEV₁ values following early childhood respiratory infection or pneumonia is stronger for adult-based studies compared to paediatric-based studies. All studies reporting adult FEV₁ data (n=6) described significant reductions in at least one exposed subgroup compared to unexposed controls,^{71,132,134,137,147,148} with four of six studies reporting significant reductions when subgroup data were pooled.^{132,134,137,148} In comparison, paediatric data were more heterogenous. Four of eight studies reported significant reductions in FEV₁ values,^{66,145,146,149} three reported non-significant reduction in FEV₁,^{133,136,143} and one reported non-significant increased FEV₁.¹⁴¹

Figure 10. Effect of early childhood pneumonia and other lower respiratory tract infections on FEV₁ in later childhood and adulthood.



*Overlapping cohorts. LRTI = lower respiratory tract infection. ^ΔLRTI including confirmed pneumonia, bronchitis, whooping cough, measles, and influenza. [#]LRTI including pneumonia, measles, whooping cough, and influenza.

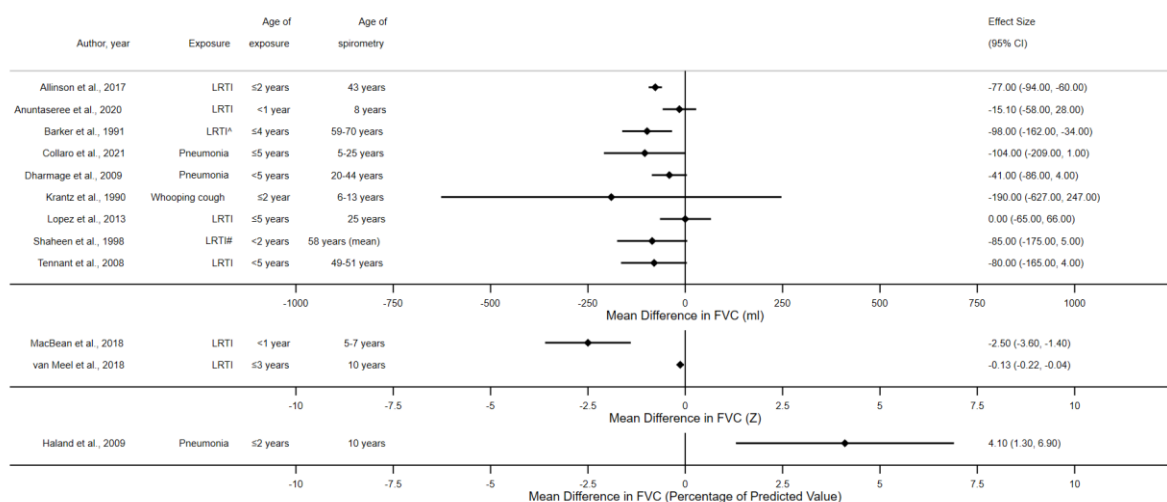
4.6.3 Overall impact of early childhood respiratory infections on FVC values

Twelve of 14 studies reported FVC values following early childhood respiratory infections or pneumonia (Figure 11). Four studies reported significant reductions in FVC ranging between -98 (95%CI -162, -34)¹³⁷ and -77 (95%CI -94, -60)¹³⁴ millilitres, and -2.5 (95%CI -3.6, -1.4)¹⁴⁶ to -0.13 (95%CI -0.22, -0.04)⁶⁶ Z-scores. A further six studies reported non-significant reductions in FVC, ranging from -190 (95%CI -627, 247)¹⁴³ and -15 (95%CI 58, 28)¹³⁶ millilitres. Four of these studies reported confidence intervals that bordered on statistical significance, and which had upper bounds ranging from 1-5 millilitres.^{132,133,147,148} One study reported no change in FVC,⁷¹ while another reported significant increases in the FVC values of children with a history of pneumonia occurring ≤2 years.¹⁴¹

Data from studies that reported subgroup FVC values are summarised in Figure 14. Six of 14 studies reported that FVC values were significantly lower among at least one exposed group (or for at least one exposed subgroup in studies reporting FVC data for multiple exposed subgroups) compared to unexposed controls. The effect sizes ranged from -77 (95%CI -94, -60)¹³⁴ to -600 (-920, -280) millilitres,¹⁴⁷ and -0.32 (95%CI -0.52, -0.11)⁶⁶ to -3.2 (95%CI -4.8, -1.6)¹⁴⁶ Z-scores. Reasons for this wide variation, such as differences in the severity of infections across studies, could not be evaluated due to the lack of data in these studies. Nine studies reported non-significant reductions in FVC values for at least one exposed group, and five studies reported non-significant increases in FVC values for at least one exposed group, with effect sizes ranging

between -15.1 (95%CI -58, 28)¹³⁶ and -190 (95%CI -627, 247) millilitres,¹⁴³ and -0.13 (95%CI -0.32, 0.06) to -0.17 (95%CI -0.42, 0.08) Z-scores.⁶⁶ The sole study that reported FVC was undertaken in children aged 10 years with a history of early childhood pneumonia at ≤ 2 years (FVC percentage of predicted difference between groups of 4.10 [95%CI 1.30, 6.90] %).¹⁴¹ This was the only study to report a significant improvement in either FEV₁ or FVC values, and the only study to report any improvement (including non-significant improvements). This study had attrition bias (from a high rate of loss to follow-up) although similar high attrition rates were observed in most of the studies included in this manuscript (Table 7).

Figure 11. Effect of early childhood pneumonia and other lower respiratory tract infections on FVC in later childhood and adulthood.



LRTI = lower respiratory tract infection. [^]LRTI including confirmed pneumonia, bronchitis, whooping cough, measles, and influenza. [#]LRTI including pneumonia, measles, whooping cough, and influenza.

Studies that reported significant and non-significant improvements to FVC values described these trends in both paediatric^{66,141} and adult^{71,137,147} data across the exposures as for FEV₁ values. Unlike for FEV₁, FVC data for adults were more heterogeneous with greater divergence in the exposed groups. Only three of six studies reported significant reductions in FVC.^{132,134,148} Also unlike FEV₁, these trends were reported in a large study (n=3828 included in regression modelling)⁶⁶ in addition to smaller studies in which FVC values for multiple exposure groups were reported.^{71,137,141,147} Small sample sizes within these multiple exposed groups contributed to imprecision within the estimated differences to unexposed controls. The effect size reported in the smallest of studies to report possible increases to FVC values (0.05 [95%CI -0.12, 0.22] z scores).¹⁴⁶ This study,¹⁴⁶ unlike several others,^{71,137,147} used contemporary early childhood

exposure data (2002-06) of children aged 10 years, and so recall bias is less likely to contribute to spurious associations.

The impact of the lower respiratory infection profiles on lung function is described below and illustrated in Figure 13 and Figure 14.

4.6.4 Pneumonia

Five included studies explicitly classified exposures in at least one subgroup as pneumonia,^{133,137,147} serious respiratory¹³² or lung infection¹⁴⁵ assessed by the researcher,¹³⁷ medical records,¹³³ or participant recall.^{132,147} One study presented combined pneumonia and bronchitis results.¹³⁷ Four of five studies reported significant reductions in FEV₁ values following early childhood pneumonia^{132,137,145,147} (compared to those without childhood pneumonia) while the fourth reported a non-significant reduction.¹³³ Two of five studies found significant reductions in FVC values,^{137,147} while two reported non-significant reductions,^{132,133} and one a significant increase in FVC values of the pneumonia group compared to the control group. One study reported significant reductions in both FEV₁ and FVC values when exposure occurred during infancy, and non-significant results in children whose exposure occurred between ages 1-4 years.¹³⁷ Three of these five studies reported adulthood spirometry values,^{132,137,147} and two reported primarily paediatric data,^{133,145} one of which was also the only study to report non-significant changes to FEV₁ values, and one of two studies to report non-significant reductions to FVC values.¹³³

4.6.5 Whooping cough

Three included studies classified exposures in at least one group as whooping cough as assessed by a researcher,¹³⁷ parental recall or positive *Bordetella pertussis* culture,¹⁴³ or parental recall alone.¹⁴⁷ Two of three studies reported whooping cough in early childhood significantly reduced FEV₁ and FVC values,^{137,143} while the third reported non-significant increases in FEV₁ and FVC¹⁴⁷ compared to those who did not have whooping cough. Two of three studies reported spirometry data of adults.^{137,147} Significant reductions, and non-significant increases in FEV₁ and FVC values were reported in adults,^{137,147} while non-significant decreases were reported in children.¹⁴³

4.6.6 Unclassified lower respiratory tract infection

Six studies reported FEV₁ values, and five studies FVC values, of at least one exposed group classified as having an otherwise undefined LRTI in early childhood using participant^{71,134} or parental recall,⁶⁶ nasopharyngeal aspirate sample following parental report,^{71,146,148} or hospital admission records.¹³⁶ Three of six studies found significant reductions in the FEV₁ values in either

children¹⁴⁶ or adults.^{134,148} Two of five studies reported significant reductions in FVC values.^{134,146} One study reported non-significant reductions to both FEV₁ and FVC values in children,¹³⁶ while two other studies reported mixed results ranging from significant reductions to non-significant improvements in FEV₁ and FVC values for children⁶⁶ or adults⁷¹ depending on the age of exposure.

4.6.7 Other respiratory infections

Several included studies reported on other explicitly defined respiratory infections assessed by researcher (measles),¹³⁷ participant recall (measles,¹⁴⁷ influenza,¹⁴⁷ rhinovirus),¹⁴⁶ and nasopharyngeal aspirate sample (tuberculosis).¹⁴⁹ Significant reductions in FEV₁ and FVC values were reported in rhinovirus and tuberculosis groups, with non-significant reductions reported for other respiratory infections.

4.7 DISCUSSION

This is the first systematic review to synthesise the evidence on the effects of early childhood pneumonia and other lower respiratory infection on later lung function. The identified 14 studies report the impact on spirometry values through the spectrum of childhood and adulthood with sample sizes ranging between 41-9175. The total number of participants in the 14 studies were 21996, including 9969 children and 13307 adults. Eight of 14 included studies reported significant FEV₁ or FVC deficits in exposed groups compared to unexposed groups. Larger effect sizes reported by several studies,^{137,143,147} ranging from between -390 (95%CI -670, -110)¹⁴⁷ to -170 (95%CI -320, -20)¹³⁷ ml for FEV₁, and -600 (95%CI -920, -280)¹⁴⁷ to -240 (95%CI -400, -70)¹³⁷ ml for FVC. These effect sizes are clinically substantial in the context of the definition of a significant bronchodilator response (≥ 200 ml in FEV₁ and/or FVC values).⁷ Other studies showed smaller effect sizes of <100 ml or <0.2 Z-scores. Due to differences in the study methods used to determine early childhood exposure, potential confounding by further infection during or after early childhood, and the large time-lag between exposure and study participation in adult-based studies, we did not pool spirometry measurements for meta-analysis.

Deficits in spirometry values related to early childhood respiratory infection observed in most studies included in this review are biologically plausible. Continued airway growth and rapid proliferation of alveoli occur in the first three-to-four years of life, and infection during this critical period of lung development may impair overall lung growth.⁶⁴ Clinically, there has been a debate as to whether reduced lung function is the result of early childhood respiratory infections or pneumonias, or if infants with low lung function are simply pre-disposed to early childhood respiratory infections. While there is some evidence for the latter,¹⁵⁰ the only prospective study

with lung function measurements collected before and after early childhood respiratory infection onset found that the lung function of South African children at six weeks of age (as measured using multiple breath washout) was not associated with increased LRTI incidence within the first year of life, but LRTIs were associated with lower lung function measured at 12 months.^{67,151} These findings suggest that, while ‘small lungs’ may predispose infants and young children to respiratory infections, such infection may further worsen subsequent lung function. Biological plausibility is further supported by animal work that showed the effect of infection and inflammation on the developing lung.¹⁵²

Most studies that investigated FEV₁ and FVC values reported similar effect sizes for both outcomes, suggesting that early childhood respiratory infection may be associated with a future restrictive lung function pattern. Static lung volume measurement would be required to determine if reduced FVC is related to a true restrictive deficit or was secondary to gas trapping and airway closure related to airway obstruction.⁷ A recent prospective study of longitudinal spirometry patterns from ages 7-53 evaluated against static lung volume and gas diffusing capacity data has shown that childhood pneumonia is associated with both a lifetime restrictive only pattern, and also with low FVC secondary to gas trapping and airway closure as in obstructive phenotypes.¹⁵³ Furthermore, reduction in total lung capacity (true restriction) has been observed in adults following early childhood pneumonia/pleurisy.⁶⁵ Based on adult spirometry data included in this review, reductions in spirometry values as a consequence of early childhood respiratory infection appear to persist into adulthood. Continuation of lung function deficits from childhood into adulthood are consistent with now well-established lung function trajectories of both FEV₁ and FVC and studies showing reduced childhood lung function predicts reduced adulthood lung function.⁵¹⁻⁵⁶ The magnitude of the deficits in this review are generally small, but are more impactful in children relative to the smaller size of lungs and airways. Currently, there is no evidence to identify minimally clinically important differences (MCIDs) in childhood lung function. The significance of the lung function deficits we report may be less important at an individual level,¹⁵⁴ but may be important at a population level due to known associations between reduced lung function and cardiopulmonary morbidity and all-cause mortality risk.^{47,51-55} These latter associations have been demonstrated in adults whose spirometry values are reduced below the population mean, but still within the clinically normal range (i.e. small reductions in spirometry values).^{47,114} In the context of the impact on lifetime lung function trajectories, appropriate treatment and ongoing management of early childhood respiratory infection is important, as an

additional trajectory describing the reversal of losses to childhood lung function leading to normalised values during the lung growth phase has now also been demonstrated.^{54,55}

The only study to include data from a developing nation, Thailand, reported small, non-significant changes in FEV₁ and FVC values.¹³⁶ Data from this study¹³⁶ were collected from a birth cohort enrolled in 2000/01, prior to the introduction of universal health coverage and vastly increased national expenditure on primary care and medicine accessibility.¹⁵⁵ We speculate that known contributors to poorer lung function such as adverse socioeconomic circumstances, malnutrition and stunting, and other early life insults such as exposure to passive smoking and high air pollution levels¹⁵⁶ may have contributed substantially to lower lung function values in Thai children during this period, and so the contribution of early childhood pneumonia may be difficult to discern. This is, however, contradicted by data from regional and remote First Nations Australian populations, who are disadvantaged¹⁵⁷ and for whom prevalence of early childhood pneumonia is comparable to rates reported in the developing world.¹²⁶ First Nations Australians have measurable reductions in lung function following early childhood pneumonia, as reported by the only study to include participants from a disadvantaged population of an affluent country.⁴⁷

Our systematic review is novel as it is the first on the subject matter, however, there are several limitations. Firstly, the global burden of early childhood respiratory infection and pneumonia occurs primarily in developing nations and disadvantaged Indigenous populations of affluent countries^{125,126} but we could only find two studies with data from a developing nation¹³⁶ or an Indigenous population.¹³³ Significant disagreement between these two studies makes the effect of early childhood pneumonia on lung function within disadvantaged populations difficult to determine. Given the overwhelming worldwide prevalence of early childhood respiratory infections and pneumonias, additional data from developing nations are needed to fully characterise the impact on lung function within these populations. Lung function optimisation and prevention of further insults to the lungs in affected children is important to reverse observed losses to lung function and to normalise values into adulthood.^{54,55}

Secondly, despite repeated attempts to contact authors of 19 studies prior to data extraction, we received information for only two studies. We were unable to include a recently published individual participant-data meta-analysis¹⁵¹ of early-life respiratory infections in 150,000 European children. The authors found a significant association between LRTIs and reduced FEV₁ and FVC¹⁵¹ but were unable to provide data after adjustment for asthma as per our protocol due to resource constraints. Thirdly, 10 of 14 included studies relied on parent- or self-reported medical histories and so reporting bias is a limitation for each, particularly for those studies of adults that

self-reported early childhood pneumonia. Further, lung function data and trajectories are complex with genetic, epigenetic, and socioeconomic determinants that cannot be examined in our systemic review.¹⁵⁸ However, as the exposed and unexposed groups were drawn from the same population, these confounding effects may be reduced. Finally, pneumonia lacks a formalised definition for epidemiological research and can be difficult to elucidate using techniques used by nearly all studies we reviewed (participant or parent questionnaires/interviews). Therefore, we elected to include all LRTIs, and undefined respiratory infection involving organisms known to cause pneumonia. We expect the inclusion of these additional data to attenuate the impact on lung function values we report in this systematic review. Our systematic review a-priori excluded studies that focused on bronchiolitis and asthma and thus our data cannot be extrapolated to wheeze and asthma target groups.

In conclusion, we observed reductions in both FEV₁ and FVC values in childhood and adult following early childhood respiratory infection, including pneumonia, that were statistically significant in the majority of included studies, and non-significant in a minority of studies. Despite the apparent impacts to lung function, the effect sizes among studies varied. However, there is substantial evidence to suggest that even small losses in lung function are associated with future cardiopulmonary morbidity, and all-cause mortality.^{47,114} Reductions in spirometry values due to early childhood pneumonia may be important in changing population risk rather than individual risk. Additional data are needed from developing countries and disadvantaged populations to determine the impacts on lung function in these populations.

4.8 SUPPLEMENTARY MATERIALS

Figure 12. Newcastle-Ottawa Scale quality assessment scale.

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average child in the community *
 - b) somewhat representative of the average child in the community *
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of the non exposed cohort
 - a) drawn from the same community as the exposed cohort *
 - b) drawn from a different source
 - c) no description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) secure record (eg surgical records) *
 - b) structured interview *
 - c) written self report
 - d) no description
- 4) Demonstration that outcome of interest was not present at start of study
 - a) yes ☐
 - b) no

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
 - a) study controls for prematurity or birthweight *
 - b) study controls for any additional factor *

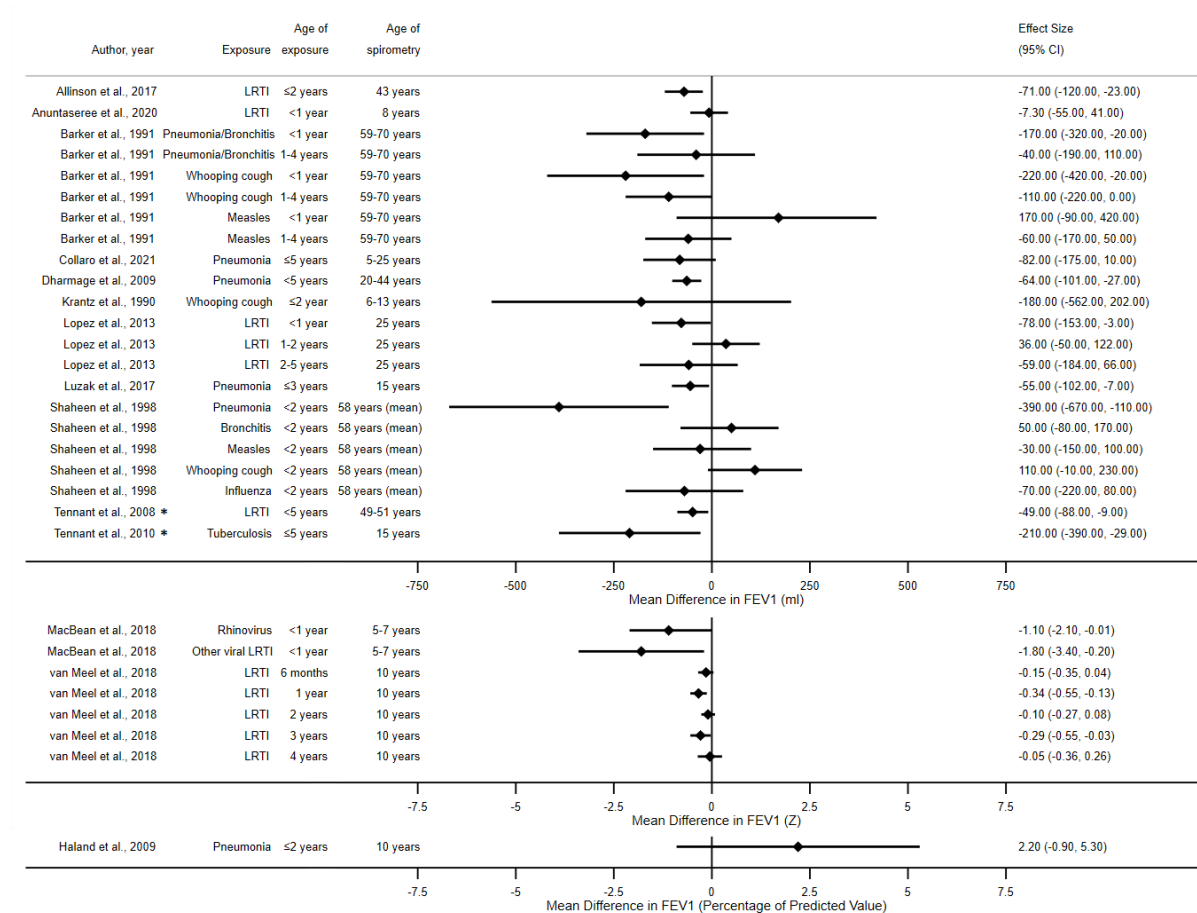
Outcome

- 1) Assessment of outcome
 - a) independent or blind assessment *
 - b) record linkage *
 - c) self report
 - d) no description
- 2) Was follow-up long enough for outcomes to occur
 - a) yes *
 - b) no
- 3) Adequacy of follow up of cohorts
 - a) complete follow up - all subjects accounted for *
 - b) subjects lost to follow up unlikely to introduce bias - >80% follow up *
 - c) follow up rate < 80% and no description of those lost
 - d) no statement

Table 7. Quality of evidence appraisals for the 14 included articles using the Newcastle-Ottawa Scale.¹³⁰

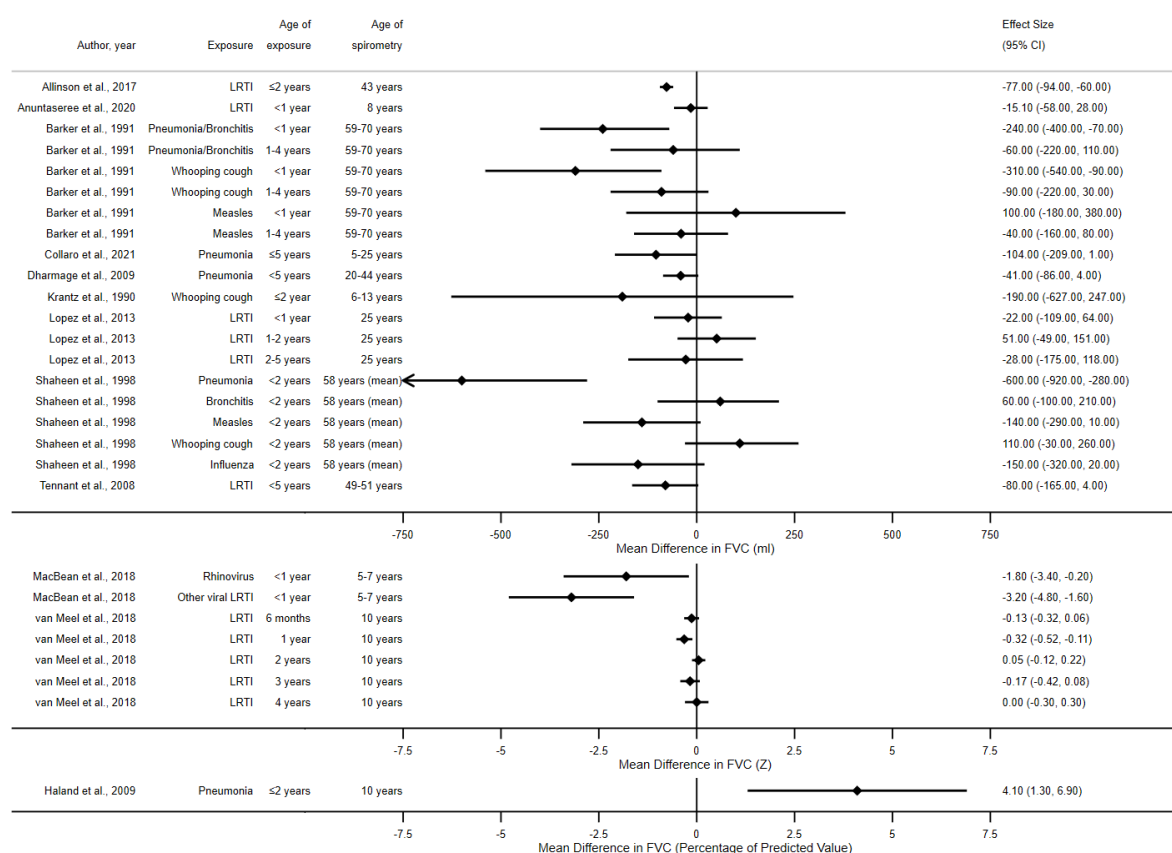
Author, Year	Selection	Comparability	Outcome	Overall	Quality
Allinson et al ¹³⁴ (2017)	3/4	2/2	3/3	8/9	High
Anuntaseree et al ¹³⁶ (2020)	4/4	1/2	2/3	7/9	High
Barker et al ¹³⁷ (1991)	4/4	2/2	2/3	8/9	High
Collaro et al ¹³³ (2021)	3/4	2/2	2/3	7/9	High
Dharmage et al ¹³² (2009)	3/4	1/2	3/3	7/9	High
Haland et al ¹⁴¹ (2009)	3/4	1/2	2/3	6/9	Moderate
Krantz et al ¹⁴³ (1990)	2/4	1/2	2/3	5/9	Moderate
Lopez Bernal et al ⁷¹ (2013)	4/4	1/2	2/3	7/9	High
Luzak et al ¹⁴⁵ (2017)	3/4	1/2	2/3	6/9	Moderate
MacBean et al ¹⁴⁶ (2018)	3/4	0/2	2/3	5/9	Moderate
Shaheen et al ¹⁴⁷ (1998)	4/4	1/2	2/3	7/9	High
Tennant et al ¹⁴⁸ (2008)	3/4	2/2	2/3	7/9	High
Tennant et al ¹⁴⁹ (2010)	4/4	1/2	2/3	7/9	High
van Meel et al ⁶⁶ (2018)	3/4	2/2	2/3	7/9	High

Figure 13. Effect of early childhood pneumonia and other lower respiratory tract infections on FEV1 in later childhood and adulthood.



*Overlapping cohorts. LRTI = lower respiratory tract infection.

Figure 14. Effect of early childhood pneumonia and other lower respiratory tract infections on FVC in later childhood and adulthood.



LRTI = lower respiratory tract infection.

Chapter 5: Culturally appropriate outreach specialist respiratory medical care improves the lung function of children in regional and remote Queensland

This chapter addresses the first part of Objective 2 outlined in Section 1.4; “Evaluate changes in spirometry values of paediatric patients treated through IROC....”. The following publication within a peer-reviewed journal was produced:

Collaro AJ, Chang AB, Marchant JM, Masters IB, Rodwell LT, Takken AJ, McElrea MS. Culturally Appropriate Outreach Specialist Respiratory Medical Care Improves the Lung Function of Children in Regional and Remote Queensland. *Lung*. 2020;198(2):361-9.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
Andrew Collaro	Drafting of manuscript, led data analysis, input into study design
Anne Chang	Reviewed draft manuscript, data collection, led study design
Julie Marchant	Reviewed draft manuscript, input into study design

Brent Masters	Reviewed draft manuscript, data collection, input into study design
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5.1 ABSTRACT

5.1.1 Background and Objectives

Indigenous Respiratory Outreach Care (IROC) is a culturally appropriate specialist respiratory service established to deliver multidisciplinary respiratory care to regional and remote Queensland communities. Our objective was to evaluate the impact of an outreach specialist respiratory service on the spirometry of children attending IROC clinics, particularly Indigenous children with asthma and bronchiectasis.

5.1.2 Methods

Retrospective single-arm cohort study of 189 children who performed spirometry at twelve sites across regional and remote Queensland between October 2010 and December 2017. Each child's baseline spirometry was compared to their best spirometry at follow-up visit occurring within (1) 12 months of their most recent visit with at least 12 months of specialist care and; (2) each year of their first 3 years of care.

5.1.3 Results

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) Z-scores improved significantly across the whole group from baseline to follow-up (change in Z-scores (Δz) of $FEV_1=0.38$, 95%CI 0.22, 0.53; $\Delta zFVC=0.36$, 95%CI 0.21, 0.51). In subgroup analyses, lung function also significantly improved in the Indigenous children ($n=141$, $\Delta zFEV_1=0.37$, 95%CI 0.17, 0.57; $\Delta zFVC=0.36$, 95%CI 0.17, 0.55) as well as those with asthma ($n=117$, $\Delta zFEV_1=0.41$, 95%CI 0.19, 0.64; $\Delta zFVC=0.46$, 95%CI 0.24, 0.68) and bronchiectasis ($n=38$, $\Delta zFEV_1=0.33$, 95%CI 0.07, 0.59; $\Delta zFVC=0.26$, 95%CI -0.03, 0.53). Significant improvements in FEV_1 and FVC were observed within the first and second years of follow-up for Indigenous children, but not for non-Indigenous children.

5.1.4 Conclusion

Using an IROC model of care in regional and remote settings leads to significant lung function improvement in Indigenous children with asthma and bronchiectasis.

5.2 INTRODUCTION

Chronic respiratory disease is estimated to represent 8% of total disease burden in Australia.² The impact of chronic respiratory illness is substantial, particularly for Aboriginal and Torres Strait Islander (here forth respectfully called Indigenous) Australians whose burden of respiratory disease is 2.5 times higher than for non-Indigenous Australians.² Indeed, respiratory illness is the most common chronic illness in Indigenous Australians aged <35 years and affects 4-13% of the Indigenous population across all age groups.⁶⁰

Indigenous Australians with respiratory disease are known to have poorer outcomes⁶⁰ as a result of many issues including poor service access, complexities surrounding medication adherence and self-discharge rates 19 times greater than non-Indigenous Australians.^{58,61} In 2011, the Indigenous Respiratory Outreach Care (IROC) program was established through Queensland Health to provide children and adults with more equitable access to multidisciplinary specialist respiratory services in regional and remote Queensland communities with high Indigenous populations.⁸¹ The model of care was a culturally appropriate service (based on our previous paediatric-only service), involving respectful community engagement with community elders and Indigenous health workers (who may refer directly to the service) and post-clinic activities.^{79,81,159} The paediatric IROC team consists of paediatric-trained clinicians from the Queensland Children's Hospital (respiratory paediatricians, nurse, scientist and physiotherapist) and an Indigenous project officer. Following IROC clinics, each child's clinical care plan is reviewed with the local teams (community doctor, nurse, and Indigenous Health Practitioner) who oversee implementation of the suggested clinical approach. An appropriate model of care that includes availability of culturally appropriate resources is known to improve clinical outcomes.^{160,161}

Asthma and bronchiectasis are the most common illnesses diagnosed and treated at paediatric IROC clinics. In these and other chronic respiratory conditions, spirometry (a lung function test) assists in the diagnosis and/or disease monitoring as part of standard care.^{86,93} Spirometry is increasingly appreciated as an important clinical tool for assessing lung function, particularly in the Indigenous Australian context. Spirometry provides an objective measurement in a setting where few validated tools exist,^{101,162} and spirometry values (particularly FEV₁) are a demonstrated independent predictor of future all-cause mortality and cardiovascular disease (the

largest cause of mortality for Indigenous Australians),⁶⁰ The Prospective Urban Rural Epidemiology (PURE) study, involving 126,359 adults (aged >35-70 years) from 17 low to high income countries, concluded any lung function impairment (even in the clinically normal range of 0 to -2 Z-scores) was an independent risk factor for increased future mortality and cardiovascular disease within a median follow-up period of 7.8 years (IQR 5.6-9.5).¹¹⁴ Finally, spirometry is an important prognostic indicator for those with asthma⁸⁶ and bronchiectasis.¹⁰¹ For both illnesses, the disease burden is higher among Indigenous Australians compared with non-Indigenous Australians.¹⁰¹ For asthma, individual patient data from paediatric randomised controlled trials found that a 10% fall in FEV₁ between measurements increased the odds by 28% for having an exacerbation within 3 months and poor asthma control within 6 months.⁸⁶ For bronchiectasis, highly prevalent in Indigenous children,¹⁶¹ optimal care is reflected in the improvement of spirometry values.⁹³ Bronchiectasis can be reversible in children who receive optimal care,^{163,164} or the disease can progress with declining lung function if unmanaged.¹⁶⁵

There are few objective Australian studies that have evaluated the impact of any model of care for chronic diseases. Currently, there is no published respiratory or lung function data that extends beyond a single region. Availability of such data informs evaluation of health services and potentially guides future strategies and policies that address the high burden of chronic respiratory diseases. Thus, we analysed the lung function data of children referred to IROC paediatric respiratory outreach clinics in Queensland. Specifically, we assessed changes in spirometry values over the course of outreach specialist care for (a) the whole cohort, (b) children with asthma and bronchiectasis and (c) Indigenous children.

5.3 METHODS

5.3.1 Study design, setting, and participants

Children were referred to IROC clinics (at 12 regional/remote sites) by general practitioners or community health workers. Although the service focused on Indigenous children, we also reviewed non-Indigenous children referred to our service. Patient demographics such as age, sex, ethnicity, height, and weight were collected, and spirometry was undertaken in all age-appropriate children by a paediatric respiratory scientist. Respiratory diagnoses confirmed by IROC paediatric respiratory specialists were recorded. For this study, we retrospectively analysed spirometry data of children (aged <18 years at first IROC clinic visit) attending our IROC clinics between October 2010 to December 2017 who were medically reviewed and had spirometry on ≥ 2 occasions over a period of ≥ 12 months. We excluded those with incomplete or missing data. Ethics approval was

granted by the Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/265).

5.3.2 Patient data

Spirometry was performed in accordance with current guidelines using a portable spirometer (detailed in Appendix A). Spirometric data was entered into a secure database and checked thoroughly for errors. Patient demographic information and respiratory diagnoses were verified against electronic medical records, clinic databases and clinical letters. Bronchiectasis diagnoses was confirmed on high resolution computed tomography. Global Lung Function Initiative (GLI) 2012⁹ reference values were used to derive Z-scores and %predicted values. Caucasian reference values were used for non-Indigenous children and 'Other' for Indigenous children.

5.3.3 Statistical analysis and definitions

FEV₁, FVC, and FEV₁/FVC% Z-scores and %predicted values at each child's first visit (baseline) were compared to follow-up (determined by the highest FEV₁ Z-score occurring within the last 12 months since their most recent clinic visit). To ensure that any improvement was not a once-off measurement, we also compared FEV₁ Z-scores (zFEV₁) at baseline with best follow-up (determined by highest zFEV₁ score) occurring within each year of their first 3 years of specialist care. Baseline and follow-up data were not normally distributed and so Wilcoxon signed-rank tests were used for comparisons. A Mann-Whitney U test was used to compare spirometry asthma and bronchiectasis diagnoses. Proportions of zFEV₁ impairment were reported using a chi-squared test, and baseline zFEV₁ for groups of children based on baseline PURE classification were compared to best follow-up occurring within each of their first 3 years of care. Current practice and ATS/ERS guidelines⁷ consider a Z-score of -1.64 SD to be the lower limit of normal (LLN) below which results are clinically abnormal. The PURE study demonstrated that FEV₁ being in the clinical normal range, (zFEV₁=0 to -1) and spanning the LLN (zFEV₁ of -1 to -2), respectively termed mild and moderate FEV₁ impairment) was associated with worse health outcomes.¹¹⁴ SPSS v25.0 (IBM Corp., Armonk, NY, USA) was used for this analysis.

5.4 RESULTS

5.4.1 Demographics and diagnoses

Of the 359 children who attended the IROC clinics over the 7-year period, 189 fulfilled the inclusion criteria for this analysis (demographics summarised in Table 8). Of those not selected, 2 children were first tested at age <3 years, and 168 children were seen for a period of <12 months.

Table 8. Demographics of 189 included in the analysis.

Measure	Median (IQR) or n (%)	
Age (years)		
Baseline	6.8 (5.2 – 9.4)	
Follow-up	9.8 (7.2 – 12.2)	
BMI (kg/m ²)		
Baseline	16.3 (15.1 – 18.0)	
Follow-up	17.6 (15.8 – 21.3)	
Duration of care (months)	21.7 (12.9 – 42.4)	
Gender	114 (60.3%) male	
Ethnicity	141 (74.6%) Indigenous	
Respiratory diagnosis	Asthma	117 (62%)
	Bronchiectasis	39 (21%)
	Bronchitis/PBB*	16 (8%)
	RCW [#]	12 (6%)
	Cough	11 (6%)

*PBB: protracted bacterial bronchitis. [#]RCW: Recurrent cough and/or wheeze not fulfilling other diagnoses.

5.4.2 Spirometry data

FEV₁ and FVC %predicted values and Z-scores (but not FEV₁/FVC%) were significantly improved at follow-up (Table 9). Similar significant changes were found when grouped by Indigenous status (n=141 Indigenous, n=48 non-Indigenous). Spirometry at best follow-up visits occurring within 1- and 2-years following baseline significantly improved for all children and the Indigenous group, but not the non-Indigenous group (Figure 15). No significant changes were observed at follow-up within year 3 of follow-up for any group. Post-bronchodilator FEV₁ and FVC values were used for 34% tests at baseline (n=64) compared to 42% of tests at follow-up (n=79).

When grouped by diagnosis, FEV₁ and FVC %predicted values and Z-scores (but not FEV₁/FVC%) significantly improved at follow-up for children with asthma and bronchiectasis (Table 10). Similar significant improvements were found in Indigenous and non-Indigenous with asthma. Non-significant improvements occurred in the FVC of Indigenous children with bronchiectasis, and for FEV₁ and FVC in the small group of non-Indigenous children with bronchiectasis.

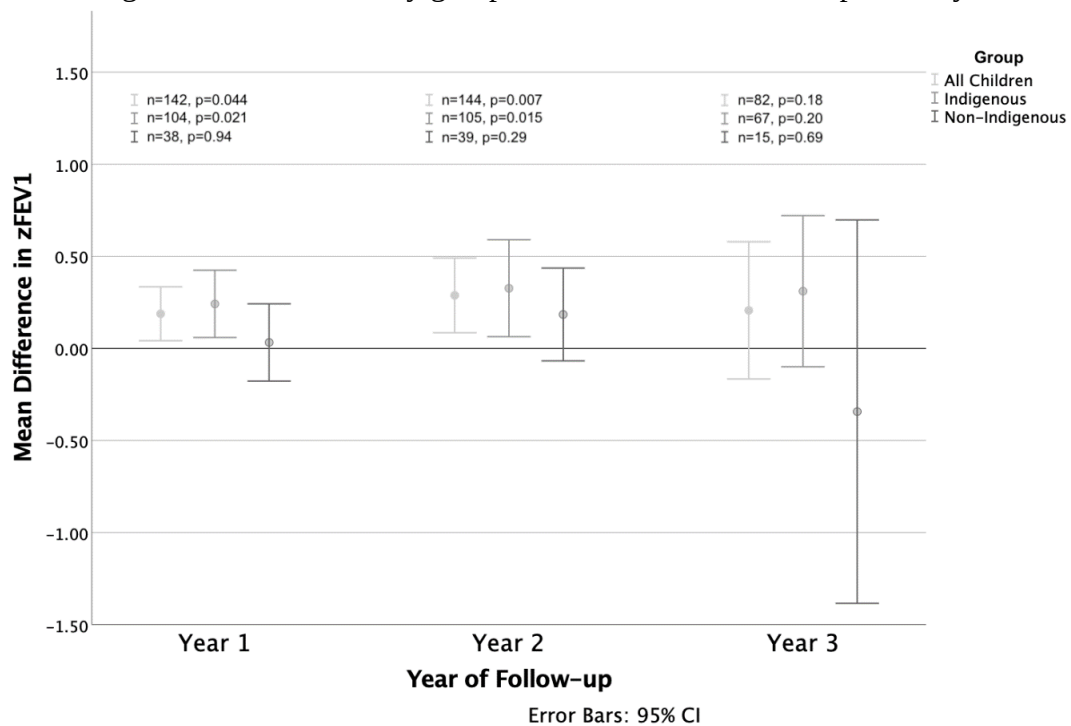
Table 9. Spirometry data for children at baseline and best follow-up visit within the last 12 months of outreach specialist care.

		Baseline	Follow-up			
		Median (IQR)		Mean Difference (95%CI)	p*	
All Children		n=189				
FEV ₁	Z-score	-0.50 (-1.33, 0.20)	-0.15 (-0.91, 0.56)	0.38 (0.22, 0.53)	<0.0001	
	%pred	94.2 (82.8, 102.3)	98.1 (89.0, 106.4)	5.00 (3.09, 6.92)	<0.0001	
FVC	Z-score	-0.42 (-1.14, 0.39)	0.02 (-0.77, 0.74)	0.36 (0.21, 0.51)	<0.0001	
	%pred	94.7 (86.3, 105.1)	100.4 (92.3, 108.4)	4.64 (2.83, 6.45)	<0.0001	
FEV ₁ /FVC %	Z-score	-0.39 (-1.11, 0.66)	-0.36 (-0.83, 0.18)	-0.02 (-0.19, 0.14)	0.85	
Indigenous		n=141				
FEV ₁	Z-score	-0.51 (-1.37, 0.20)	-0.18 (-0.92, 0.56)	0.37 (0.17, 0.57)	0.0002	
	%pred	93.4 (82.6, 102.3)	97.7 (88.8, 106.4)	4.98 (2.53, 7.44)	0.0001	
FVC	Z-score	-0.43 (-1.28, 0.41)	-0.11 (-0.81, 0.72)	0.36 (0.17, 0.55)	0.0008	
	%pred	94.7 (84.2, 105.1)	98.8 (91.7, 108.1)	4.52 (2.26, 6.78)	0.0003	
FEV ₁ /FVC %	Z-score	-0.37 (-1.04, 0.76)	-0.36 (-0.82, 0.29)	-0.02 (-0.23, 0.19)	0.83	
Non-Indigenous		n=48				
FEV ₁	Z-score	-0.36 (-1.27, 0.21)	-0.13 (-0.87, 0.59)	0.40 (0.21, 0.58)	0.0002	
	%pred	95.3 (84.0, 102.6)	98.4 (89.5, 107.1)	5.08 (2.75, 7.40)	0.0002	
FVC	Z-score	-0.41 (-0.79, 0.36)	0.15 (-0.62, 0.80)	0.38 (0.17, 0.58)	0.001	
	%pred	94.6 (90.1, 105.0)	102.1 (92.9, 110.3)	4.99 (2.28, 7.70)	0.001	
FEV ₁ /FVC %	Z-score	-0.48 (-1.17, 0.24)	-0.46 (-0.95, -0.02)	-0.03 (-0.28, 0.22)	0.992	

*Comparison with baseline spirometry.

The asthma and bronchiectasis groups (including Indigenous and non-Indigenous children) were compared. At baseline, the FVC of the asthma group was significantly higher than in the bronchiectasis group (p=0.042), however there was no significant difference in zFEV₁ or FEV₁/FVC% Z-scores (p=0.072; p=0.87). At follow-up, the asthma group had significantly higher FEV₁ and FVC values than the bronchiectasis group (p=0.006; p=0.002), with no difference between FEV₁/FVC% Z-score (p=0.55).

Figure 15. Change in FEV₁ Z-scores by group from baseline to follow-up over 3 years.



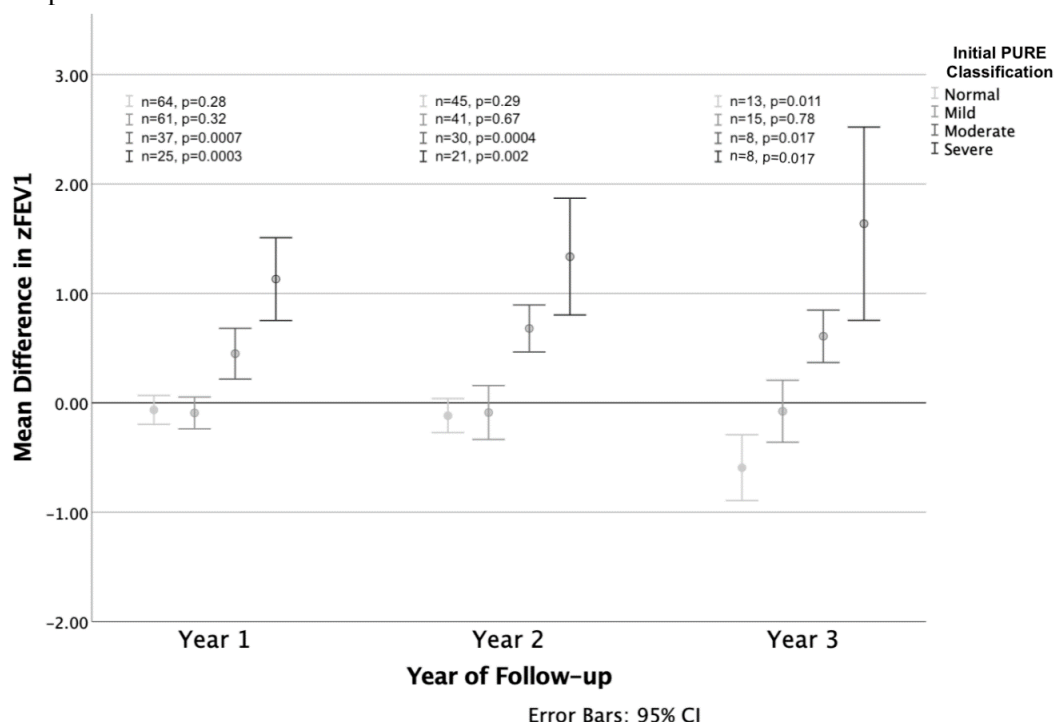
Using the PURE study¹¹⁴ classification for lung impairment, there were significantly fewer children with impaired FEV₁ by follow-up (baseline=125, follow-up=103, p=0.021). Children with moderate and severe impairment at baseline had significantly higher zFEV₁ across all 3 years of follow-up (Figure 16). Children with no impairment at baseline showed significantly lower zFEV₁ by the third year of follow-up.

Table 10. Spirometry data for children with asthma and bronchiectasis at baseline and best follow-up visit within the previous 12 months.

		Baseline	Follow-up			Baseline	Follow-up		
		Median (IQR)		Mean Difference (95%CI)	p*	Median (IQR)		Mean Difference (95%CI)	p*
All Children		Asthma (n=117)				Bronchiectasis (n=38)			
FEV ₁	Z-score	-0.35 (-1.25, 0.30)	0.05 (-0.68, 0.68)	0.41 (0.19, 0.64)	0.0002	-0.68 (-1.87, -	-0.41 (-1.10, 0.21)	0.33 (0.07, 0.59)	0.010
	%pred	95.3 (84.5, 103.7)	100.1 (91.7, 108.4)	5.36 (2.57, 8.16)	0.0002	0.03) 91.4 (75.6, 99.5)	94.9 (86.8, 102.5)	4.70 (1.41, 7.99)	0.005
FVC	Z-score	-0.27 (-1.08, 0.47)	0.16 (-0.59, 0.93)	0.46 (0.24, 0.68)	0.0002	-0.76 (-1.59, 0.03)	-0.47 (-1.03, 0.21)	0.26 (-0.03, 0.53)	0.048
	%pred	96.6 (86.9, 105.6)	102.1 (94.1, 111.7)	5.70 (3.05, 8.34)	0.0001	91.6 (82.1, 100.3)	94.9 (88.3, 103.9)	3.98 (0.61, 7.34)	0.025
FEV ₁ /FVC%	Z-score	-0.27 (-1.04, 0.74)	-0.36 (-0.81, 0.17)	-0.11 (-0.31, 0.09)	0.60	0.10 (-1.13, 0.80)	-0.46 (-0.81, 0.39)	-0.08 (-0.51, 0.35)	0.98
Indigenous		Asthma (n=89)				Bronchiectasis (n=29)			
FEV ₁	Z-score	-0.41 (-1.25, 0.33)	0.01 (-0.68, 0.67)	0.39 (0.11, 0.67)	0.007	-0.66 (-1.97, -	-0.63 (-1.07, 0.13)	0.30 (-0.02, 0.63)	0.048
	%pred	94.3 (84.5, 104.3)	100.0 (91.6, 108.0)	5.16 (1.61, 8.70)	0.006	0.01) 91.7 (74.4, 99.8)	92.5 (87.2, 101.6)	4.27 (0.21, 8.33)	0.028
FVC	Z-score	-0.21 (-1.21, 0.50)	0.10 (-0.61, 0.96)	0.46 (0.18, 0.74)	0.003	-0.76 (-1.45, 0.09)	-0.49 (-1.04, 0.22)	0.20 (-0.13, 0.54)	0.18
	%pred	97.6 (86.3, 105.9)	101.4 (94.1, 111.8)	5.57 (2.30, 8.85)	0.003	91.5 (83.1, 101.1)	94.9 (88.6, 102.9)	3.11 (-0.90, 7.12)	0.10
FEV ₁ /FVC%	Z-score	-0.27 (-0.98, 0.76)	-0.38 (-0.84, 0.17)	-0.12 (-0.37, 0.13)	0.68	-0.20 (-1.42, 0.83)	-0.43 (-0.82, 0.37)	-0.09 (-0.63, 0.44)	0.97
Non-Indigenous		Asthma (n=28)				Bronchiectasis (n=9)			
FEV ₁	Z-score	-0.33 (-1.25, 0.20)	0.20 (-0.68, 0.86)	0.48 (-0.21, 0.75)	0.002	-0.73 (-2.07, 0.03)	-0.33 (-1.71, 0.21)	0.42 (-0.00, 0.85)	0.066
	%pred	95.7 (84.3, 102.4)	102.3 (91.9, 110.8)	6.01 (2.57, 9.45)	0.002	91.1 (73.0, 100.4)	96.1 (79.4, 102.6)	6.09 (0.09, 12.1)	0.051
FVC	Z-score	-0.44 (-0.73, 0.16)	0.17 (-0.54, 0.90)	0.45 (0.14, 0.75)	0.006	-0.61 (-1.92, 0.08)	-0.19 (-1.48, 0.49)	0.48 (-0.04, 0.99)	0.066
	%pred	94.3 (90.2, 101.9)	103.6 (93.7, 111.8)	6.10 (2.08, 10.1)	0.006	92.1 (74.6, 101.2)	97.3 (84.4, 107.3)	6.77 (-0.28, 13.8)	0.066
FEV ₁ /FVC%	Z-score	-0.29 (-1.18, 0.70)	-0.33 (-0.74, 0.10)	-0.08 (-0.42, 0.26)	0.72	0.15 (-0.77, 0.37)	-0.49 (-0.85, 0.81)	-0.05 (-0.75, 0.66)	0.77

*Comparison with baseline spirometry.

Figure 16. Change in FEV₁ Z-scores by PURE study¹¹⁴ criteria classification at baseline over 3 years of follow-up.



5.5 DISCUSSION

We report for the first time the change in objective lung function data of children managed by a specialist respiratory paediatric outreach team. Data from 189 children treated through IROC clinics based in regional and remote Queensland showed that FEV₁ and FVC Z-scores and %predicted values, but not FEV₁/FVC% Z-scores, significantly improved at their follow-up visit after ≥ 12 months of specialist care, and at follow-up visits within years 1 and 2 following initial presentation. Similar lung function improvements were observed in the spirometry of Indigenous children exclusively and those with asthma or bronchiectasis. When applying the PURE study criteria¹¹⁴ to our cohort, a high proportion (66.1%) of children had impaired FEV₁ at baseline, and significantly fewer children (54.5%) had impaired FEV₁ at follow-up. Significant improvements in zFEV₁ for children with moderate and severely impaired FEV₁ at baseline were found across 3 years of follow-up.

Our study is clinically important for several reasons. It is the first study that has provided objective data on the impact on respiratory function of a respiratory outreach service to remote and rural Indigenous communities. Secondly, we have shown that spirometry of children with lung disease can be improved with appropriate care in a regional-remote setting. Thirdly, Indigenous children with bronchiectasis have significantly improved spirometry values when diagnosed early

and managed appropriately, despite the high incidence (>75%) of FEV₁ impairment at first referral.

Significant improvements in FEV₁ and FVC values of Indigenous children seen at IROC are clinically important. Indigenous adults seen at a specialist outreach service in the Northern Territory had moderately severe lung function abnormalities by ATS/ERS criteria⁷ (mean FEV₁=55% predicted; FVC=61% predicted) despite the young adult cohort (mean age=49 years, $\pm$ 12.9 SD).¹⁰⁰ Further, the lung function of Indigenous adults with bronchiectasis has been shown to be in the severe⁷ range (median FEV₁=30% predicted; FVC=41% predicted), with a median age of respiratory-related death (48.8 years, IQR 36.4, 52.9) 20 years lower than for their non-Indigenous counterparts (69.6 years, IQR 64.2, 75.1).¹⁰¹ Within our cohort, children with asthma had significantly better lung function than children with bronchiectasis at follow-up, and these values are substantially better than those reported in Indigenous adults with bronchiectasis.¹⁰¹ Current data shows that optimal care may prevent further deterioration in lung function of children with bronchiectasis,^{166,167} and so we believe early diagnosis and better management is important for the future lung health of these children. The model of care used is likely important and improvements in the provision and access to the outreach specialist service may be effective in preventing a debilitating lung function decline in adulthood. However, improvement of services needs to occur concurrently with numerous other risk factors relating to socio-economic determinants of health (e.g. over-crowding).¹⁶¹

The importance of improving lung function (and hence its trajectory) is reflected in the published literature such as the PURE study that, consistent with other published data, found that FEV₁ is an independent predictor of future all-cause mortality and cardiovascular disease, even with FEV₁ Z-scores of 0 to -2 (generally considered clinically normal).¹¹⁴ While these adult outcomes are not relevant to our cohort (and not the focus of our study), examining our data using the PURE criteria is important in terms of lung function trajectories. Recent work has shown that lung function is very much set in childhood but there is a single trajectory (one of 6) where lung function can be improved and protective of future adult lung disease.⁵⁴ When classifying our cohort using these novel criteria,¹¹⁴ we found that significantly fewer children had impaired FEV₁ at follow-up, and that children with moderate or severely impaired FEV₁ at baseline had significantly improved zFEV₁ across 3 years of follow-up. While representing an important reduction, the number of children with continuing FEV₁ impairment remains high, placing these children at significantly higher risk for future cardiovascular disease and all-cause mortality. At our cohort's median age of ~10 years at follow-up, their lung function will likely have the same trajectory, or

possibly deteriorate. In the PURE study, the risk of lung function impairment (Z-score <0) for future all-cause mortality, respiratory disease and cardiovascular disease was even higher than that for traditionally-known factors (tobacco smoking, hypertension and previous cardiovascular disease).¹¹⁴ In the context of the very high burden of cardiovascular disease and premature mortality in Indigenous adults,^{60,61} there is a need to obtain relevant cohort data relating lung function with the future health of Indigenous people, in addition to optimising the lung function of children.

The GLI 2012⁹ lung function reference set used for Indigenous children in this study was ‘Other’, recently found to be the most appropriate for Indigenous children and young adults.²⁰ Validation of this reference set for Indigenous children allowed us to describe with confidence the lung function of Indigenous children seen at IROC clinics. Using Caucasian-based references would result in lower FEV₁ and FVC %predicted and Z-scores whilst retaining the significant changes in the lung function and proportions. However, the number with impaired lung function would be substantially higher than that described in the results.

There are several limitations to our study. Firstly, this is a retrospective single-arm cohort study and is therefore a noncomparative study. Secondly, we cannot be certain that the improvement may not be, in part, secondary to a learning effect through repetition of the spirometry test over repeated clinic visits, raising an artificially lowered baseline FVC. This learning effect may explain why no significant changes were observed in FEV₁/FVC% values were found across groups. Sub-maximal inhalation and reduced forced expiratory time (FET) may lower FVC values and it is known that children who are naïve spirometry subjects may exhibit sub-maximal inhalations and reduced FET relative to experienced subjects.¹⁶⁸ While all spirometry was performed by experienced paediatric respiratory scientists, these spirometry results are clinically reported values and few may not have met full ATS/ERS criteria.¹⁰ Thirdly, we cannot discount the influence of survivorship bias in our analysis of 3 years of follow-up. For several reasons including IROC clinic scheduling, patient discharge and children lost to follow-up, not all children were seen in each of the 3 years following their initial clinic visit. For example, we found children with no FEV₁ impairment at baseline showed significant zFEV₁ regression by Year 3 of follow-up. This is likely because of a smaller sample size in Year 3 (n=82 compared to 142-144 in Years 1 and 2) and attrition effects where children no longer require specialist care are discharged from the IROC service back to primary health care. The latter point is supported by our finding that children with severe impairment at baseline had significantly higher zFEV₁ across all

3 years of follow-up. However, without analysis and reporting of patient outcomes, we cannot be certain of the influence survivorship bias and attrition effects have on this data.

In conclusion, the lung function of children managed through IROC specialist respiratory outreach clinics in regional and remote Queensland communities significantly improves over a minimum of 12-month period of care. Specifically, the lung function of Indigenous children and children with asthma and bronchiectasis improved significantly following at least 12 months of specialist care in conjunction with local services. When applying the PURE study criteria¹¹⁴ to this cohort of children, we found a significant number of children with impaired FEV₁, particularly among children with bronchiectasis. Thus, more needs to be done to reduce their heightened risk of future all-cause mortality and cardiovascular and respiratory disease. Using an IROC model and/or similar culturally appropriate health services may help improve short and long-term clinical outcomes of Indigenous people.

5.6 SUPPLEMENTARY MATERIALS

Spirometry was performed in seated position with a nose clip according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines [12]. An Easy on-PC spirometer (ndd Medizintechnik AG, Zurich, Switzerland) was used, and calibration was validated immediately prior to each clinic using a 3-litre syringe. In the presence of airway obstruction, confirmed or suspected asthma, or if otherwise clinically indicated, post-bronchodilator spirometry was performed 10 minutes after 400 micrograms of salbutamol delivered through a spacer. In instances where pre- and post-bronchodilator spirometry were performed, the best score (either pre- or post-bronchodilator) as determined by FEV₁ was used for that visit.

All children who met inclusion criteria were analysed, followed by subgroups of Indigenous and non-Indigenous children and those with confirmed asthma or bronchiectasis. Where ethnic, diagnostic, spirometry test data or information necessary to generate predicted values were missing, children were excluded from analysis.

Chapter 6: Pediatric patients of outreach specialist Queensland clinics have lung function improvement comparable to that of tertiary pediatric patients

This chapter addresses Objective 2 outlined in Section 1.4; “Evaluate changes in spirometry values of paediatric patients treated through IROC and compare these changes to those seen in tertiary paediatric facilities”, through the following peer-reviewed published article:

Collaro AJ, Chang AB, Marchant JM, Rodwell LT, Masters IB, Chatfield MD, McElrea MS. Pediatric Patients of Outreach Specialist Queensland Clinics Have Lung Function Improvement Comparable to That of Tertiary Pediatric Patients. *Chest*. 2020;158(4):1566-75.

The following editorial¹⁶⁹ accompanied this article, and is available in Appendix E:

Kasi AS, Lesnick BL. Can We Prevent COPD by Reaching Out to Children at Risk? *Chest*. 2020;158(4):1327-8.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
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Andrew Collaro	Drafting of manuscript, led data analysis, input into study design
Anne Chang	Reviewed draft manuscript, data collection, led study design
Julie Marchant	Reviewed draft manuscript, input into study design
Brent Masters	Reviewed draft manuscript, data collection, input into study design
Leanne Rodwell	Reviewed draft manuscript, data collection, input into study design
Mark Chatfield	Reviewed draft manuscript, assisted with data analysis
Margaret McElrea	Reviewed draft manuscript, data collection, input into study design

6.1 ABSTRACT

6.1.1 Background

Inequitable access to quality healthcare contributes to the known poorer outcomes of people living in regional/remote areas (c.f. urban-based), especially for First Nations people. Integration of specialist outreach services within primary care is one strategy that can reduce the inequity when modelled to the needs and available resources of target communities.

6.1.2 Research Question

To evaluate whether respiratory outreach clinics in regional and remote Queensland are as effective as tertiary respiratory services at improving the lung function of children.

6.1.3 Study Design and Methods

From existing databases, we obtained spirometry data of children (aged 3-18 years) seen at Indigenous-focused outreach clinics in regional and remote Queensland and Brisbane-based paediatric tertiary hospitals over the same contemporary period (October 2010 to July 2019). We compared the change in spirometry Z-scores (Δz) at follow-up for both groups of children.

6.1.4 Results

Lung function significantly improved in both groups: Tertiary hospital (n=2249; Δz forced expiratory volume in 1 second (FEV1)=0.22, 95%CI 0.17, 0.27; Δz forced vital capacity (FVC)=0.23, 95%CI 0.18, 0.28); Outreach (n=252; FEV1=0.35, 95%CI 0.22, 0.48; FVC=0.36, 95%CI 0.23, 0.50). There were no significant intergroup differences in Δz FEV1 (0.13, 95%CI -0.02, 0.28, p=0.10) or Δz FVC (0.14, 95%CI -0.02, 0.29, p=0.08) improvement from baseline. In both groups, the proportion of children with z FEV1 >0 at follow-up (hospital=31.7%,

outreach=46.8%) significantly increased (hospital $p=0.001$, outreach $p=0.009$) from baseline (hospital=27.2%, outreach=35.3%). Numbers of children with $zFEV_1 >0$ significantly increased for asthma and bronchiectasis outreach sub-groups, and for children with asthma in the hospital-based group.

6.1.5 Interpretation

Comparable significant lung function improvement of children was seen in Indigenous-focused outreach remote/regional clinics and paediatric tertiary hospitals. This suggests that effective clinical care is achievable within the outreach setting.

6.2 INTRODUCTION

Although the health of Australians has improved with longer life expectancies and more years at full health than previous generations,⁵⁷ gaps between regional and urban areas, and Indigenous and non-Indigenous Australians remain.¹⁷⁰ Australia is geographically expansive, with population densities as low as <1 person/square km in some remote Queensland communities.¹⁷¹ Ensuring equal access to quality health services for regional and remote communities is challenging. An outreach specialist service integrated with primary care is one strategy that delivers healthcare directly to people living in these isolated communities, and has been shown to have significant potential for delivering quality care when modelled to the needs of target communities and available resources to support health workers.^{76,77} Reducing obstacles to healthcare access including logistics, distance, and cost of travel⁴ may encourage health-seeking behaviours and improve health outcomes. For Indigenous populations, there is additional cultural complexity, and so culturally appropriate services are needed and have been shown to improve outcomes within these communities.^{160,161} While there is now data on the benefits of such services,¹⁷² there are no objective respiratory-based data comparing the health outcomes of service provision in regional and remote areas to urban centres.

Australia has provided public funding for outreach services since 2000 through the establishment of the Medical Specialist Outreach Assistance Program, and in Queensland this has been complemented by funding provided by state government. Indigenous Respiratory Outreach Care (IROC) is a respiratory outreach service funded since 2011 through the National Indigenous Health Partnership Agreement to Close the Gap, delivering multidisciplinary specialist respiratory care to regional and remote Queensland communities with high Indigenous populations.⁸¹ The paediatric IROC team was modelled on our culturally-informed respiratory outreach service to the Torres Straits region operational since the late 1990s.⁷⁹ The outreach team consists of paediatric-

trained clinicians based at the Queensland Children's Hospital (QCH), and includes paediatric-trained respiratory medical specialists, nurses, scientists, physiotherapists, and Indigenous project officers. Following each clinic, every child's clinical care plan is reviewed with local treating teams (community doctor, nurse, and Indigenous health worker) who implement the suggested clinical approach. Our recent evaluation of the spirometry of newly referred children attending IROC found significantly improved forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) values following at least 12 months of specialist care among these children.¹⁷² While these findings are promising, how these results compare to respiratory services offered by paediatric tertiary facilities in Queensland has yet to be determined.

Spirometry is an important clinical tool that assists in the diagnosis and continued monitoring of respiratory disease.^{86,93} The importance of spirometry values in adults (>35 years) as an independent predictor of all-cause future mortality and morbidity (cardiovascular disease events and respiratory hospitalisation) has recently been further consolidated in the comprehensive Prospective Urban Rural Epidemiology (PURE) study, involving 126,359 participants aged 35-70 years from 17 low to high income countries.¹¹⁴ The PURE study found FEV₁ Z-scores <0 (termed FEV₁ impairment), even within the clinically normal range of 0 to -1.64, were associated with increased risk of all-cause mortality and cardiovascular and respiratory morbidity within a median follow-up period of 7.8 years (IQR 5.6-9.5), where the size effect was higher than most traditional risk factors (e.g. smoking, hypertension).¹¹⁴

To our knowledge, no respiratory outreach service has been evaluated against a complementary tertiary hospital service with respect to lung function. Availability of such data could inform evaluation of health services and guide future policy decisions with global implications for achieving equity in health service delivery for people living in remote regions. Therefore, we expanded upon our previous analysis of IROC spirometry,¹⁷² and compared the values to the spirometry of children tested at tertiary respiratory clinics in Brisbane over the same time period (8.8 years). The aim of our study was to evaluate whether respiratory outreach clinics in regional and remote Queensland are as effective as respiratory tertiary hospital clinics at improving the lung function of children. We assessed changes in spirometry, and compared these changes between the two groups, over the course of specialist care for (i) all children tested and (ii) children with confirmed asthma and bronchiectasis.

6.3 METHODS

6.3.1 Study design, setting, and participants

Inclusion criteria were children aged 3-18 years at first clinic visit (either IROC or tertiary hospital), who were medically reviewed and had performed spirometry on ≥ 2 occasions over a period of ≥ 12 -months. Spirometry of children attending IROC clinics between October 2010 and July 2019 were compared to spirometry data collected from paediatric tertiary hospital clinics in Brisbane for the same period. Our previous IROC-based data included 190 children seen between October 2010-December 2017.¹⁷² Where children were seen at both IROC and tertiary settings, a judgement was made taking into consideration the clinical situation (e.g. tertiary centre visit for imaging or bronchoscopy, but usually seen at IROC).

Paediatric IROC clinics occurred at twelve regional/remote Queensland locations (Bamaga, Cherbourg, Cloncurry, Charleville, Cunnamulla, Doomadgee, Mount Isa, Longreach, Mornington Island, Thursday Island, Weipa and Woorabinda). In both outreach and tertiary settings, patient demographics including age, sex, ethnicity, height, and weight were collected and spirometry was performed by experienced paediatric respiratory scientists. Ethics approval for this study was granted by the Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/265).

6.3.2 Spirometry testing

Spirometry was performed in a seated position with a nose clip according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines^{7,8} in both outreach and tertiary hospital settings. For outreach clinics, an Easy on-PC spirometer (ndd Medizintechnik AG, Zurich, Switzerland) was used, while tertiary hospital spirometry was performed with various equipment dependent upon on the site. Calibration/validation of devices occurred daily and followed manufacturer guidelines. In both outreach and tertiary settings, post-bronchodilator spirometry was performed 10 minutes after delivery of 400mcg of salbutamol through a spacer in the presence of airway obstruction, confirmed or suspected asthma, or if otherwise clinically indicated. Global Lung Function Initiative (GLI) 2012⁹ reference values were applied to spirometry from each testing site to derive Z-scores and %predicted values. For Indigenous children, the 'Other' classification was used for calculating reference values as we recently found this to be most appropriate for use in this population.²⁰

6.3.3 Data verification

IROC spirometry paper reports were transcribed into an electronic database and checked for data entry errors. Each child's information including demographic data and respiratory diagnosis was verified against electronic medical records, clinic databases and letters. Further information regarding the extraction and verification of tertiary hospital data is available within the supplement. Asthma diagnoses were based on specialist respiratory paediatrician's diagnosis and bronchiectasis based on high resolution computed-tomography findings. Where demographic, diagnostic, or test data that was mandatory for the calculation of reference values or statistical analysis was missing and unable to be retrieved or verified, these children were excluded from the study.

6.3.4 Statistical analysis and definitions

Data distributions were examined visually using Q-Q plots, and numerically using Shapiro-Wilk and Kolmogorov-Smirnov tests. Non-parametric tests were used for non-normally distributed data whilst parametric tests used for normally distributed data. Baseline (first visit) and follow-up data were not normally distributed thus median and interquartile ranges (IQR) were reported.

Where pre- and post-bronchodilator spirometry were performed, the best test as determined by highest FEV₁ Z-score (zFEV₁) was used for that visit. To quantify any potential bias introduced, the percentage of post-bronchodilator spirometry used for baseline and follow-up results is reported. For both clinic types, FEV₁, FVC, and FEV₁/FVC% Z-scores and %predicted values from each child's first clinic visit (baseline) were compared to follow-up (determined by the highest zFEV₁ occurring within the previous 12 months from their most recent clinic visit) using a paired Wilcoxon signed-rank test. Changes in FEV₁, FVC, and FEV₁/FVC% were compared using an independent samples t-test.

Baseline zFEV₁, zFVC and FEV₁/FVC% z-scores were compared using a Mann-Whitney U test. To account for potential differences age and duration of care between both clinic types, a linear model was used to determine whether these factors influence any spirometric change observed at follow-up for the whole group, and asthma/bronchiectasis sub-groups.

We then compared the proportion of children with FEV₁ impairment (determined by zFEV₁) between IROC and tertiary hospital groups according to the PURE study criteria¹¹⁴ using a chi-squared test. The PURE study termed FEV₁ <0 as "impaired" whether in the clinical normal range or spanning the LLN (zFEV₁ 0 to -1 and -1 to -2), respectively termed mild and moderate FEV₁

impairment.¹¹⁴ SPSS v25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses; 2-tailed p-values <0.05 were considered significant.

6.4 RESULTS

6.4.1 Demographics and diagnosis

The demographics and diagnosis of the 252 children tested at IROC clinics and 2249 children tested at tertiary hospital clinics are summarised in Table 11.

Table 11. Demographics of children analysed at Indigenous Respiratory Outreach Care (IROC) and tertiary hospital clinics.

	Outreach (IROC) Clinics Median (IQR) or n (%)		Tertiary Respiratory Clinics Median (IQR) or n (%)	
N	252 including Indigenous n=183 (73%)		2249	
Age (years)				
Baseline	6.5 (5.0 – 9.2)		7.9 (5.4 – 11.7)	
Follow-up	9.6 (7.4 – 12.1)		11.4 (8.2 – 15.1)	
BMI (kg/m ²)				
Baseline	16.4 (15.2 – 18.8)		16.6 (15.3 – 19.1)	
Follow-up	18.0 (16.0 – 22.2)		18.1 (15.8 – 21.4)	
Duration of care (months)	27.5 (15.5 – 44.7)*		28.0 (16.6 – 43.4)*	
Sex	156 (62%) male		1290 (57%) male	
Common diagnosis (% of children seen)	Asthma	154 (61%)	Asthma	681 (30%)
	Cystic fibrosis	4 (1.6%)	Cystic fibrosis	434 (19%)
	Bronchiectasis	46 (18%)	Bronchiectasis	185 (8.2%)
	Airway malacia	6 (2.4%)	Airway malacia	153 (6.8%)
	Cough#	15 (6.0%)	Cough#	141 (6.3%)
	NMD	0 (0%)	NMD	132 (5.9%)
	Bronchitis/PBB	22 (8.7%)	Bronchitis/PBB	99 (4.4%)

PBB=protracted bacterial bronchitis. NMD=Neuromuscular diseases (including the various muscular dystrophies).

*No significant differences were observed in duration of care between clinic types. #Cough=not related to any other diagnosis and unspecified.

Table 12. Spirometry data for children at baseline and after at least 12 months specialist care at either outreach or tertiary hospitals.

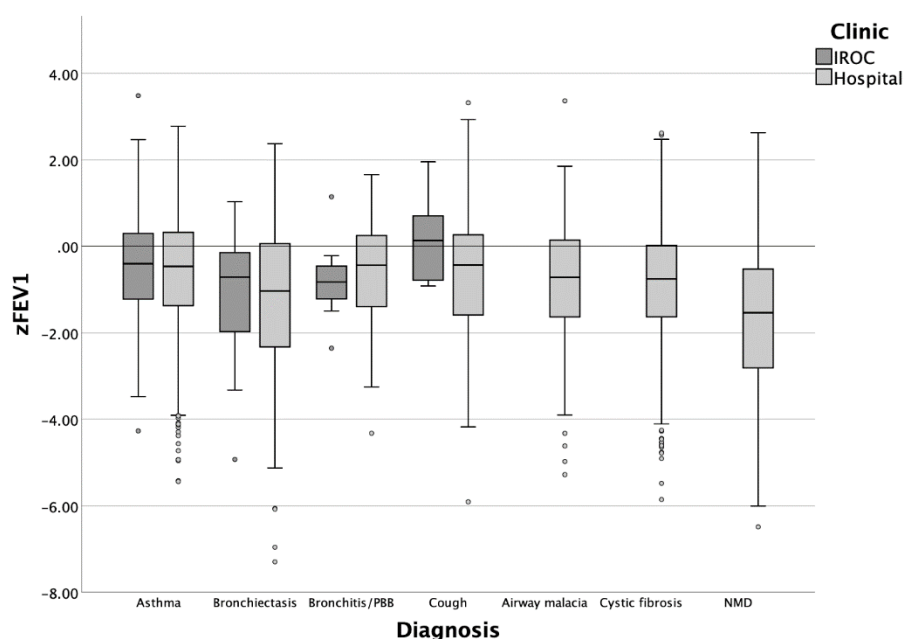
		Outreach (IROC) Clinics				Tertiary Hospital Clinics				
		Baseline	Follow-up			Baseline	Follow-up			
		Median (IQR)		p*	Mean Change (95%CI)	Median (IQR)		p*	Mean Change (95%CI)	p#
Whole cohort		n=252				n=2249				
FEV ₁	Z-score	-0.41 (-1.28, 0.26)	-0.09 (-0.85, 0.54)	<0.0001	0.35 (0.22, 0.48)	-0.81 (-1.97, 0.08)	-0.61 (-1.68, 0.25)	<0.0001	0.22 (0.17, 0.27)	0.10
	%predicted	94.8 (83.9, 103.2)	99.0 (90.0, 106.5)	<0.0001	4.6 (3.0, 6.3)	90.0 (76.0, 100.9)	92.6 (80.0, 102.9)	<0.0001	2.9 (2.3, 3.5)	0.08
FVC	Z-score	-0.32 (-1.13, 0.46)	0.05 (-0.78, 0.70)	<0.0001	0.36 (0.23, 0.50)	-0.53 (-1.63, 0.30)	-0.29 (-1.35, 0.55)	<0.0001	0.23 (0.18, 0.28)	0.08
	%predicted	96.0 (86.3, 105.8)	100.5 (91.2, 108.0)	<0.0001	4.7 (3.0, 6.3)	93.3 (79.9, 103.9)	96.5 (84.2, 106.6)	<0.0001	3.1 (2.5, 3.7)	0.10
FEV ₁ /FVC%	Z-score	-0.38 (-1.07, 0.66)	-0.36 (-0.85, 0.29)	0.70	-0.04 (-0.17, 0.09)	-0.44 (-1.30, 0.43)	-0.49 (-1.21, 0.22)	0.50	-0.04 (-0.09, 0.01)	0.97
Asthma		n=154				n=681				
FEV ₁	Z-score	-0.39 (-1.21, 0.29)	0.00 (-0.63, 0.62)	<0.0001	0.41 (0.24, 0.58)	-0.47 (-1.39, 0.32)	-0.15 (-0.91, 0.57)	<0.0001	0.42 (0.33, 0.51)	0.94
	%predicted	95.2 (85.0, 103.5)	100.0 (92.5, 107.5)	<0.0001	5.3 (3.2, 7.4)	94.3 (83.2, 103.9)	98.2 (89.1, 106.7)	<0.0001	5.3 (4.2, 6.4)	1.00
FVC	Z-score	-0.24 (-1.07, 0.50)	0.11 (-0.50, 0.83)	<0.0001	0.43 (0.26, 0.59)	-0.13 (-1.06, 0.63)	0.22 (-0.67, 0.89)	<0.0001	0.39 (0.30, 0.47)	0.67
	%predicted	97.0 (86.6, 106.2)	101.2 (94.1, 109.6)	<0.0001	5.3 (3.3, 7.3)	98.5 (86.7, 107.8)	102.6 (92.2, 110.7)	<0.0001	4.8 (3.8, 5.79)	0.69
FEV ₁ /FVC%	Z-score	-0.32 (-1.08, 0.68)	-0.32 (-0.81, 0.18)	0.65	-0.07 (-0.23, 0.09)	-0.55 (-1.40, 0.34)	-0.57 (-1.18, 0.11)	0.38	0.03 (-0.05, 0.11)	0.28
Bronchiectasis		n=46				n=185				
FEV ₁	Z-score	-0.64 (-1.87, -0.03)	-0.30 (-1.26, 0.32)	0.044	0.35 (0.03, 0.67)	-0.96 (-2.30, 0.17)	-0.59 (-1.65, 0.37)	<0.0001	0.41 (0.25, 0.57)	0.76
	%predicted	92.1 (75.6, 99.5)	96.5 (84.9, 104.1)	0.028	4.9 (0.9, 9.0)	87.7 (71.8, 102.0)	92.8 (79.0, 104.5)	<0.0001	5.5 (3.4, 7.5)	0.82
FVC	Z-score	-0.75 (-1.59, 0.03)	-0.42 (-1.19, 0.46)	0.036	0.33 (0.03, 0.63)	-0.72 (-1.99, 0.26)	-0.21 (-1.28, 0.64)	<0.0001	0.45 (0.29, 0.62)	0.50
	%predicted	91.5 (82.1, 100.3)	95.3 (86.6, 105.9)	0.021	4.6 (0.9, 8.4)	90.8 (75.3, 103.4)	97.4 (84.5, 107.7)	<0.0001	6.0 (3.9, 8.0)	0.56
FEV ₁ /FVC%	Z-score	0.05 (-1.12, 0.80)	-0.32 (-0.82, 0.35)	0.93	-0.02 (-0.35, 0.30)	-0.53 (-1.28, 0.22)	-0.62 (-1.19, 0.10)	0.55	-0.06 (-0.23, 0.10)	0.84

*Comparison of baseline and follow-up spirometry. #Comparison of mean difference in baseline and follow-up spirometry between outreach and tertiary hospital clinics.

6.4.2 Spirometry data

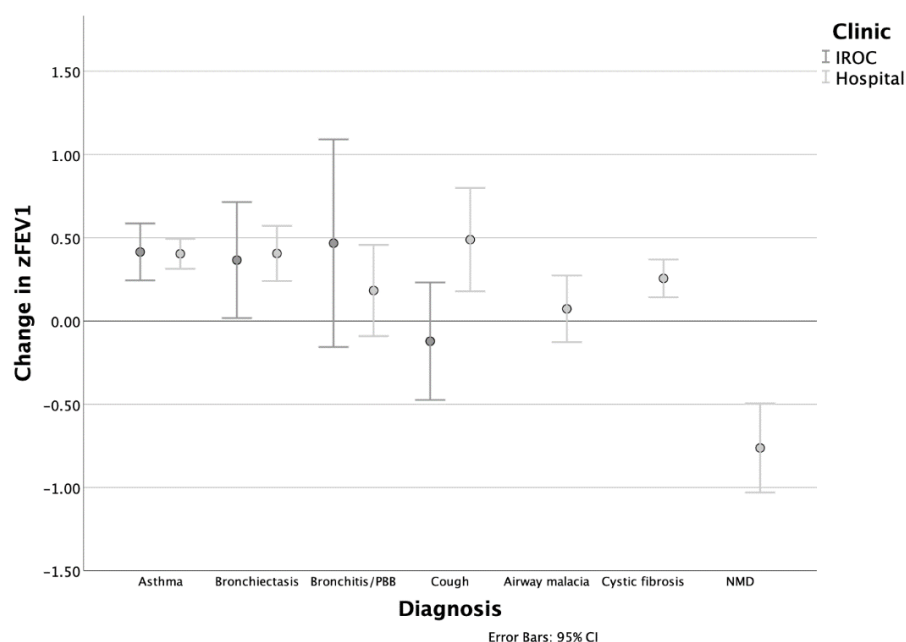
Post-bronchodilator spirometry was more frequently used for IROC spirometry than tertiary hospital spirometry, for both baseline (32.9% vs. 20.6%) and follow-up (44% vs. 21.2%) measures. zFEV₁ and zFVC (Table 12) values for whole cohorts at IROC and tertiary hospitals improved significantly between baseline and follow-up visits. No significant changes occurred in zFEV₁/FVC%. This pattern was also observed for children with asthma and bronchiectasis at both clinic types. The improvements in zFEV₁ and zFVC from baseline to follow-up of children tested at IROC were not significantly different to those tested at tertiary hospital clinics. The difference in the mean scores between groups were zFEV₁=0.13 (95%CI -0.02, 0.28); zFVC=0.14 (95%CI -0.02, -0.29).

Figure 17. Baseline FEV₁ Z-scores grouped by respiratory diagnosis at tertiary hospital and Indigenous Respiratory Outreach Care (IROC) clinics. [Data presented as boxplots (median, quartiles, and outliers) as the data was not normally distributed]



Mean baseline zFEV₁ for diagnosis subgroups are depicted in Figure 17, while changes in zFEV₁ for diagnoses subgroups are depicted in Figure 18. There were no significant differences between improvements in children with asthma (zFEV₁=-0.01, 95%CI -0.21, 0.20, p=0.94; zFVC=0.10, 95%CI -0.15, 0.24, p=0.67) and bronchiectasis (zFEV₁=-0.07, 95%CI -0.44, 0.30, p=0.70; zFVC=-0.16, 95%CI -0.52, 0.21, p=0.40) between clinic types. Only minor improvements and regressions were noted in FEV₁/FVC%, with non-significant differences between children seen at IROC and tertiary hospital clinics.

Figure 18. Change (follow-up minus first-visit baseline) in FEV1 Z-scores grouped by respiratory diagnosis at tertiary hospital and Indigenous Respiratory Outreach Care (IROC) clinics. [Data presented as mean and 95%CI]



Comparison of baseline spirometry data, and linear modelling of improvements to zFEV₁ and zFVC for the whole group, and asthma/bronchiectasis sub-groups are detailed in the Supplementary Material. We determined that adjustment for the age of children at baseline, and the duration of their care had little influence on our findings, and that improvement to zFEV₁ and FVC were not significantly different between clinic types.

Applying the PURE study criteria for FEV₁ impairment (Table 13), a significant increase in the number of children with zFEV₁ ≥ 0, was observed in both IROC and tertiary hospital groups. This pattern was also observed among children with diagnosis of asthma, however only the IROC bronchiectasis sub-group showed a significant increase in the number of children with zFEV₁ ≥ 0. This was coupled with significant decreases in the number of children with zFEV₁ < -2, with the exceptions of children with asthma (analysis not possible due to n < 5 at follow-up) and bronchiectasis within the IROC group. Despite this improvement, a substantial proportion of children had zFEV₁ scores < 0 at follow-up (53.2-67.3%).

Table 13. Comparison of spirometry impairment based on PURE study criteria¹¹⁴ at baseline follow-up visits at either outreach or tertiary hospital.

Classification of FEV ₁ impairment based on PURE study criteria ¹⁴	Outreach (IROC) Clinics				Tertiary Hospital Clinics			
	Baseline n (%)	Follow-up n (%)	Change ±n	p*	Baseline n (%)	Follow-up n (%)	Change ±n	p*
Whole cohort	n=252				n=2249			
No impairment (Z-score ≥0)	89 (35.3%)	118 (46.8%)	+29	0.0086	611 (27.2%)	714 (31.7%)	+103	0.0008
Mild (Z-score 0 to -1)	85 (33.7%)	84 (33.3%)	-1	0.93	620 (27.5%)	653 (29.0%)	+33	0.27
Moderate (Z-score -1 to -2)	45 (17.9%)	39 (15.5%)	-6	0.47	467 (20.8%)	438 (19.5%)	-29	0.28
Severe (Z-score <-2)	33 (13.1%)	11 (4.4%)	-22	0.0005	551 (24.5%)	444 (19.8%)	-107	<0.0002
Asthma	n=154				n=681			
No impairment (Z-score ≥0)	56 (36.4%)	77 (50.0%)	+21	0.016	238 (34.9%)	297 (43.6%)	+59	0.0011
Mild (Z-score 0 to -1)	53 (34.4%)	56 (36.4%)	+3	0.72	209 (30.7%)	234 (34.4%)	+25	0.15
Moderate (Z-score -1 to -2)	28 (18.2%)	19 (12.3%)	-9	0.15	128 (18.8%)	97 (14.2%)	-31	0.024
Severe (Z-score <-2)	17 (11.0%)	2 (1.3%)	-15	-	106 (15.6%)	53 (7.8%)	-53	<0.0002
Bronchiectasis	n=46				n=185			
No impairment (Z-score ≥0)	11 (23.9%)	21 (45.7%)	+10	0.029	53 (28.6%)	62 (33.5%)	+9	0.31
Mild (Z-score 0 to -1)	18 (39.1%)	10 (21.7%)	-8	0.070	42 (22.7%)	47 (25.4%)	+5	0.54
Moderate (Z-score -1 to -2)	6 (13.0%)	8 (17.4%)	+2	0.56	32 (17.3%)	39 (21.1%)	+7	0.36
Severe (Z-score <-2)	11 (23.9%)	7 (15.2%)	-4	0.29	58 (31.4%)	37 (20.0%)	-21	0.013

*Comparison of baseline and follow-up spirometry.

6.5 DISCUSSION

We report for the first time how the spirometry of children (n=252) managed by specialist paediatric respiratory outreach teams compares to that of children seen at paediatric tertiary hospitals (n=2249). Significant improvements in spirometry Z-scores and %predicted values for FEV₁ and FVC were seen in both clinic settings (mean Δ zFEV₁=0.35, 4.6%; Δ zFVC=0.36, 4.7% at IROC vs. Δ zFEV₁=0.22, 2.9%; Δ zFVC=0.23, 3.1% at tertiary hospitals) with no significant differences in improvements between both groups. We found significant increases in the number of children with no FEV₁ impairment (as determined by PURE study criteria)¹¹⁴ following specialist care at both clinic types (29 of 163 with impairment at baseline (18%) at IROC and 103 of 1638 (6.3%) at tertiary hospitals), as well as for children with asthma seen at both clinic types. For children with bronchiectasis, the number with no FEV₁ impairment increased significantly among those seen at IROC but there was no significant change in the tertiary hospital group.

Our study is novel and important for several reasons. We found that children seen at IROC clinics in regional and remote Queensland have significantly improved lung function following ≥ 12 months of specialist care which is comparable to improvements in children seen at respiratory clinics in paediatric tertiary hospitals in Brisbane. Secondly, the findings suggest that the outreach services can deliver effective care while reducing or eliminating many of the hurdles to accessing specialist care faced by those in regional and remote settings. Finally, cultural complexity is not an insurmountable obstacle to offering a high-quality service when effort is made to engage communities and tailor the service appropriately. These results have implications, globally, for equity in health service delivery for people living in remote regions.

When applying PURE study criteria¹¹⁴ for FEV₁ impairment to both outreach and tertiary hospital groups, we observed a significant increase in the number of children with FEV₁ ≥ 0 . While this result is promising, there remains a large percentage of children with some level of FEV₁ impairment for both IROC and tertiary hospital groups. Graded increases in the risk of mortality, cardiovascular events, and respiratory hospitalisation occur with worsening FEV₁ impairment,¹¹⁴ and it is known that mortality rates, risk of hospitalisation, and engagement in high risk behaviour such as smoking and alcohol consumption increase with geographic remoteness.¹⁷⁰ These issues are further compounded by Indigenous status, whose burden of respiratory disease is 2.5 times higher than non-Indigenous Australians,² in addition to higher burden of cardiovascular disease and mortality.^{3,61}

Indigenous adults with bronchiectasis are reported to have lung function in the severe⁷ range (median FEV₁=30%; FVC=41% predicted), where their median age of respiratory-related death (48.8 years, IQR 36.4, 52.9) is 20 years earlier than for non-Indigenous adults (69.6 years, IQR 64.2, 75.1).¹⁰¹ The values we report for children with bronchiectasis seen at IROC clinics are substantially higher at follow-up (median FEV₁=96.5%; FVC=95.3% predicted) than the adult data. In addition, we report a significant increase in the number of these children with no FEV₁ impairment after specialist care (baseline=11, follow-up=21, p=0.029). Current data shows that children with bronchiectasis who do not receive optimal care deteriorate.^{166,167} In this context, the IROC model of care is important for the continued optimisation of lung function in children who are disadvantaged by remoteness and further disadvantaged by being Indigenous (73% of children seen), and may help to prevent continued decline into adulthood. Long term ready access to specialist respiratory care services for remote and tertiary centre patients may prevent the drastic deterioration in lung function seen in poorly treated bronchiectasis. Other risk factors associated with socio-economic determinants of health such as overcrowding must be concurrently addressed to further improve outcomes.

Lung function trajectory from child to adulthood has received substantial attention of late.⁵¹⁻⁵⁶ Lung function (FEV₁) trajectories, beginning with below average (but still within normal range) or abnormally low FEV₁ in childhood or young adulthood with/without accelerated FEV₁ decline, are now well-supported within the literature and are associated with increased cardiopulmonary and all-cause mortality.⁵¹⁻⁵⁵ Significant associations between chronic obstructive pulmonary disease (COPD) prevalence in adulthood and several abnormal trajectories have been demonstrated in those with below average or low childhood FEV₁, which are further strengthened when followed by accelerated decline occurring as a result of aggravation in adulthood (i.e. smoking or environmental stimuli).^{51,54} There is some evidence catch-up growth may occur,^{55,56,59} and so early identification and management of chronic respiratory illness in childhood/young adulthood may change the lung function trajectory of children treated. Associations with COPD diagnosis in adulthood are particularly relevant in the Indigenous Australian population, who are 2.9 times more likely to smoke⁵⁷ and disproportionately affected by COPD, with incidence rates 2.5 times higher than non-Indigenous Australians.⁵⁸

GLI 2012⁹ reference values were used in this study, with the 'Other' reference set applied for children who were parent self-identified as Indigenous (the majority of whom were seen at IROC clinics). The 'Other' category was recently found to be the most appropriate for children

and young adults within this population²⁰, allowing us to describe the lung function of these children with confidence. Thus, we believe the validation of this category was important to ensure conclusions from this study are meaningful. Future evaluation of adult IROC and other Australian respiratory outreach services with significant numbers of Indigenous patients would benefit from validation of current reference sets to the adult Australian Indigenous population, or the development of a new reference set based on the testing of healthy Indigenous Australian adults.

Regarding diagnoses in the two settings, there is greater heterogeneity in the respiratory diagnoses of children seen at tertiary respiratory clinics compared with IROC clinics. Neuromuscular disease and cystic fibrosis are examples of groups well represented in tertiary hospital clinics that require complex care which is outside the scope of outreach clinics and are characterised by worsening lung function as the disease progresses. Further, we expect that for each disease group, the most severe cases are likely to end up within tertiary care. Therefore, we expected tertiary hospital spirometry to be significantly lower than IROC spirometry, which is what we observed. Comparison of children with specific diagnoses such as asthma and bronchiectasis allowed us to draw meaningful conclusions by minimising confounding factors such as disease heterogeneity and instead compare like-to-like, as well as ensuring the analysis has sufficient sample size by using groups well represented at both clinic types, but we cannot correct for disproportionate representation of severe disease within tertiary care relative to the outreach setting.

Our study has several other limitations. Firstly, this is a retrospective analysis. Secondly, we cannot measure the influence of learning effect on the spirometry of children seen in outreach or tertiary settings. This would have the effect of raising an artificially lowered baseline FVC, caused by sub-maximal inhalation and reduced forced expiratory time. This effect has been previously observed in naïve spirometry subjects when compared to experienced spirometry subjects.¹⁶⁸ This may explain the absence of significant change in FEV₁/FVC% values observed across both clinic types. Further, while all spirometry was performed by experienced paediatric respiratory scientists, these spirometry results are clinically reported values and few may not have met full ATS/ERS criteria.¹⁰

In conclusion, we have demonstrated that our model of paediatric respiratory outreach clinics offering specialist care to regional and remote Queensland communities results in improvement in spirometry comparable to that seen in paediatric tertiary hospital patients in Brisbane. Despite significant improvements in the lung function of children in both outreach

and tertiary hospital groups at follow-up, a substantial number of children have impaired FEV₁. This is particularly important for children disadvantaged by both remoteness and Indigenous status, who are already at increased risk of cardiovascular disease, respiratory hospitalisation, and mortality. Thus, while this high-quality model of care that improves lung function is important, particularly in the context of recent research in establishing lung function trajectories and COPD prevalence, addressing other risk factors associated with non-attainment of optimal lung function within these populations must be addressed concurrently.

6.6 SUPPLEMENTARY MATERIAL

6.6.1 Data verification

Tertiary hospital clinic data was extracted from electronic databases and combined into a single electronic database. Consideration was given to differences in clinic operation and structure at the three separate tertiary sites in addition to information availability. Data from each site was verified separately with available supporting evidence for patient diagnosis. Data from former paediatric tertiary facilities was verified against electronic medical records, clinic letters, and respiratory nurse records. It was considered that QCH data did not require verification of diagnosis associated with the lung function test due to the increased level of nursing support and availability of information to respiratory scientists at the time of testing.

6.6.2 Spirometry data

Median zFEV₁, zFVC and zFEV₁/FVC% values of whole cohort children (Table 12) tested at IROC were significantly higher than in the whole cohort of children tested at tertiary hospitals at both baseline ($p<0.0001$; $p=0.001$; $p=0.034$) and at follow-up ($p<0.0001$; $p<0.0001$; $p=0.039$) visits. At their baseline, children at IROC and tertiary hospitals with a diagnosis of asthma had similar zFEV₁ and zFVC values ($p=0.26$; $p=0.62$), however children at IROC had significantly higher zFEV₁/FVC% ($p=0.007$). Children with bronchiectasis had similar zFEV₁ and zFVC at baseline for both clinic types ($p=0.47$; $p=0.92$), however children at IROC had significantly better zFEV₁/FVC% ($p=0.041$).

6.6.3 Regression

When adjusting for differences between clinic types in the age of children at baseline, and the duration of their care, we found there were no significant intergroup differences within the whole group for Δ zFEV₁ (0.04, 95%CI -0.19, 0.11, $F(1,2497)=0.217$, $p=0.64$) and Δ zFVC (0.03, 95%CI -0.12, 0.18, $F(1, 2497)=0.139$, $p=0.71$). There were no significant differences between clinic types in children with asthma for both Δ zFEV₁ (-0.04, 95%CI -0.24, 0.16, $F(1,$

831)=0.234, $p=0.67$) and $\Delta zFVC$ (-0.03, 95%CI -0.22, 0.17), and in children with bronchiectasis for $\Delta zFEV_1$ (-0.07, 95%CI -0.43, 0.29, $F(1, 227)=0.155$, $p=0.69$) and $\Delta zFVC$ (-0.17, 95%CI -0.02, 0.61, $F(1, 227)=0.895$, $p=0.35$).

Chapter 7: Determinants and follow-up of lung function data from a predominantly First Nations cohort of adults referred to specialist respiratory outreach clinics in regional and remote Queensland

This chapter addresses the first part of Objective 3 outlined in Section 1.4; “Evaluate determinants and changes in lung function ... in adults treated through IROC”. The following publication within a peer-reviewed journal was produced:

Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Dent A, Blake T, Mawn P, Fong K, McElrea MS. Determinants and Follow-up of Lung Function Data from a Predominantly First Nations Cohort of Adults Referred to Specialist Respiratory Outreach Clinics in Regional and Remote Queensland. *Lung*. 2021;199(4):417-25.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

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Margaret McElrea	Reviewed draft manuscript, input into study design

7.1 ABSTRACT

7.1.1 Purpose

Northern Territory (NT)-based clinical service data suggest substantial lung function impairment among First Nations adults as young as 18-40 years. Our objectives were to describe the burden of disease and lung function of adults living in regional-remote Queensland, identify determinants of lung function, and evaluate the impact of a specialist respiratory outreach service on their lung function.

7.1.2 Methods

Retrospective 8-year cohort study (February 2012-March 2020) of 1765 adults (1113 First Nations Australians) referred to specialist respiratory outreach clinics at regional-remote sites across Queensland.

7.1.3 Results

In the combined cohort, the forced expiratory volume in 1 second (FEV₁) was clinically abnormal for 53% of patients (54% of First Nations patients), forced vital capacity (FVC) for 42% (46%), FEV₁/FVC% for 32% (30%), and gas diffusing capacity (D_{LCO}) for 42% (44%). A respiratory diagnosis was assigned by a respiratory physician in 77% of patients. First Nations lung function was higher than that reported by other similar cohort studies in the NT. Smoking, second-hand household smoke exposure, below normal BMI, and respiratory disease

were associated with reduced lung function. In the 40% (709/1765) followed-up, FEV₁ and FVC significantly improved (mean change: zFEV₁=0.15 [95%CI 0.10-0.20]; zFVC=0.25 [0.20, 0.31]), FEV₁/FVC% significantly reduced (mean=-0.10 [95%CI -0.07 to -0.03]), with no significant change in D_{LCO}. Patients with COPD had less FEV₁ improvement, while underweight and obese patients had less FVC improvement.

7.1.4 Conclusion

Regional/remote First Nations adult Queenslanders have higher lung function than previously reported, and those followed up had improved lung function following specialist outreach care.

7.2 INTRODUCTION

Australians are among the healthiest people in the world, comparing favourably to other countries in all areas except for alcohol consumption and rate of obesity.⁵⁷ Continued improvements to life expectancy have been coupled with reduced years at ill health, but these improvements are not ubiquitous. For the 29% of Australians living in rural and remote areas,⁵⁷ there is significantly increased risk of disease-associated morbidity and mortality (up to 1.7 times in outer regional and remote areas) relative to Australians living in urban areas.¹⁷⁰ Reasons for this health inequality are complex; contributing factors include financial and logistical barriers to accessing healthcare and social determinants of health.¹⁷⁰

Health gaps are further heightened among Aboriginal and/or Torres Strait Islander Australians (henceforth respectfully referred to as First Nations), who are disproportionately affected by a range of chronic diseases that account for 77% of the mortality gap between First Nations and non-First Nations peoples.⁴ There are many reasons for this gap but the lack of culturally-appropriate services is one factor that likely contributes to inadequate healthcare access.¹⁶¹ Within the literature, culturally appropriate outreach services have been shown to improve outcomes.^{160,161} Indigenous Respiratory Outreach Care (IROC), a culturally appropriate specialist respiratory service that delivers care to regional and remote Queensland communities with high proportions of First Nations Australians, was established in 2011.⁸¹ IROC, staffed by First Nations project officers and respiratory physicians, nurses, physiotherapists, and respiratory scientists, engages with community Elders groups and works closely with local primary care teams (community doctor, nurse, and First Nations health workers). These local teams refer patients to the IROC service and implement the delivery of the suggested clinical management. The value of IROC has been objectively demonstrated for

children where it was found that the spirometric lung function of First Nations children with asthma and bronchiectasis significantly improved following at least 12 months of IROC-specialist care service.¹⁷³ We further showed that these improvements were comparable to those of children seen at tertiary paediatric facilities in Brisbane.¹⁷⁴ To date, there has been no published objective evaluation of any culturally appropriate respiratory service for First Nations adults.

The two largest reported contributors to lung disease in First Nations adults are chronic obstructive pulmonary disease (COPD)⁵⁷ and asthma (3 and 1.9 times more common in First Nations compared with non-First Nations Australians⁴ respectively).⁹⁴ These data were obtained from epidemiological studies which may be inaccurate as both conditions have high disease misclassification (as high as 31% for COPD).⁹⁵ Accurate diagnostic data from a large cohort of adults would contribute to the current sparsity of First Nations specific data.

Lung function tests are important for diagnosing and monitoring lung disease.^{8,41} Further, spirometry values (particularly forced expiratory volume in 1 second, FEV₁) independently predict future respiratory and cardiovascular morbidity and all-cause mortality, with an effect size greater than traditional risk factors such as smoking and hypertension.¹¹⁴ These relationships are particularly important to First Nations Australians, who have a high respiratory and cardiovascular disease morbidity and mortality burden.⁴ Despite its importance, published lung function data for First Nations adults is sparse. Existing data suggests that significant lung function derangement is common among First Nations adults as young as 18-40 years,¹⁰⁰ particularly in the presence of bronchiectasis and COPD where severe airflow limitation is present in the majority of patients seen at respiratory clinics.^{101,102}

To address these important knowledge gaps, we evaluated the lung function data of 1765 adults (1113 First Nations Australians) who received specialist clinical care through IROC clinics. Our study's objectives were to (i) describe the lung function and burden of respiratory disease within these populations, (ii) determine factors that impact upon lung function, given its importance to overall health and utility as a predictor of future outcomes,⁹⁵ and (iii) determine whether the IROC service has any impact on the lung function of adults treated by analysing follow-up spirometry.

7.3 METHODS

7.3.1 Study design, setting, and participants

This was an 8-year cohort study (February 2012–March 2020) of adults referred to the IROC service through their primary care physicians, First Nations health workers, or self-referral. Data were prospectively collected as part of the service.

Clinics were held in regional and remote Queensland communities. Inclusion criteria were adults aged >18 years at first IROC clinic visit, who were medically reviewed and had spirometry and/or gas diffusion tests performed by a respiratory scientist. Although IROC focuses on First Nations Australians, non-First Nations adults within these communities were also referred to the service. Ethical approval was granted by The Prince Charles Hospital Human Research Ethics Committee (HREC/2019/QPCH/58452).

7.3.2 Lung function testing

Spirometry and gas diffusion testing were performed according to American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria^{8,41} on either EasyOne Lab or EasyOne Pro Lab (nidd Medizintechnik) portable machines. Global Lung Function Initiative (GLI) 2012 reference values⁹ were applied to spirometry tests, and GLI 2017 reference values⁴³ were applied to gas diffusion tests, to derive Z-scores for each patient (see the supplement for more information on Z-score usage in lung function testing). This study uses re-calculated gas diffusion reference values issued in a correction by the GLI in October 2020.¹⁷⁵ For patients >85 years, the Miller 1983 reference equations were used for gas diffusion tests.¹⁷⁶ The GLI 2012 “Other/mixed” classification was used for spirometry for patients who self-identified as First Nations.²⁰ For all other patients, the “Caucasian” classification was used. Pre-bronchodilator spirometry was used for all lung function analysis except for Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹¹ staging, where post-bronchodilator spirometry was used.

7.3.3 Data verification

Patient demographics, lung function data, respiratory diagnosis as confirmed by a respiratory physician, comorbidities, smoking behaviours, and secondary smoke exposure were collected at each clinic visit and stored electronically. Missing information was filled where possible using electronic and paper chart medical records. Patients were excluded from the study if there were gaps in data.

7.3.4 Statistical analysis and definitions

Data distributions were examined visually and numerically. Non-parametric tests were used for non-normally distributed data whilst parametric tests were used for normally distributed data. Pre-bronchodilator spirometry and gas diffusion measurements at baseline and follow-up were normally distributed. Pre-bronchodilator spirometry data was used for both baseline and follow-up visits. Follow-up spirometry and gas diffusion values were determined by highest $zFEV_1$ and zD_{LCO} values occurring within the last 12 months of care, and at least 3 months after baseline spirometry. GLI 2012 derived Z-scores were used for statistical analysis; however, we also present baseline lung function as percentages of predicted (% predicted) values for various diagnoses to enable comparison with other cohort studies using % predicted values (see the supplement for more information).

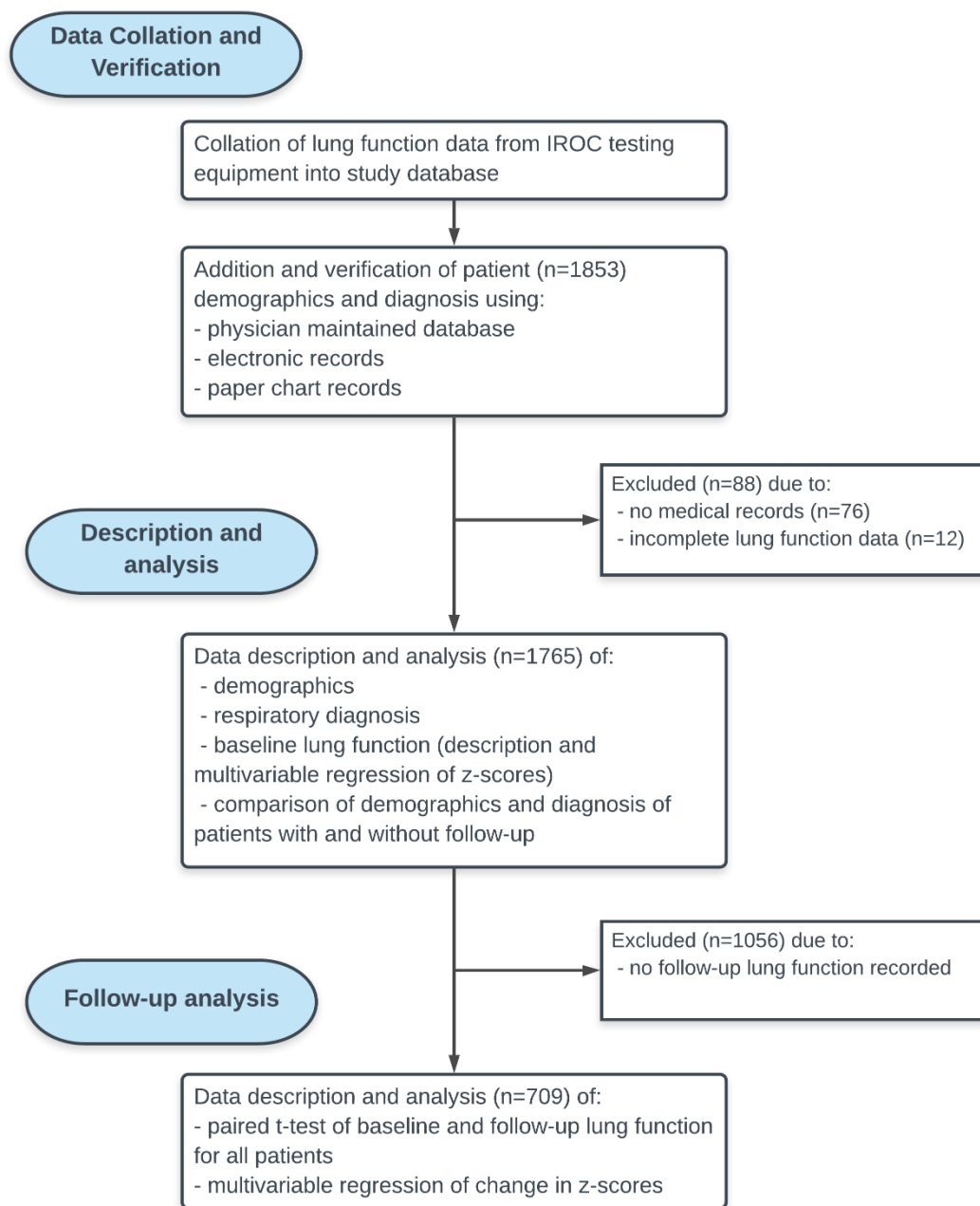
Baseline spirometry and gas diffusion data were examined using multivariable regression modelling. Regression coefficients and their associated 95% confidence intervals (95%CI) and p-values were reported. Change (Δ) in Z-scores was modelled similarly, with length of care as an added covariate. Stata 16.1 (StataCorp LLC) was used for statistical analyses; 2-tailed p-values <0.05 were considered significant.

7.4 RESULTS

7.4.1 Cohort summary

Of the 1853 patients with lung function data, our final cohort consisted of 1765 adults (Figure 19). Demographic and respiratory diagnosis data for the cohort ($n=1765$) are summarised in Table 14, with baseline lung function including GOLD¹¹ staging for COPD summarised in Table 15. First Nations adults were younger, more likely female, and more likely to smoke and be exposed to second-hand household smoke when compared to non-First Nations adults.

Figure 19. Flow diagram of study data collection, verification, and analysis.



7.4.2 Spirometry and gas diffusing capacity

Multivariable regression showed that BMI, First Nations status, smoking (including second-hand household exposure) and respiratory diagnosis significantly influenced lung function (Table 16). Those with COPD (mean FEV_1 =58% predicted, SD=21; FVC=74% predicted, SD=19; FEV_1/FVC =62%, SD=16; D_{LCO} =64% predicted, SD=22), bronchiectasis (mean FEV_1 =63% predicted, SD=25; FVC=73% predicted, SD=23; FEV_1/FVC =67%, SD=13, D_{LCO} =77% predicted, SD=26) and pulmonary hypertension (mean FEV_1 =55% predicted,

SD=21; FVC=65% predicted, SD=19; FEV₁/FVC=66%, SD=13; D_{LCO}=63% predicted, SD=24) had significantly poorer lung function compared with those without these diseases.

Table 14. Summary of patient demographics and lung function at first presentation to IROC clinics.

		Whole Group n=1765	First Nations n=1117	Non-First Nations n=648
		Median (IQR) or n (%)		
Age (years)		57 (48 – 67)	55 (45 – 64)	63 (53 – 72)
BMI (kg/m ²)	Underweight (<18.5)	83 (5%)	55 (5%)	28 (4%)
	Normal (18.5-24.9)	340 (19%)	198 (18%)	142 (22%)
	Overweight (25-29.9)	428 (24%)	247 (22%)	181 (28%)
	Obese (≥30)	914 (52%)	617 (55%)	297 (46%)
Female		1027 (58%)	689 (62%)	338 (52%)
Smoking	Current	606/1585 (38%)	477/1044 (46%)	129/541 (24%)
	Former	565/1585 (36%)	327/1044 (31%)	238/541 (44%)
	Never	414/1585 (26%)	240/1044 (23%)	174/541 (32%)
Household smoke		570/1396 (41%)	447/945 (47%)	123/451 (27%)
Respiratory disease burden	No diagnosis	399 (23%)	246 (22%)	153 (24%)
	1 diagnosis	851 (48%)	561 (50%)	290 (45%)
	2 diagnosis	409 (23%)	262 (25%)	147 (23%)
	3+ diagnosis	106 (6%)	48 (4%)	58 (9%)
Common respiratory diagnoses*	COPD	623 (35%)	394 (35%)	229 (35%)
	Asthma	574 (33%)	379 (34%)	195 (30%)
	OSA	352 (20%)	242 (22%)	110 (17%)
	Bronchiectasis	70 (4%)	39 (4%)	31 (5%)
	Pulm hypertension	39 (2%)	20 (2%)	19 (3%)

*Patients may have concurrent respiratory diagnoses. Abbreviations: COPD, chronic obstructive pulmonary disease. OSA, obstructive sleep apnoea.

7.4.3 Follow-up

Of the 1765 patients in the cohort, 709 (40%) attended clinically for follow-up review visits. The median duration of care (from baseline to last visit to IROC) was 17 months (IQR 6, 36). Of the 709 patients who were followed-up, 698 had spirometry performed. Patients lost to follow-up.

Table 18 within the supplement compares the demographics and lung function data of those patients who were followed-up to those who were not. Patients followed-up clinically were more likely to have respiratory disease and associated poorer lung function.

Table 15. Summary of lung function at first presentation to IROC clinics, including GOLD staging of patients with COPD.

		Whole Group n=1765	First Nations n=1117	Non-First Nations n=648
		Mean (SD)		
Spirometry (n=1734)	FEV ₁ (% pred)	72 (23)	72 (22)	72 (25)
	FEV ₁ (Z-score)	-1.81 (1.43)	-1.84 (1.41)	-1.76 (1.49)
	FVC (% pred)	80 (19)	80 (19)	81 (19)
	FVC (Z-score)	-1.44 (1.38)	-1.53 (1.44)	-1.27 (1.27)
	FEV ₁ /FVC (%)	71 (14)	73 (13)	69 (15)
	FEV ₁ /FVC (Z-score)	-1.06 (1.64)	-1.01 (1.64)	-1.56 (1.64)
Gas diffusing capacity (n=1297)	D _{LCO} (% pred)	81 (25)	81 (24)	82 (26)
	D _{LCO} (Z-score)	-1.45 (1.92)	-1.51 (1.87)	-1.34 (1.99)
GOLD (post-bronchodilator)		n (%)		
COPD & FEV ₁ /FVC <0.70				
GOLD 1 (Mild)	FEV ₁ ≥80% pred	64/375 (17%)	48/248 (19%)	16/127 (13%)
GOLD 2 (Moderate)	FEV ₁ 50-79% pred	203/375 (54%)	137/248 (55%)	66/127 (52%)
GOLD 3 (Severe)	FEV ₁ 30-49% pred	84/375 (22%)	51/248 (21%)	33/127 (26%)
GOLD 4 (Very Severe)	FEV ₁ <30% pred	24/375 (6%)	12/248 (5%)	12/127 (9%)

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease. COPD, chronic obstructive pulmonary disease. Pred, predicted.

Over the duration of treatment, we observed significant increases in mean zFEV₁ and zFVC, and a significant decrease in zFEV₁/FVC (Table 17). Regression analyses found improvements to FEV₁ and FVC at follow-up to be similar for most demographic factors and respiratory diagnosis. However, we found weak evidence that for the overweight and obese groups, increases in FVC were significantly lower ($\beta=-0.38$, $p<0.01$; $\beta=-0.21$, $p=0.02$) than the normal group (full regression presented in Table 4), and decreases in FEV₁/FVC were greater for First Nations patients ($\beta=-0.17$, $p=0.03$).

Follow-up gas diffusion testing of 253 of 709 patients showed no significant changes in zD_{LCO}. This result was similar across demographic and respiratory diagnosis categories except for former smokers (vs. never smokers) ($\beta=-0.46$, $p=0.02$).

Table 16. Regression testing the effects of demographics and respiratory diagnoses on baseline lung function Z-scores.

		zFEV ₁ (n=1734)		zFVC (n=1734)		zFEV ₁ /FVC% (n=1734)		zD _{LCO} (n=1297)	
		β (95%CI)	p	β (95%CI)	p	β (95%CI)	p	β (95%CI)	p
Age (10 years)		-0.04 (-0.08, 0.01)	0.13	-0.05 (-0.09, 0.00)	0.07	-0.02 (-0.07, 0.00)	0.43	-0.23 (-0.30, -0.17)	<0.01
BMI*	Underweight	-0.47 (-0.78, -0.15)	<0.01	-0.40 (-0.72, -0.08)	0.02	-0.24 (-0.59, 0.11)	0.18	-1.17 (-1.60, -0.73)	<0.01
	Normal	Reference	-	Reference	-	Reference	-	Reference	-
	Overweight	0.20 (0.01, 0.38)	0.08	0.11 (-0.09, 0.30)	0.28	0.30 (0.09, 0.51)	<0.01	0.31 (0.04, 0.57)	0.02
	Obese	0.08 (-0.09, 0.25)	0.60	-0.13 (-0.31, 0.05)	0.15	0.46 (0.26, 0.65)	<0.01	0.83 (0.58, 1.08)	<0.01
Sex	Female	0.06 (-0.07, 0.19)	0.36	-0.02 (-0.15, 0.12)	0.80	0.21 (0.07, 0.35)	<0.01	-0.05 (-0.22, 0.13)	0.60
First Nations		-0.08 (-0.21, 0.06)	0.27	-0.26 (-0.40, -0.12)	<0.01	0.11 (-0.05, 0.26)	0.17	-0.44 (-0.62, -0.25)	<0.01
Smoking	Current	-0.30 (-0.48, -0.12)	<0.01	-0.15 (-0.33, 0.04)	0.13	-0.31 (-0.52, -0.11)	<0.01	-0.12 (-0.37, 0.13)	0.33
	Former	-0.30 (-0.48, -0.13)	<0.01	-0.15 (-0.33, 0.03)	0.09	-0.40 (-0.59, -0.20)	<0.01	-0.22 (-0.46, 0.02)	0.07
	Never	Reference	-	Reference	-	Reference	-	Reference	-
Household smoke		-0.20 (-0.35, -0.06)	<0.01	-0.23 (-0.38, -0.08)	<0.01	-0.02 (-0.18, 0.14)	0.80	-0.16 (-0.35, 0.04)	0.11
Asthma (n=574)		-0.29 (-0.43, -0.15)	<0.01	-0.06 (-0.20, 0.08)	0.40	-0.55 (-0.71, -0.40)	<0.01	0.58 (0.39, 0.77)	<0.01
COPD (n=623)		-1.07 (-1.22, -0.92)	<0.01	-0.58 (-0.73, -0.43)	<0.01	-1.27 (-1.44, -1.11)	<0.01	-1.40 (-1.60, -1.20)	<0.01
OSA (n=352)		0.10 (-0.07, 0.26)	0.24	-0.07 (-0.24, 0.10)	0.42	0.29 (0.11, 0.48)	<0.01	0.29 (0.07, 0.51)	0.01
Bronchiectasis (n=70)		-0.44 (-0.76, -0.12)	<0.01	-0.44 (-0.77, -0.12)	<0.01	-0.32 (-0.68, 0.03)	0.07	-0.10 (-0.53, 0.33)	0.65
Pulm htn (n=39)		-0.84 (-1.21, -0.48)	<0.01	-0.82 (-1.26, -0.37)	<0.01	-0.36 (-0.84, 0.12)	0.14	-1.10 (-1.69, -0.52)	<0.01

Regression model adjusted for patient age. *BMI categories: Underweight (<18.5kg/m²), Normal (18.5-24.9 kg/m²), Overweight (25-29.9 kg/m²), Obese (≥30 kg/m²).

Abbreviations: COPD, chronic obstructive pulmonary disease. OSA, obstructive sleep apnoea. Pulm htn, pulmonary hypertension.

Table 17. Mean changes in lung function Z-scores from baseline to follow-up visit with regression testing.

		$\Delta zFEV_1$ (n=698)		$\Delta zFVC$ (n=698)		$\Delta zFEV_1/FVC\%$ (n=698)		ΔzD_{LCO} (n=253)	
Paired sample t-test		Mean Δ (95%CI)	p	Mean Δ (95%CI)	p	Mean Δ (95%CI)	p	Mean Δ (95%CI)	p
		0.15 (0.10, 0.26)	<0.01	0.25 (0.20, 0.31)	<0.01	-0.10 (-0.17, -0.03)	<0.01	0.08 (-0.05, 0.21)	0.22
Regression		β (95%CI)	p	β (95%CI)	p	β (95%CI)	p	β (95%CI)	p
Age (10 years)		-0.01 (-0.05, 0.04)	0.75	-0.01 (-0.05, 0.04)	0.84	-0.01 (-0.07, 0.05)	0.72	0.02 (-0.10, 0.15)	0.69
Duration of Care#		0.06 (0.04, 0.08)	<0.01	0.06 (0.04, 0.08)	<0.01	0.03 (0.01, 0.05)	0.01	0.04 (0.00, 0.08)	0.03
BMI*	Underweight	-0.19 (-0.43, 0.05)	0.12	-0.38 (-0.66, -0.10)	<0.01	0.23 (-0.09, 0.55)	0.20	-0.11 (-0.80, 0.58)	0.76
	Normal	Reference	-	Reference	-	Reference	-	Reference	-
	Overweight	-0.11 (-0.27, 0.05)	0.18	-0.16 (-0.34, 0.02)	0.08	-0.03 (-0.24, 0.18)	0.83	0.09 (-0.32, 0.51)	0.66
	Obese	-0.14 (-0.29, 0.01)	0.08	-0.21 (-0.38, -0.03)	0.02	-0.05 (-0.25, 0.15)	0.65	0.00 (-0.42, 0.43)	0.98
Sex	Female	0.02 (-0.08, 0.13)	0.67	-0.02 (-0.14, 0.10)	0.74	0.00 (-0.14, 0.14)	1.00	0.08 (-0.19, 0.36)	0.55
First Nations		-0.05 (-0.16, 0.07)	0.42	0.05 (-0.08, 0.18)	0.46	-0.17 (-0.32, -0.02)	0.03	0.10 (-0.20, 0.40)	0.52
Smoking	Current	-0.10 (-0.25, 0.05)	0.20	-0.13 (-0.30, 0.04)	0.14	0.02 (-0.18, 0.21)	0.85	-0.31 (-0.73, 0.11)	0.15
	Former	-0.04 (-0.18, 0.10)	0.58	-0.09 (-0.25, 0.07)	0.25	0.09 (-0.09, 0.27)	0.34	-0.46 (-0.85, -0.07)	0.02
	Never	Reference	-	Reference	-	Reference	-	Reference	-
Household smoke		0.06 (-0.05, 0.17)	0.30	0.03 (-0.10, 0.15)	0.66	0.05 (-0.09, 0.20)	0.48	-0.27 (-0.55, 0.02)	0.07
Asthma (n=262)		0.05 (-0.07, 0.17)	0.40	0.08 (-0.05, 0.22)	0.20	0.14 (-0.01, 0.29)	0.07	0.10 (-0.22, 0.43)	0.52
COPD (n=299)		-0.13 (-0.26, -0.01)	0.04	-0.06 (-0.21, 0.08)	0.38	-0.13 (-0.29, 0.03)	0.12	0.07 (-0.25, 0.37)	0.68
OSA (n=195)		-0.05 (-0.18, 0.07)	0.42	-0.05 (-0.19, 0.10)	0.50	0.01 (-0.15, 0.18)	0.88	0.20 (-0.13, 0.54)	0.23
Bronchiectasis (n=42)		0.13 (-0.08, 0.35)	0.22	0.35 (-0.01, 0.72)	0.26	0.16 (-0.12, 0.44)	0.68	0.22 (-0.36, 0.79)	0.46
Pulm htn (n=18)		0.28 (-0.04, 0.60)	0.08	0.36 (-0.02, 0.75)	0.07	-0.02 (-0.46, 0.42)	0.93	0.21 (-0.92, 0.50)	0.57

#Duration of care from baseline to best follow-up visit occurring within last 12 months of care. *BMI categories: Underweight (<18.5kg/m²), Normal (18.5-24.9 kg/m²), Overweight (25-29.9 kg/m²), Obese ($\geq$ 30 kg/m²). Regression model adjusted for patient age and length of care. Abbreviations: COPD, chronic obstructive pulmonary disease. OSA, obstructive sleep apnoea. Pulm htn, pulmonary hypertension.

7.5 DISCUSSION

In our study involving spirometry and gas diffusing capacity of 1765 adults (approximately two-thirds First Nations) managed by specialist respiratory outreach teams in Queensland, we found baseline FEV₁ Z-scores were below the clinical normal range (defined as -1.64 and above) for the 52% of the whole cohort, and for 54% of the First Nations group (Table 2). Baseline FVC Z-scores were clinically abnormal for 42% of patients (46% First Nations), baseline FEV₁/FVC% for 32% (30% First Nations), and gas diffusing capacity (D_{LCO}) for 42% (44% First Nations). Baseline mean FVC, FEV₁/FVC, and D_{LCO} Z-scores were within the clinically normal range. The majority (77%) of patients were assigned a respiratory diagnosis, with COPD, asthma, and OSA the most common diagnoses seen and treated. Diagnosed respiratory disease, smoking, second-hand household smoke exposure, and below normal BMI were associated with reduced lung function. At follow-up, there were statistically significant improvements in lung function, with increased mean FEV₁ and FVC and significant decline in FEV₁/FVC%, while D_{LCO} was unchanged ($p>0.05$).

Our study of adults managed at a specialist respiratory outreach service within an IROC model is the first such report in Australia. To our knowledge, only two similar Australian studies exist^{100,102} but neither examined follow-up data or factors that influenced lung function data. Both previous studies were retrospective and reported on First Nations patients seen at respiratory outreach services within the Northern Territory (NT).^{100,102} The NT-based study's findings were different to ours in the following ways: (i) the mean FEV₁ values reported (55%¹⁰⁰ and 42%¹⁰² predicted) were well below that of the First Nations adults at IROC clinics (72% predicted) despite similar age distributions,^{100,102} and (ii) marked differences in bronchiectasis incidence (4%) compared to the NT studies that reported 19% and 50% respectively.^{100,102} In one instance, the reference values used were not disclosed by the authors,¹⁰² while the National Health and Nutrition Examination Survey III (NHANES III)¹⁷⁷ values, without ethnic correction, were used in another.¹⁰⁰ NHANES III reference values give higher predicted values and therefore lower Z-scores than the GLI 2012 "Other/mixed" for any given raw value, and so these differences in reported lung function between our study and previous NT studies are likely overestimated. These differences therefore detract from the comparability of absolute values Z-scores and %predicted values reported. Possible reasons for actual disparity in lung function may include timelier referral by primary care physicians and IHWs in the Queensland model, and differences in patient sampling (a proportion of patients are referred for respiratory health checks).

Our clinical review follow-up cohort was small (only 40% of IROC patients had follow-up lung function) and had poorer lung function than those not followed-up. Reasons for the relatively small group include: (i) patients (n=253) not assigned a respiratory diagnosis (many of whom were respiratory health check referrals), were more likely to be discharged back to their primary care team and not seen for follow-up, (ii) 11% (n=201) of patients included at baseline are known to have died at the time of writing, and (iii) some had moved away from IROC clinic sites.

Changes in follow-up spirometry (improvements in zFEV₁ and zFVC, reduction in zFEV₁/FVC%) were similar across most demographic factors and respiratory diagnosis, except for COPD and underweight patients where changes in zFEV₁ and zFVC were smaller respectively, and First Nations patients who had a larger reduction in zFEV₁/FVC%. The prognostic value of lung function, particularly FEV₁ as a prognostic marker of mortality, has been well established within the literature,¹¹⁰ and was demonstrated clearly in the PURE¹¹⁴ study. Given the importance of lung function, particularly within at-risk populations such as those in regional and remote areas¹⁷⁰ and First Nations Australians,⁴ it is promising that lung function decline associated with chronic respiratory disease appears to have been somewhat halted through specialist care at IROC. We do, however, interpret these changes with caution, and several study limitations should be considered.

We cannot be certain that these improvements to FEV₁ and FVC parameters may not be, in part, secondary to a learning effect through repetition and improvement in technique over repeated clinic visits. While all lung function testing was performed by experienced respiratory scientists, these results are clinically reported values and a minority may not meet full ATS/ERS criteria.^{8,41} We also cannot discount the influence of survivorship bias, as there were a significant number of patients who were lost to follow-up (Supplement Table S1) for many reasons including those previously mentioned, such as discharge of healthy patients back to primary care, and high First Nations mobility. Without analysis and reporting of patient outcomes, we cannot measure the influence of these effects. Further, while the “Other/mixed” GLI 2012 spirometry reference set has been found to be appropriate for use in First Nations children and young adults (3-25 years), no such reference set validation has been done for spirometry or gas diffusion testing in First Nations adults. Finally, our data includes First Nations adults seen in regional and remote Queensland only. Additional data from other Australian regions are needed to confirm the generalisability of our findings.

Our study has highlighted the demographics and lung function of adults seen at specialist respiratory outreach clinics in regional and remote Queensland. When compared to similar studies

of respiratory outreach services within the NT, adults (including First Nations) seen at IROC had significantly better lung function even at baseline. We determined that patients who are underweight, smoke, are exposed to second-hand household smoking and who are assigned a respiratory diagnosis have significantly poorer lung function. In the 40% of patients seen in which follow-up lung function had been performed, FEV₁ and FVC significantly improved, FEV₁/FVC% reduced significantly, while *D*_{LCO} was unchanged. Given the nature of chronic respiratory diseases present in this population, we suggest that providing culture-appropriate services for adults with respiratory illness may halt the decline in lung function typically seen when diseases such as COPD and bronchiectasis are sub-optimally managed.

7.6 ACKNOWLEDGEMENTS

We acknowledge and thank the First Nations Health Workers, First Nations project officers, doctors, nurses, and clinical measurements scientists on the IROC program for their tireless efforts.

7.7 SUPPLEMENTARY MATERIAL

7.7.1 Lung function Z-scores

Z-scores indicate how many standard deviations away from the predicted value the raw lung function measurement lies. Abnormality in lung function values may be defined in several ways. Some parameters such as spirometric measurements are one-tailed, where abnormality defined by the lower 5th centile (or -1.64 Z-scores) of healthy individuals.⁹ These tests are influenced by several factors, including a person's age, sex, height and ethnicity.¹³⁻¹⁶ The Global Lung Function Initiative (GLI) recommends the use of Z-scores as a superior alternative to % predicted values, as the latter has been associated with age- and height-related biases.¹⁷⁸

We acknowledge other cohort studies, including Australian studies referenced in our article, examine lung function using % predicted values. Therefore, in any instance where we compare our findings to that of other studies, we present lung function in % predicted values for ease of reading. Given the advantages of Z-scores in eliminating bias, we use Z-scores in all our statistical analyses.

7.7.2 Patients lost to follow-up.

Table 18. Comparison of Indigenous Respiratory Outreach Care (IROC) patients seen only once versus those patients seen for follow-up.

Measure		Followed-up (n=709)	Not followed-up (n=1056)
Age (years)		57.9 (49.9 – 67.5)	56.6 (45.3 – 66.7)
BMI (kg/m ²)	Underweight (<18.5)	35 (5%)	48 (5%)
	Healthy (18.5-24.9)	121 (17%)	219 (21%)
	Overweight (25-29.9)	172 (24%)	256 (24%)
	Obese (≥30)	381 (52%)	533 (51%)
Female		412 (58%)	615 (58%)
First Nations		473 (67%)	644 (61%)
Smoking	Current	243/680 (36%)	363/905 (40%)
	Former	256/680 (38%)	309/905 (34%)
	Never	181/680 (27%)	233/905 (25%)
Household smoke	Yes	293/651 (45%)	277/745 (37%)
	No	358/651 (55%)	468/745 (62%)
Respiratory disease burden	No diagnosis	73 (10%)	326 (31%)
	1 diagnosis	365 (52%)	486 (46%)
	2 diagnosis	205 (29%)	204 (19%)
	3+ diagnosis	66 (9%)	40 (5%)
Common respiratory diagnosis*	Asthma	270 (38%)	304 (29%)
	COPD	304 (43%)	319 (30%)
	OSA	195 (28%)	157 (15%)
	Bronchiectasis	42 (6%)	28 (3%)
	Pulm htn	20 (3%)	19 (2%)
Lung function		Mean (SD)	
Spirometry	FEV ₁ (% predicted)	68 (23)	75 (22)
	FEV ₁ (Z-score)	-2.05 (1.45)	-1.65 (1.40)
	FVC (% predicted)	78 (19)	82 (19)
	FVC (Z-score)	-1.62 (1.40)	-1.32 (1.36)
	FEV ₁ /FVC (%)	69 (15)	73 (14)
	FEV ₁ /FVC (Z-score)	-1.28 (1.73)	-0.92 (1.56)
Gas diffusing capacity	D _{LCO} (% predicted)	79 (25)	83 (24)
	D _{LCO} (Z-score)	-1.64 (2.04)	-1.33 (1.82)

*Patients may have concurrent respiratory diagnoses. Abbreviations: COPD, chronic obstructive pulmonary disease. OSA, obstructive sleep apnoea. Pulm, pulmonary. Htn, hypertension.

Chapter 8: Is lung function associated with future cardiovascular morbidity and overall mortality in a predominantly First Nations population?

This chapter addresses the second part Objective 3 outlined in Section 1.4; “Evaluate ... associations between reduced lung function and cardiovascular morbidity in adults treated through IROC”. The following publication within a peer-reviewed journal was produced:

Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Dent A, Blake T, Mawn P, Fong K, McElrea MS. Associations between lung function and future cardiovascular morbidity and overall mortality in a predominantly First Nations population: a cohort study. *Lancet Reg Health West Pac*. 2021;13:100188.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
Andrew Collaro	Drafting of manuscript, led data analysis, input into study design
Anne Chang	Reviewed draft manuscript, data collection, led study design
Julie Marchant	Reviewed draft manuscript, input into study design

Mark Chatfield	Reviewed draft manuscript, assisted with data analysis, input into study design
Annette Dent	Reviewed draft manuscript, data collection, input into study design
Tamara Blake	Reviewed draft manuscript, input into study design
Patsi Mawn	Reviewed draft manuscript, data collection
Kwun Fong	Reviewed draft manuscript, data collection, led study design
Margaret McElrea	Reviewed draft manuscript, input into study design

8.1 ABSTRACT

8.1.1 Background

Spirometric lung function impairment is an independent predictor of respiratory and cardiovascular disease, and mortality across a broad range of socioeconomic backgrounds and environmental settings. No contemporary studies have explored these relationships in a predominantly regional/remote Indigenous population, whose health outcomes are generally worse than for non-Indigenous populations, and Indigenous people living in urban centres.

8.1.2 Methods

This was a retrospective cohort study of 1,734 adults (1,113 First Nations) referred to specialist respiratory outreach clinics in the state of Queensland, Australia from February 2012 to March 2020. Regression modelling was used to test associations between lung function and mortality and cardiovascular disease.

8.1.3 Findings

At the time of analysis (August 2020), 189 patients had died: 88 (47%) from respiratory causes and 38 (20%) from cardiovascular causes. When compared with the normal/mild range of >0 to -1 Z-scores, forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) Z-scores <-1 were associated with elevated mortality risk ($HR=3.2$, 95%CI 1.9-5.4; $HR=3.5$, 95%CI 2.3-5.4), and elevated cardiovascular disease risk ($OR=1.7$, 95%CI 1.2-2.4; $OR=1.9$, 95%CI 1.4-2.5). $FEV_1/FVC\%$ Z-scores <-1 were associated with increased overall mortality ($HR=1.7$, 95%CI 1.3-2.4), but not cardiovascular disease ($OR=1.0$, 95%CI 0.8-1.3). Repeat analysis of the First Nations Australians subgroup produced similar results.

8.1.4 Interpretation

Reduced lung function even in the clinically normal range is associated with increased mortality, and cardiovascular and respiratory disease in First Nations Australians. These findings highlight the importance of lung function optimisation and inform the need for future investment to improve outcomes in Indigenous populations.

8.2 RESEARCH IN CONTEXT

8.2.1 Evidence before this study

We searched PubMed for relevant publications exploring associations between lung function and cardiovascular disease, and mortality. We searched for articles published between database inception to February 2020, using search terms “spirometr*”, “lung function”, “cardiovascular”, “mortality”, and “survival”. We found analyses of data from large-scale cohort studies, literature reviews, and a meta-analysis that examined these associations. One large-scale cohort study included participants from a diverse range of socioeconomic backgrounds and environments. Across all studies, strong associations between FEV₁ and FVC indices were found. Individually, however, there is disagreement as to whether only FEV₁, FVC, or both, independently predict mortality and cardiovascular disease. Notably, we found only one study published in 1988 that included predominantly Indigenous participants; this was the only study to have found any association between FEV₁/FVC% and mortality, but not for other spirometry lung indices. Limitations of that study include that it is no longer contemporary (spirometry data collected in 1970/71), reference values applied were not reported, and other likely confounders (e.g., tobacco smoking, co-morbidities) were not accounted for.

8.2.2 Added value of this study

In this cohort of predominantly First Nations Australians, we found that any lung function impairment, even within the clinical normal range of 0 to -1.64 Z-scores, is associated with increased respiratory and cardiovascular disease risk, and mortality. We provide supportive evidence that both FEV₁ and FVC independently predict these outcomes, and to our knowledge, this is only the second study to find a significant association between FEV₁/FVC% and mortality. Furthermore, this is the only study to establish this association while correcting for factors such as smoking, BMI, and co-morbidities.

8.2.3 Implications of all the available evidence

Our findings highlight the importance of lung function optimisation, particularly in the First Nations Australian population, who like other global Indigenous populations, are at heightened

risk of chronic respiratory and cardiovascular diseases, and early mortality. In the context of recent research findings which show that lung function catch-up growth is possible in children, it is vital that preservation and optimisation of lung function occurs in Indigenous children to alter lung function trajectories and prevent adverse outcomes in adulthood.

8.3 INTRODUCTION

It is increasingly accepted that lung function is an independent prognostic marker not only of respiratory conditions but also of cardiovascular disease and overall mortality^{109,111} even in asymptomatic people without respiratory disease.¹¹³ The relationship between forced expiratory volume in 1 second (FEV₁) and cardiovascular disease mortality has been explored in several large population-based cohort studies.¹⁰⁹⁻¹¹² The prospective urban rural epidemiology (PURE) study with lung function data from 126,359 people from 17 countries found that reduced FEV₁ (even within the clinically normal range) was associated with increased mortality and cardiovascular disease, with an effect size greater than conventional risk factors such as smoking and hypertension.¹¹⁴ Similar correlations have been observed with forced vital capacity (FVC) measurements, and less frequently with the FEV₁/FVC ratio.¹¹¹⁻¹¹⁴

Several mechanisms have been put forward to explain the relationship between lung function and cardiovascular disease. Systemic inflammation,¹⁰⁹ when associated with chronic lung conditions such as chronic bronchitis,¹⁷⁹ has emerged as the most likely mechanism. Furthermore, airflow limitation is an independent predictor of vascular injury and atherosclerosis.^{110,180} The strong associations of both FEV₁ and FVC impairments with coronary artery disease are present even among lifetime non-smokers.¹⁸¹ More recently, lung function impairment has also been associated with congestive heart failure after adjusting for left ventricular function and cardiac stress.¹¹¹

Several large population-based cohort studies have included participants from a range of socioeconomic backgrounds and environmental settings.^{109,114} While the PURE study¹¹⁴ findings were similar among high and low income countries as well as across urban and rural areas, only one previously published study has specifically examined data from Indigenous populations.¹⁸² This is particularly important as First Nations people are among the most disadvantaged groups¹⁵⁷ and First Nations Australians are more affected by chronic disease than their non-First Nations counterparts.⁴ Chronic respiratory disease among First Nations peoples is approximately 2.5 times higher than for non-First Nations,² while cardiovascular disease burden is 1.2 times higher and cardiovascular-related mortality 1.6 times higher.⁴ The relative poorer health of First Nations

Australians is further worsened with increasing geographical remoteness.¹⁸³ Thus, it is important to confirm the prognostic value of lung function in First Nations people, particularly those in regional and remote areas.

Since 2011, we have been part of the Indigenous Respiratory Outreach Care (IROC) program, a specialist respiratory outreach service in Queensland that delivers care directly to regional and remote communities with high First Nations populations. The visiting specialist teams consist of a First Nations project officer, respiratory physician, nurse, and respiratory scientist. Lung function testing is routinely performed by patients at IROC clinics before physician consultation. Using data of adults treated at IROC clinics, we evaluated spirometric measures of lung function, co-morbidities, and demographic factors as predictors of cardiovascular and respiratory morbidity and mortality of the cohort. Our study's aims were to, firstly, determine what demographic and disease factors are associated with reduced lung function, and secondly, to evaluate the prognostic value of spirometric lung function with future cardiovascular disease and mortality.

8.4 METHODS

8.4.1 Study design, setting, and participants

This is an eight-year retrospective cohort study (February 2012-March 2020) of adults referred to the IROC service through their primary care physicians, First Nations health workers or self-referral. Clinics were held in regional and remote Queensland communities. Inclusion criteria were adults aged 18-95 years at IROC clinic visit, who were medically reviewed and had spirometry performed by a trained respiratory scientist. Ethical approval for this study was granted by The Prince Charles Hospital Human Research Ethics Committee (reference: HREC/2019/QPCH/58452).

8.4.2 Lung function testing

Spirometry was performed according to American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria^{8,41} using an EasyOne Pro or EasyOne Pro Lab (ndd Medizintechnik) portable machines. Patients were tested with a nose clip while seated. Global Lung Function Initiative (GLI) 2012 reference values⁹ were applied to spirometry tests to derive Z-scores for each patient. For patients who self-identified as First Nations, the GLI 2012 “Other/mixed” classification was chosen,²⁰ while the “Caucasian” classification was used for non-First Nations patients.

8.4.3 Data verification

Patient demographics, lung function data, respiratory diagnosis, smoking and household smoking status, and comorbidities recorded by a respiratory physician for each patient were collected. Data for mortality and cause of death data was censored in August 2020 and collected from electronic medical records, using death certificates where available, or discharge summaries. Where cause of death was unclear or no information was available, cause of death was flagged as “unknown”. All information was transferred into a separate study database, and missing information was completed where possible using electronic and paper chart medical records.

8.4.4 Definitions and statistical analysis

Pre-bronchodilator spirometry at first visit to IROC was used as the baseline for this study. We analysed the data using categories described by the PURE study¹¹⁴ where FEV₁ Z-scores ≥ 0 are grouped as “no impairment”, <0 to -1 as “mild impairment”, <-1 to -2 as “moderate impairment”, and <-2 as “severe impairment”. We note that only Z-scores ≤ -1.64 (lowest 5% of the reference population) are considered clinically abnormal.⁹

Chronic respiratory disease includes respiratory physician diagnoses of chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, or other chronic pulmonary disease. Cardiovascular disease includes ischaemic heart disease, congestive heart failure, stroke or transient ischaemic attack (TIA), and cardiac valve disease.

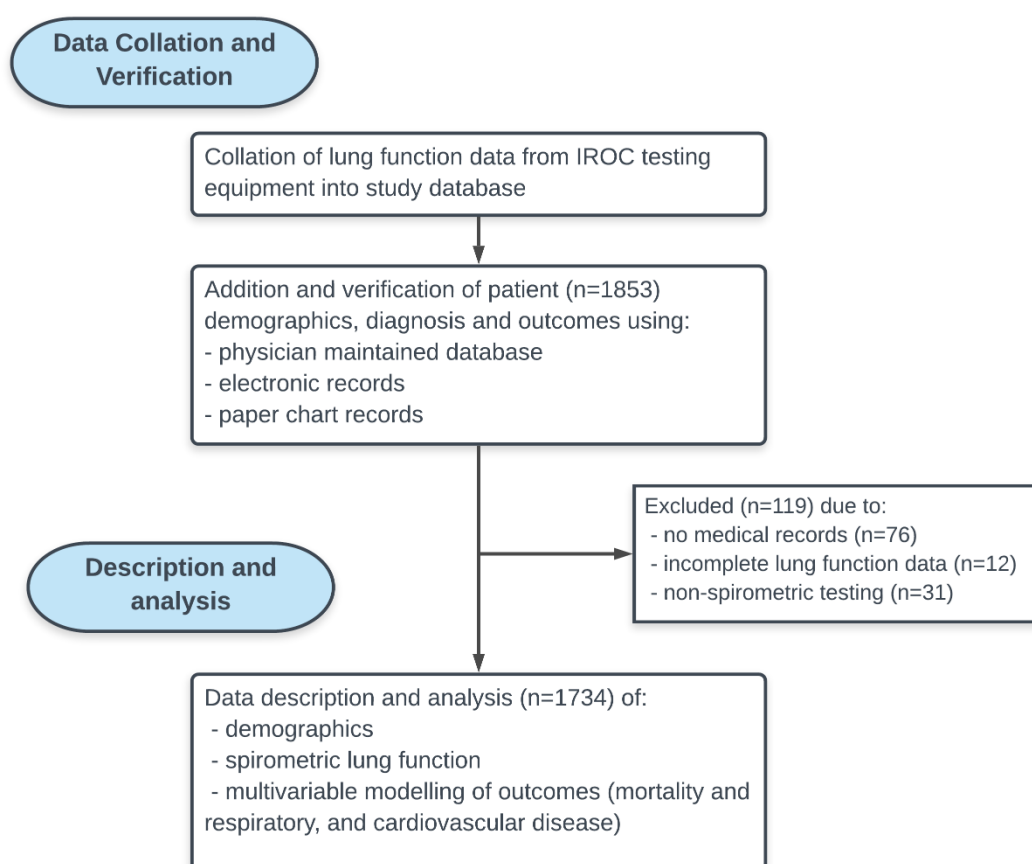
Adjusted hazard ratios (HRs) for mortality were calculated for patient demographics, baseline lung function status, arterial hypertension, and type 2 diabetes using a multivariable Cox proportional hazards model after testing the proportional hazards assumption. Due to small event numbers, patients within the no impairment and mild impairment groups were combined into a single category for the survival analysis. Multivariable logistic regression modelling was used to generate odds ratios (ORs) for respiratory and cardiovascular disease. Main effects were fit for age, sex, First Nations status, body mass index (BMI), smoking status, lung function, hypertension, and type 2 diabetes. To assess data relating only to First Nations, we repeated these models on the subgroup consisting of First Nations patients only. Stata16.1 (StataCorp LLC) was used for statistical analyses; 2-tailed p-values <0.05 were considered significant.

8.5 RESULTS

Of the 1,853 patients with lung function data, we were unable to obtain medical records for 76 patients while 43 patients had lung function data that was incomplete or did not include spirometry (Figure 20). Spirometry, demographic, chronic respiratory disease, and comorbidity

data for the cohort included in this analysis are summarised in Table 19 and categorised by FEV₁ Z-scores. The median age of the remaining patients included in this cohort (n=1,734) was 57 years (IQR 48-67) (First Nations=55 years, IQR 46-64; non-First Nations=63 years, IQR 53-72); 1,013 (58%) were females and 1,113 (64%) First Nations Australians. The median follow-up time was 4 years (IQR 2-5) from the time patients were first seen at IROC, to the time of collation and verification (August 2020) of the data. During this period, 189 (11%) patients died; 88 (47%) from respiratory causes, 38 (20%) from cardiovascular causes, 38 (20%) from other causes including renal disease, non-pulmonary cancers, and 25 (13%) from unknown causes.

Figure 20. Flow diagram of data collection, verification, and analysis of study data.



With worsening lung function (lower Z-score categories), the proportion of patients with chronic respiratory disease and cardiovascular disease increased, as well as the number of deaths (Table 20). The frequency of cardiovascular disease (ischaemic heart, heart failure) and mortality (all, respiratory, and cardiovascular) based on baseline FEV₁ categories depict graded increases with decreasing FEV₁ (Figure 21). Likewise, there were graded increases with decreasing FVC (Supplement Figure S1).

Table 19. Summary of patient demographics by zFEV₁.

	Clinically normal range		Clinically abnormal range	
	zFEV ₁ ≥ 0 (n=173)	zFEV ₁ < 0 to -1 (n=326)	zFEV ₁ < -1 to -2 (n=469)	zFEV ₁ < -2 (n=766)
	Median (IQR) or n (%)			
FEV ₁ (% predicted)	107.0 (102.8-112.3)	91.4 (88.5-95.2)	78.7 (74.8-82.2)	54.0 (40.9-63.7)
FVC (% predicted)	107.4 (100.6-112.6)	93.3 (88.1-98.9)	82.2 (76.8-88.6)	66.9 (56.7-75.9)
FEV ₁ /FVC < LLN (Z < -1.64)	0.82 (0.78-0.86) 3 (<1%)	0.80 (0.75-0.83) 20 (<1%)	0.77 (0.70-0.82) 76 (16%)	0.65 (0.52-0.75) 450 (59%)
Sex				
Female	108 (62%)	192 (59%)	281 (59.9%)	432 (56%)
Male	65 (38%)	134 (41%)	188 (40.1%)	334 (44%)
First Nations	97 (56%)	200 (61%)	319 (68.0%)	497 (65%)
Age (years)	53 (40-63)	55 (45-66)	57 (46-68)	59 (51-68)
BMI (kg/m ²)				
Underweight (<18.5)	1 (<0.1%)	10 (<1%)	21 (5%)	49 (6%)
Healthy (18.5-24.9)	33 (19%)	63 (19%)	70 (15%)	167 (22%)
Overweight (25-29.9)	49 (28%)	75 (23%)	111 (24%)	182 (24%)
Obese (≥30)	90 (52%)	178 (55%)	267 (57%)	368 (48%)
Smoking (n=1571)				
Current	27 (16%)	97 (30%)	175 (37%)	303 (40%)
Former	43 (25%)	98 (30%)	151 (32%)	270 (35%)
Never	76 (44%)	93 (29%)	115 (25%)	123 (16%)
Household smoke (n=1396)				
Yes	43 (25%)	96 (29%)	150 (32%)	280 (37%)
No	88 (51%)	158 (49%)	247 (53%)	330 (43%)
Hypertension	40 (23%)	101 (31%)	174 (37%)	307 (40%)
Chronic respiratory disease	104 (60%)	218 (67%)	360 (77%)	663 (87%)
Cardiovascular disease	29 (17%)	48 (15%)	96 (21%)	218 (29%)
Cancers	13 (6%)	14 (4%)	14 (<1%)	44 (6%)
Deaths	1 (<1%)	15 (5%)	32 (7%)	141 (18%)

Clinically normal range encompasses Z-scores ≥ -1.64.

Cox regression analyses of baseline spirometry data (FEV₁, FVC, and FEV₁/FVC%) relating to mortality are presented in

Table 21.

Like the data for frequency of disease, there were graded increases in mortality with decreasing FEV₁, FVC, and FEV₁/FVC% Z-scores. Risk of death for First Nations patients was similar to their non-First Nations counterparts, and further modelling exclusively on the First Nations subgroup yielded similar results (Table 24). Adjusted HRs also depict a significant reduction in risk for patients who were overweight or obese, while underweight patients and patients with type 2 diabetes were at significantly increased mortality risk. When compared to a combined normal/mild group (≥ -1 Z-score), patients in a combined moderate/severe group (< -1 Z-scores) for either FEV₁ or FVC were at >3 times higher risk of mortality (HR 3.2, 95%CI 1.9-5.4; HR=3.5, 95%CI 2.3-5.4), and 1.7 times higher risk with moderate/severe FEV₁/FVC% (HR=1.7, 95%CI 1.3-2.4).

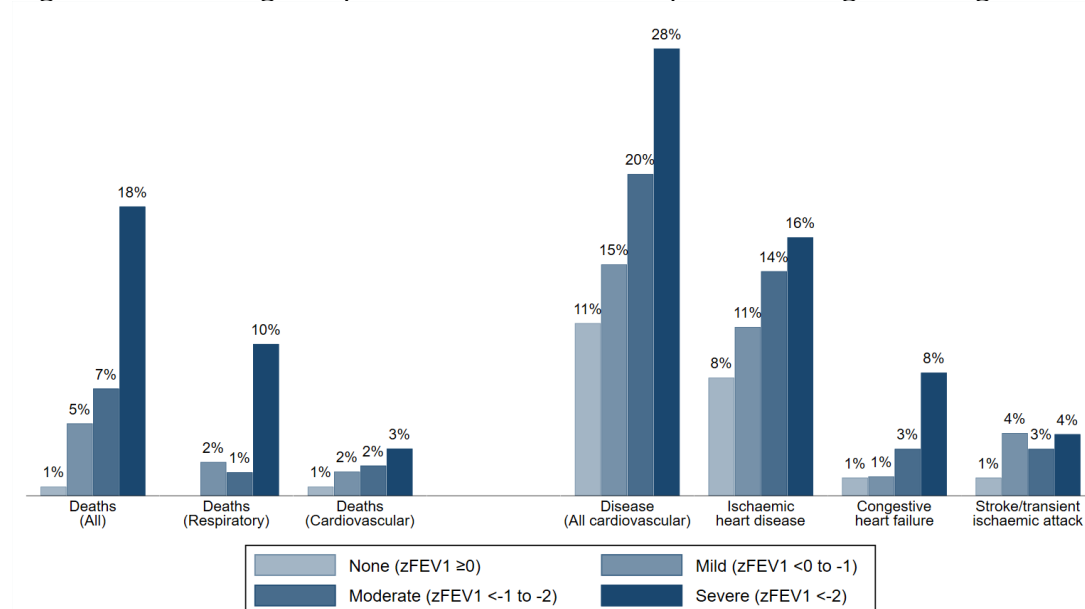
Table 20. Summary of outcomes by First Nations status by FEV1 category.

	Clinically normal range		Clinically abnormal range	
	zFEV ₁ ≥ 0	zFEV ₁ < 0 to -1	zFEV ₁ < -1 to -2	zFEV ₁ < -2
	n (%)			
Deceased				
First Nations	.	9/200 (5%)	20/319 (6%)	77/497 (15%)
Non-First Nations	1/76 (1%)	5/125 (5%)	12/150 (8%)	64/269 (24%)
Respiratory disease				
First Nations	33/97 (34%)	134/200 (67%)	242/319 (76%)	427/497 (86%)
Non-First Nations	40/76 (54%)	84/126 (67%)	118/150 (79%)	236/269 (88%)
Cardiovascular disease				
First Nations	10/97 (10%)	26/200 (13%)	69/319 (22%)	133/497 (27%)
Non-First Nations	9/76 (12%)	22/126 (17%)	27/150 (18%)	85/269 (32%)

For respiratory disease, logistic regression showed increased risk in patients with any FEV₁ (Table 22), FVC (Table 23), or FEV₁/FVC% (Supplement Table S2) impairment. Adjusted risk of cardiovascular disease was higher for all patients with any FEV₁ or FVC impairment, current and former smokers, and patients with hypertension and/or type 2 diabetes. First Nations patients were at similar risk for both outcomes as their non-First Nations counterparts. We also found females were at significantly reduced risk of cardiovascular disease. When compared to a combined normal/mild group (≥ -1 Z-score), patients in a combined moderate/severe group (< -1 Z-scores) were at greater risk of cardiovascular disease for both FEV₁ and FVC (HR 1.7, 95%CI 1.2-2.4; HR=1.9, 95%CI 1.4-2.5). We found no relationship between impaired FEV₁/FVC% and

cardiovascular disease. Further modelling found associations between FEV₁, FVC, and FEV₁/FVC% parameters and respiratory, cardiovascular disease were also true for First Nations patients (Supplement Tables S3, S4, and S5).

Figure 21. Percentages of patients within zFEV₁ impairment categories assigned to each outcome.



8.6 DISCUSSION

In our study of 1,734 adults (approximately two-thirds First Nations Australians), we found that any FEV₁, FVC, and FEV₁/FVC% impairment, even within clinically normal ranges, was associated with significantly increased risk of all-cause mortality. Type 2 diabetes (T2DM) and low BMI were associated with increased risk, while obesity was associated with decreased risk of overall mortality. In multivariable regression of respiratory and cardiovascular disease, we found that FEV₁, FVC, and FEV₁/FVC% impairment were associated with increased risk of respiratory disease, whilst FEV₁ and FVC impairment, male sex, ever-smoker status, and co-morbidities (T2DM and hypertension) were associated with increased cardiovascular disease risk. First Nations status did not alter risk of respiratory or cardiovascular disease, or mortality. Notably, in our unique cohort, our findings were similar to that of the recent PURE study, which suggested FEV₁ and FVC, even within the clinically normal ranges, were associated with mortality and cardiovascular disease risk in their large prospective cohort of 126,359 adults.¹¹⁴

Table 21. Hazard ratios (HR) for mortality in three multivariable models.

			FEV ₁		FVC		FEV ₁ /FVC%	
			HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Age (per 10-year increase)			1·85 (1·61, 2·11)	<0·01	1·89 (1·65, 2·17)	<0·01	1·85 (1·62, 2·12)	<0·01
Sex	Female		0·76 (0·56, 1·02)	0·07	0·75 (0·56, 1·00)	0·05	0·81 (0·60, 1·09)	0·17
First Nations status			0·92 (0·67, 1·28)	0·63	0·85 (0·62, 1·17)	0·32	0·97 (0·70, 1·34)	0·87
BMI	Underweight		1·82 (1·07, 3·08)	<0·01	1·79 (1·06, 3·04)	<0·01	1·85 (1·09, 3·14)	<0·01
	Normal		Reference		Reference		Reference	
	Overweight		0·77 (0·53, 1·13)		0·79 (0·54, 1·16)		0·73 (0·50, 1·06)	
	Obese		0·45 (0·31, 0·66)		0·43 (0·29, 0·62)		0·45 (0·31, 0·66)	
Smoking* (n=1571)	Current		1·57 (0·98, 2·50)	0·13	1·62 (1·02, 2·58)	0·09	1·71 (1·07, 2·75)	0·06
	Former		1·50 (0·96, 2·34)		1·57 (1·01, 2·45)		1·62 (1·04, 2·54)	
	Never		Reference		Reference		Reference	
Spirometry		Z-score						
Clinically normal		≥0 to -1	Reference	<0·01	Reference	<0·01	Reference	<0·01
		<-1 to -2	1·74 (0·95, 3·18)		2·30 (1·40, 3·76)		1·56 (1·05, 2·32)	
Clinically abnormal		<-2	4·00 (2·37, 6·75)		4·65 (2·97, 7·29)		1·86 (1·31, 2·65)	
Hypertension			1·36 (1·00, 1·84)	0·048	1·35 (1·00, 1·84)	0·05	1·30 (0·96, 1·77)	0·09
Type 2 diabetes			1·67 (1·19, 2·36)	<0·01	1·51 (1·07, 2·13)	0·02	1·81 (1·28, 2·57)	<0·01

Patients with missing smoking data (n=163) included in modelling but excluded from global Wald test.

Table 22. Odds ratios (ORs) for respiratory and cardiovascular disease in two multivariable models with FEV₁.

			Respiratory disease		Cardiovascular disease	
			OR (95%CI)	p	OR (95%CI)	p
Age (per 10-year increase)			1·21 (1·10, 1·32)	<0·01	1·57 (1·41, 1·75)	<0·01
Sex	Female		0·98 (0·76, 1·26)	0·85	0·69 (0·54, 0·89)	<0·01
First Nations status			0·96 (0·73, 1·26)	0·76	1·08 (0·82, 1·43)	0·59
BMI	Underweight		0·99 (0·54, 1·81)	0·38	1·01 (0·53, 1·92)	0·15
	Normal		Reference		Reference	
	Overweight		1·12 (0·77, 1·62)		1·45 (0·98, 2·15)	
	Obese		1·31 (0·94, 1·82)		1·07 (0·74, 1·55)	
Smoking* (n=1571)	Current		1·07 (0·76, 1·50)	0·25	1·70 (1·16, 2·48)	0·02
	Former		1·33 (0·94, 1·88)		1·50 (1·05, 2·16)	
	Never		Reference		Reference	
FEV ₁		Z-score				
Clinically normal		≥0	Reference	<0·01	Reference	<0·01
		<0 to -1	1·16 (0·76, 1·77)		1·15 (0·62, 2·13)	
		<-1 to -2	1·68 (1·12, 2·53)		1·46 (0·82, 2·61)	
Clinically abnormal		<-2	3·58 (2·36, 5·43)		2·16 (1·23, 3·80)	
Hypertension			1·25 (0·92, 1·70)	0·15	2·15 (1·63, 2·83)	<0·01
Type 2 diabetes			0·95 (0·68, 1·32)	0·75	2·45 (1·83, 3·28)	<0·01

* Patients with missing smoking data (n=163) included in modelling but excluded from global Wald test.

Our study is novel for several reasons. Firstly, our data confirms the applicability of the PURE study¹¹⁴ findings of the relationship of lung function to future cardiovascular and respiratory morbidity, and mortality in a predominantly Indigenous population in a regional/remote setting. Secondly, we also found that in addition to the well-known importance of FEV₁ and FVC, the FEV₁/FVC ratio has an equally significant association with mortality. Finally, our study is one of the first, and the only contemporaneous study, to be largely based on a First Nations population. This is important as the burden of chronic illness among First Nations Australians is high and cardiovascular illness is the largest cause of mortality.¹¹⁴ Confirming the applicability of international studies to First Nations Australians is evidence that may promote strategic resource allocation to improve outcomes for this population.

Table 23. Odds ratios (ORs) for respiratory and cardiovascular disease in two multivariable models with FVC.

			Respiratory disease		Cardiovascular disease	
			OR (95%CI)	p	OR (95%CI)	p
Age (per 10-year increase)			1·24 (1·14, 1·36)	<0·01	1·60 (1·43, 1·78)	<0·01
Sex	Female		1·05 (0·58, 1·91)	0·86	0·69 (0·53, 0·89)	<0·01
First Nations status			0·96 (0·73, 1·26)	0·79	1·06 (0·80, 1·40)	0·69
BMI	Underweight		1·05 (0·58, 1·91)	0·59	0·98 (0·50, 1·91)	0·11
	Normal		Reference		Reference	
	Overweight		1·07 (0·75, 1·54)		1·45 (0·98, 2·14)	
	Obese		1·24 (0·89, 1·71)		1·03 (0·71, 1·49)	
Smoking* (n=1571)	Current		1·23 (0·88, 1·70)	0·09	1·76 (1·21, 2·56)	<0·01
	Former		1·47 (1·04, 2·08)		1·55 (1·08, 2·22)	
	Never		Reference		Reference	
FVC		Z-score				
Clinically normal		≥0	Reference	<0·01	Reference	<0·01
		<0 to -1	1·32 (0·91, 1·91)		1·11 (0·67, 1·83)	
		<-1 to -2	1·39 (0·96, 2·00)		1·60 (1·00, 2·56)	
Clinically abnormal		<-2	2·33 (1·60, 3·40)		2·45 (1·55, 3·85)	
Hypertension			1·30 (0·96, 1·75)	0·09	2·18 (1·65, 2·87)	<0·01
Type 2 diabetes			0·91 (0·66, 1·25)	0·55	2·28 (1·70, 3·06)	<0·01

*Patients with missing smoking data (n=163) included in modelling but excluded from global Wald test.

Our findings are concordant with data from the Whitehall II Study (n=4,817) in which mean baseline FEV₁ and FVC were significantly lower (-0.4 litres, p<0.001; -0.5 litres, p<0.001) among those participants who were deceased at census.¹⁰⁹ While FEV₁ often receives greater attention within the literature, FVC has also been strongly associated with survival outcomes.^{113,182,184,185} An analysis of 7,489 participants in the Atherosclerosis Risk in Communities (ARIC) study by Burney et al. found higher FVC significantly reduced mortality risk (HR 0.90, 95%CI 0.81-1.00), while higher FEV₁ (HR 0.98, 95%CI 0.80-1.07) did not.¹¹³ The relationship between FEV₁/FVC% and mortality is often unexplored except for a small number of studies. An analysis 12,703 participants from the Gutenberg Health Study by Magnussen et al, found no association between FEV₁/FVC% with survival (HR 0.94, 0.85-1.04).¹¹¹ To our knowledge, the only study that has demonstrated a significant association between FEV₁/FVC% and mortality was a study of two Indigenous populations in Papua New

Guinea, where the mean FEV₁/FVC% was significantly greater at baseline in those participants who were still alive at census versus those who had died (difference=6.5%, $p<0.001$).

We observed similar results when analysing cardiovascular outcomes, where any FEV₁ or FVC impairment, even within the clinically normal range, significantly increased cardiovascular disease risk, independent of other factors such as age, sex, smoking status, and BMI. This relationship is now well supported by numerous studies, summarised in a recent review.¹¹² The Coronary Artery Risk Development in Young Adults (CARDIA) study ($n=3,000$) found that subclinical lung function decline was associated with two distinct cardiopulmonary disease states at follow-up.¹⁸⁶ FEV₁ and FVC decline with preserved FEV₁/FVC%, a restrictive spirometry pattern, was associated with left ventricular (LV) hypertrophy (LV mass in grams, $\beta=3.84$, $p<0.0001$) at year 25 of follow-up.¹⁸⁶ Decline in FEV₁, with associated FEV₁/FVC% decline, was associated with lowered cardiac output at year 5 (LV cardiac output in litres/minute, $\beta=-0.07$, $p=0.03$) and lowered left atrial internal dimension (LAID) at year 25 (LAID in cm, $\beta=-0.034$, $p=0.0001$) of follow-up.¹⁸⁶ Our data are consistent with the notion that graded increases in cardiovascular disease prevalence occur with increasing FEV₁ and FVC impairment. Indeed, a meta-analysis of 12 datasets found that patients with COPD were more likely to have cardiovascular disease than controls or the general population (OR 2.46, 95%CI 2.02–3.00).¹⁸⁷

Findings for First Nations patients within this cohort were similar to the whole group, confirming the applicability of lung function as a predictor of future outcomes to the First Nations population of Australia. First Nations status did not significantly influence mortality, nor cardiovascular or respiratory disease risk. This is likely due to First Nations individuals making up most of the whole group. For this study we used the “Other/mixed” GLI category to produce reference values and Z-scores, based on previous findings that this is the most suitable ethnic category for First Nations children.²⁰ Currently, this category has yet to be validated for use in the adult First Nations population and so lung function interpretation within this population is more difficult. We also note that First Nations representation increased with worsening FEV₁ impairment and was highest in the moderate and severe FEV₁ categories of impairment.

Our study supports existing evidence within the literature that spirometric lung function is an independent predictor of future mortality and cardiovascular disease risk and provides up-to-date evidence that these findings are applicable in First Nations populations. This highlights the importance of lung function optimisation, particularly in First Nations populations that continue to be at heightened risk of respiratory and cardiovascular diseases, and reduced life expectancies.⁴ Recent research in lung function trajectories suggests that impaired (but still clinically normal) FEV₁ in childhood or young adulthood are associated with lower lung function in adulthood, and associated increased cardiopulmonary and all-cause mortality.^{51,52,54,55} Importantly, there is now evidence that early identification and management of respiratory illness in early life may precipitate catch-up growth, and alter the lung function trajectories of children treated.^{55,56} We have previously shown that specialist respiratory outreach services that are tailored to the needs of target communities can significantly improve the lung function of children in Indigenous communities.¹⁷⁴ Continued optimisation of lung function in children and adults in Indigenous populations through services such as these, while concurrently addressing other risk factors such as those identified in our study (e.g. smoking, hypertension, type 2 diabetes) are important to improve future outcomes for this at-risk population.

Our study has several limitations. Firstly, our analysis is limited somewhat by a smaller sample size when compared to other larger-scale epidemiological studies discussed above. Secondly, while all lung function testing was performed by experienced respiratory scientists, these results are clinically reported values and a minority may not meet full ATS/ERS criteria.^{8,41} Finally, death certificate data was not available for all patients via electronic medical records, and in many instances discharge summaries were used instead.

Our study supports previously published findings that spirometric lung function is a prognostic indicator of mortality and cardiovascular disease. We determined that patients with FEV₁ or FVC impairment, still within the clinically normal range, were at increased risk of death and cardiovascular disease. Notably, we found an association between FEV₁/FVC% and survival not found in other studies. Patients with common comorbidities such as diabetes and hypertension were at significantly increased risk of cardiovascular disease, while no association with respiratory disease was found. Our findings are applicable to both First Nations (approximately two-thirds of this study

cohort) and non-First Nations adults living in rural-remote areas, although we note increased representation of First Nations patients in the moderate and severely impaired FEV₁ categories.

In conclusion, our findings suggest that reduced FEV₁, FVC, and FEV₁/FVC%, even within the clinically normal range, are independently associated with increased mortality, while reduced FEV₁ and FVC are independently associated with increased cardiovascular disease risk. In the content of recent research into lung function trajectories, these findings highlight a need for significant emphasis to be placed on lung function optimisation in children and young adults, particularly in Indigenous populations who have a substantially heightened risk of chronic lung and heart disease, and early mortality, in adulthood. ‘Closing the gap’ for First Nations Australians requires a broad socioeconomic approach,¹⁸⁸ as well as attention to factors that influence lung trajectories, much of which occurs in utero and early childhood.⁵⁵

8.7 ACKNOWLEDGEMENTS

We acknowledge and thank the Indigenous Health Workers, doctors, nurses, and clinical measurements scientists on the IROC program for their tireless efforts.

8.8 SUPPLEMENTARY MATERIAL

Figure 22. Percentages of patients within each FVC Z-scores (zFVC) category assigned to each outcome.

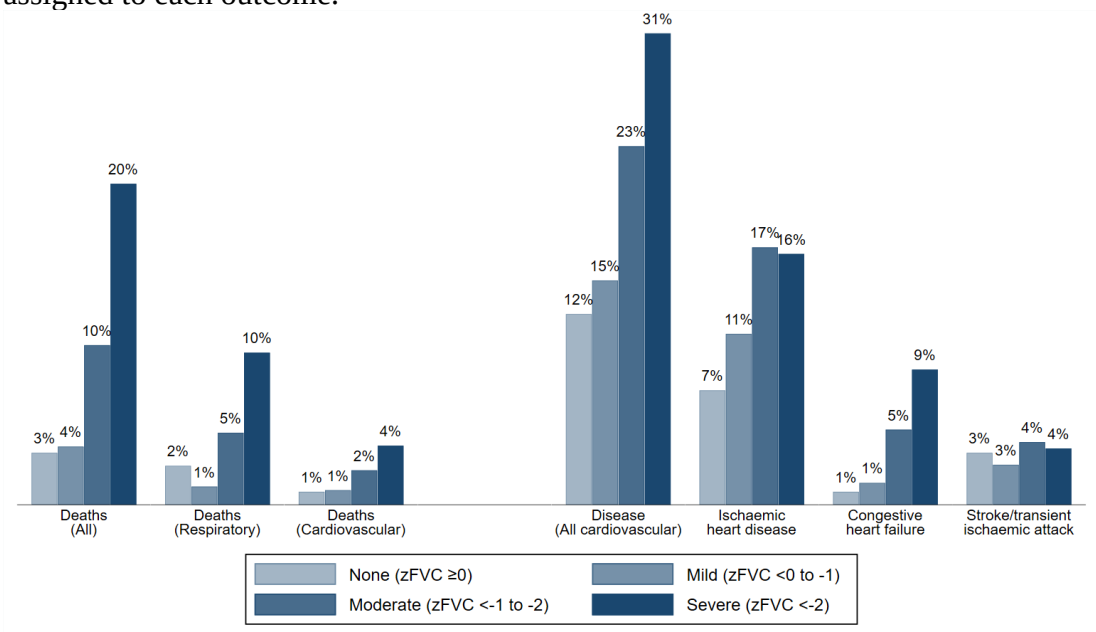


Table 24. Adjusted hazard ratios (HR) for mortality of First Nations patients from 3 multivariable models.

		FEV ₁		FVC		FEV ₁ /FVC%		
		HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	
Age (per 10-year increase)		1·95 (1·62, 2·35)	<0·01	1·94 (1·61, 2·32)	<0·01	1·95 (1·62, 2·34)	<0·01	
Sex	Female	0·76 (0·52, 1·13)	0·18	0·77 (0·52, 1·14)	0·19	0·78 (0·53, 1·16)	0·22	
BMI	Underweight	2·66 (1·45, 4·90)	<0·01	2·69 (1·46, 4·95)	<0·01	2·66 (1·45, 4·88)	<0·01	
	Normal	Reference		Reference		Reference		
	Overweight	0·66 (0·39, 1·14)		0·64 (0·37, 1·10)		0·60 (0·35, 1·02)		
	Obese	0·43 (0·25, 0·72)		0·41 (0·25, 0·70)		0·41 (0·24, 0·69)		
Smoking* (n=1040)	Current	1·67 (0·93, 3·00)	0·23	1·75 (0·97, 3·13)	0·17	1·67 (0·92, 3·02)	0·06	
	Former	1·42 (0·79, 2·55)		1·49 (0·83, 2·68)		1·45 (0·80, 2·62)		
	Never	Reference		Reference		Reference		
Spirometry		Z-score						
Clinically normal		≥0 to -1	Reference	<0·01	Reference	<0·01	Reference	<0·01
		<-1 to -2	1·32 (0·59, 2·95)		1·95 (0·95, 3·99)		1·48 (0·88, 2·50)	
Clinically abnormal		<-2	2·89 (1·43, 5·84)		3·97 (2·09, 7·55)		1·58 (0·99, 2·52)	
Hypertension			1·26 (0·83, 1·92)	0·28	1·32 (0·86, 2·03)	0·05	1·18 (0·77, 1·82)	0·44
Type 2 diabetes			1·60 (1·05, 2·44)	0·03	1·45 (0·95, 2·22)	0·03	1·64 (1·07, 2·51)	0·02

Three multivariable Cox proportional hazards models, fit for age, sex, First Nations status, body mass index (BMI), smoking status, hypertension, type 2 diabetes, and each of FEV₁, FVC and FEV₁/FVC lung function parameters. *First Nations patients with missing smoking data (n=73) included in modelling but excluded from global Wald test.

Table 25. Adjusted odds ratios (ORs) for respiratory and cardiovascular disease in two multivariable models, with FEV₁/FVC% as the focus.

			Respiratory disease		Cardiovascular disease	
			OR (95%CI)	p	OR (95%CI)	p
Age (per 10-year increase)			1·22 (1·11, 1·33)	<0·01	1·61 (1·44, 1·80)	<0·01
Sex	Female		1·07 (0·79, 1·32)	0·86	0·70 (0·54, 0·90)	<0·01
First Nations status			1·01 (0·76, 1·33)	0·97	1·10 (0·83, 1·46)	0·49
BMI	Underweight		1·07 (0·58, 1·97)	0·09	1·05 (0·55, 2·01)	0·20
	Normal		Reference		Reference	
	Overweight		1·19 (0·82, 1·73)		1·38 (0·93, 2·03)	
	Obese		1·52 (1·08, 2·15)		1·01 (0·70, 1·45)	
Smoking* (n=1571)	Current		1·06 (0·76, 1·48)	0·32	2·01 (1·37, 2·95)	0·01
	Former		1·29 (0·91, 1·83)		1·70 (1·19, 2·44)	
	Never		Reference		Reference	
FEV ₁ /FVC%		Z-score				
Clinically normal		≥0	Reference	<0·01	Reference	0·91
		<0 to -1	1·63 (1·20, 2·21)		0·92 (0·65, 1·31)	
		<-1 to -2	2·17 (1·54, 3·06)		1·01 (0·70, 1·47)	
Clinically abnormal		<-2	5·79 (3·81, 8·81)		0·91 (0·64, 1·31)	
Hypertension			1·26 (0·93, 1·71)	0·14	2·20 (1·67, 2·89)	<0·01
Type 2 diabetes			1·15 (0·83, 1·60)	0·41	2·45 (1·82, 3·28)	<0·01

Two multivariable logistic regression models, fit for age, sex, First Nations status, body mass index (BMI), smoking status, hypertension, type 2 diabetes, and FEV₁/FVC%. *Patients with missing smoking data (n=163) included in modelling but excluded from global Wald test.

Table 26. Adjusted odds ratios (ORs) for respiratory and cardiovascular disease, in two multivariable models of First Nations patients, with FEV₁ as the focus.

			Respiratory disease		Cardiovascular disease	
			OR (95% CI)	p	OR (95%CI)	p
Age (per 10-year increase)			1·21 (1·07, 1·36)	<0·01	1·49 (1·29, 1·71)	<0·01
Sex	Female		1·02 (0·74, 1·04)	0·90	0·86 (0·62, 1·19)	0·36
BMI	Underweight		0·90 (0·44, 1·87)	0·66	1·49 (0·69, 3·22)	0·12
	Normal		Reference		Reference	
	Overweight		1·18 (0·73, 1·89)		1·70 (1·02, 2·82)	
	Obese		1·25 (0·82, 1·92)		1·13 (0·70, 1·83)	
Smoking* (n=1040)	Current		0·90 (0·59, 1·38)	0·40	1·72 (1·08, 2·76)	0·04
	Former		1·19 (0·75, 1·87)		1·73 (1·09, 2·76)	
	Never		Reference		Reference	
FEV ₁ /FVC%		Z-score				
Clinically normal		≥0	Reference	<0·01	Reference	0·01
		<0 to -1	0·92 (0·52, 1·63)		1·06 (0·44, 2·57)	
		<-1 to -2	1·27 (0·73, 2·18)		1·73 (0·76, 3·96)	
Clinically abnormal		<-2	2·72 (1·56, 4·74)		2·22 (0·99, 5·00)	
Hypertension			1·15 (0·79, 1·70)	0·46	2·69 (1·88, 3·84)	<0·01
Type 2 diabetes			0·83 (0·57, 1·20)	0·31	2·57 (1·81, 3·65)	<0·01

Two multivariable logistic regression models, fit for age, sex, body mass index (BMI), smoking status, hypertension, type 2 diabetes, and FEV₁. *Patients with missing smoking data (n=73) included in modelling but excluded from global Wald test.

Chapter 9: Association of gas diffusing capacity of the lung for carbon monoxide with cardiovascular morbidity and survival in a disadvantaged clinical population

This chapter addresses the second part Objective 3 outlined in Section 1.4; “Evaluate ... associations between reduced lung function and cardiovascular morbidity in adults treated through IROC”. The following publication within a peer-reviewed journal was produced:

Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Dent A, Fong KM, McElrea MS. Association of Gas Diffusing Capacity of the Lung for Carbon Monoxide with Cardiovascular Morbidity and Survival in a Disadvantaged Clinical Population. *Lung*. 2022;200(6):783-92.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
Andrew Collaro	Drafting of manuscript, led data analysis, input into study design
Anne Chang	Reviewed draft manuscript, data collection, led study design
Julie Marchant	Reviewed draft manuscript, input into study design

Mark Chatfield	Reviewed draft manuscript, assisted with data analysis, input into study design
Annette Dent	Reviewed draft manuscript, data collection, input into study design
Kwun Fong	Reviewed draft manuscript, data collection, led study design
Margaret McElrea	Reviewed draft manuscript, input into study design

9.1 ABSTRACT

9.1.1 Purpose

Low diffusing capacity of the lung for carbon monoxide (D_{LCO}) and spirometry values are associated with increased mortality risk. However, associations between mortality risk and cardiovascular disease with the transfer coefficient of the lung for carbon monoxide (K_{CO}) and alveolar volume (V_A) are unknown. This cohort study: (i) evaluated whether D_{LCO} , K_{CO} , and V_A abnormalities are independently associated with cardiovascular morbidity and/or elevated mortality risk and, (ii) compared these associations with those using spirometry values.

9.1.2 Methods

Gas diffusing capacity and spirometry data of 1165 adults seen at specialist respiratory outreach clinics over an eight-year period (241 with cardiovascular disease; 108 deceased) were analysed using multivariable Cox and logistic regression.

9.1.3 Results

D_{LCO} , K_{CO} , and V_A values below the lower limit of normal (<-1.64 Z-scores) were associated with elevated cardiovascular disease prevalence (respective odds ratios of 1.83 [95%CI 1.31-2.55], 1.56 [95%CI 1.08-2.25], 2.20 [95%CI 1.60-3.01]) and increased all-cause mortality risk (respective hazard ratios of 2.99 [95%CI 1.83-4.90], 2.14 [95%CI 1.38-3.32], 2.75 [95%CI 1.18-2.58]), after adjustment for factors including age, personal smoking, and respiratory disease. Compared to similar levels of spirometry abnormality, D_{LCO} , K_{CO} , and V_A were associated with similar or greater mortality risk, and similar cardiovascular disease prevalence. Analysis of only those patients with clinical normal spirometry values ($n=544$) showed these associations persisted for D_{LCO} .

9.1.4 Conclusion

Low D_{LCO} , K_{CO} , and V_A measurements are associated with cardiovascular disease prevalence. As risk factors of all-cause mortality, they are more sensitive than spirometry even among patients with no diagnosed respiratory disease.

9.2 INTRODUCTION

There is a growing evidence that low spirometric lung function is independently associated with increased future cardiovascular morbidity,^{111,114} and overall mortality.^{109,111,113,114} These associations have been demonstrated in asymptomatic patients without respiratory disease,¹¹³ and in patients whose spirometry Z-scores are reduced below zero but still within the clinically normal range (0 to -1.64 Z-scores).^{47,114} Comparatively fewer studies have reported on the association between diffusing capacity of the lung for carbon monoxide (D_{LCO}) and mortality.^{115,116} Limited existing data suggests clinically abnormal D_{LCO} is associated with elevated mortality risk with greater effect size than for spirometry,^{115,116} even in the absence of diagnosed respiratory disease.¹¹⁵ As yet, no studies have reported on associations between D_{LCO} and overall cardiovascular morbidity. Furthermore, other key parameters of the diffusing capacity test, i.e., the transfer coefficient of the lung for carbon monoxide (K_{CO}) and alveolar volume (V_A), remain entirely unexplored for their association with either overall cardiovascular morbidity or all-cause mortality.

K_{CO} is the rate of carbon monoxide (CO) removal from alveolar gas during the single breath hold manoeuvre,⁴² and is thus the change in log concentration of CO in the inspired gas volume (V_I) divided by the breath hold time (10 ± 2 seconds⁴¹ for an acceptable manoeuvre). Despite controversy surrounding the diagnostic utility of the K_{CO} ,¹⁸⁹⁻¹⁹¹ it is useful in discerning patterns of parenchymal or obstructive pathologies.^{190,192} V_A is an estimate of the volume of gas accessible to surfaces of gas exchange (the respiratory membrane that forms the alveolar wall) and equates to V_I minus the volume of gas remaining in the large and small airways that does not participate in gas exchange.⁴² The product of the K_{CO} and V_A is then adjusted for pressure to give the D_{LCO} . The K_{CO} and V_A provide complementary information to the D_{LCO} and afford insight into the root cause of D_{LCO} abnormality, and both should be reported alongside the D_{LCO} according to the current standard.⁴¹ Given the clinical utility of these measurements and their availability to clinicians interpreting test results, assessing whether these parameters are also associated with future mortality risk would add valuable knowledge.

We utilised the data from regional and remote clinical populations seen and treated at specialist respiratory outreach clinics over an eight-year period to evaluate whether D_{LCO} , K_{CO} , and V_A abnormalities are associated with future outcomes. The majority of participants were First Nations Australians who are, compared to non-First Nations people, at significantly increased risk of chronic respiratory² and cardiovascular disease⁴ amongst other health disparities.¹⁵⁷ Investigating this question in an at-risk population is important, as such investigations are more likely to uncover significant associations. The objectives of our study were to (i) determine whether D_{LCO} , K_{CO} , and V_A abnormalities are associated with cardiovascular morbidity and/or elevated mortality risk independent of other factors e.g., concurrent respiratory disease, and (ii) compare these associations with those involving FEV_1 , FVC, and $FEV_1/FVC\%$ values obtained from spirometry testing.

9.3 MATERIALS AND METHODS

9.3.1 Study design, setting, and participants

This is an eight-year retrospective analysis of adults referred to Indigenous Respiratory Outreach Care (IROC) clinics in regional and remote Queensland through their primary care physicians, community health workers, or self-referral. Inclusion criteria were adults aged 18-85 years at IROC clinic visit, who were medically reviewed with acceptable and repeatable⁴¹ gas diffusing capacity and spirometry testing performed by a trained respiratory scientist between February 2012 and March 2020. Ethical approval for this study was granted by The Prince Charles Hospital Human Research Ethics Committee (reference: HREC/2019/QPCH/58452).

9.3.2 Lung function testing

Gas diffusing capacity (single breath) and spirometry testing were performed according to European Respiratory Society (ERS) and American Thoracic Society (ATS) criteria.^{8,41} Patients were tested using an EasyOne Pro Lab (nidd Medizintechnik). Global Lung Function Initiative (GLI) multi-ethnic reference equations for spirometry (GLI-2012)⁹ were used to generate predicted values for spirometry tests using the ‘other/mixed’ category, as this was found to be most suitable for use in First Nations Australian children and young adults.²⁰ GLI reference equations for gas diffusing capacity testing (GLI-2017), including the 2020 corrections,¹⁷⁵ were applied to tests to derive Z-scores for each patient’s values.^{9,43} Notably, no ethnic correction is available. We used the American Thoracic Society (ATS)/European Respiratory Society (ERS)⁷ four-tier grading with approximated Z-score equivalents proposed by Miller and Cooper¹¹⁶ where GLI-derived⁴³ Z-scores ≥ -1.64 were graded as normal, -1.64 to -3 as mild, -3 to -5 as moderate, and < -5 as severe.¹¹⁶

9.3.3 Data verification and definitions

Patient demographics, gas diffusing capacity and spirometry test data, cardiovascular disease, personal smoking status, household smoking data, and comorbidities recorded by a respiratory physician at baseline (first visit to IROC clinic) for each patient were collected. Mortality data was censored in August 2020, with both cause (where available) and date of death collected. Electronic and paper chart medical records were used to verify patient demographic, medical, personal smoking, and household smoking data.

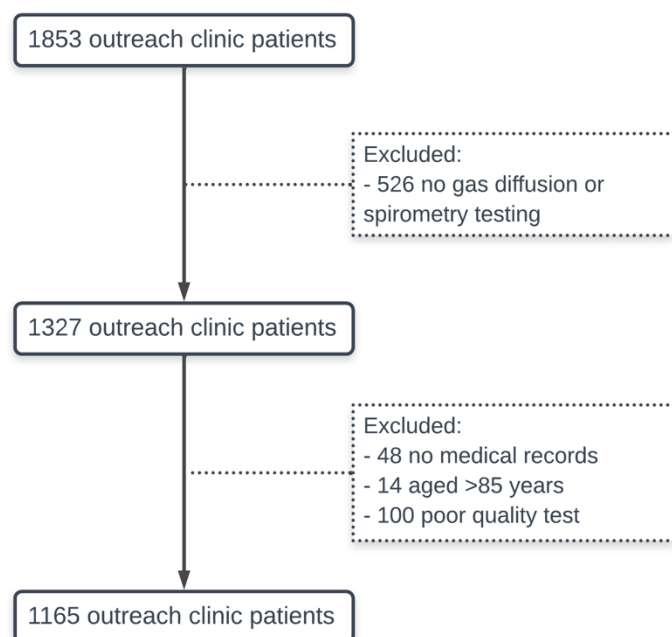
Mortality data were collected from electronic medical records, using death certificates where available, or discharge summaries. Where cause of death was unclear or no information was available, cause of death was categorised as ‘unknown’. Chronic respiratory disease included respiratory physician diagnoses of chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, or other chronic pulmonary disease, and cardiovascular disease included ischaemic heart disease, congestive heart failure, stroke or transient ischaemic attack, and cardiac valve disease.

9.3.4 Statistical analysis

Gas diffusing capacity and spirometry data at first visit to IROC was used as the baseline for each patient included in this analysis. Odds ratios (ORs) for cardiovascular disease were calculated for gas diffusing capacity and spirometry Z-score tiers using logistic regression. Hazard ratios (HRs) for mortality events were calculated for baseline gas diffusing capacity and spirometry status using a Cox proportional hazards (PH) model after testing the PH assumption through visual inspection of log-log plots. Adjusted survival curves were generated assuming a Weibull distribution. Variables with $p < 0.2$ for any level on univariable modelling were included in final adjusted models. These variables included age, sex, personal smoking status, body mass index (BMI), First Nations status, and respiratory disease. Global Wald testing was performed on categorical variables. Stata17 (StataCorp LLC) was used for statistical analyses; 2-tailed p -values < 0.05 were considered significant.

9.4 RESULTS

Figure 23. Summary of included outreach clinic patients.



Over an eight-year period, 1853 patients were seen at adult IROC clinics. Of these, 1327 patients had gas diffusion capacity testing. We excluded 48 patients with no paper chart or electronic medical records, 14 patients aged >85 years, and a further 100 who did not meet acceptability and repeatability criteria for gas diffusion capacity⁴¹ or spirometry testing⁸ (Figure 23). Thus, a total of 1165 patients were included in this analysis where their demographic and gas diffusing capacity data are summarised in Table 27. The median time from baseline visit to data census was 3.5 years (IQR 2 – 5). Excluded participants were similar in age (59 years) with similar proportions of females (51%), were less likely to be current (24%) or former (24%) smokers but had similar cardiovascular disease prevalence (20%).

Gas diffusing capacity values for included patients were below the lower limit of normal (-1.64 Z-score) for 517 (40%) D_{LCO} , 298 (23%) K_{CO} , and 451 (35%) V_A results. Summary cardiovascular disease and mortality data for included patients are shown in Table 28.

Table 27. Summary data of 1165 patients at initial specialist respiratory outreach clinic visit.

	All patients (n=1165)	Deceased patients (n=108)
	Median (IQR) or n (%)	
Age, years	57 (48, 66)	66 (57, 75)
Female	651 (56%)	42 (39%)
First Nations	763 (65%)	62 (57%)
Smoking Status		
Current	434 (37%)	42 (39%)
Former	393 (34%)	39 (36%)
Never	248 (21%)	16 (15%)
Unknown	90 (8%)	11 (10%)
Body mass index, (kg/m ²)		
Underweight (<18.5)	56 (5%)	12 (11%)
Healthy (18.5-24.9)	192 (16%)	30 (28%)
Overweight (25-29.9)	284 (24%)	35 (32%)
Obese (≥30)	633 (54%)	31 (29%)
Cardiovascular disease	241 (21%)	58 (54%)
Respiratory disease	904 (76%)	93 (86%)
D_{LCO}		
Z	-1.21 (-2.37, -0.11)	-3.16 (-4.77, -1.79)
% Predicted	82 (67, 98)	57 (37, 73)
K_{CO}		
Z	-0.26 (-1.51, 0.72)	-2.07 (-3.57, -0.51)
% Predicted	96 (78, 111)	69 (49, 92)
V_A		
Z	-1.18 (-2.03, -0.31)	-1.68 (-2.70, -0.91)
% Predicted	86 (77, 96)	81 (69, 89)
FEV ₁		
Z	-1.62 (-2.67, -0.81)	-2.64 (-3.45, -1.57)
% Predicted	76 (60, 89)	58 (41, 74)
FVC		
Z	-1.27 (-2.16, -0.46)	-2.10 (-2.99, -1.17)
% Predicted	82 (70, 94)	69 (56, 81)
FEV ₁ /FVC%		
Z	-0.86 (-2.05, -0.08)	-1.43 (-3.28, -0.08)
Raw	75 (65, 81)	67 (54, 79)

D_{LCO} = diffusing capacity of the lung for carbon monoxide, K_{CO} = transfer coefficient of the lung for carbon monoxide, V_A = alveolar volume, FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity.

9.4.1 Cardiovascular morbidity

A total of 241 (21%) of patients had diagnosed cardiovascular disease at baseline. Our adjusted models showed abnormal D_{LCO} (OR=1.83, 95%CI 1.31, 2.55), K_{CO} (OR=1.56, 95%CI 1.08, 2.25), and V_A (OR=2.20, 95%CI 1.60, 3.01) were each associated with cardiovascular disease, independent of smoking status. Complete per-tier modelling is shown in Table 29.

Table 28. Summary baseline lung function grading data, cardiovascular disease, and subsequent survival data for 1165 patients seen at specialist respiratory outreach clinics.

	Normal (Z $\geq$ -1.64)	Abnormal (Z $<$ -1.64)		
		Mild (Z -1.64 to -3)	Moderate (Z -3 to -5)	Severe (Z $<$ -5)
D_{LCO}				
n (%)	697 (60%)	270 (23%)	147 (13%)	51 (4%)
CVD (%)	103/697 (15%)	57/270 (21%)	64/147 (44%)	17/51 (33%)
Deaths (%)	24/697 (3%)	24/270 (9%)	37/147 (25%)	23/51 (45%)
K_{CO}				
n (%)	901 (77%)	149 (13%)	97 (8%)	18 (2%)
CVD (%)	157/901 (17%)	41/149 (28%)	39/97 (40%)	4/18 (22%)
Deaths (%)	49/901 (5%)	19/149 (13%)	29/97 (30%)	11/18 (61%)
V_A				
n (%)	753 (65%)	324 (28%)	84 (7%)	4 ($<$ 1%)
CVD (%)	121/753 (23%)	90/324 (28%)	29/84 (35%)	1/4 (25%)
Deaths (%)	53/753 (7%)	37/324 (11%)	17/84 (20%)	1/4 (25%)
FEV_1				
n (%)	590 (51%)	364 (31%)	200 (17%)	11 (1%)
CVD (%)	96/590 (16%)	87/364 (24%)	55/300 (28%)	3/11 (27%)
Deaths (%)	30/590 (5%)	33/364 (9%)	43/200 (22%)	2/11 (18%)
FVC				
n (%)	708 (61%)	341 (29%)	111 (10%)	5 ($<$ 1%)
CVD (%)	115/708 (16%)	90/341 (26%)	35/111 (32%)	1/5 (20%)
Deaths (%)	40/708 (6%)	41/341 (12%)	26/111 (23%)	1/5 (20%)
$FEV_1/FVC\%$				
n (%)	802 (69%)	199 (17%)	151 (13%)	13 (1%)
CVD (%)	158/802 (20%)	42/199 (21%)	40/151 (26%)	1/13 (8%)
Deaths (%)	60/802 (7%)	19/199 (10%)	26/151 (17%)	3/13 (23%)

CVD = cardiovascular disease, D_{LCO} = diffusing capacity of the lung for carbon monoxide, K_{CO} = transfer coefficient of the lung for carbon monoxide, V_A = alveolar volume.

When we limited the gas diffusing capacity data to those whose FEV_1 and FVC values were within the clinically normal range (n=544 patients including 26 deceased), D_{LCO} (p=0.01) and V_A (p=0.04) were still significantly associated with cardiovascular disease, while K_{CO} (p=0.14) was not.

Table 29. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals for cardiovascular disease from logistic regression and global Wald testing using Z-scores derived from Global Lung Function Initiative reference values.⁴³

		Unadjusted		Adjusted*	
D_{LCO} (Z)	n	OR (95%CI)	p	OR (95%CI)	p
Normal (≥ -1.64)	697	Reference	<0.001	Reference	<0.001
Mild (-1.64 to -3)	270	1.54 (1.08, 2.21)		1.27 (0.86, 1.88)	
Moderate (-3 to -5)	147	4.45 (3.02, 6.55)		3.31 (2.12, 5.19)	
Severe (< -5)	51	2.88 (1.55, 5.35)		2.77 (1.30, 5.91)	
K_{CO} (Z)					
Normal (≥ -1.64)	901	Reference	<0.001	Reference	0.03
Mild (< -1.64 to ≥ -3)	149	1.80 (1.21, 2.68)		1.28 (0.82, 2.00)	
Moderate (< -3 to ≥ -5)	97	3.19 (2.05, 4.95)		2.18 (1.30, 3.66)	
Severe (< -5)	18	1.35 (0.44, 4.17)		1.41 (0.39, 5.09)	
V_A (Z)					
Normal (≥ -1.64)	753	Reference	<0.001	Reference	<0.001
Mild (< -1.64 to ≥ -3)	324	2.01 (1.47, 2.74)		2.05 (1.46, 2.88)	
Moderate (< -3 to ≥ -5)	84	2.75 (1.69, 4.50)		2.78 (1.63, 4.77)	
Severe (< -5)	4	1.74 (0.18, 16.9)		3.10 (0.27, 35.9)	
FEV_1 (Z)					
Normal (≥ -1.64)	590	Reference	0.002	Reference	0.03
Mild (< -1.64 to ≥ -3)	364	1.62 (1.17, 2.24)		1.36 (0.95, 1.94)	
Moderate (< -3 to ≥ -5)	200	1.95 (1.34, 2.85)		1.61 (1.06, 2.45)	
Severe (< -5)	11	1.93 (0.50, 7.40)		4.68 (1.12, 19.6)	
FVC (Z)					
Normal (≥ -1.64)	708	Reference	<0.001	Reference	<0.001
Mild (< -1.64 to ≥ -3)	341	1.85 (1.35, 2.53)		1.77 (1.26, 2.48)	
Moderate (< -3 to ≥ -5)	111	2.37 (1.52, 3.71)		2.59 (1.59, 4.21)	
Severe (< -5)	5	1.29 (0.14, 11.6)		2.61 (0.27, 25.5)	
$FEV_1/FVC\%$ (Z)					
Normal (≥ -1.64)	802	Reference	0.19	Reference	0.52
Mild (< -1.64 to ≥ -3)	199	1.09 (0.74, 1.60)		0.81 (0.53, 1.23)	
Moderate (< -3 to ≥ -5)	151	1.47 (0.98, 2.19)		0.91 (0.58, 1.44)	
Severe (< -5)	13	0.34 (0.04, 2.63)		0.28 (0.03, 2.27)	

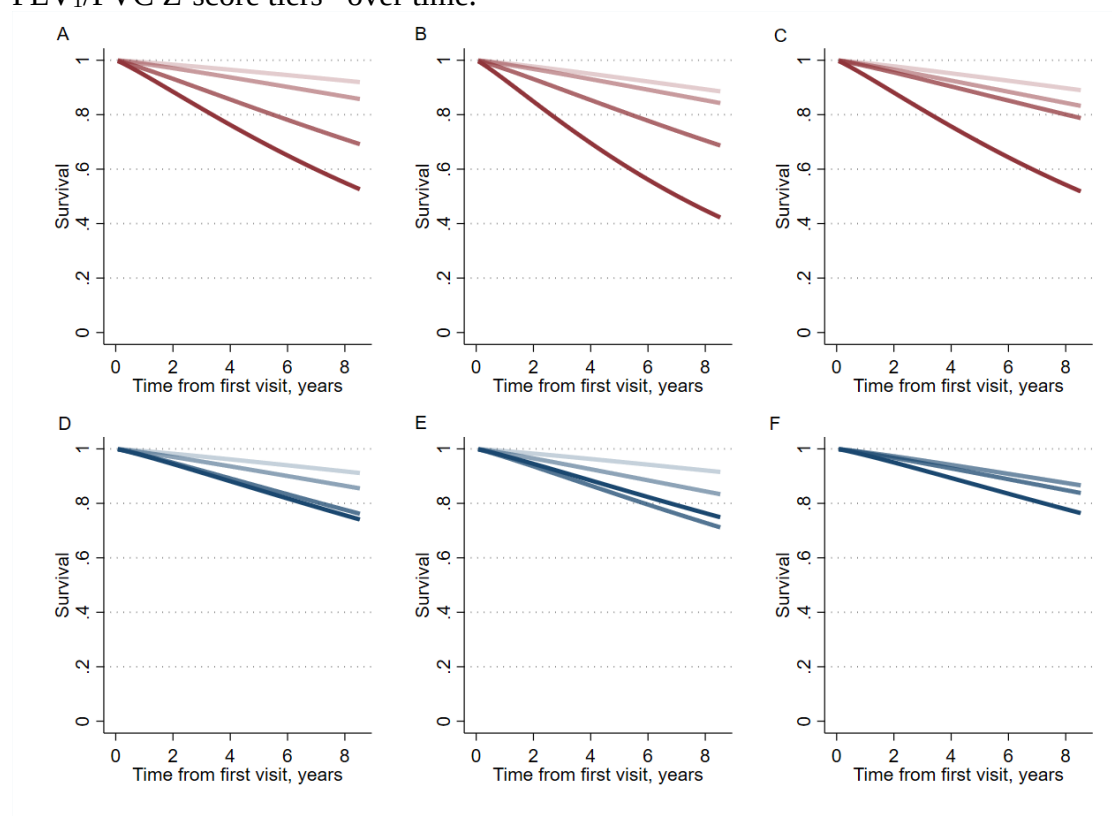
D_{LCO} = diffusing capacity of the lung for carbon monoxide, K_{CO} = transfer coefficient of the lung for carbon monoxide, V_A = alveolar volume. FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity.

*Adjusted for age, sex, smoking status, body mass index, First Nations status, and respiratory disease.

9.4.2 Mortality and survival distributions

By August 2020, 108 (9%) patients had died. Respiratory-related death occurred in 42 (39%) patients, cardiovascular-related death in 25 (23%) patients, and other causes of death in 15 (14%), while we were unable to retrospectively determine cause of death in 16 (15%) patients. Adjusted survivor functions for gas diffusing capacity and spirometry Z-score tiers are graphed in Figure 24. The set of four curves appeared similar between gas diffusing capacity and spirometry tests, although the proportion of patients surviving appeared significantly less for severe D_{LCO} , K_{CO} , or V_A grading. Of 84 patients with a D_{LCO} below the lower limit of normal at baseline, only two had a lower K_{CO} Z-score, and 10 a lower V_A Z-score.

Figure 24. Survival estimates for (A) D_{LCO} , (B) K_{CO} , (C) V_A , (D) FEV_1 , (E) FVC , and (F) FEV_1/FVC Z-score tiers* over time.



D_{LCO} = diffusing capacity of the lung for carbon monoxide, K_{CO} = transfer coefficient of the lung for carbon monoxide, V_A = alveolar volume, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity.

*Severity tiers for Z-scores; normal (>-1.64), mild (<-1.64 to -3), moderate (-3 to -5) and severe (<-5) are shown on graph as lightest to darkest.

9.4.3 Multivariable survival modelling

D_{LCO} (HR=2.99, 95%CI 1.83, 4.90), K_{CO} (HR=2.14, 95%CI 1.38, 3.32), V_A (HR=1.75, 95%CI 1.18, 2.58) Z-scores below the lower limit of normal were associated with increased risk of all-cause mortality after adjustment for age, sex, smoking status, body mass index, First Nations status, and respiratory disease. Full per-tier modelling is available in Table 30, and adjusted survivor functions are plotted in Figure 24.

Analysis restricted to only patients with normal FEV_1 and FVC values showed that D_{LCO} (p=0.03) was still associated with increased overall mortality risk, while K_{CO} (p=0.16) and V_A (p=0.08) were not.

9.4.4 Comparison to spirometry

Median spirometry values were above the lower limit of normal (-1.64 Z-score), with 575 (49%) FEV_1 , 457 (39%) FVC, and 363 (31%) $FEV_1/FVC\%$ results falling below the lower limit. Abnormal FEV_1 (OR=1.45, 95%CI 1.06, 1.97) and FVC (OR=1.93, 95%CI 1.42, 2.63) were both associated with cardiovascular disease, with adjusted effect sizes for each tier similar to those seen for gas diffusing capacity measurements (Table 29). Abnormal FEV_1 (HR=2.21, 95%CI 1.41, 3.47), and FVC (HR=2.57, 95%CI 1.71, 3.86) were also associated with elevated mortality risk, with adjusted effect sizes similar or less than equivalent gas diffusing capacity tiers (Table 30). We observed no associations between $FEV_1/FVC\%$ and either cardiovascular disease prevalence (OR=0.84, 95%CI 0.60, 1.18) or elevated mortality risk (HR=1.13, 95%CI 0.75, 1.70). In the subgroup of patients with normal spirometry, data relating to their gas diffusing capacity values with cardiovascular morbidity and adjusted survival curves and modelling were presented above.

Table 30. Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals for mortality from Cox regression for baseline lung function Z-scores*.

		Unadjusted		Adjusted*	
D_{LCO} (Z)	n	HR (95%CI)	p	HR (95%CI)	p
Normal (≥ -1.64)	697	Reference	<0.001	Reference	<0.001
Mild (< -1.64 to ≥ -3)	270	2.47 (1.40, 4.35)		1.86 (1.03, 3.34)	
Moderate (< -3 to ≥ -5)	147	7.49 (4.48, 12.5)		4.40 (2.51, 7.69)	
Severe (< -5)	51	15.0 (8.45, 26.5)		7.86 (3.84, 16.1)	
K_{CO} (Z)					
Normal (≥ -1.64)	901	Reference	<0.001	Reference	<0.001
Mild (< -1.64 to ≥ -3)	149	2.49 (1.47, 4.24)		1.39 (0.79, 2.44)	
Moderate (< -3 to ≥ -5)	97	6.32 (3.99, 10.0)		3.11 (1.82, 5.32)	
Severe (< -5)	18	14.1 (7.31, 27.1)		6.97 (3.08, 15.8)	
V_A (Z)					
Normal (≥ -1.64)	753	Reference	0.011	Reference	0.014
Mild (< -1.64 to ≥ -3)	324	1.49 (0.98, 2.26)		1.59 (1.03, 2.45)	
Moderate (< -3 to ≥ -5)	84	2.40 (1.39, 4.16)		2.09 (1.19, 3.66)	
Severe (< -5)	4	2.81 (0.39, 20.4)		5.75 (0.76, 43.6)	
FEV_1 (Z)					
Normal (≥ -1.64)	590	Reference	<0.001	Reference	<0.001
Mild (< -1.64 to ≥ -3)	364	1.83 (1.05, 2.84)		1.68 (1.00, 2.83)	
Moderate (< -3 to ≥ -5)	200	4.07 (2.55, 6.50)		2.98 (1.79, 4.96)	
Severe (< -5)	11	2.90 (0.69, 12.2)		3.46 (0.78, 15.4)	
FVC (Z)					
Normal (≥ -1.64)	708	Reference	<0.001	Reference	<0.001
Mild (< -1.64 to ≥ -3)	341	2.04 (1.32, 3.16)		2.10 (1.33, 3.30)	
Moderate (< -3 to ≥ -5)	111	3.68 (2.24, 6.05)		4.00 (2.37, 6.76)	
Severe (< -5)	5	2.34 (0.32, 17.1)		3.40 (0.44, 26.3)	
$FEV_1/FVC\%$ (Z)					
Normal (≥ -1.64)	802	Reference	<0.001	Reference	0.63
Mild (< -1.64 to ≥ -3)	199	1.33 (0.80, 2.24)		1.00 (0.58, 1.69)	
Moderate (< -3 to ≥ -5)	151	2.55 (1.61, 4.04)		1.22 (0.74, 2.02)	
Severe (< -5)	13	4.55 (1.42, 14.6)		2.01 (0.60, 6.79)	

D_{LCO} = diffusing capacity of the lung for carbon monoxide, K_{CO} = transfer coefficient of the lung for carbon monoxide, V_A = alveolar volume. FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity.

*Adjusted for age, sex, smoking status, body mass index, First Nations status, and respiratory disease. *Z-scores are derived from Global Lung Function Initiative reference values⁴³.

9.5 DISCUSSION

In this study of 1165 predominantly First Nations Australian patients seen at specialist respiratory outreach clinics in regional and remote Queensland, we found that D_{LCO} , K_{CO} , V_A , FEV_1 , and FVC values below the clinically normal range were associated with cardiovascular disease and mortality. This finding was independent of factors such as age, sex, personal smoking, BMI, and concurrent respiratory disease. Mortality risk almost doubled for each category increase in D_{LCO} , K_{CO} , and V_A tier (normal, mild, moderate, and severe) based on Z-scores in unadjusted but not adjusted models. While two other studies^{115,116} have reported similar findings with respect to the association of low diffusing capacity with future mortality, our study provides the first evidence that the K_{CO} and V_A , in addition to the D_{LCO} , are each independent prognostic markers of mortality. Further, our data suggests estimated survival is similar or lower for gas diffusing capacity compared to equivalent spirometry Z-score tiers, suggesting that the former is more sensitive than the latter.

Neas et al. investigated pulmonary function as a predictor of mortality using First National Health and Nutrition Examination Survey (NHANES I) data¹¹⁵ Their analysis showed each 10% decrement in D_{LCO} percentage predicted below the lower limit of normal was associated with increased mortality (risk ratio [RR]=1.33, 95%CI 1.21, 1.45), with a greater effect size than for either FEV_1 (RR=1.15, 95%CI 1.10, 1.19) or FVC (RR=1.15, 95%CI 1.10, 1.20).¹¹⁵ This association persisted after including only participants with an FEV_1 >90% predicted (RR=1.30, 95%CI 1.08, 1.56).¹¹⁵ Our similar analysis with stricter criteria, requiring both normal FEV_1 and FVC, support and extend this existing evidence and showed D_{LCO} values below the lower limit of normal were still significantly associated with mortality.

Recent analysis by Miller and Cooper¹¹⁶ explored several grading schemes and showed the ATS/ERS four-tier system in combination with GLI reference equations⁴¹ was best related to survival in a large (n=13829) clinical population and so were chosen for our analysis. Miller and Cooper reported a similarly large increase in risk related to D_{LCO} Z-score abnormality (mild: HR=2.0, 95%CI 1.8, 2.1; moderate: HR=3.4, 95%CI 3.2, 3.7; severe: HR=6.2, 95%CI 6.0, 7.3)¹¹⁶ and these hazard ratios were consistently higher than those for FEV_1 and FVC across the each tier of Z-score grading.¹¹⁶ In concordance in our study, the largest effect across both cardiovascular morbidity and survival analysis were seen in the D_{LCO} , except for the mild tier in which there was significant variation. Our effect size estimates have wide confidence intervals that make differences in the associations of outcomes with gas diffusing capacity and spirometry measurements difficult to discern, however estimates for the severe Z-score tier appear much

larger for gas diffusing capacity measurements than for spirometry. Taken together with previously published evidence,^{115,116} our study supports that associations between cardiovascular morbidity and overall survival to D_{LCO} , K_{CO} , V_A are similar or stronger than for equivalent FEV_1 , FVC, and $FEV_1/FVC\%$ values.

Our data supports a small but growing body of evidence that suggests that lung function impairment, as measured by spirometry and gas diffusing capacity, is associated with poor patient outcomes and this remains true in the absence of diagnosed respiratory disease.^{113,115} The limitations of diagnostic labels have, in part, given rise to the treatable traits paradigm, where clinical interventions are guided by genetic, phenotypic, and biomarker characteristics amongst others.^{22,193} Airflow limitation, eosinophilic airway inflammation, and emphysema¹⁹³ are examples of treatable traits that are identifiable using lung function testing, and our findings suggest these tests could also be applied outside of the respiratory clinic domain. Portability, (relative) low cost, standardisation, and well-defined guidelines for interpretation are key strengths of lung function tests that enable their use in a range of settings, including within office-based and outreach clinics. Broad application of the treatable traits approach necessitates the use of identification markers that are not isolated to large tertiary facilities in urban centres, but those that are ubiquitous and practical across the spectrum of clinical settings.

Our study has several important limitations. Firstly, we cannot discount the possibility of spectrum bias influencing our data, owing to the large number of clinic locations throughout Queensland. We are also reliant on mortality data reported in paper charts and electronic medical records, and so there may be a minority of deaths in this cohort that have not been accounted for. Secondly, although the GLI-2012 ‘other/mixed’ reference category has been found to be suitable for use in First Nations Australian children and young adults, we cannot be certain about its suitability to the adult population. GLI-2017 reference values were developed using participants of European ancestry and no ethnic correction is available.⁴³ It is unlikely these values are suitable for use in First Nations Australians. Thirdly, although we found significant associations, our data is limited by sample size, particularly within the severe Z-score tier of some measurements. This limits our ability to compare associations with outcome between gas diffusing capacity and spirometry measurements. Finally, our data includes adults seen in regional and remote Queensland, and so we cannot be certain about the generalisability of our findings to other populations more broadly.

In conclusion, our data suggests D_{LCO} , K_{CO} , and V_A measurements below the clinically normal range are associated with cardiovascular disease and all-cause mortality. These associations are independent of factors such as age, personal smoking, and concurrent respiratory disease and persist even when spirometry values are normal. Our data also shows D_{LCO} , K_{CO} , and V_A measurements were associated with similar or elevated mortality risk compared to spirometry equivalent spirometry Z-score tiers. Overall, D_{LCO} , K_{CO} , and V_A are prognostic markers of cardiovascular disease and all-cause mortality, with D_{LCO} the most capable measurement for this purpose as an additional prognostic marker available to clinicians.

9.6 ACKNOWLEDGEMENTS

We thank the staff and patients who participated in IROC clinics, and their supporting local communities.

Chapter 10: Fractional exhaled nitric oxide (FeNO) cut-off values in First Nations Australian children and adults

This chapter addresses Objective 4 outlined in Section 1.4; to “Develop reference values for ... exhaled nitric oxide (FeNO) lung function tests, for use in First Nations Australian children and adults”. The following publication within a peer-reviewed journal was produced:

Collaro AJ, Chang AB, Marchant JM, Vicendese D, Chatfield MD, Cole JF, Blake TL, McElrea MS. Developing Fractional Exhaled Nitric Oxide Predicted and Upper Limit of Normal Values for a Disadvantaged Population. *Chest*. 2022. In Press.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
Andrew Collaro	Drafting of manuscript, data collection, led data analysis, input into study design
Anne Chang	Reviewed draft manuscript, data collection, led study design
Julie Marchant	Reviewed draft manuscript, input into study design
Don Vicendese	Reviewed draft manuscript, assisted with data analysis

Mark Chatfield	Reviewed draft manuscript, assisted with data analysis
Johanna Cole	Reviewed draft manuscript, data collection
Tamara Blake	Data collection, input into study design
Margaret McElrea	Reviewed draft manuscript, led data collection, input into study design

10.1 TAKE-HOME POINT

10.1.1 Study Question

What are suitable predicted and upper limit of normal (ULN) FeNO values in healthy First Nations Australian children and adults, and how do they relate to current guidelines that suggest single or all-age based cut-off values?

10.1.2 Results

We developed FeNO predicted and ULN values that account for non-linear associations with age and height for First Nations Australians aged 4-76 years, and current interpretive guidelines do not adequately describe normal and abnormal FeNO values in this population.

10.1.3 Interpretation

Single paediatric, adult, or all-age FeNO cut-off values used by current interpretive guidelines to define abnormality fail to account for factors that modify FeNO values; creating height-for-age predicted and ULN values could be considered for other ethnicities.

10.2 ABSTRACT

10.2.1 Background

Fractional exhaled nitric oxide (FeNO), used as a biomarker, is influenced by several factors including ethnicity. Normative data are essential for interpretation, and currently single cut-off values are used in children and adults.

10.2.2 Research Question

Accounting for factors that influence FeNO, (a) what are appropriate predicted and upper limit of normal (ULN) FeNO values in an under-served population (First Nations Australians), (b) how do these values compare to age-based interpretive guidelines, and (c) what factors influence FeNO and what is the size of the effect?

10.2.3 Study Design and Methods

FeNO data of First Nations Australians (aged <16-years: n=862, ≥16-years: n=348) were obtained. Medical history using participant questionnaires and medical records were used to define healthy participants. Flexible regression using spline functions, as used by the Global Lung Function Initiative, were used to generate predicted and ULN values.

10.2.4 Results

Look-up tables for predicted and ULN values using age (4-76 years) and height (100-200cm) were generated and are supplied with a calculator for clinician use. In healthy First Nations children (aged <18 years), ULN values ranged between 25-60 parts per billion (ppb) when considering only biologically plausible age and height combinations. For healthy adults, ULN values ranged between 39-88ppb. Neither the current FeNO interpretation guidelines, nor the currently recommended cut-off of 50ppb for First Nations children ≤16-years were appropriate for use in this cohort. Our modelling revealed predicted and ULN values of healthy participants varied non-linearly with age and height.

10.2.5 Interpretation

As single paediatric, adult, or all-age FeNO cut-off values used by current interpretive guidelines to define abnormality fail to account for factors that modify FeNO values, we propose predicted and ULN values for First Nations Australians aged 4-76 years. Creating age and height adjusted predicted and ULN values could be considered for other ethnicities.

10.3 INTRODUCTION

Fractional exhaled nitric oxide (FeNO) is a non-invasive tool used increasingly as a biomarker to identify and monitor asthma²¹ and eosinophilic airway inflammation as a treatable trait, in order to provide individualised care.²² Non-suppression of FeNO despite corticosteroid use may also assist identification of a type 2 immune response within the airways.¹⁹⁴ Age and height are known to be independently associated with FeNO values,^{35,36} and there is now evidence that ethnic differences modify FeNO values.³⁷ Males may have higher FeNO values than females,³⁸ but current evidence is limited.³⁵ Despite the apparent impact of some of these factors on FeNO values in healthy people, current guidelines propose either age-based cut-off values^{21,25,26} or a single cut-off value for use in all individuals.²⁷ Results above the upper limit of normal (ULN) values are considered abnormal/suggestive of eosinophilic inflammation. These cut-off values are based only on data from Caucasian populations³⁷ and have been shown to be unsuitable for use in some ethnic groups whose healthy subpopulation have generally higher values than healthy White

populations,¹⁸ increasing the likelihood of disease misclassification, unnecessary investigations and/or treatment or non-treatment, possibly leading to harm.

Despite evidence to suggest age, height, and ethnicity modify FeNO values,³⁵⁻³⁷ these factors are not utilised within current interpretive guidelines. Data from the National Health and Nutrition Examination Survey (NHANES) 2007-12 were used to generate normative height-for-age FeNO data for Non-Hispanic white, non-Hispanic black, Hispanic, and other/multi-racial Americans using generalised additive modelling for location, scale, and shape (GAMLSS), a statistical technique recommended by the World Health Organization (WHO) and Global Lung Function Initiative (GLI).²⁴ To our knowledge, there are no published look-up tables or software usable by clinicians to interpret FeNO, and only Jacinto et al²⁴ have previously modelled normative FeNO values using this method,¹⁹⁵ however a shortcoming of their analysis was lack of control for atopy, a factor known to confound FeNO values. Numerous other factors may influence FeNO values, including smoking,²⁹⁻³¹ dietary caffeine³² and nitrates³³, and alcohol consumption.³⁴ Recent intake in the lead-up to FeNO testing should be considered in the clinical interpretation of results.

Availability of appropriate and inclusive predicted values are important for an accurate interpretation of results. Particularly for FeNO which is used increasingly in diagnosis, treatment and follow-up in clinical practice as well as a biomarker within the treatable traits paradigm.^{22,196} In the context of the high burden of respiratory disease among Aboriginal and/or Torres Strait Islander peoples¹⁹⁷ (henceforth respectfully referred to as First Nations), we previously determined spirometry reference values²⁰ and FeNO data³⁹ of healthy children (3-16 years). We found the most appropriate published guideline for identifying healthy First Nations children was 50 parts-per-billion (ppb)³⁹ proposed by the Global Initiative for Asthma (GINA),²⁷ a value substantially higher than those recommended by other published guidelines (as low as 25 ppb).^{21,25,26} This single cut-off value is unlikely to be well-suited for all First Nations children, and may overestimate the ULN for young children of shorter stature, and underestimate the ULN for older children of larger stature. Similarly, it is unlikely to be suitable for use in First Nations adults as most current guidelines suggest different cut-offs for children and adults.^{21,25,26}

In the context of the increasing importance of using FeNO values in clinical practice for tailoring individualised approaches, we determined FeNO predicted and ULN values in an under-served population. Our study may also serve as a model for developing FeNO predicted and ULN values for other ethnicities. From 1165 participants, we aimed to provide (a) look-up tables and a calculator to determine predicted and ULN values in this under-served population, (b) relate these values to published age-based guidelines, and (c) determine factors that modify these values (age,

biological sex, height, and ethnicity [Aboriginal, Torres Strait Islander, and both Aboriginal and Torres Strait Islander Australians]).

10.4 MATERIALS AND METHODS

10.4.1 Study design, setting, and participants

To determine normative FeNO values in healthy First Nations adults, we recruited 348 First Nations aged ≥ 18 years from six Queensland and Northern Territory communities and sites between August 2019 and November 2021 as part of the Healthy Indigenous Lung Function Testing in Adults (HILTA) study. Also included are data from our previous Indigenous Respiratory Reference Values (IRRV)³⁹ study of First Nations children and young adults recruited from nine Queensland and Northern Territory communities in Australia between June 2015 and October 2017. Informed written consent was obtained for participation in both studies; from parent/guardian for participants < 18 years, and from adults aged ≥ 18 years. Ethical approval was obtained from Education Queensland, and the Children's Health Queensland (HREC/14/QRCH/111), Far North Queensland (HREC/14/QCH/96-929), Darling Downs (HREC/15/QTDD/27), and Menzies School of Health Research (HREC-2017-2833) Human Research Ethics Committees.

10.4.2 Participant selection

Repeatable FeNO measurements (within 10% or 2ppb for measurements < 10 ppb)²⁸ were included in this analysis. Participants were excluded if they had no recorded FeNO result, non-repeatable FeNO measurements, or did not identify as First Nations Australians.

Table 31. Criteria for assignment of participants into sub-groups.

Sub-group	Criteria
Asthma	Either (or both): Medical record documented asthma Doctor-confirmed asthma on participant questionnaire
Atopy (no asthma)	Participant does not meet criteria for asthma sub-group, but has at least one of doctor-confirmed: Hay fever Chronic rhinorrhoea Eczema
Other respiratory disease	Participant does not meet criteria for asthma, or atopy (no asthma) sub-groups, but has or has had other doctor-confirmed respiratory disease. Examples provided on participant questionnaire include chronic obstructive pulmonary disease and bronchiectasis.
Smoking history only	Participant does not meet criteria for asthma, atopy (no asthma), or other respiratory disease sub-groups, but indicated on participant questionnaires they are a current or former smoker.
Healthy	Participant does not meet criteria for any other above sub-group.

10.4.3 Data collection

Medical and smoking histories for all participants were obtained from medical history and modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires (parent-completed for participants <18 years), as well as medical charts. Where there was disagreement, medical chart data was used. Participants were stratified by age (<12 years, 12-16 years, and >16 years), and then allocated into sub-groups according to medical history. Criteria for assignment of participants into sub-groups are given in Table 31.

10.4.4 FeNO measurements

NIOX MINO (Aerocrine AB, Sweden) handheld devices were used to measure FeNO for the IRRV study. NIOX VERO (Circassia, UK) handheld devices were used to obtain FeNO measurements for the HILTA study. The newer NIOX VERO devices have been shown to be clinically equivalent to the older MINO devices.¹⁹⁸ For both studies, FeNO was performed by the patient exhaling into the device through a filtered mouthpiece (online technique) at a

controlled flow rate (50 mL s⁻¹) and pressure (10-20 cm H₂O) for 6 seconds (children <12 years of age) or 10 seconds (children and adults ≥12 years of age). This methodology is according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.²⁸ At least two measurements were made during the testing session and the mean value was used as per current guidelines.²⁸

10.4.5 Spirometry measurements

Spirometry was performed according to ATS/ERS guidelines for preschool children,¹¹⁹ and for school-age children and adults,^{8,10} using portable Easy on-PC spirometers (nidd, Zurich, Switzerland). Z-scores and percentage-predicted (pp) values for spirometry tests were generated for the 'Other/mixed' Global Lung Function Initiative (GLI) 2012⁹ ethnic category, as this was previously found to be most appropriate in First Nations Australian children and young adults²⁰ and is recommended by the GLI for ethnic groups who have no GLI ethnic-specific equation.¹⁹⁹

10.4.6 Statistical methods

Prior to conducting the predictive modelling of FeNO ranges, we explored the associations between FeNO and age and height using general additive quantile regression for the 50th (predicted) and 95th (upper limit of normal) percentiles. We explored the univariate associations between the 5th, 50th (predicted values) and 95th percentiles (upper limit of normal) of FeNO and age and height using additive quantile regression which indicated that the associations were non-linear. The results are presented graphically.

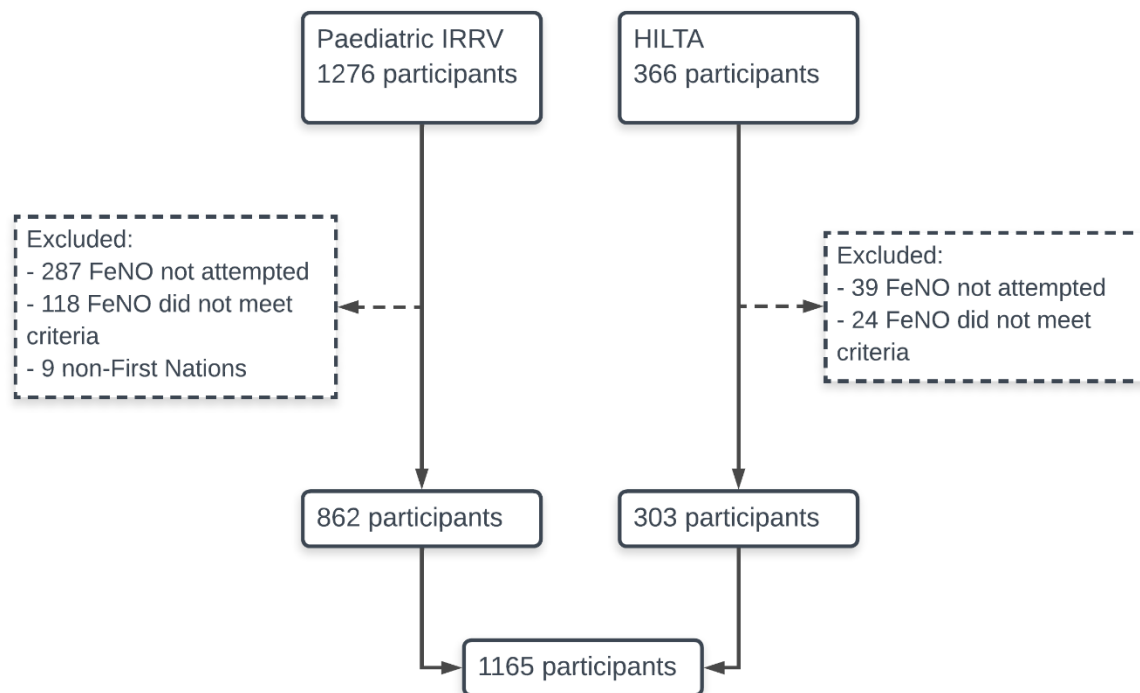
To estimate the centile reference ranges we used a GAMLSS model.^{200,201} A full description of the methods used are available in Supplementary Materials A. Briefly, this is an approach recommended by the WHO Child Growth Standards for reference centile estimation²⁰² and has been used for reference ranges for spirometry²⁰³ and FeNO.²⁴ We used penalised smoothing splines of natural log transformed age and height to model the location, scale and shape of natural log transformed FeNO.²⁴ The smoothing parameter and effective degrees of freedom for the splines were estimated using the local maximum likelihood method.²⁰⁰

Results of our modelling are supplied as look up tables with an accompanying calculator coded in Microsoft Excel (Redmond, Washington, US). The *gamlss*,²⁰⁴ *qgam*,²⁰⁵ and *ggplot*²⁰⁶ libraries in R²⁰⁷ were used for the GAMLSS, additive quantile regressions and their graphs, respectively.

10.5 RESULTS

Sequential exclusion from study participants to obtain the study cohort are summarised in Figure 25, with their demographic and FeNO data described in Table 32. Of the 142 participants unable to achieve FeNO testing that met criteria, 79 were aged <12 years, 29 were aged 12-16 years, and 34 were aged >16 years.

Figure 25. Sequential exclusion of participants from IRRV and HILTA datasets.



FeNO = fractional exhaled nitric oxide. IRRV = Indigenous Respiratory Reference Values. HILTA = Healthy Indigenous Lung Function Testing in Adults.

Table 32. Demographic data and FeNO values by sub-group of 1165 participants with repeatable FeNO results.

	All participants (n=1165)	Participants aged <12 years (n=486)	Participants aged 12-16 years (n=331)	Participants aged >16 years (n=348)
	n (%) or Median (IQR)			
Age, years	13 (9 – 21)	9 (7 – 10)	14 (13 – 16)	37 (23 – 53)
Female	620 (53%)	248 (51%)	164 (50%)	208 (60%)
Height, cm	157 (136 – 167)	133 (123 – 143)	163 (158 – 169)	167 (161 – 175)
Ever-smoker	176 (15%)	0 (0%)	36 (11%)	140 (40%)
Ethnicity				
Aboriginal	430 (37%)	163 (34%)	104 (31%)	163 (47%)
Torres Strait Islander	394 (38%)	142 (29%)	132 (40%)	120 (34%)
Both	341 (29%)	181 (37%)	95 (29%)	65 (19%)
Sub-groups	n (%) or Median (IQR)			
Healthy	582 (50%)	273 (56%)	166 (50%)	143 (41%)
FeNO, ppb	12 (8 – 21)	10 (7 – 14)	11 (8 – 22)	19 (13 – 30)
95 th percentile, ppb	57	52	57	62
Abnormal spirometry*	7 (1%)	0 (0%)	0 (0%)	7 (5%)
Asthma	205 (18%)	73 (15%)	58 (18%)	74 (21%)
FeNO	18 (11 – 32)	16 (9 – 31)	20 (11 – 35)	18 (13 – 29)
95 th percentile, ppb	88	79	116	97
Abnormal spirometry*	10 (5%)	0 (0%)	0 (0%)	10 (14%)
Atopy (no asthma)	131 (11%)	50 (10%)	48 (15%)	33 (9%)
FeNO, ppb	15 (10 – 30)	15 (10 – 35)	15 (10 – 37)	14 (12 – 23)
95 th percentile, ppb	71	56	76	50
Abnormal spirometry*	3 (2%)	0 (0%)	0 (0%)	3 (9%)
Other respiratory disease	141 (12%)	90 (19%)	36 (11%)	15 (4%)
FeNO, ppb	11 (7 – 18)	11 (7 – 16)	12 (6 – 19)	18 (8 – 31)
95 th percentile, ppb	37	30	52	61
Abnormal spirometry*	4 (3%)	0 (0%)	0 (0%)	4 (3%)
Smoking history only	106 (9%)	0 (0%)	23 (7%)	83 (24%)
FeNO, ppb	15 (10 – 26)	-	12 (9 – 18)	16 (12 – 25)
95 th percentile, ppb	48	-	35	49
Abnormal spirometry*	6 (6%)	-	0 (0%)	6 (7%)

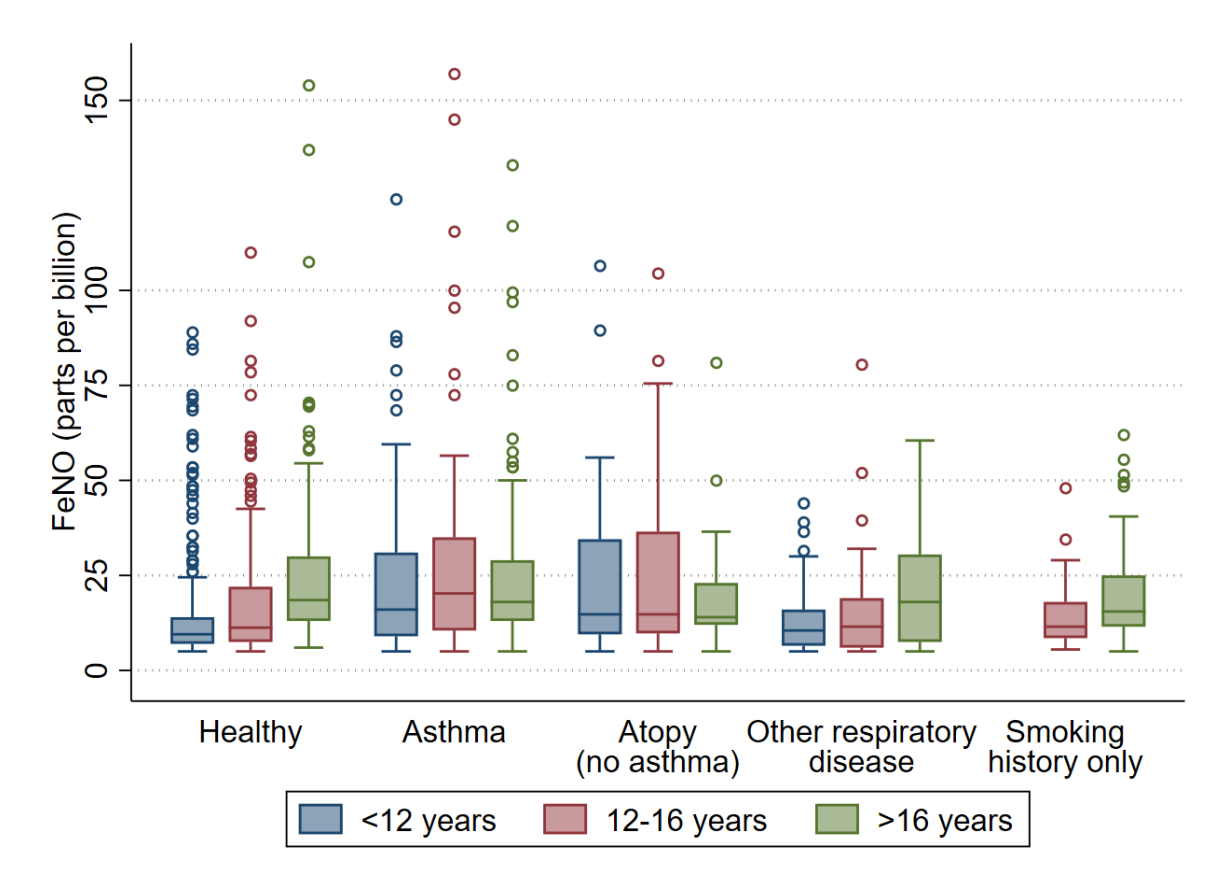
FeNO = fractional exhaled nitric oxide. Both = Aboriginal and Torres Strait Islander. ppb = parts per billion.

*Abnormal spirometry defined as any of FEV₁, FVC, or FEV₁/FVC values < -1.64 Z-scores using the GLI-2012

‘Other/mixed’ ethnic category.⁹

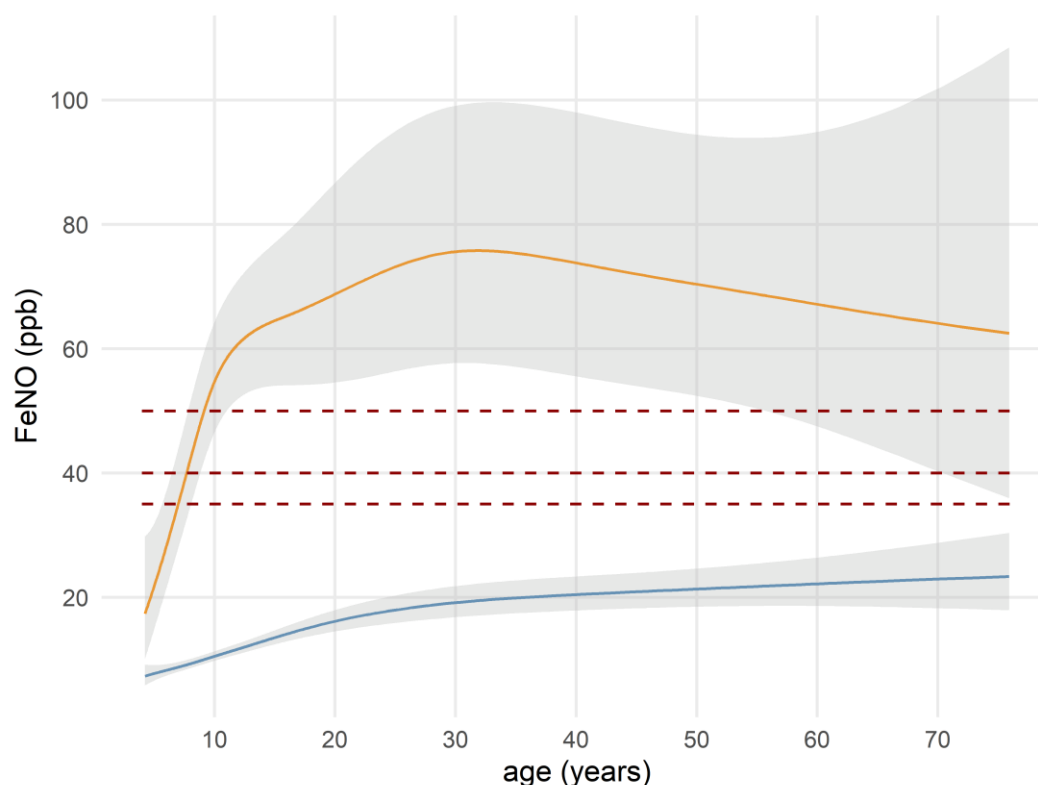
Half (n=582, 50%) of all included participants were classified as healthy, with a greater proportion of younger participants classified as healthy (56% aged <12 years and 50% aged 12-16 years) compared to the adult group (41% aged >16 years). Seven of 582 (1%) of healthy participants had either abnormal FEV₁, FVC, or FEV₁/FVC values (< -1.64 Z-scores), proportionally less than for the other sub-groups. FeNO distributions for each sub-group are plotted in Figure 26. For healthy, ‘other respiratory disease’, and ‘smoking history only’ groups, FeNO was lowest among the youngest age group (<12 years), and highest among the late adolescent and adult group (>16 years). For asthma and atopy (without asthma) groups, FeNO was highest among children aged 12-16 years.

Figure 26. Box and whisker plots of FeNO results for First Nations Australians across five sub-groups.



10.5.1 FeNO predicted and ULN values in using healthy participants (n=582)

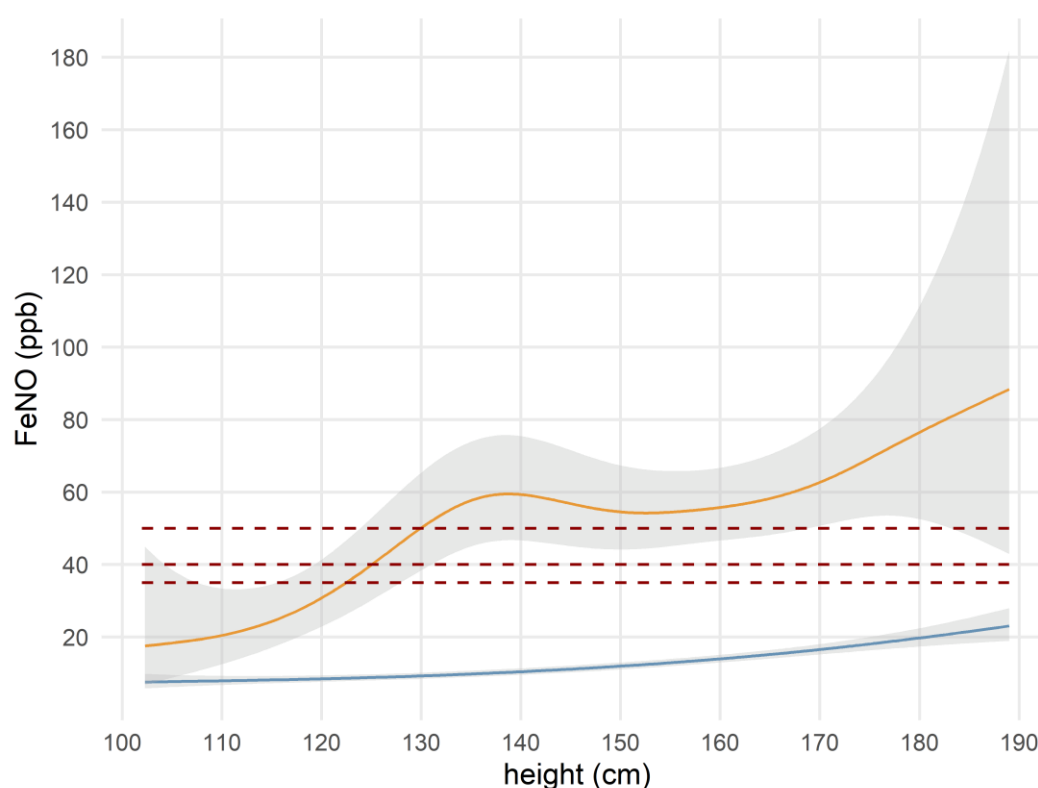
Figure 27. Univariable quantile generalised additive modelling of FeNO (ppb) predicted and upper limit of normal values as a function of age (years) for 582 healthy First Nations Australians.



Modelling of FeNO predicted (blue) and upper limit of normal (orange) values as a function of age are indicated by smoothed lines generated using quantile generalised additive regression. The shaded areas indicate 95% confidence intervals. Dashed red lines reflect 35, 40, and 50ppb cut-offs proposed by current interpretive guidelines. P-values for each model fit were <0.001.

Univariable generalised additive modelling of predicted and ULN FeNO values as a function of age is shown in Figure 27, and height in Figure 28, with reference lines reflecting paediatric, adult, and all-age cut-offs proposed by current interpretive guidelines.^{21,25-27} Age and height were both found to be independently associated with FeNO values within our cohort (Table 33), and so were selected as explanatory variables within GAMLSS modelling of FeNO percentiles. A heat map of FeNO ULN values for biologically plausible age and height combinations is shown in Figure 29, and all age and height combinations in Figure 30. Look-up tables for age (per 0.5 years) and height (per 2cm) combinations, and a FeNO predicted and ULN value calculator using age and height inputs, are available in Supplementary Materials B.

Figure 28. Univariable quantile generalised additive modelling of FeNO (ppb) predicted and upper limit of normal values as a function of height (cm) for 582 healthy First Nations Australians.



Modelling of FeNO predicted (blue) and upper limit of normal (orange) values as a function of age are indicated by smoothed lines generated using quantile generalised additive regression. The shaded areas indicate 95% confidence intervals. Dashed red lines reflect 35, 40, and 50ppb cut-offs proposed by current interpretive guidelines. P-values for each model fit were <0.001.

10.5.2 Relation to current interpretive guidelines

FeNO value distributions of healthy First Nations Australians by age bracket and ethnicity are plotted in Figure 31. The GINA²⁷ all-age and ATS²¹ adult cut-offs of 50ppb classified 9% of healthy participants aged >16 years; 13% of Aboriginal, 7% of Torres Strait Islander, and 4% of both Aboriginal and Torres Strait Islander participants aged >16 years as having ‘abnormal’ FeNO values. In comparison, a 50ppb cut-off classified 4% of children <12 years, and 8% of children aged 12-16 years as having ‘abnormal’ FeNO values. Using the 40ppb cut-off proposed by the National Institute for Health and Care Excellence (NICE)²⁵ and British Thoracic Society (BTS)/ Scottish Intercollegiate Guidelines Network (SIGN)²⁶

guidelines, 15% of healthy participants aged >16 years were classified as having ‘abnormal’ FeNO values.

Table 33. Univariable and multivariable regression modelling of FeNO (ppb) in 582 healthy First Nations Australians.

	Univariable (n=582)		Multivariable (n=582)	
	GMR (95%CI)	p	GMR (95%CI)	p
Age (per 10 year increase)	1.07 (1.06, 1.09)	<0.001	1.04 (1.02, 1.06)	<0.001
Female	0.97 (0.95, 1.02)	0.26		
Height (per 10 cm increase)	1.05 (1.04, 1.07)	<0.001	1.04 (1.02, 1.05)	<0.001
Ethnicity				
Aboriginal	Reference	-	Reference	-
Torres Strait Islander	1.02 (0.96, 1.09)	0.16	1.01 (0.95, 1.07)	0.82
Both	0.92 (0.86, 0.98)	0.01	0.96 (0.90, 1.02)	0.17

GMR = geometric mean ratio.

10.6 DISCUSSION

Using data of 582 healthy First Nations Australians, we present the first look-up tables, and an accompanying calculator that accepts age and height inputs that may be used to generate FeNO predicted and ULN values. While this was generated for an underserved population (First Nations children and adults aged 4-76 years), we believe such methods could be used to generate predicted and ULN values for other populations. Cut-off values suggested from existing guidelines^{21,25-27} may either under- or over-estimate FeNO ULN values, depending on the age and height of the individual. Comparing simple calculations of 95th percentiles in Table 32 to the GINA or adult ATS cut-off of 50ppb, we found 9% of healthy adults in our study were within the inflammatory zone, and when we applied the 40ppb cut-off proposed for adults by NICE²⁵ and BTS/SIGN²⁶ guidelines, 15% of healthy adult First Nations participants fell within the inflammatory zone, suggesting neither cut-off is suitable for this population even without more sophisticated modelling of ULN values.

In the context of disproportionate respiratory disease burden among First Nations Australians,^{197,208} and the utility of FeNO as a tool used to assist in airway diagnosis and monitoring,²¹ accurate and comprehensive guidelines for interpretation of FeNO results are needed. Current FeNO guidelines are deficient in several ways. We present an all-age FeNO 95th percentile value for healthy First Nations Australians, including age-specific 95th percentile values for individuals aged <12 years, 12-16 years, and >16 years (Table 32), in much the same way as existing FeNO interpretive guidelines do. However, our data suggest

the modelled ULN values within Supplement B be used in preference to the 95th percentile of these age-groups. To illustrate, among children aged <12, the 95th percentile was 52ppb. In our modelling, depending on the exact age and height of the child, the ULN ranges between 25ppb and 60ppb when considering biologically plausible age and height combinations of children aged 4-11.9 years. For participants aged >16 years, our modelling suggests a range of values between 39-88ppb for individuals ranging from 140-180cm in height (as per look-up tables contained within Supplementary Materials B). Use of more sophisticated techniques in the development of FeNO reference values that incorporate known confounders may enhance the sensitivity and specificity of this test and improve confidence of clinicians in FeNO testing, enhancing its clinical utility. Our research demonstrates that currently, clinicians should be aware of significant limitations in the use of single cut-off values for large populations of patients.

Our data is concordant with previous works that suggest age and height independently modify FeNO values.^{35,36} Biologically, this is plausible as cumulative nitric oxide synthase activity within the airway epithelium is related to total airway surface area.²⁴ Yet, current guidelines for FeNO interpretation present only a single paediatric, adult, or all-age cut-off value. This contrasts with spirometry where reference values vary with age, height, biological sex, and ethnicity. Lastly, current guidelines are based solely on data collected from White populations despite evidence suggesting that ethnicity is a determinant of FeNO values.³⁷ The effect of ethnicity may be a function of differences in nitric oxide synthase activity and allele frequency between ethnic groups.²⁰⁹⁻²¹¹

In addition to age and height, numerous other medical and lifestyle factors may modify FeNO values. Among First Nations children and adolescents, FeNO values appeared elevated in children with doctor-diagnosed asthma, or atopy (defined as hay fever, rhinorrhoea, or eczema) without concurrent asthma. Among asthmatic adult participants, the FeNO ULN was 97ppb (Table 32). Other factors such as respiratory disease and infection²¹² and cigarette smoking history³¹ may also modify FeNO.²⁹⁻³¹ Each of these factors, and their effects on FeNO, should be considered in the clinical interpretation of results. For patients with respiratory disease, atopy, or recent smoking history, any published cut-off value, even reference and ULN values provided within Supplementary Materials B, should be used with caution. Further, our modelling of predicted and ULN FeNO values in this population should be used only as supporting evidence in the overall clinical picture, and patient values that fall above or below

the suggested ULN provided in Supplement B does not by itself indicate the presence or absence of disease.

The use of ethnicity-specific equations or correction in clinical algorithms is the subject of debate within the literature, and there are calls to remove ethnic correction from spirometry reference values^{213,214} and in other fields of medicine.^{215,216} These arguments centre around practical issues inherent with ethnic correction including that little consideration is usually given to socioeconomic determinants of health when collecting and analysing data from racial or ethnic groups, possibly normalising abnormal results in disadvantaged populations. There is evidence to suggest that socioeconomic determinants impact spirometry values within racial and ethnic groups,^{217,218} however, evidence is lacking for FeNO. Analysis of 6717 children aged 6 years within the Generation R study cohort found that while FeNO values varied between ethnicities, neither socioeconomic, nor sociodemographic factors influenced FeNO values.²¹⁹ There is a need for further data, particularly across the age spectrum, to better understand the impacts of socioeconomic determinants of health on FeNO values. A limitation of our work is the inability to explore these effects due the lack of socioeconomic data collected.

Our study has several other limitations. Our data is reliant on self-reported and medical record information rather than direct measurements to ascertain the presence of asthma, atopy, and other respiratory disease. Thus, we cannot exclude the possibility of asthmatic or atopic individuals being inappropriately included/excluded from the healthy group. We attempted to minimize this risk by utilizing multiple sources of data to ensure the healthy group is representative of the healthy First Nations population. Secondly, we were unable to account for numerous other factors that may confound FeNO such as dietary caffeine³² and nitrate³³ intake, and excessive alcohol consumption.³⁴ Thirdly, given that our data describes the distribution of FeNO values for healthy individuals, it cannot be used to predict corticosteroid responsiveness for which data from a clinical population is required. Finally, our data has been obtained from First Nations populations in Queensland and the Northern Territory, and we cannot be certain of the generalisability of our findings and look-up tables to First Nations populations of other states and territories within Australia. While our sample of healthy participants is much smaller than the cohort used to generate the Global Lung Function Initiative (GLI) 2012 equations for spirometry testing, it is larger than the current recommended number (n=300) recommended by the GLI.⁹

This is the first study to develop look-up tables and a calculator to generate predicted and ULN values for use in a clinical population, using only healthy participants with no history of asthma, atopy, smoking, or any other chronic respiratory disease. Predicted and ULN values presented account for both age and height, which were found to modify FeNO values in a non-linear fashion. We determined that ULN values contained within published guidelines, and a 50ppb cut-off previously recommended for First Nations children, may result in either under- or over-diagnosis of eosinophilic airway inflammation in First Nations children and adults. Whether these methods should be generated for other ethnicities remains to be determined. Significant work is required to develop more reliable FeNO interpretation guidelines that accurately account for modifying factors, to aid clinicians in using FeNO as a robust tool to identify eosinophilic airway inflammation. Data from a clinical population is required to understand how data presented in this study relates to corticosteroid responsiveness.

10.7 ACKNOWLEDGEMENTS

The authors would like to acknowledge the invaluable assistance of Vera Assan (Indigenous Healthworker), Lesley Versteegh (Aboriginal Research Nurse), Allan Takken and Brian Peacock (Indigenous Project Officers, IROC Program) in completing this study. We also thank the study participants, families, schools, community elders and leaders for their support and participation.

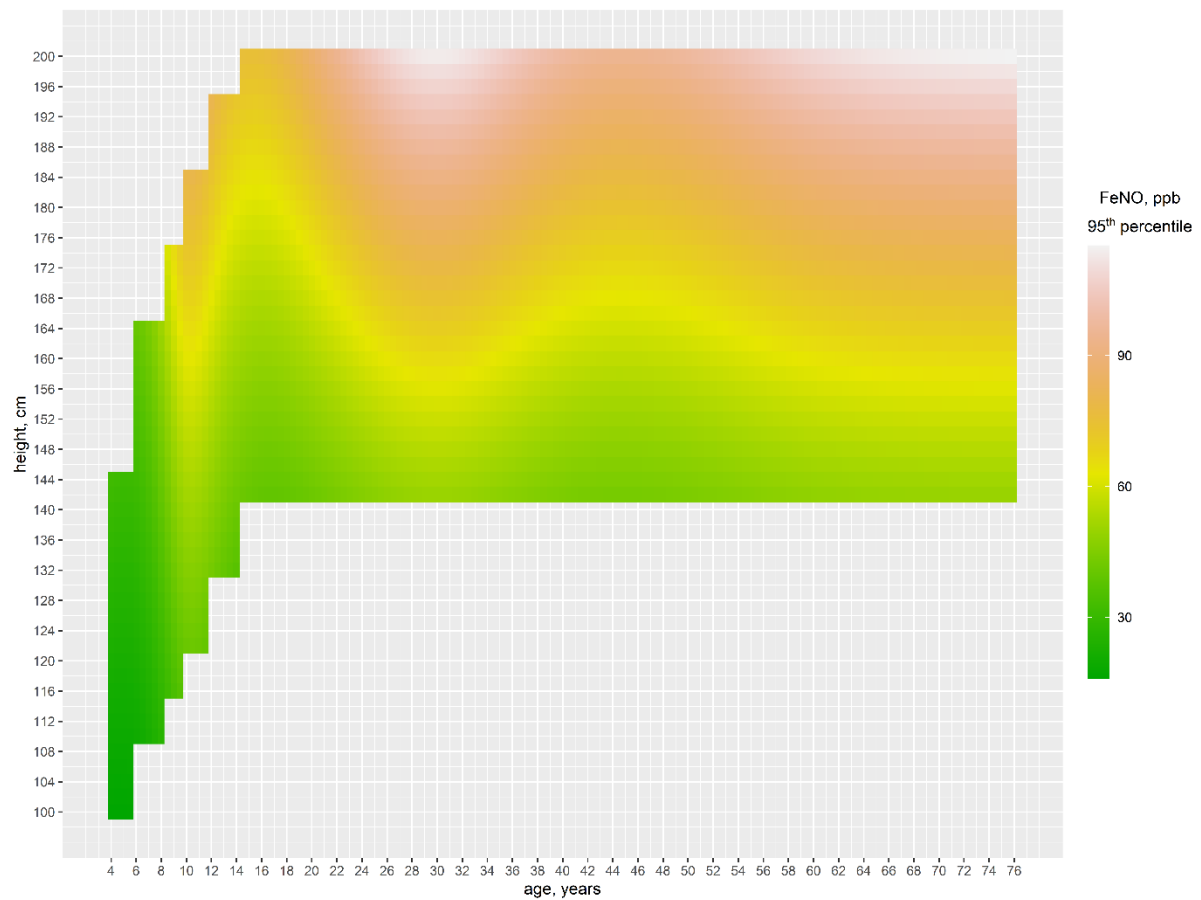
10.8 SUPPLEMENTARY MATERIALS A

To estimate the centile reference ranges we used a generalized additive model for location, scale, and shape (GAMLSS).²²⁰ This is an approach recommended by the World Health Organization (WHO) Child Growth Standards for reference centile estimation²⁰² and has been used for reference ranges for spirometry²⁰³ and, recently, exhaled FeNO.²⁴ The approach is thoroughly described in the four previous citations but briefly, the mean or median (location), variability (scale) and skewness (shape) of the outcome distribution, conditioned on the required covariates, are each directly modelled using a flexible general additive approach that can allow for any non-linearity. The smoothing parameter and effective degrees of freedom for the splines are estimated automatically using the local maximum likelihood method.²²⁰ The results from GAMLSS are similar to quantile regression.²²¹ They both are powerful and robust methods that offer an in-depth view of the association between predictors and the outcome but, in some cases, GAMLSS may have the advantage of statistical efficiency, that is, more precise estimates.²²²

For adult spirometry, Cole showed that a multiplicative model was required to represent the change in outcome based on age and size. That is, the outcome was proportional to $f_1(\text{age}) \times f_2(\text{size})$ where f_1 and f_2 are arbitrary functions and represent the spline fits for age and size.²²³ This specification assumes an allometric law between outcome and size and is widely applied for body size scaling both between and within species.²²⁴ This is the approach used by WHO.²⁰³ Jacinto et al. argued cogently that, as cumulative nitric oxide synthase activity within the airway epithelium is related to total airway surface area, it would be expected that a multiplicative model would apply also to reference values for FeNO.²⁴ Furthermore, a recent systematic review regarding reference values for FeNO remarked on the importance of accounting for allometric scaling and added that this area of research was in need of standardization of technical and statistical methods.¹⁹⁵ Because of the need to respect allometric scaling, and a recent study used the multiplicative approach for FeNO reference values, and the importance of standardisation of statistical methods, we decided to also specify a multiplicative model. The multiplicative approach is applied efficiently by logarithmic transformation of the outcome FeNO, and our two predictor variables, height and age, to which an additive model is applied and then the results are exponentiated back to their original scale for ease of interpretation.^{220,225} This can be done because of the invariance of quantiles under monotone transformation.

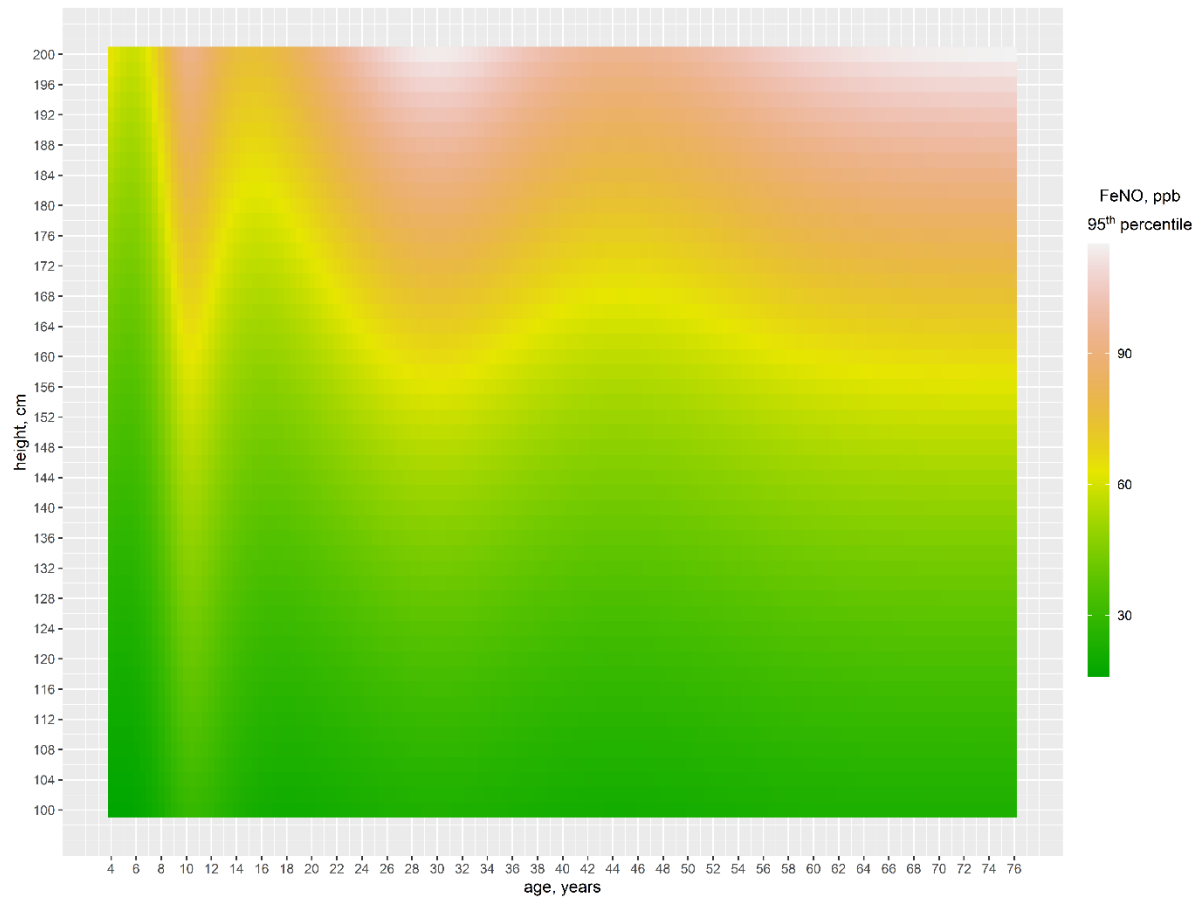
The use of GAMLSS begins with a choice of distribution for the specified model and following WHO recommendations and previous studies^{24,202,203} we tested model fit with the Box-Cox Cole-Green, Box-Cox Cole-Green original, Box-Cox power exponential, Box-Cox power exponential original, Box-Cox t and Box-Cox t original distributions.²²⁶ Based on both the Akaike Information and Bayesian Information Criteria (AIC, BIC) the Box-Cox power exponential original was chosen. Residual density plots, quantile-quantile plots and worm plots were also checked to assess model fit.²²⁰ The model was used to provide predicted reference ranges for median and ULN exhaled FeNO (converted back to its original scale (parts per billion, ppb) based on both age and height, also in their original scales (years and centimetres, respectively).

Figure 29. Heat map of FeNO (ppb) upper limit of normal values in 582 healthy First Nations Australians for biologically plausible height-for-age combinations, generated using generalised additive modelling for location, scale, and shape.



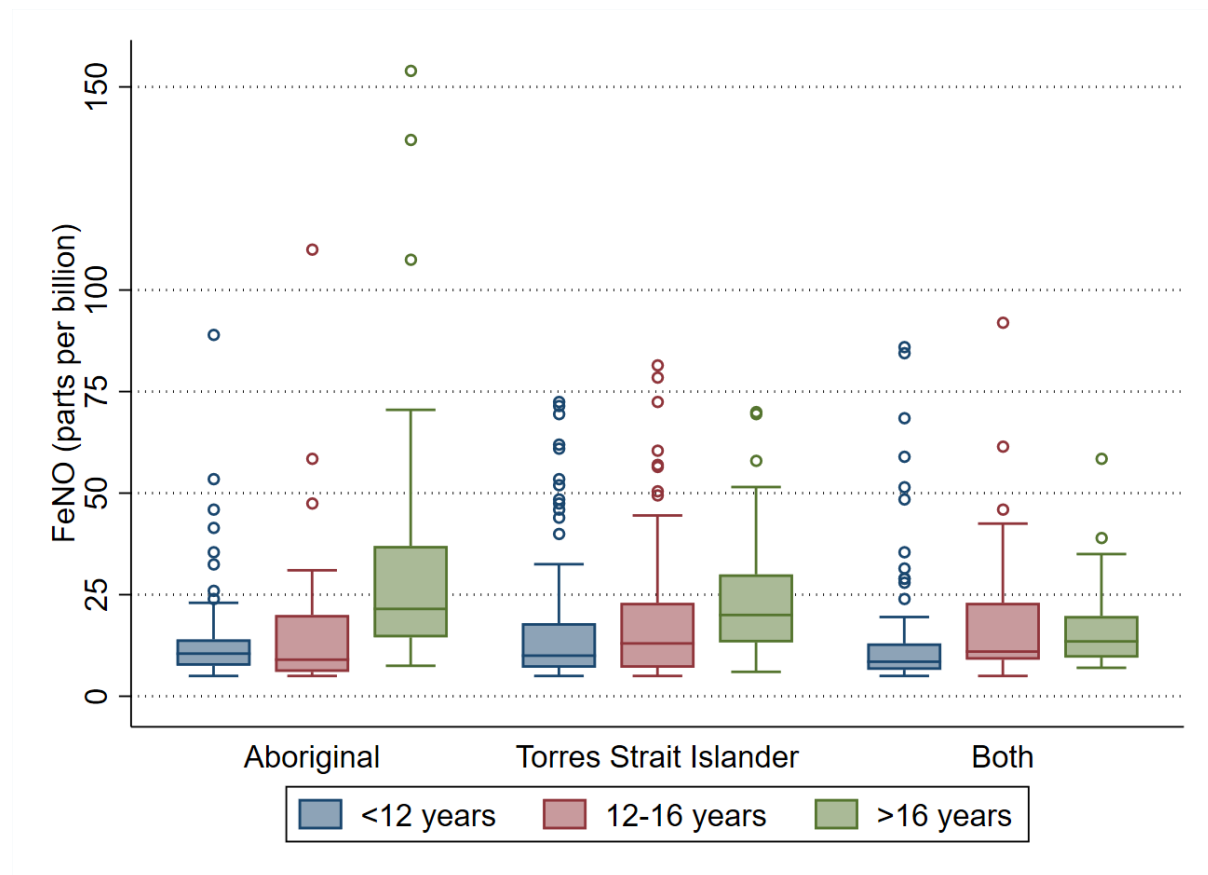
FeNO upper limit of normal in ppb, represented in colour, against age (years) and height (cm).

Figure 30. Heat map of height-for-age FeNO (ppb) upper limit of normal values in First Nations Australians generated using GAMLSS modelling.



FeNO upper limit of normal in ppb, represented in colour, against age (years) and height (cm).

Figure 31. Box and whisker plots of FeNO results for 582 healthy First Nations Australians, by age bracket and ethnicity.



10.9 SUPPLEMENTARY MATERIALS B

Macro-enabled Excel worksheet available online at
<https://doi.org/10.1016/j.chest.2022.10.014>

Chapter 11: Spirometry reference values in First Nations Australian children and adults

This chapter addresses Objective 4 outlined in Section 1.4; “Develop reference values for spirometry ... lung function tests, for use in First Nations Australian children and adults”. This manuscript is being prepared for submission to a peer-reviewed journal and may differ from the final published version.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
Andrew Collaro	Drafting of manuscript, data collection, led data analysis, input into study design
Rachel Foong	Reviewed draft manuscript, data collection, assisted with data analysis, input into study design
Anne Chang	Reviewed draft manuscript, data collection, led study design
Julie Marchant	Reviewed draft manuscript, input into study design

Tamara Blake	Reviewed draft manuscript, data collection
Johanna Cole	Reviewed draft manuscript, data collection
Glenn Pearson	Data collection, input into study design
Rebecca Hii	Data collection, input into study design
Mark Chatfield	Reviewed draft manuscript, assisted with data analysis
Graham Hall	Reviewed draft manuscript, data collection, assisted with data analysis, input into study design
Margaret McElrea	Reviewed draft manuscript, led data collection, led study design

11.1 ABSTRACT

11.1.1 Background

Spirometry is routinely used to diagnose and monitor respiratory disease. There has been no study of reference values in Aboriginal, Torres Strait Islander, and both Aboriginal and Torres Strait Islander (First Nations) Australians with no respiratory disease, symptomology, or smoking history.

11.1.2 Methods

We combined data collected within Queensland, Northern Territory, and Western Australia, between June 2015 and July 2022. Demographic, medical history, and spirometry data of 2662 First Nations Australians were collected, quality assessed, and categorized into ‘healthy’ or ‘not healthy’ groups using pre-defined criteria. Suitability of the Global Lung Function Initiative 2012 (GLI-2012) ‘Other/mixed’ reference equation was assessed using Z-score distributions and multivariable regression.

11.1.3 Results

Acceptable and repeatable spirometry data from 1444 healthy First Nations Australian children and adults aged 3-91 years were available. The GLI-2012 ‘Other/mixed’ reference equation provided an overall good fit for the data. First Nations Australian spirometry values were 9% lower when using ‘Caucasian’ predicted values, a smaller deficit than 20-30% previously reported in studies that did not exclude ever-smokers or participants with respiratory disease. Participants in rural areas had significantly lower FEV₁ ($\beta = -0.40$, 95%CI -0.27, -0.53)

and FVC ($\beta = -0.44$, 95%CI -0.32, -0.57) Z-scores than their urban counterparts, and this deficit increased with age for FEV₁ (β per 10 years = -0.13, 95%CI -0.22, -0.04) and FVC (β per 10 years = -0.16, 95%CI -0.24, -0.08).

11.1.4 Conclusion

Use of appropriate reference values to assist clinical interpretation is important for minimising under- or over-diagnosis of disease. The GLI-2012 ‘Other/mixed’ reference equation should be used for spirometry testing in First Nations Australian children and adults.

11.2 INTRODUCTION

Spirometry is a lung function test routinely performed in outreach, office, and hospital settings for the diagnosis and ongoing monitoring of airway obstruction,^{11,12} a treatable trait.¹⁹³ Age, height, biological sex, and ethnicity are factors known to influence spirometry values, and are used in Global Lung Function Initiative (GLI)-2012⁹ reference equations to generate predicted values to which results are then compared to aid clinician interpretation. Four ethnic groups represented are Caucasian, African American, North- and South-East Asian, with a fifth group, ‘Other’, created as an average of the four groups for individuals who do not fit into these categories, or who are of mixed ethnic origin.⁹

There have been numerous attempts to describe spirometry reference values for Aboriginal and Torres Strait Islander (henceforth respectfully referred to as First Nations) Australians, all of which suggest the spirometry of these populations are 15-30% lower than for Caucasian Australians.^{18,227} Common to nearly all are methodological flaws such as the inclusion of smokers, and failure to collect detailed respiratory history or symptomology. Previously, we collected data of >1200 First Nations children and young adults aged 3-25 from regional and remote Queensland communities and schools. For 930 children and young adults whose spirometry met acceptability and repeatability criteria^{8,10} and had no respiratory disease, spirometry values were only 7-8% lower when using Caucasian specific reference ranges, with the ‘Other/mixed’ category providing the best overall fit.²⁰ Currently, the Australia and New Zealand Society of Respiratory Science recommend the use of ‘Other/mixed’ for ethnic groups such as First Nations Australians who have no GLI ethnic-specific equation.¹⁹⁹

While most Australians (including First Nations Australians) are urban-based, a significantly higher proportion of First Nations Australians reside in rural and remote areas.¹⁷⁰ Australians living in rural and remote areas are at substantially higher risk of disease-associated morbidity and mortality (up to 1.7 times in rural and remote areas).¹⁷⁰ Socioeconomic

determinants are known to affect lung function within racial and ethnic groups,^{217,218} and these factors, amongst others, are currently not accounted for in reference equations. We hypothesise that ‘healthy’ urban-based First Nations Australians may have spirometry values higher than their rural and remote counterparts.

Underestimation of normal spirometry values in First Nations Australians increases the potential for underdiagnosis or disease misclassification, leading to harm. To accurately describe normative spirometry data and determine if GLI-2012 reference values should be used for First Nations Australians of all ages, we combined previously collected paediatric data²⁰ with adult data collected from urban and rural Queensland, Northern Territory, and Western Australia. Our objectives were to determine whether: (a) the ‘Other/mixed’ category is appropriate for use in First Nations Australians across the lifespan, including Aboriginal, Torres Strait Islander, and both Aboriginal and Torres Strait Islanders; and (b) to determine whether the spirometry values of rural based First Nations Australians differ from those in urban areas, and if so, to quantify these differences.

11.3 MATERIALS AND METHODS

11.3.1 Study design, setting, and participants

This was a cross-sectional study of spirometry data collected from First Nations Australian children and adults across three datasets. The first dataset was the Indigenous Respiratory Reference Values (IRRV)³⁹ study, which included First Nations children and young adults aged 3-25 years recruited from childcare centres and schools from nine Queensland and Northern Territory communities in Australia between June 2015 and October 2017. The second dataset is the Healthy Indigenous Lung Function Testing in Adults (HILTA) study, which included First Nations children and young adults aged ≥ 12 years from six Queensland and Northern Territory communities and sites recruited between August 2019 and July 2022. Also included were adults aged ≥ 18 years seen for respiratory health checks at Indigenous Respiratory Outreach Care specialist respiratory clinics in regional and remote Queensland. The third dataset is the Many Healthy Lungs (MHL) study, which included First Nations children and adults aged ≥ 5 years from Perth, Broome, and the Kimberley in Western Australia recruited between October 2018 and November 2021.

All participants above 18 years of age provided informed consent. For children <18 years, parent or guardian written consent was obtained. Ethical approval for the IRRV and HILTA studies were obtained from Education Queensland, and the Human Research Ethics

Committees of Children’s Health Queensland, Far North Queensland, Darling Downs, Townsville, and Menzies School of Health Research/Northern Territory, while for the MHL study, this was obtained through the Western Australian Aboriginal Health Ethics Council (reference HREC707) and the Curtin University Human Research Ethics Committee (reference HR89/2016).

11.3.2 Inclusion criteria

Participants were included in the final analysis of spirometry data if they met all criteria set out in Table 34. Participants were classified as urban or rural depending on where they were tested. Urban sites included Brisbane, Darwin, Perth, Caboolture, and Townsville. Rural sites included Dalby, Cherbourg, Bamaga, Woorabinda, Thursday Island, Broome, and the Kimberley. Body mass index (BMI) criteria were enforced for participants aged ≥ 30 years as obesity is known to affect lung function.²²⁸ Significant recruitment occurred at sporting events featuring young athletes who often had high BMIs due to differences in body composition, and so these criteria were not enforced for participants below age 30 years.

Table 34. Criteria for inclusion in the ‘healthy’ group of participants.

Category	Criteria
Spirometry	Spirometry testing meets current American Thoracic Society (ATS)/European Respiratory Society (ERS) standards ^{8,10}
Respiratory disease	No physician-confirmed respiratory disease on participant questionnaires or on medical chart records.
Symptomology	No disclosure of respiratory symptomology on study questionnaires (difficulty breathing, dyspnoea, wheeze)
Body mass index (BMI)	BMI ≤ 30 for participants aged ≥ 30 .
Smoking	Total lifetime cigarettes numbered fewer than 100 (cigarettes/day multiplied by estimated number of days smoking).

11.3.3 Medical data collection

Medical and smoking histories for all participants were obtained from self-administered (parent or guardian-completed for children < 18 years) questionnaires, and in medical charts where possible.

11.3.4 Anthropometric and spirometry data collection

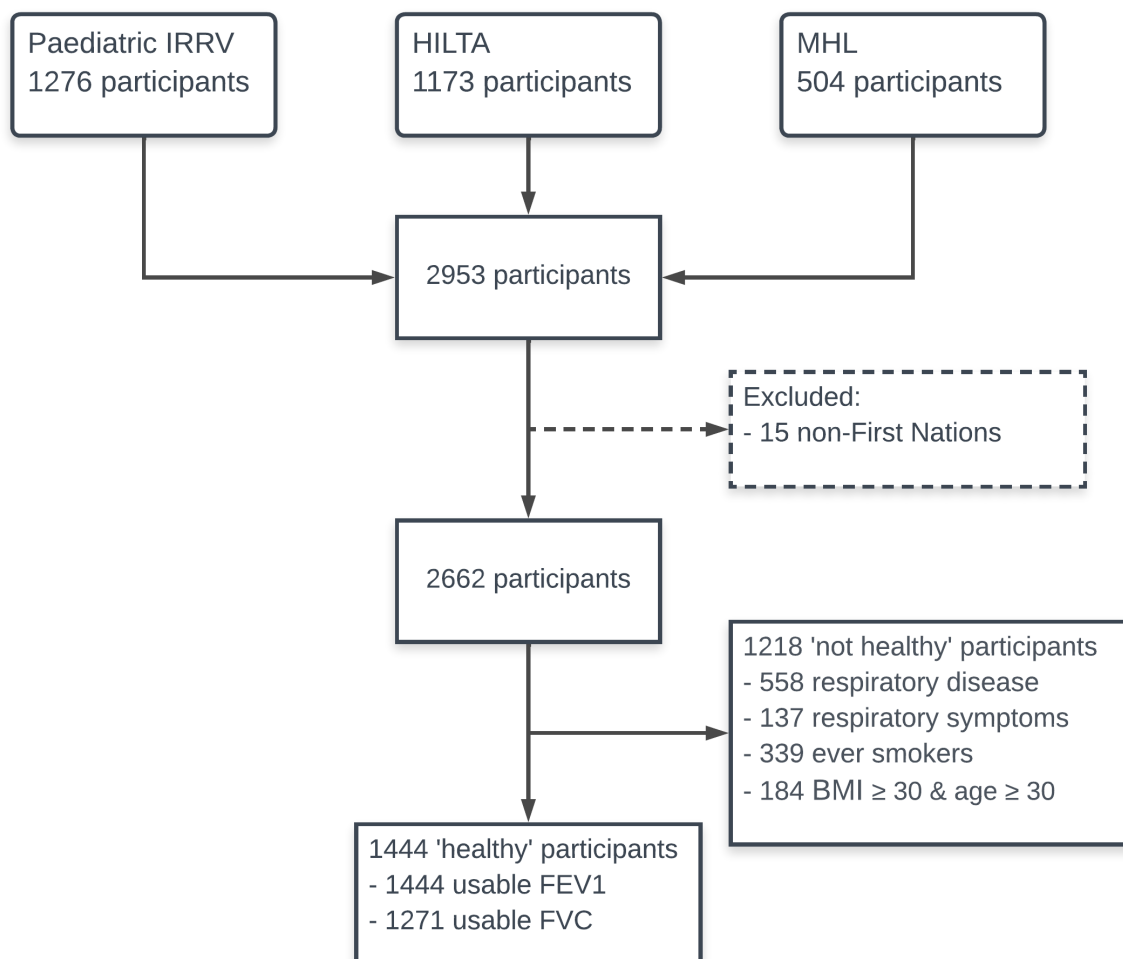
Standing height was measured using a Seca 217 stadiometer (Seca, Hamburg, Germany) prior to testing. Weight was measured except within Queensland schools or childcare centres as Education Queensland did not grant permission to do so. Spirometry was performed according to ATS/ERS guidelines for preschool children,¹¹⁹ and for school-age children and adults,^{8,10} using portable Easy on-PC spirometers (nidd, Zurich, Switzerland).

11.3.5 Statistical analysis

Z-scores and percentage-predicted (% predicted) values for spirometry tests were generated using the ‘Other/mixed’ Global Lung Function Initiative (GLI) 2012⁹ reference equation. Mean Z-scores and standard deviations (SD) for males and females of each ethnicity (Aboriginal, Torres Strait Islander, or Aboriginal and Torres Strait Islander) were also calculated. Mean Z-scores of zero (with a maximum difference of ± 0.5), an SD of 1, and approximately 10% of results falling within 1.64 Z-scores from the centre of normal curve suggests an overall good fit.²⁰ GLI2012_DataConversion (Quanjer, Stanojevic, Cole, Stocks) software was used to calculate M and S coefficients for the ‘healthy’ and ‘not healthy’ groups. Multivariable regression modelling was used to determine whether age, sex, and height are sufficiently accounted for in this population using the ‘Other/mixed’ reference equation. Differences in Z-scores between ethnicities, and between urban and rural participants also were assessed in this way, with and without age, sex, and height as included factors. Additional modelling with added interaction terms were used to assess the impact of ethnicity on age-related changes in spirometry Z-scores. Data were analysed using Stata17 (StataCorp LLC); 2-tailed p-values <0.05 were considered significant.

11.4 RESULTS

Figure 32. Flow diagram of participant inclusion and categorisation of ‘healthy’ and ‘not healthy’ participants.



A flow diagram of IRRV, HILTA and MHL study participants and categorisation of ‘healthy’ and ‘not healthy’ participants is shown in Figure 32. Among First Nations Australian participants with at least an acceptable and repeatable FEV₁, 1062 of 1358 (78%) children aged <18 years were classified as healthy, while 382 of 1304 (29%) of adults aged ≥18 years were classified as healthy. Demographic and spirometry outcomes of ‘healthy’ participants and ‘not healthy’ participants are summarised in Table 35. 1271/1444 (88%) of ‘healthy’, and 1170/1218 (96%) of ‘not healthy’ participants had acceptable and repeatable FVC values. Among ‘healthy’ participants, the youngest age was 3 years, and the oldest was 91 years. Participants classified as ‘not healthy’ were older, more likely to be female, more likely to identify as Aboriginal, and had overall lower FEV₁, FVC, and FEV₁/FVC. Compared to Caucasians, FEV₁ and FVC values of ‘not healthy’ participants were 19% and 18% lower,

respectively. Z-score distributions for healthy and not healthy participants are plotted in Figure 33.

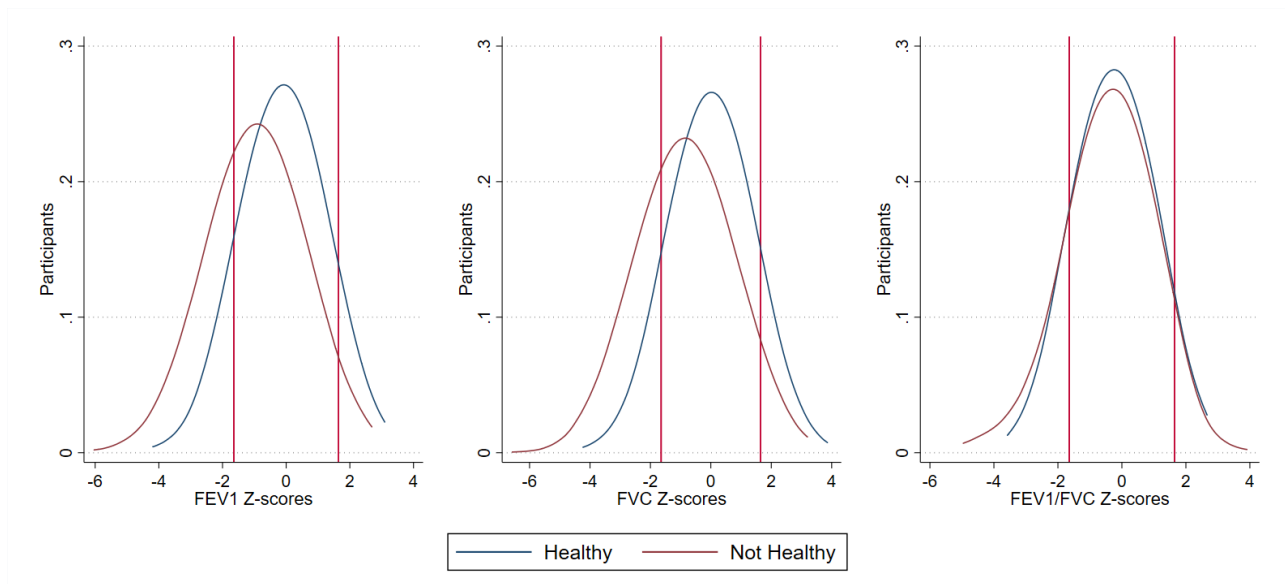
Table 35. Summary of healthy and not healthy participant demographics and spirometry values generated using the ‘Other/mixed’ and ‘Caucasian’ GLI-2012 reference equations.

		All healthy n=1444	Urban healthy n=431	Rural healthy n=1013	Not healthy n=1218
		n (%), or Median (IQR)			
Age (years)		12 (9 – 19)	20 (12 – 25)	11 (8 – 15)	40 (19 – 55)
Female		755 (53%)	234 (56%)	521 (51%)	766 (63%)
Height (cm)		154 (132 – 166)	164 (151 – 175)	147 (129 – 162)	163 (157 – 171)
Ethnicity	Aboriginal	781 (54%)	373 (87%)	408 (40%)	881 (72%)
	Torres Strait Islander	351 (24%)	23 (5%)	328 (32%)	206 (17%)
	Both	312 (22%)	35 (8%)	277 (27%)	131 (11%)
GLI-2012 ‘Other/mixed’		Mean (SD)			
FEV ₁ Z-score		-0.09 (1.02)	0.05 (1.03)	-0.15 (1.01)	-0.95 (1.27)
FEV ₁ % predicted		99 (13)	100 (13)	98 (13)	87 (18)
FVC* Z-score		0.01 (1.07)	0.20 (1.12)	-0.07 (1.04)	-0.85 (1.34)
FVC* % predicted		100 (13)	102 (13)	99 (12)	89 (17)
FEV ₁ /FVC* Z-score		-0.25 (0.90)	-0.31 (0.91)	-0.22 (0.90)	-0.41 (1.13)
FEV ₁ /FVC* %		86 (6)	85 (6)	87 (6)	81 (9)
GLI-2012 ‘Caucasian’		Mean (SD)			
FEV ₁ Z-score		-0.65 (0.96)	-0.52 (0.96)	-0.70 (0.95)	-1.41 (1.17)
FEV ₁ % predicted		92 (12)	94 (12)	91 (12)	81 (17)
FVC* Z-score		-0.64 (0.95)	-0.48 (0.99)	-0.72 (0.93)	-1.36 (1.17)
FVC* % predicted		92 (12)	94 (12)	91 (11)	82 (16)
FEV ₁ /FVC* Z-score		-0.07 (0.86)	-0.14 (0.86)	-0.04 (0.86)	-0.24 (1.06)
FEV ₁ /FVC* % predicted		86 (6)	85 (6)	87 (6)	81 (9)

*FVC and FEV₁/FVC values for 1271 ‘healthy’ and 1170 ‘not healthy’ participants are reported. GLI = Global

Lung Function Initiative. Both = Aboriginal and Torres Strait Islander.

Figure 33. Kernel density plots for FEV₁, FVC, and FEV₁/FVC% Z-scores generated using the ‘Other/mixed’ GLI-2012 reference equation, for healthy and not healthy participants.



FEV₁, FVC, and FEV₁/FVC Z-scores and percent-predicted values for Aboriginal, Torres Strait Islander, and both Aboriginal and Torres Strait Islander participants were generated using the GLI-2012 ‘Other/mixed’ reference equation are summarised in Table 36, and distributions are plotted in Figure 34. FEV₁, FVC, and FEV₁/FVC were within the maximum difference of ± 0.5 Z-scores for both males and females of each ethnicity. Spirometry Z-scores for males and females of each ethnicity appear to be normally distributed. M and S coefficients generated using GLI software suggest healthy First Nations Australians have 9% lower FEV₁ and FVC values, and 1% lower FEV₁/FVC values than the predicted values for Caucasians. The ‘not healthy’ group had 20%, 18%, and 3% lower FEV₁, FVC, and FEV₁/FVC values than the Caucasian predicted values, respectively (Table 37).

Table 36. Summary of healthy participant demographics and spirometry values generated using the ‘Other/mixed’ GLI-2012 reference equation.

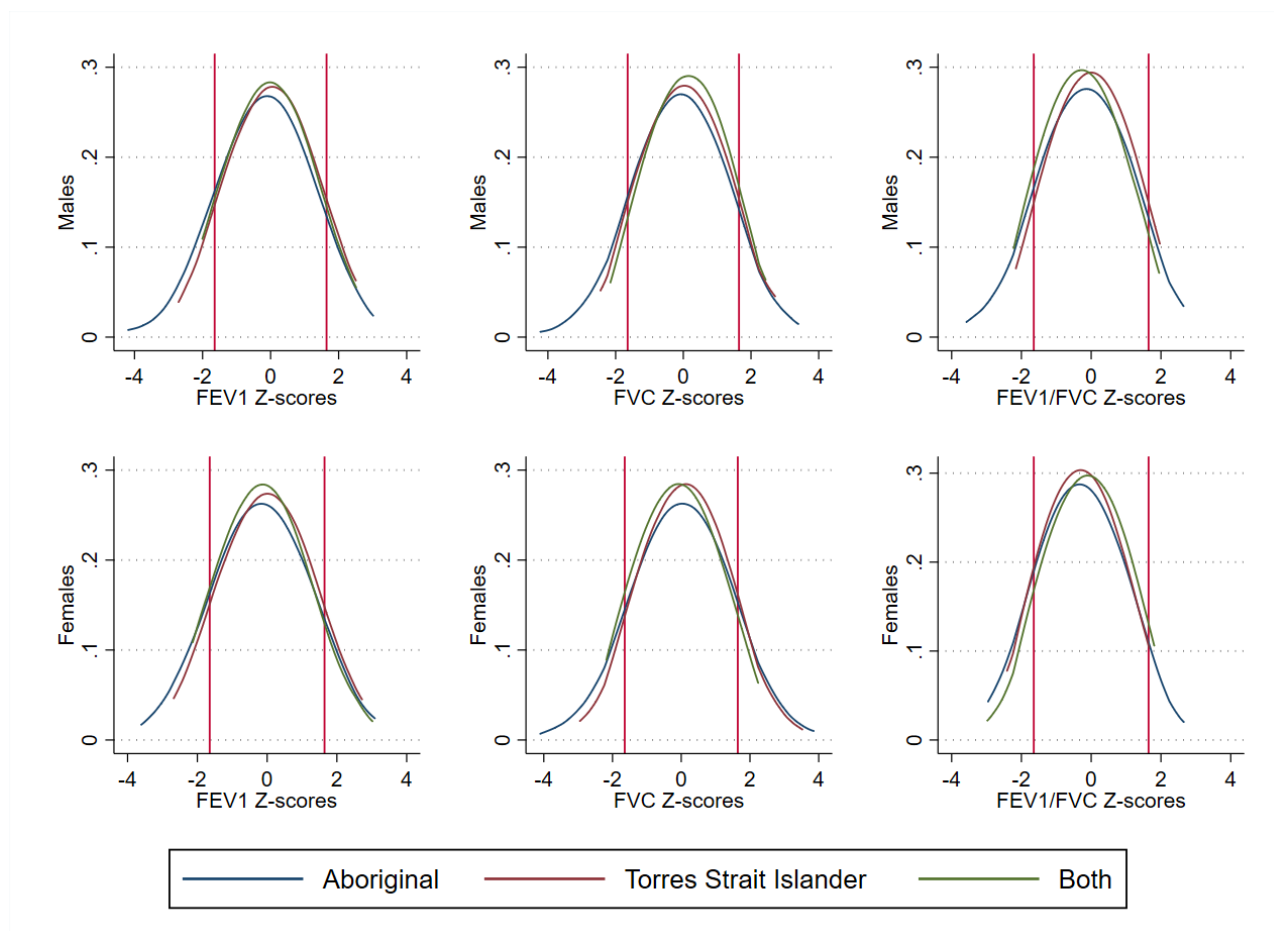
		FEV ₁			FVC			FEV ₁ /FVC		
		Aboriginal	Torres Strait Islander	Both	Aboriginal	Torres Strait Islander	Both	Aboriginal	Torres Strait Islander	Both
Males (n=689)	Z-score*	-0.16	0.05	-0.00	-0.10	0.05	0.19	-0.19	-0.00	-0.33
	SD	1.09	0.94	0.89	1.13	0.99	0.91	1.03	0.84	0.83
	% < -1.64	7%	4%	3%	7%	4%	3%	8%	2%	4%
	% > 1.64	3%	3%	3%	5%	5%	6%	3%	2%	1%
Females (n=755)	Z-score*	-0.14	-0.00	-0.11	0.03	0.11	-0.07	-0.35	-0.35	-0.16
	SD	1.11	0.99	0.90	1.16	0.99	0.97	0.89	0.73	0.85
	% < -1.64	8%	5%	3%	7%	3%	3%	8%	2%	4%
	% > 1.64	5%	5%	3%	6%	5%	5%	2%	1%	1%

GLI = Global Lung Function Initiative. Both = Aboriginal and Torres Strait Islander. pp = Percentage of predicted value. *Mean Z-score.

Table 37. M and S coefficients for ‘healthy’ and ‘not healthy’ First Nations Australians generated using the GLI software.

		Healthy (n=1444)	Not healthy (n=1217)
FEV ₁	M	-0.09	-0.2038
	S	0.0114	0.0114
FVC	M	-0.0865	-0.1813
	S	-0.0503	-0.0503
FEV ₁ /FVC	M	-0.0107	-0.0309
	S	-0.086	-0.086

Figure 34. Kernel density plots for FEV₁, FVC, and FEV₁/FVC% Z-scores generated using the ‘Other/mixed’ GLI-2012 reference equation, for healthy males and females of each ethnicity.



Vertical red lines reference -1.64 and 1.64 Z-scores, respectively.

FEV₁ and FVC Z-scores for Torres Strait Islander, and both Aboriginal and Torres Strait Islander participants, respectively, were significantly higher than for Aboriginal participants. No significant differences were observed for FEV₁/FVC. Our modelling suggests the GLI-2012 ‘Other/mixed’ reference equation underestimates the decline of FEV₁ and FVC values with age, and to a lesser extent, increases in FEV₁ and FVC values with height in this population (Table 38).

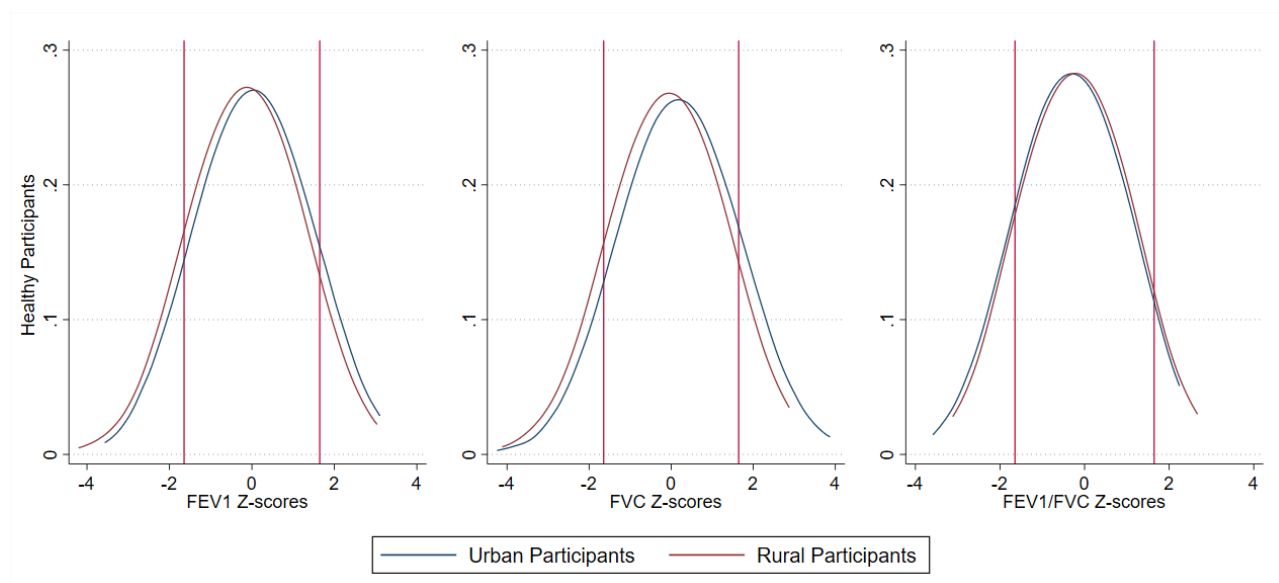
Table 38. Multivariable regression modelling of FEV₁, FVC, and FEV₁/FVC Z-scores in 1444 healthy First Nations Australians.

	FEV ₁ (Z)		FVC (Z)		FEV ₁ /FVC (Z)	
	Model A	Model B	Model A	Model B	Model A	Model B
	β (95%CI)		β (95%CI)		β (95%CI)	
Age (per 10 years)	-0.11 (-0.15, -0.06)		-0.12 (-0.17, -0.08)		0.01 (-0.03, 0.05)	
Sex						
Male	Reference		Reference		Reference	
Female	-0.02 (-0.13, 0.08)		0.01 (-0.10, 0.13)		-0.12 (-0.22, -0.02)	
Height (per 10cm)	-0.03 (-0.06, -0.00)		-0.04 (-0.08, -0.00)		0.03 (-0.01, 0.05)	
Site Type						
Urban	Reference	Reference	Reference	Reference	Reference	Reference
Rural	-0.44 (-0.57, -0.31)	-0.33 (-0.45, -0.20)	-0.55 (-0.69, -0.40)	-0.40 (-0.54, -0.26)	0.12 (-0.01, 0.25)	0.08 (-0.04, 0.20)
Ethnicity						
Aboriginal	Reference	Reference	Reference	Reference	Reference	Reference
TSI	0.31 (0.18, 0.45)	0.31 (0.17, 0.44)	0.30 (0.15, 0.45)	0.28 (0.13, 0.44)	0.05 (-0.08, 0.18)	0.06 (-0.07, 0.19)
Both	0.15 (0.01, 0.29)	0.21 (0.07, 0.35)	0.16 (0.00, 0.32)	0.23 (0.07, 0.39)	0.02 (-0.12, 0.16)	0.00 (-0.13, 0.14)

GLI = Global Lung Function Initiative. Both = Aboriginal and Torres Strait Islander. pp = Percentage of predicted value.

11.4.1 Urban and rural spirometry in ‘healthy’ participants

Figure 35. Kernel density plots for FEV₁, FVC, and FEV₁/FVC% Z-scores generated using the ‘Other/mixed’ GLI-2012 reference equation, for healthy rural and urban participants.



Urban and rural participant FEV₁, FVC, and FEV₁/FVC Z-scores kernel density plots are shown in Figure 35. With and without population-specific adjustment for age, sex, and height, FEV₁ and FVC Z-scores were significantly lower among rural participants compared to their urban counterparts (Table 38), while no significant difference was found in FEV₁/FVC Z-scores. For rural participants, deficits compared to urban participants increased with age for FEV₁ (β per 10 years = -0.13, 95%CI -0.21, -0.04) and FVC (β per 10 years = -0.14, 95%CI -0.23, -0.05) Z-scores, but not FEV₁/FVC (β per 10 years = -0.01, 95%CI -0.09, 0.07) Z-scores.

11.5 DISCUSSION

Using the data of 1444 healthy participants aged 3-91 years, spirometry values of First Nations Australians were 9% lower when using Caucasian reference equations compared to using 'Other/mixed' ethnicity reference equations. Our findings suggest that the 'Other/mixed' ethnic reference equations provide an overall good fit for Aboriginal and Torres Strait Islander Australians. We determined this in a rigorously screened population with no respiratory disease or symptomology, who have never smoked, were not obese, and whose spirometry met ATS/ERS criteria^{8,10} for acceptability and repeatability. Spirometry values of Torres Strait Islander, and both Aboriginal and Torres Strait Islander participants were measurably higher than for Aboriginal participants. Spirometry data of excluded ‘not healthy’ participants were 18-20% lower when using Caucasian-specific reference equations, consistent with normative

data reported in previous articles that did not adequately exclude unhealthy (from a respiratory perspective) participants.^{18,227} Finally, we have shown there are measurable gaps in lung function between urban and rural-based First Nations Australians following early childhood, that appears to increase throughout the lifespan. Our data has several key strengths, including the large sample of healthy participants (far in excess of the minimum of 300 data points suggested by the GLI),⁹ the rigorous exclusion of participants whose spirometry data may not be truly reflective of the broader healthy population, and the inclusion of spirometry data from urban and rural communities of three regions (Queensland, Northern Territory, and Western Australia) which greatly enhances the generalisability of our findings.

Within the context of disproportionate respiratory disease burden among First Nations Australians,^{197,208} and the reliance on spirometry testing in the diagnosis and ongoing monitoring of chronic respiratory disease, it is important that reference values accurately reflect the spirometry of healthy individuals within this population. In most previous attempts to describe normative data, unhealthy participants or smokers were included in the final data,^{88,96,227,229,230} and most lacked sufficient numbers^{88,227,229,230} according to GLI criteria. Unsurprisingly, First Nations Australian spirometry values were reported to be up to 20-30% lower than Caucasians.^{18,88,96,227,229,230} In each of these reports, insufficient care was taken to ensure data was truly representative of the healthy population, and use of these recommendations' risks normalising abnormal lung function, possibly leading to harm through reduced level of care. Unsurprisingly, these deficits are consistent with those observed in our 'not healthy' group, for whom spirometry values were 18-19% lower than for Caucasians. The only other analysis to have excluded smokers and participants with respiratory disease, to our knowledge, was an analysis of 87 children and adults aged 5-76 years from two remote communities.²³¹ The authors reported a mean Z-score of -1.49 (SD 1.14) when using the GLI-2012 'Other/mixed' reference category. These are substantially lower than our results, though the small sample size is well below GLI recommendations and was acknowledged as a study limitation.²³¹

While Z-scores generated using GLI-2012 reference equations consider the influence of age, biological sex, and height on spirometry values, we hypothesised these associations may not be a perfect fit for First Nations Australians. Our modelling revealed that decline in FEV₁ and FVC values with age is underestimated in this population, as >0.10 Z-scores were lost for each decade of life in healthy individuals. Similarly, the effects of increasing height on FEV₁ and FVC values appears to be overestimated, and our analysis suggests ≥ 0.03 Z-score

overshoot for each 10cm in height. We have shown previously that body proportions are measurably different in this population when compared to Caucasians, with sitting height contributing significantly less to overall standing height.²³² While this a plausible explanation for overestimation of the effects of height, we are unable to explain the underestimation of decline with age. We speculate this may due, in part, to the cumulative effects of socioeconomic disadvantage.

The use of ethnic correction in clinical algorithms, including in lung function testing, has been subject of debate and it has been suggested that ethnic classification should be removed from spirometry reference values,^{213,214} and from algorithms used in other fields of medicine including renal function testing.^{215,216} Even after ensuring reference data is truly representative of the healthy population, as has not previously been the case for First Nations Australian lung function, there are numerous other issues related to ethnic correction, including that little consideration is usually given to determinants of health when surveying racial or ethnic groups to produce ethnic adjustments, possibly normalising abnormal results in disadvantaged populations. While our analysis is far from an exhaustive analysis of the impact of socioeconomic determinants, an important limitation of our study, our findings suggest lung function of First Nations Australians is lower with the increasing disadvantage associated with living in rural areas, and that our data suggests the GLI-2012 ‘Other/mixed’ reference equation is suitable for use in either urban or rural participants. Our data does suggest that predicted values calculated without ethnic correction would have been more representative of First Nations Australian spirometry values than values 20-30% lower as described previously, highlighting the importance of comprehensive exclusion of data that may not be representative of the healthy population.

Another limitation of our analysis are the smaller numbers of adults compared to children. While recruitment was approximately equal between children and adults, a substantially higher proportion of adults were excluded due to respiratory disease or symptomology, obesity, and smoking. Thus, the number of adults included in our analysis of only healthy participants were smaller than for children.

In conclusion, we determined spirometry values of First Nations Australian children and adults were approximately 8% lower than for Caucasians, using the data of 1444 healthy participants aged 3-91 years from Queensland, Northern Territory, and Western Australia. This was in stark contrast to previous reports that suggest a deficit of 20-30%. Spirometry values of Torres Strait Islander, and both Aboriginal and Torres Strait Islander participants were higher

than for Aboriginal participants. Spirometry values were measurably lower for rural participants compared to their urban counterparts following early childhood, and this deficit further increased with age. Differences between urban and rural participants are likely due to known increased socioeconomic burden in rural areas. We found the GLI-2012 ‘Other/mixed’ reference equation provided a good fit for both groups, and so should be used where possible in in spirometry testing of First Nations Australians.

11.6 ACKNOWLEDGEMENTS

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Chapter 12: How do Cormic Index profiles contribute to differences in spirometry values between White and First Nations Australian children?

This chapter addresses Objective 5 outlined in Section 1.4; “Investigate the influence of anthropometric differences between First Nations children and their non-First Nations counterparts, and how this accounts for known differences in lung function between healthy children of both ethnicities”. The following publication within a peer-reviewed journal was produced:

Collaro AJ, Chang AB, Marchant JM, Chatfield MD, Blake TL, McElrea MS. How do Cormic Index profiles contribute to differences in spirometry values between White and First Nations Australian children? *Pediatr Pulmonol*. 2021;56(12):3966-74.

The following editorial²³³ accompanied this article and is available in Appendix F.

Mozun R, Berger F, Singer F. One size does not fit all-Why do pediatric spirometry estimates vary across populations "down under"? *Pediatr Pulmonol*. 2022;57(2):345-6.

The authors listed below have certified that:

1. They meet the criteria for authorship and 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.

Contributor	Statement of Contribution
Andrew Collaro	Drafting of manuscript, led data analysis, input into study design
Anne Chang	Reviewed draft manuscript, data collection, led study design
Julie Marchant	Reviewed draft manuscript, input into study design
Mark Chatfield	Reviewed draft manuscript, assisted with data analysis
Tamara Blake	Reviewed draft manuscript, data collection
Margaret McElrea	Reviewed draft manuscript, led data collection, input into study design

12.1 ABSTRACT

12.1.1 Background

Spirometry values of First Nations Australian children are lower than White children. One explanation relates to differences in sitting-height/standing-height ratio (Cormic Index), as this accounts for up to half the observed differences in spirometry values between White children and other ethnicities. We investigated whether the Cormic Index of First Nations children differs from White children, and if this explains the lower spirometry values of First Nations children.

12.1.2 Methods

First Nations children (n=619) aged 8-16 years were recruited from nine Queensland communities. Their spirometry and Cormic Index data were compared to that of White children (n=907) aged 8-16 years from the NHANES III dataset.

12.1.3 Results

FEV₁ and FVC of First Nations children was 8% lower for children aged 8-11.9 years, and 9-10% lower for children aged 12-16 years. The Cormic Index was statistically lower in the First Nations 8-11.9 years group (median=0.515, IQR 0.506-0.525) compared with White children (0.519, IQR 0.511-0.527), and this difference was greater in the 12-16 years group (0.505, IQR 0.492-0.516; 0.520, IQR 0.510-0.529). Adjusting for age, sex, and standing height, lower Cormic Index of First Nations children accounts for 14% (95%CI 7-21%) of FEV₁ and

15% (95%CI 8-21%) of FVC differences in the younger group, and 26% (95%CI 16-37%) of FEV₁ and 31% (95%CI 19-42%) of FVC differences in the older group.

12.1.4 Conclusion

Ethnic differences in Cormic Index partly account for why healthy First Nations Australian children have lower spirometry values than White children. As childhood spirometry values impact adult health, other contributing factors require attention.

12.2 INTRODUCTION

Spirometry is a gold-standard tool used for diagnosing and monitoring various respiratory diseases in a wide variety of settings.^{7,8} To interpret spirometry, reference values are required and are dependent on age, sex, standing height, and ethnicity. Currently, the most widely used reference values are those published by the Global Lung Function Initiative (GLI) in 2012 for four different ethnicities (Caucasian, North East Asian, South East Asian, and African American), and a fifth equation that is an averaging of these (other/mixed).⁹ Effects of ethnicity on lung function have been reported since the early twentieth century. In a recent review, 85% of the 226 included studies reported that non-white racial and ethnic groups have comparatively lower lung function compared to White children.²³⁴ Possible explanations include inherent, anthropometric, environmental, and social factors. Of these, anthropometric difference was the most frequently cited likely reason for differences in lung function between racial and ethnic groups.

Differences in body proportions such as sitting-height/standing-height ratio (Cormic Index), chest circumference, and chest depth/width ratio between ethnic groups have been demonstrated in primary school-aged children in the United Kingdom for four of the five GLI ethnic categories.²³⁵ Only the Cormic Index has been shown to contribute significantly to differences in lung function observed between ethnicities in children, accounting for 8% to 46% of observed differences in spirometry values depending on the study population.^{15,235} Anthropometric differences are also present in adulthood, with 35-39% of the 12% lower spirometry values in African Americans, relative to White children, attributable to differences in Cormic Index.²³⁶ Data from both children and adults suggest that, compared to differences in sitting height, impact of differences in socioeconomic circumstances between ethnic groups makes a comparatively smaller contribution to disparities in lung function, with one analysis of White and African-American participants from the Third National Health and Nutrition

Examination Survey (NHANES III) dataset estimating poverty index accounted for 7.5% and 2.5% of lung function deficits in African-American women and men, respectively.²³⁶

In the Australian context, the GLI Caucasian reference set was found to be suitable for use in the White population.⁹⁵ For Australian First Nations children, the GLI 2012 ‘other/mixed’ ethnic category was found to be the most appropriate for use in First Nation Australian children and young adults (aged 3-25 years), whose spirometric values were 7-8% lower overall than the White reference set.²⁰ In contrast, older studies (between 1979-2002) have reported First Nations spirometric values to be 15-30% lower.¹⁸ Serious methodological flaws were present in each of the older studies, e.g., the inclusion of smokers and participants with respiratory illnesses. Reasons for the lower spirometric values in healthy First Nations children compared to White children are unknown. While differences in anthropometric measurements between White and First Nations Australians may account for the above as has been shown in other ethnic groups,^{15,235,236} this has not been explored.

To address this knowledge gap, our study aimed to determine what influence anthropometric factors have on the differences in observed lung function between Australian First Nations and White children. We used data of healthy First Nations Australian children previously collected for the paediatric Indigenous Respiratory Reference Values (IRRV) study²⁰ to compare with data of healthy White children collected as part of the NHANES III in USA.²³⁷ NHANES III is the most contemporary, large-scale dataset featuring sitting height measurements in White children. Further, standing height and lung function data from the survey was used in the creation of GLI 2012 multi-ethnic reference equations. Our objectives were to (i) determine how the Cormic Index differs between Australian First Nations children and White children, (ii) determine how much of the observed differences in lung function can be explained by differences in the Cormic Index, and (iii) determine how Cormic Index differences and the effects on lung function change throughout middle childhood and adolescence.

12.3 MATERIALS AND METHODS

12.3.1 Study design, setting, and participants

This was a cross-sectional study of children aged 8-16 years using two datasets. The first dataset comprises children from the IRRV dataset,²⁰ which included First Nations participants recruited from childcare centres and schools from nine Queensland and Northern Territory communities in Australia between June 2015 and October 2017. The second dataset were

children from the NHANES III dataset, recruited between 1988 and 1994 using a multistage probability sampling design.²³⁷ Ethical approval for development of the IRRV dataset was obtained from Education Queensland, and the Human Research Ethics Committees of Children's Health Queensland, Far North Queensland, Darling Downs, Townsville, and Menzies School of Health Research/Northern Territory, and parent/guardian consent was obtained for all children within the study. Ethical approval for the NHANES III survey granted by the National Center for Health Statistics Research Ethics Review Board, and parent consent was provided for all children within the survey.

12.3.2 Participant selection

All children in the IRRV study dataset are First Nations Australians, and so none were excluded based on ethnicity. Children with current or previous respiratory disease, smoking history, and whose spirometry did not meet acceptability or repeatability criteria were already excluded from the finalised IRRV dataset, and so only children outside the 8-16-year age range were excluded. Only White children from the NHANES III dataset were selected for analysis. We excluded those outside the 8–16-year age range, who had respiratory disease, did not meet the acceptability or repeatability criteria for spirometry or did not have a standing and sitting height measurement recorded.

Children were separated into two groups within each dataset: 8-11.9 years and 12-16 years, to represent middle childhood and adolescence, respectively.

12.3.3 Definitions

Within the IRRV dataset, respiratory disease included asthma, bronchiectasis, bronchitis, bronchiolitis, pneumonia, and chronic neonatal lung disease. Respiratory disease was assigned using a combination of medical records and parent/guardian completed questionnaires. Respiratory disease was assigned to children within the NHANES III dataset where a parent/guardian indicated the child had ever been treated for asthma (question E3, g) or chronic bronchitis (question E3, h).

12.3.4 Measurements

Spirometry and anthropometric data were obtained from the original datasets, and spirometry testing was performed as originally described.^{20,238} Spirometry Z-scores and % predicted values were re-calculated for this study using White values from the GLI 2012 reference equations, including for First Nations children so as to measure the lung function deficit in this population. For the IRRV study, sitting height was obtained by measuring the

distance between the sitting surface to the top of the head, ensuring the participant's thighs were positioned horizontally. The seating surface (metallic stool) used was the same for all children. Methodology for obtaining sitting height in the NHANES III study was as described within the study anthropometry manual,²³⁹ and was comparable to techniques used in the IRRV study except for differences in the specific equipment used. Z-scores for standing and sitting heights were calculated using the British 1990 growth reference²⁴⁰ and the lmsGrowth software (Medical Research Council, UK). While the specific equipment used to obtain these measurements was not identical between both studies, the methodology is the same (including identical patient posture during measurement), and so are sufficiently comparable.

12.3.5 Statistical analysis

Mann-Whitney U tests were used to compare anthropometric measurements between the First Nations and White children. Multivariable regression modelling was used for FEV₁ and FVC Z-score outcomes. Age sex, and standing height (potential confounders), Cormic Index (predictor), and study dataset (exposure) were included in Model 1. Models were then re-run without Cormic Index adjustment, to determine how the Cormic Index contributes to the difference in spirometric lung function seen between First Nations and White children (Model 2). Percentages were calculated using the β coefficient for study dataset (IRRV First Nations children, with NHANES III White children as a reference) according to the formula: percentage = $100 \left(\frac{\text{Model 2 } \beta - \text{Model 1 } \beta}{\text{Model 2 } \beta} \right)$. Bootstrap resampling (1000 iterations) was used to calculate 95% confidence intervals for these percentages. Statistical analyses were repeated without Cormic Index outliers to determine what impact their exclusion has on our findings.

While Z-scores calculated through GLI reference equations already account for age, sex, and height, we elected to adjust for these factors to eliminate any age, sex, or height related biases specific to First Nations children, for whom GLI reference equations were not developed. Data were analysed using Stata16.1 (StataCorp LLC); 2-tailed p-values <0.05 were considered significant.

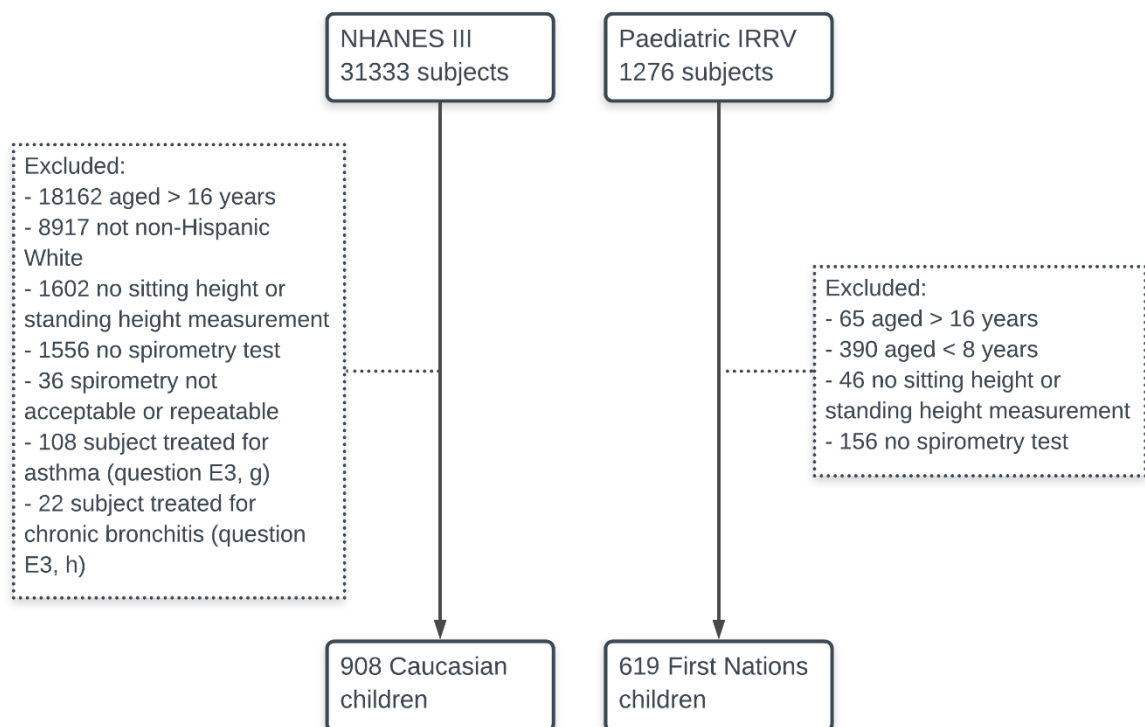
12.4 RESULTS

12.4.1 Study population

Subjects from the paediatric IRRV and NHANES III datasets were sequentially excluded using criteria as shown in Figure 36. Sequential exclusion of subjects from Third National Health and Nutrition Examination Survey (NHANES III) and Indigenous Respiratory

Reference Values (IRRV) datasets., leaving 619 First Nations children and 908 White children. Their demographic data, anthropometric, and spirometric measurements are summarised in Table 39 and further summarised by sex in Table 42 and Table 43.

Figure 36. Sequential exclusion of subjects from Third National Health and Nutrition Examination Survey (NHANES III) and Indigenous Respiratory Reference Values (IRRV) datasets.



12.4.2 Anthropometric measurements

Sitting and standing heights for First Nations and White children are plotted in Figure 37, Cormic Index and age are plotted in Figure 38, and sub-grouped by sex in Figure 39 and Figure 40.

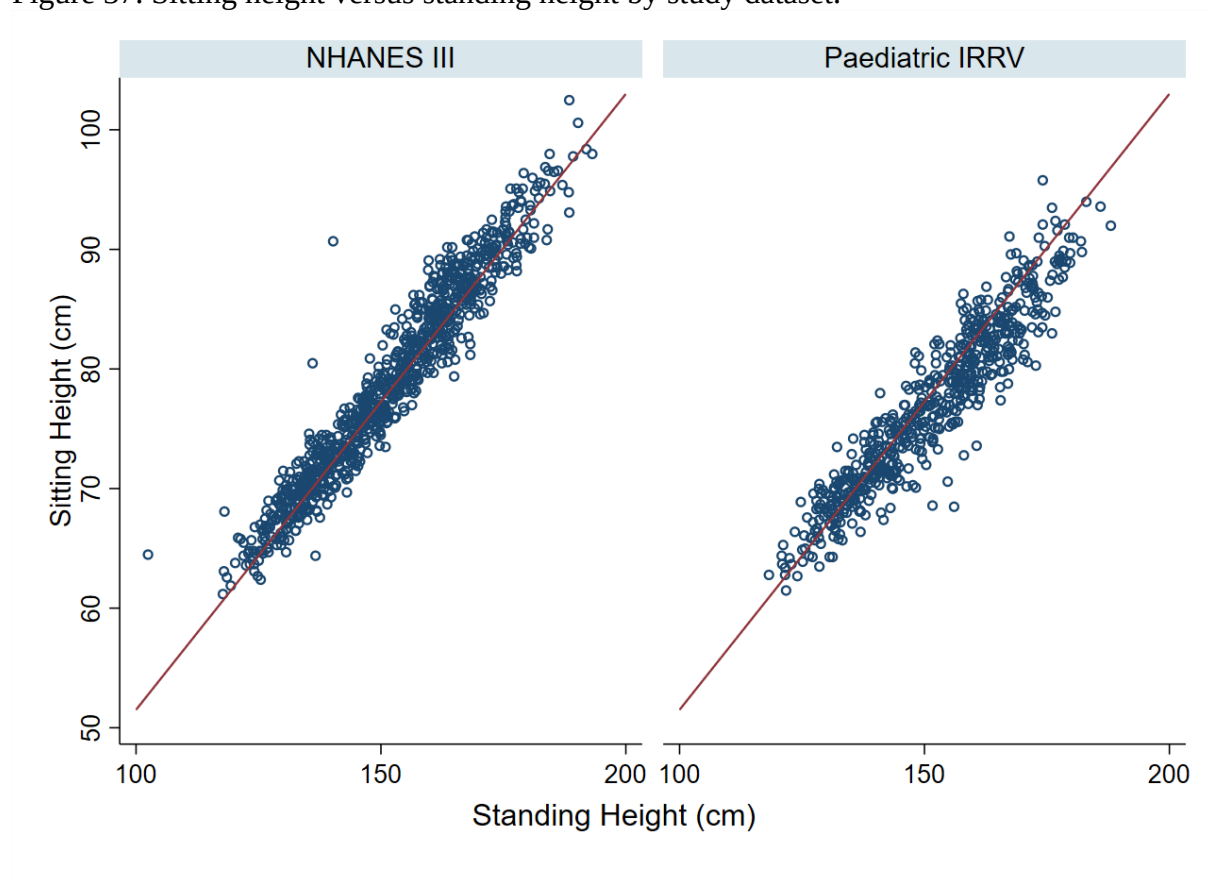
Table 39. Demographic data, anthropometric, and spirometric measurements of subjects from NHANES III and IRRV datasets.

		8–11.9 years		12–16 years	
		White ^a n=476	First Nations ^b n=312	White ^a n=432	First Nations ^b n=307
		n (%), Median (IQR) or Mean (95%CI)			
Median Age (years)		10.0 (9.0 – 11.0)	10.0 (8.9 – 11.0)	14.5 (13.3 – 15.8)	14.0 (13.0 – 15.5)
Female		241 (51%)	155 (50%)	237 (55%)	143 (47%)
Sitting height	Median (cm)	72.5 (69.4 – 75.9)	71.5 (69.0 – 75.2)	85.7 (82.0 – 88.9)	82.4 (79.0 – 85.0)
	Mean (Z-score)	0.27 (0.17, 0.36)	0.31 (0.18, 0.44)	0.02 (-0.08, 0.13)	0.03 (-0.09, 0.14)
Standing height	Median (cm)	139.5 (133.2 – 146.9)	140.0 (132.8 – 146.6)	163.7 (158.2 – 170.3)	162.5 (157.6 – 169.0)
	Mean (Z-score)	-0.21 (-0.30, -0.11)	-0.36 (-0.48, -0.24)	0.11 (0.01, 0.22)	-0.36 (-0.48, -0.24)
Cormic Index		0.519 (0.511 – 0.527)	0.515 (0.506 – 0.525)	0.520 (0.510 – 0.529)	0.505 (0.492 – 0.516)
FEV ₁	Litres (L)	1.97 (1.75 – 2.25)	1.84 (1.59 – 2.09)	3.29 (2.83 – 3.73)	2.87 (2.49 – 3.30)
	Z-score	0.06 (-0.60 – 0.72)	-0.64 (-1.14 – 0.04)	-0.02 (-0.56 – 0.65)	-0.82 (-1.35 – -0.19)
	% Predicted	100.6 (93.0 – 108.1)	92.4 (86.9 – 100.4)	99.8 (93.4 – 107.5)	90.3 (84.1 – 97.8)
FVC	Litres (L)	2.27 (1.99 – 2.63)	2.08 (1.85 – 2.43)	3.77 (3.20 – 4.29)	3.30 (2.90 – 3.77)
	Z-score	0.09 (-0.52 – 0.73)	-0.61 (-1.12 – 0.03)	0.02 (-0.60 – 0.69)	-0.75 (-1.38 – -0.25)
	% Predicted	101.1 (93.9 – 108.7)	93.0 (87.0 – 100.4)	100.2 (93.0 – 108.0)	91.2 (84.1 – 97.1)

GLI 2012 “Caucasian” reference equation used to generate FEV₁ Z-scores.³ Sitting and standing height Z-scores calculated using British 1990 growth reference set.¹⁴

^aCaucasian children from NHANES III dataset.¹¹ ^bFirst Nations children from IRRV dataset.⁹

Figure 37. Sitting height versus standing height by study dataset.



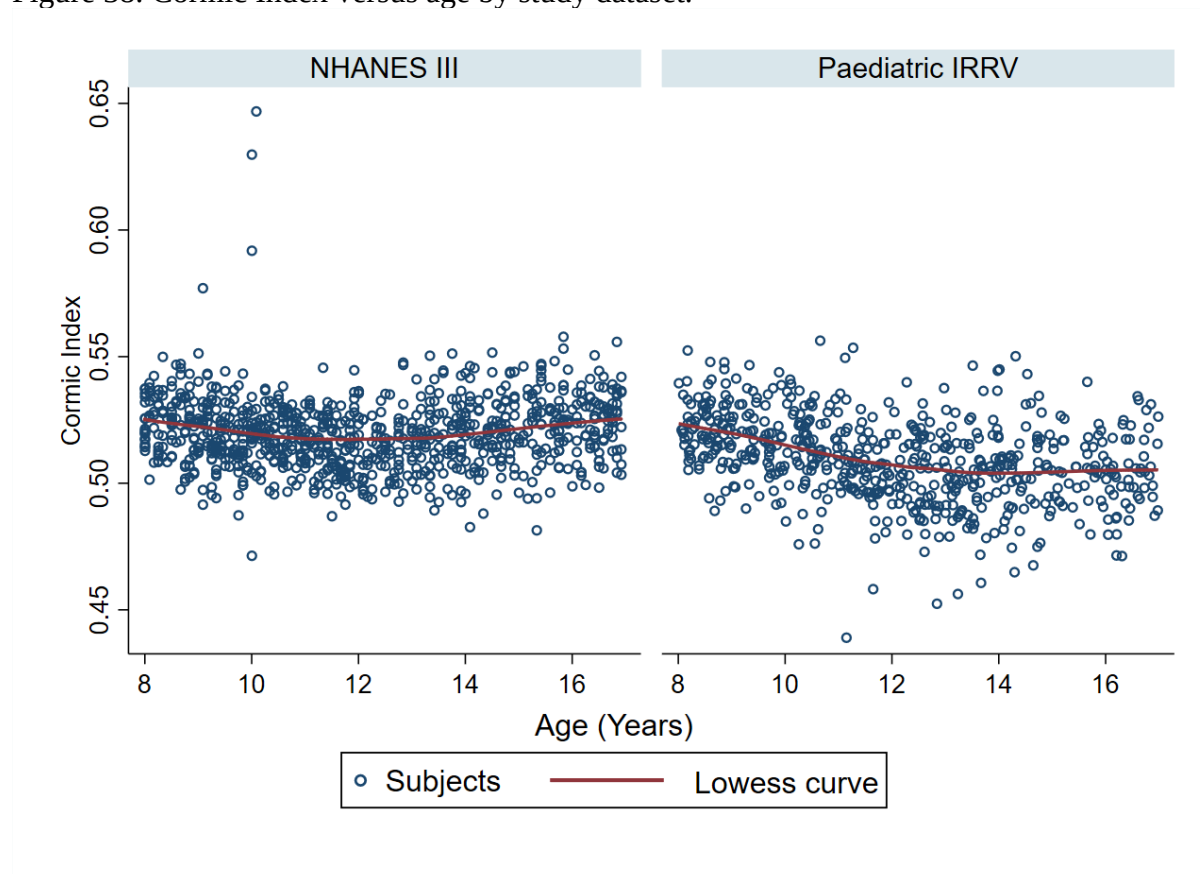
IRRV, Indigenous Respiratory Reference Values; NHANES III, Third National Health and Nutrition Examination Survey.

For children aged 8-11.9 years, no significant differences were observed between subjects within First Nations and White groups for either standing (median=140cm [IQR 132.8-146.6] vs. 139.5cm [IQR 133.2-146.9], $p=0.12$) or sitting heights (median=71.5cm [IQR 69.0-75.2] vs. 72.5cm [IQR 69.4-75.9], $p=0.95$). However, the Cormic Index was statistically significantly lower in First Nations children compared to White children (median=0.515 [IQR 0.506-0.525] vs. 0.519 [0.511-0.527], $p<0.001$). No sex differences were found in the Cormic Index for either First Nations (male median=0.515 [IQR 0.506-0.526] vs. females=0.515 [IQR 0.506-0.525], $p=0.80$) or White (male median=0.518 [IQR 0.510-0.527] vs. females=0.520 [IQR 0.511-0.528], $p=0.27$) children.

For children aged 12-16 years, White children, compared to First Nations, had significantly higher standing (median=163.7cm [IQR 158.2-170.3] vs. 162.5cm [IQR 157.6-169.0] respectively, $p=0.047$) and sitting heights (median=85.7cm [IQR 82.0-88.9] vs. 82.4cm [IQR 79.0-85.0], $p<0.001$), and Cormic Index (median=0.520 [IQR 0.510-0.529] vs. 0.505 [IQR 0.492-0.516], $p<0.001$). In both ethnic groups, the Cormic Index was significantly higher

in females than males (First Nations females=0.510 [IQR 0.500-0.519] vs. male median=0.499 [IQR 0.489-0.508], $p<0.001$; White females=0.524 [IQR 0.516-0.534] vs. male median=0.515 [IQR 0.506-0.523], $p=0.001$).

Figure 38. Cormic Index versus age by study dataset.



IRRV, Indigenous Respiratory Reference Values; NHANES III, Third National Health and Nutrition Examination Survey.

12.4.3 Spirometry

Multivariable regression of FEV₁ and FVC Z-scores (Model 1, Table 40 and Table 41) of both ethnic groups showed that First Nations children aged 8-11.9 years and 12-16 years had significantly lower FEV₁ ($\beta=-0.59$ [95%CI -0.73, -0.46], $p<0.01$; $\beta=-0.56$ [95%CI -0.70, -0.42], $p<0.01$) and FVC ($\beta=-0.58$ [95%CI -0.70, -0.46], $p<0.01$; $\beta=-0.54$ [95%CI -0.69, -0.40], $p<0.01$) Z-scores, compared to Whites, after adjustment for age, sex, standing height, and Cormic Index. For all children aged 8-16 years from both datasets, median FEV₁ and FVC Z-scores were significantly reduced with increasing age, and significantly increased with increasing standing height and Cormic Index.

Table 40. Multivariable regression modelling FEV1 Z-scores for combined dataset, and absolute and percentage reductions explained by ethnic differences.

	8-11.9 years (n=788)		12-16 years (n=739)	
	Model 1 (R ² = 0.22)	Model 2 (R ² = 0.13)	Model 1 (R ² = 0.22)	Model 2 (R ² = 0.18)
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
Age (per 1 year increase)	-0.14 (-0.22, -0.06)*	-0.17 (-0.25, -0.09)*	-0.09 (-0.14, -0.03)*	-0.05 (-0.11, -0.00)*
Female	-0.03 (-0.16, 0.09)	-0.02 (-0.16, 0.11)	0.03 (-0.10, 0.17)	0.16 (0.03, 0.30)*
Standing height (per 1 cm increase)	0.015 (0.006, 0.025)*	0.007 (0.003, 0.017)*	0.020 (0.011, 0.028)*	0.017 (0.009, 0.026)*
Cormic Index (per 0.01 increase)	0.21 (0.17, 0.26)*	-	0.14 (0.09, 0.18)*	-
First Nations children	-0.59 (-0.73, -0.46)*	-0.69 (-0.83, -0.55)*	-0.56 (-0.70, -0.42)*	-0.76 (-0.89, -0.63)*
	Effect of Cormic Index on Z-scores in First Nations children		Effect of Cormic Index on Z-scores in First Nations children	
	β (95%CI)		β (95%CI)	
	0.10 (0.05, 0.15)*		0.20 (0.13, 0.28)*	
Absolute reduction	0.10 (0.05, 0.15)*		0.20 (0.13, 0.28)*	
Percentage reduction ^a	14 (7, 21)*		26 (16, 37)*	

*p<0.05. GLI 2012 “Caucasian” reference equation used to generate FEV₁ Z-scores.³ Z-scores for standing and sitting heights were calculated using the British 1990 growth reference.¹⁴ ^aObserved percentage reduction = 100(Model 2 β - Model 1 β)/Model 2 β. R² provided are adjusted.

Table 41. Multivariable regression modelling FVC Z-scores for combined dataset, and absolute and percentage reductions explained by ethnic differences.

	8-11.9 years (n=788)		12-16 years (n=739)	
	Model 1 (R ² = 0.24)	Model 2 (R ² = 0.15)	Model 1 (R ² = 0.22)	Model 2 (R ² = 0.18)
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
Age (per 1 year increase)	-0.14 (-0.21, -0.07)*	-0.18 (-0.25, -0.10)*	-0.06 (-0.12, -0.01)*	-0.03 (-0.08, 0.03)
Sex (Female)	-0.00 (-0.12, 0.12)	-0.01 (-0.12, 0.14)	0.03 (-0.11, 0.17)	0.18 (0.04, 0.32)*
Standing height (per 1 cm increase)	0.013 (0.004, 0.022)*	0.005 (-0.004, 0.015)	0.015 (0.006, 0.023)*	0.012 (0.003, 0.021)*
Cormic Index (per 0.01 increase)	0.22 (0.17, 0.26)*	-	0.16 (0.11, 0.20)*	-
First Nations children	-0.58 (-0.70, -0.46)*	-0.68 (-0.81, -0.55)*	-0.54 (-0.69, -0.40)*	-0.78 (-0.91, -0.65)*
	Effect of Cormic Index on Z-scores in First Nations children		Effect of Cormic Index on Z-scores in First Nations children	
	Observed β (95%CI)		Observed β (95%CI)	
Absolute reduction	0.10 (0.05, 0.15)*		0.24 (0.15, 0.32)*	
Percentage reduction ^a	15 (8, 21)*		31 (19, 42)*	

*p<0.05. GLI 2012 “Caucasian” reference equation used to generate FEV₁ Z-scores.³ Z-scores for standing and sitting heights were calculated using the British 1990 growth reference.¹⁴ ^aObserved percentage reduction = 100(Model 2 β - Model 1 β)/Model 2 β. R² provided are adjusted.

12.4.4 Effects of sitting-height/standing-height ratio on differences in FEV₁ and FVC Z-scores between the ethnic groups

In the 8-11.9 years age group, the lower Cormic Index observed in First Nations children explained 14% (95%CI 7-21%) of the difference in FEV₁ Z-scores observed between the two study groups, and 15% (95%CI 8-21%) of the difference in FVC Z-scores. In the 12-16 years age group, lower Cormic Index explained 26% (95%CI 16-37%) of the ethnic difference observed in FEV₁ Z-scores and 31% (95%CI 19-42%) of differences in FVC Z-scores.

We repeated our analysis of children aged 8-11.9 years after removing two Cormic Index outliers within the NHANES III group (Figure 3, Cormic Index >0.60). Exclusion of these children had a negligible impact on our findings, and so these analyses are not presented.

12.5 DISCUSSION

In this comparative study of 619 healthy First Nations Australian children from the IRRV dataset and 908 healthy White children from the NHANES III dataset, we found the Cormic Index, and the spirometry values (after adjustment in multivariable modelling) of First Nations children to be significantly lower in both the 8-11.9 years and 12-16 years age groups after adjustment for age, sex, and standing height. Differences in Cormic Index explained 14% and 15% of the disparity in FEV₁ and FVC measurements in children aged 8-11.9 years, rising to 26% and 31% respectively in children aged 12-16 years. Our study is the first to examine the relationship between the Cormic Index and spirometric lung function in First Nations Australian children.

First Nations Australian children have lower spirometry values²⁰ than their White counterparts. Understanding reasons for this disparity is important as it is now well acknowledged that lung function trajectories are determined in childhood and reduced (even in the clinically normal range) FEV₁ and FVC values in childhood may also impact adulthood lung function and outcomes.⁹⁵ Associations with chronic obstructive pulmonary disease (COPD) and several abnormal trajectories, beginning with reduced childhood FEV₁ and strengthened by accelerated decline due to aggravating factors in adulthood have been established.^{51,54} The prospective urban rural epidemiology (PURE) study involving 126,259 adults aged 35-70, found that those whose FEV₁ Z-scores were in the clinically normal range (0 to -1) had increased cardiovascular disease morbidity (OR=1.18, 95%CI 1.10-1.26) and all-cause mortality (HR=1.27, 95%CI 1.18-1.36), with further increased risk for Z-scores below the lower limit of normal (OR=2.02, 95%CI 1.75-2.32; HR=2.54, 95%CI 2.26-2.86).¹¹⁴ Our recent data on First Nations adults suggests both FEV₁ and FVC Z-scores below <-1 were associated with elevated mortality risk (HR=3.2, 95%CI 1.4-

7.4; HR=2.6, 95%CI 1.3-5.1), and elevated cardiovascular disease risk (OR=1.5, 95%CI 1.1-2.2; OR=1.6, 95%CI 1.2-2.3).⁴⁷ Further to this, FEV₁/FVC% Z-scores <-1 were associated with increased overall mortality (HR=1.6, 95%CI 1.1-2.3), an association not found in other populations. These findings highlight the importance of childhood spirometry values and understanding determinants of lower lung function, particularly in at-risk populations such as First Nations Australians.

The contribution of the Cormic Index to spirometric values in 8-11.9 year old First Nations children (14-15%) is comparable to that in similarly aged children in other populations. The Size and Lung function In Children (SLIC) study involving spirometry of 1901 children aged 5-11 years showed that ethnic differences in FEV₁ and FVC values for African American, South-East Asian, and 'other/mixed' children are consistent with GLI offsets.²³⁵ The overall contribution of the sitting height to these differences were significant for each category; 11% of 1.32 FEV₁ Z-score and 14% of 1.27 FVC Z-score differences in African American, 13% of 1.27 FEV₁ Z-score and 16% of 0.95 FVC Z-score differences in South-East Asian, and 10% of 0.51 FEV₁ Z-score and 11% of 0.47 FVC Z-score differences in 'other/mixed' children. Socioeconomic factors such as family affluence made only minor, non-significant differences to Z-scores (≤ 0.02 Z-score differences for FEV₁ and FVC across each ethnicity). In contrast, the Determinants of Adolescent Social well-being and Health (DASH) study showed that differences between ethnic groups in the sitting height accounted for 26-41% of the differences in FEV₁ across groups.¹⁵ Socioeconomic differences contributed a further 6-10% across groups, primarily through overcrowding. Taken together with our findings, encompassing both middle childhood and adolescence, there is evidence that heterogeneity in changes to body proportions in early adolescence between ethnic groups plays an increased role in lung function disparities as children move into adolescence.

Although the SLIC and DASH studies included anthropometric factors and socioeconomic determinants within their models, a significant portion of lung function differences (>50%) in children remains unexplained. Analysis of adult subjects in the NHANES III dataset²³⁶ also failed to account for 50% of lung function differences. Use of ethnic correction in clinical algorithms has been subject of growing debate within the literature, and there are now calls to remove racial classification from spirometry reference values^{213,214} and algorithms used in other fields of medicine.^{215,216} Central to these arguments are practical issues inherent with ethnic correction, including (i) the inability to account for mixed parentage, ancestry, and genetic diversity more generally, and (ii) that little consideration has been given to determinants of health when surveying racial or ethnic groups to produce ethnic adjustments, possibly normalising abnormal results in

disadvantaged populations. Our data suggests other inherent ethnic differences play a significant role through childhood in lung development as it affects spirometry values. This is particularly true for pre-adolescents, where lung function differences are just as significant, but are less attributable to differences in body proportions. Ethnic correction is one way to account for inherent differences, but efforts to measure and adjust for confounding factors that contribute to disadvantage and lower lung function could increase the overall accuracy of ethnic correction and reduce the risk of normalising abnormal results, as there is some evidence that socioeconomic determinants impact lung function even within racial and ethnic groups.^{217,218}

Our study has several limitations. Firstly, our modelling was limited to variables collected in both IRRV and NHANES III datasets, and we were unable to make any adjustment for socioeconomic factors. Secondly, the NHANES III dataset used to represent White children is no longer contemporary. GLI multi-ethnic equations utilised data collected through NHANES III, and so it provides an excellent fit for White children included in this study. Further, these equations have been previously found to correlate well with White Australians.⁹⁵ Despite this, we cannot be certain spirometry and, in particular, Cormic Index measurements are entirely representative of Australian White children today due to the large (>20 year) gap between studies and the possibility of changes occurring to body proportions, as has been demonstrated in other populations.²⁴¹ Thirdly, while pubertal status was assessed during the NHANES III survey, this data was not collected for children within the IRRV study and so stratification of children was based on age instead. Finally, while the IRRV data was collected across a wide range of Queensland communities and schools, we cannot be certain of the generalisability of this data to First Nations children Australia-wide.

In conclusion, we have demonstrated that differences in spirometric values, and the Cormic Index between White and First Nations Australian children are significant across the two age groups in the 8-16 year age range, and that differences in the Cormic Index account for 14-26% of the observed difference in FEV₁, and 15-30% of the difference in FVC values across middle childhood and adolescence. Our findings suggest that a large proportion of differences in lung function between these two populations are due to other possibly inherent or socioeconomic factors. Care should be taken during the development of reference values to identify differences in anthropometric measures such as Cormic Index and collect and adjust for other determinants of lung function to increase the overall accuracy and minimise the normalisation of abnormal results in disadvantaged populations.

12.6 SUPPLEMENTARY MATERIALS

Table 42. Summary of demographic data, anthropometric, and spirometric measurements of children aged 8-11.9 years from NHANES III and IRRV datasets by sex.

		Caucasian ^a (n=476)		First Nations ^b (n=312)	
		Males (n=235)	Females (n=241)	Males (n=157)	Females (n=155)
		Median (IQR)			
Median Age (years)		10.0 (9.0, 10.9)	10.0 (9.1, 11.1)	10.0 (8.9, 11.1)	10.0 (9.0, 10.7)
Sitting height	Median (cm)	72.6 (69.9, 75.7)	72.4 (68.9, 76.4)	71.5 (68.7, 74.6)	71.5 (69.4, 75.6)
	Mean (Z-score)	-0.22 (-0.34, -0.09)	-0.20 (-0.34, -0.06)	-0.43 (-0.59, -0.28)	-0.29 (-0.47, -0.11)
Standing height	Median (cm)	139.9 (134.4, 146.4)	138.7 (132.6, 147.7)	139.7 (132.5, 146.0)	140.0 (133.2, 147.0)
	Mean (Z-score)	0.29 (0.15, 0.42)	0.25 (0.12, 0.39)	0.22 (0.06, 0.38)	0.40 (0.20, 0.60)
Cormic Index		0.518 (0.510, 0.527)	0.520 (0.511, 0.528)	0.515 (0.506, 0.526)	0.515 (0.506, 0.525)
FEV ₁	Litres (L)	2.00 (1.80, 2.29)	1.93 (1.73, 2.21)	1.88 (1.67, 2.15)	1.79 (1.56, 2.06)
	Z-score	0.02 (-0.63, 0.62)	0.10 (-0.56, 0.81)	-0.55 (-1.11, 0.16)	-0.69 (-1.15, -0.04)
	% Predicted	100.2 (92.8, 107.5)	101.1 (93.4, 109.4)	93.6 (87.6, 101.8)	91.8 (84.1, 97.8)
FVC	Litres (L)	2.37 (2.10, 2.71)	2.18 (1.94, 2.51)	2.17 (1.93, 2.50)	2.03 (1.78, 2.34)
	Z-score	0.04 (-0.51, 0.68)	0.16 (-0.52, 0.77)	-0.57 (-1.11, -0.04)	-0.64 (-1.13, 0.04)
	% Predicted	100.4 (93.9, 107.9)	101.9 (93.9, 109.2)	93.5 (87.3, 99.5)	92.3 (86.8, 100.4)

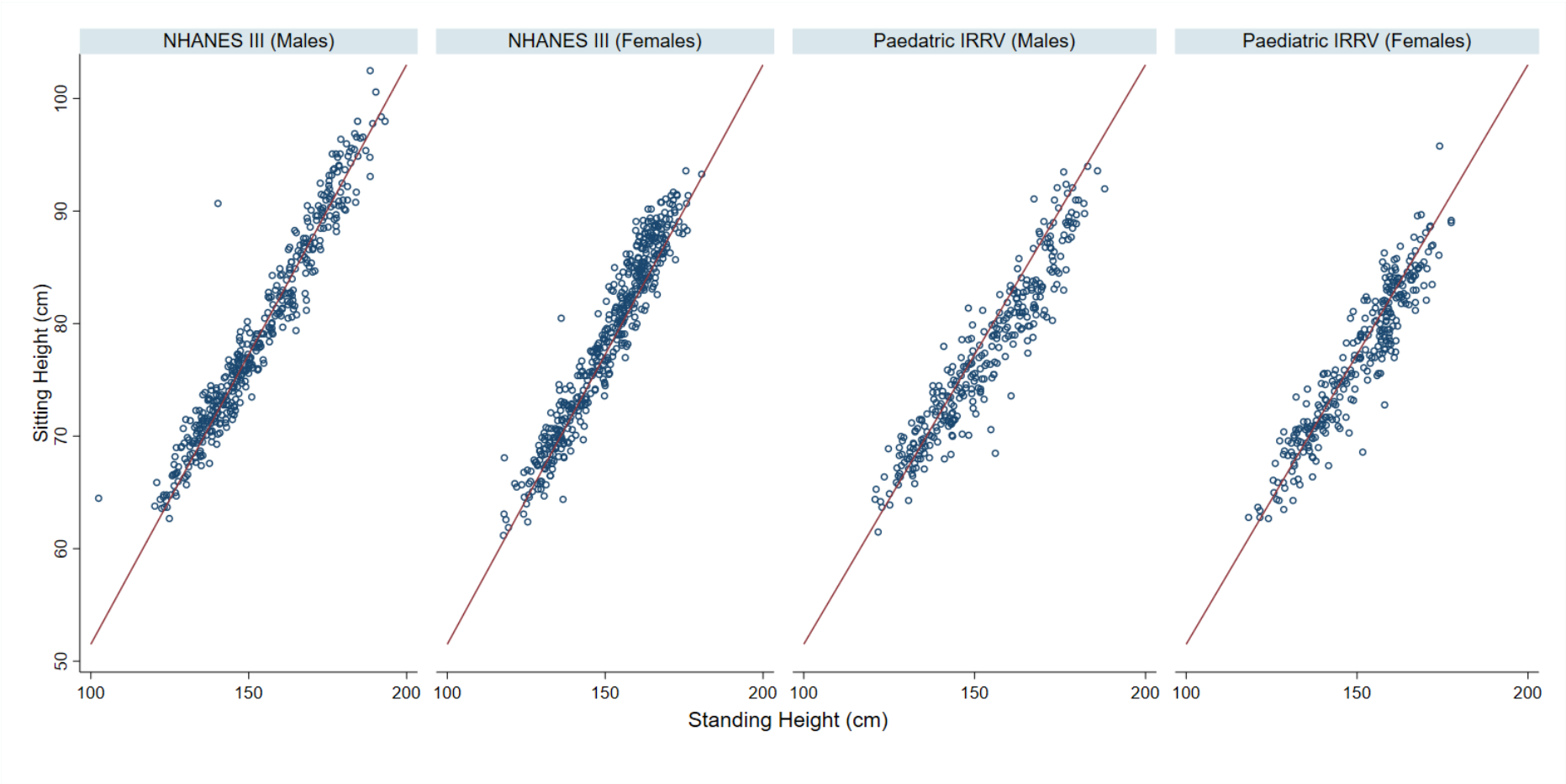
Sitting and standing height Z-scores calculated using British 1990 growth reference set.²⁴⁰ ^aCaucasian children from NHANES III dataset.²³⁷ ^bFirst Nations children from IRRV dataset.²⁰

Table 43. Summary of demographic data, anthropometric, and spirometric measurements of children aged 12-16 years from NHANES III and IRRV datasets by sex.

		Caucasian ^a (n=432)		First Nations ^b (n=307)	
		Males (n=195)	Females (n=237)	Males (n=164)	Females (n=143)
		Median (IQR)			
Median Age (years)		14.5 (13.2, 15.8)	14.4 (13.3, 15.8)	14.0 (13.1, 15.6)	14.0 (13.0, 15.2)
Sitting height	Median (cm)	86.7 (81.9, 91.0)	85.4 (82.3, 87.8)	82.3 (79.0, 86.8)	82.4 (79.5, 84.4)
	Mean (Z-score)	0.35 (0.20, 0.49)	-0.08 (-0.23, 0.06)	-0.51 (-0.68, -0.34)	-0.51 (-0.71, -0.31)
Standing height	Median (cm)	168.3 (160.5, 176.4)	162.1 (157.0, 166.2)	165.5 (158.7, 172.6)	160.0 (157.4, 165.6)
	Mean (Z-score)	0.51 (0.38, 0.65)	-0.38 (-0.52, 0.23)	0.25 (0.10, 0.39)	-0.22 (-0.41, -0.04)
Cormic Index		0.515 (0.506, 0.523)	0.524 (0.516, 0.534)	0.499 (0.489, 0.508)	0.510 (0.500, 0.519)
FEV ₁	Litres (L)	3.57 (2.89, 4.27)	3.18 (2.80, 3.46)	3.06 (2.49, 3.69)	2.78 (2.49, 3.10)
	Z-score	-0.05 (-0.61, 0.60)	0.01 (-0.51, 0.68)	-0.83 (-1.37, -0.19)	-0.82 (-1.34, -0.15)
	% Predicted	99.4 (92.9, 107.2)	100.1 (94.0, 107.9)	90.0 (83.8, 97.7)	90.4 (84.2, 98.3)
FVC	Litres (L)	4.20 (3.39, 4.96)	3.53 (3.13, 3.99)	3.48 (2.96, 4.26)	3.18 (2.83, 3.41)
	Z-score	-0.04 (-0.64, 0.63)	0.06 (-0.54, 0.71)	-0.83 (-1.50, -0.30)	-0.72 (-1.30, -0.18)
	% Predicted	99.5 (92.7, 107.3)	100.7 (93.6, 108.7)	90.5 (82.8, 96.5)	91.5 (84.7, 97.8)

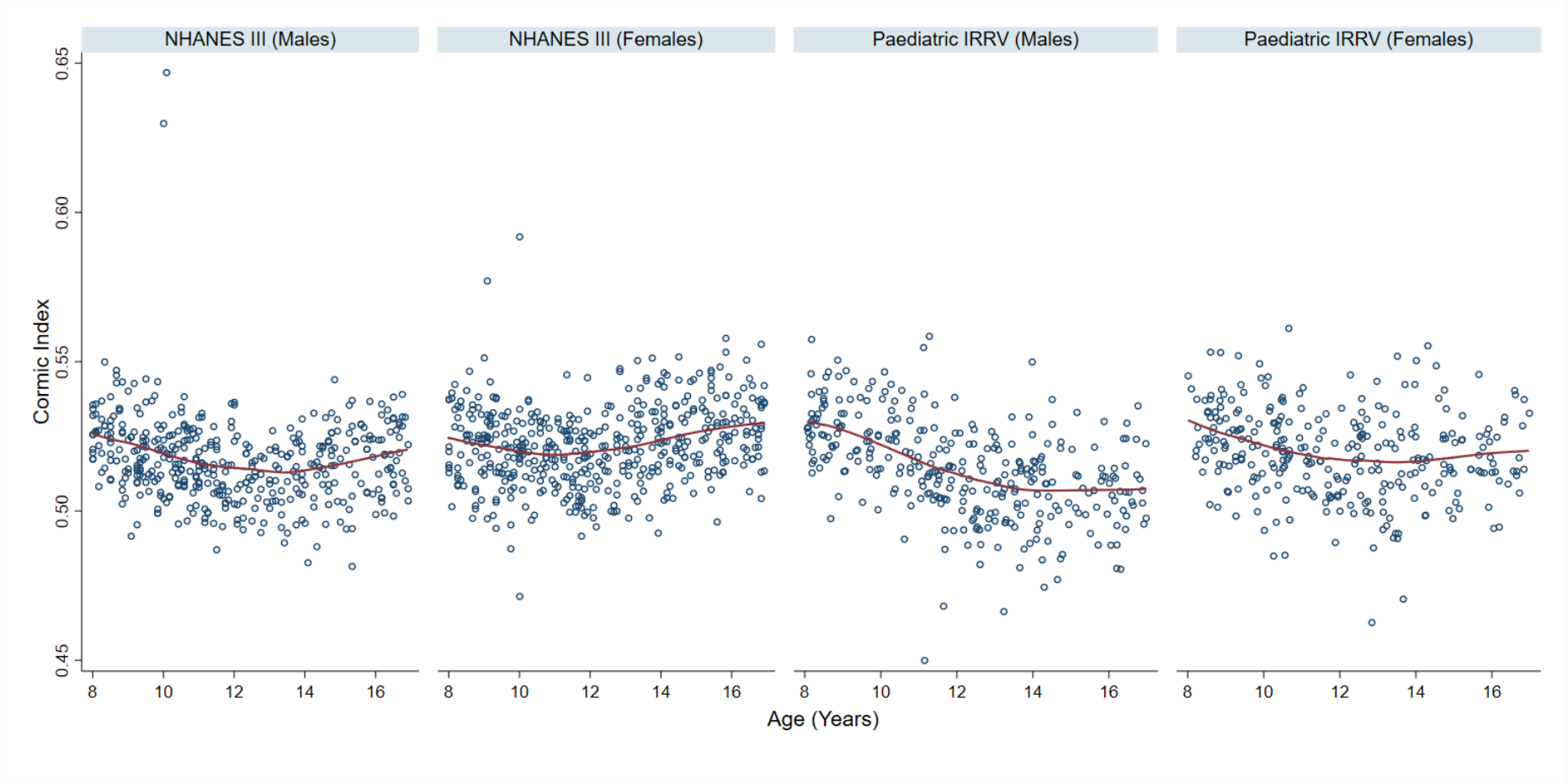
Sitting and standing height Z-scores calculated using British 1990 growth reference set.²⁴⁰ ^aCaucasian children from NHANES III dataset.²³⁷ ^bFirst Nations children from IRRV dataset.²⁰

Figure 39. Sitting height versus standing height by study dataset and sex.



Straight line describes: sitting-height/standing-height = 0.52

Figure 40. Cormic versus age by study dataset and sex.



Lowess curves fit for each dataset and sex.

Chapter 13: Conclusion

13.1 SUMMARY OF FINDINGS

The overall aims of my thesis were to improve interpretation of lung function testing, to understand determinants of lung function, and to relate lung function to clinical outcomes in First Nations Australian children and adults. To achieve these aims, five research objectives were formulated. These questions, and a summary of findings, are summarised below.

13.1.1 Objective 1: Determine the impact of early childhood pneumonia on lung function in later childhood in First Nations Australian children, and on children and adults more generally (Chapters 3 and 4)

Utilising the spirometry data of First Nations Australian children and young adults aged 3-25 years, this study used a combination of linear regression and generalised additive modelling to assess the impact of pneumonia occurring in early childhood, at or before five years, on spirometry values in later childhood and early adulthood.¹³³ After adjustment for potential confounding factors such as age at which spirometry testing occurred, household smoking, gestational age, hay fever, and early childhood wheeze, children with a history of early childhood pneumonia were shown to have lower FEV₁ and FVC values.

Early childhood pneumonia is a public health issue of international concern, yet evidence on its impact on lung function had yet to be systematically reviewed and synthesised. I thus undertook a systematic review of all available published and grey literature. This systematic review included 14 studies^{66,71,132-134,136,137,141,143,145-149} with data from the United Kingdom, Europe, North America, India, Thailand, and Australia/New Zealand. Despite early childhood pneumonia disproportionately affecting children from developing nations, and from disadvantaged communities of affluent countries, only two of 14 included studies were from a developing nation¹³⁶ (Thailand in the year 2000), or a disadvantaged population¹³³ (First Nations Australians). Meta-analysis of 11 studies showed significant reductions in the FEV₁ values of children and adults with a history of early childhood pneumonia, while meta-analysis of 9 studies showed significant reductions in the FVC values of adults, and non-significant reductions in the FVC values of children.

13.1.2 Objective 2: Evaluate changes in spirometry values of paediatric patients treated through IROC and compare these changes to those seen in tertiary paediatric facilities (Chapters 5 and 6)

Utilising the demographic, medical history, and spirometry data of 189 children seen at paediatric IROC clinics between October 2010 and December 2017, the study formally evaluated the efficacy of IROC clinics, using changes in spirometry values as an outcome measure.¹⁷³ For both First Nations and non-First Nations, FEV₁ and FVC values were significantly improved by most recent follow-up, including within each of the first three years of follow-up clinic visits. These findings suggested that treating patients through IROC clinics improved the spirometry values of children. An important limitation of this analysis was the lack of comparative data, or a control arm.

To address this limitation, and provide more context for the changes in spirometry values, Chapter 6 expanded this analysis to include IROC data up to July 2019 (n=252), and added children seen at paediatric tertiary hospital facilities in Brisbane, Queensland as a second arm (n=2249) in a two-arm cohort study.¹⁷⁴ While the average age of children seen and treated at IROC was lower than that for tertiary hospital clinics (6.5 versus 7.9 years), the average duration of care was similar across both clinic types (27.5 versus 28 months). For diagnosis such as asthma and bronchiectasis that are well represented at both clinic types, improvements in the spirometry values of children seen at IROC clinics were comparable to improvements seen in children tested at paediatric tertiary hospital clinics.

13.1.3 Objective 3: Evaluate determinants and changes in lung function and associations between reduced lung function and cardiovascular morbidity and all-cause mortality in adults treated through IROC (Chapters 7, 8, and 9)

Utilising the demographic, medical history, spirometry, and D_{LCO} data of 1734 First Nations Australian adults seen between February 2012 and March 2020, Chapter 7 explored the determinants of lung function. Within this population, BMI (underweight and obese patients), First Nations status, personal smoking, and concurrent respiratory disease were significantly associated with reduced lung function. Notably, spirometry values of adults in this analysis were higher than previously reported by similar studies in the Northern Territory. FEV₁ and FVC values were significantly improved from baseline to most-recent follow-up (17 months on average).⁴⁶ FEV₁/FVC values were reduced overall, while no measurable change occurred in D_{LCO} values. I modelled this change and found each year under the care of IROC was associated with significant increases to FEV₁, FVC, FEV₁/FVC, and D_{LCO} values, except for patients with a diagnosis of COPD, whose FEV₁ values were stagnant from baseline to follow-up. Of note is that the majority

of adults followed-up (561/698) had a primary diagnosis of either asthma (n=262) or COPD (n=299), and lung function impairment was primarily obstructive in nature.

Survival analysis showed that for each single Z-score reduction in spirometry values below 0, there were marked increases in cardiovascular disease incidence, including ischaemic heart disease and congestive heart failure, and all-cause mortality risk, even within the clinically normal range of >-1.64 Z-scores.⁴⁷ Similar analysis of D_{LCO} , K_{CO} , and V_A values revealed clinically abnormal values were associated with significantly elevated cardiovascular disease prevalence, and all-cause mortality risk, independently of age, personal smoking, and diagnosed respiratory disease. Importantly, these associations persisted for D_{LCO} in patients whose spirometry values were within the clinically normal range of >-1.64 Z-scores.

13.1.4 Objective 4: Develop reference values for spirometry and fractional exhaled nitric oxide (FeNO) lung function tests, for use in First Nations Australian children and adults (Chapters 10 and 11)

In 582 healthy participants aged 4-76 years, both linear and generalised additive modelling revealed increases in age and height were each associated with increases in FeNO values. These associations meant reporting a single cut-off value, as is currently done in FeNO interpretive guidelines, is of questionable significance and so advanced statistical methods previously employed by the World Health Organization and the GLI were used to develop two age-for-height look-up tables: the first for predicted values, the second for the ULN. To assist clinician use of these look-up tables, I developed a calculator in Microsoft Excel that accepts date of birth (age) and height inputs to calculate predicted and ULN FeNO values for First Nations Australians aged 4-76 years. Previous analysis of FeNO values in healthy First Nations Australian children aged up to 16 years suggested a 50ppb cut-off is suitable for use.³⁹ My analysis suggests that, dependent on the age and height of the child, ULN values range from 25-60ppb, while for adults ULN values range from 39-88ppb.

Spirometry values collected from 1444 healthy First Nations Australians aged 3-91 years recruited in three states/territories, showed values were approximately 8% lower than for Caucasians. GLI recommendations were used to assess whether the ‘Other/mixed’ category, previously recommended for use in First Nations Australian children and young adults aged 5-25 years,²⁰ is currently the most appropriate for use across the lifespan. Mean Z-scores of approximately zero with a maximum difference of ± 0.5 , an SD of 1, and approximately 10% of results falling within 1.64 Z-scores from the centre of normal curve suggests an overall good fit.²⁰ This analysis demonstrated that the GLI-2012⁹ ‘Other/mixed’ ethnic category is suitable for use

in this population (FEV₁ Z= -0.09, SD 1.02; FVC Z= 0.01, SD 1.07; FEV₁/FVC -0.25, SD 0.90). Rural participants had overall lower FEV₁ and FVC than for urban participants, and this deficit increased with age following early childhood. Despite these deficits, the GLI-2012 ‘Other/mixed’ ethnic category also provided an overall good fit for rural participants.

13.1.5 Objective 5: Investigate the influence of anthropometric differences between First Nations children and their non-First Nations counterparts, and how this accounts for known differences in lung function between healthy children of both ethnicities (Chapter 12)

Spirometry and anthropometric data of 619 healthy First Nations Australian children aged 8-16 years were compared to 919 healthy Caucasian children aged 8-16 extracted from the NHANES III dataset. For children aged 8-16 years, there were significant differences in the Cormic Index (sitting height as a proportion of standing height) of First Nations and Caucasian children. While standing heights were largely similar between the two groups, sitting heights were lower on average for First Nations children, reflecting differences in body proportions between the two groups. For children aged 8-11.9 years, approximately 14-15% Z-score differences in between First Nations and Caucasian children was found to be due to differences in the Cormic Index. For children aged 12-16 years, approximately 26-30% of Z-score differences were explained by differences in the Cormic Index. A substantial proportion (14-30%) of the differences in spirometry values between First Nations Australian and Caucasian children are due to differences in the Cormic Index.

13.2 IMPLICATIONS AND RECOMMENDATIONS

Through addressing knowledge gaps identified within the literature, my PhD improves the interpretation of lung function testing, understanding of determinants of lung function, and relates lung function to clinical outcomes in First Nations Australians. The implications and recommendations arising from the ten studies that form the body of this thesis are numerous and detailed discussion for each study can be found within each chapter and are summarised below.

In the analysis of spirometry data of First Nations Australian children and young adults showed that in a population at high risk of pneumonia, pneumonia occurring during periods of critical lung development has a lasting impact on spirometry values through childhood into adulthood, and so may increase risk of future cardiopulmonary disease, and all-cause mortality risk.^{47,114} In the context of increasing evidence that childhood lung function follows defined trajectories into adulthood⁵¹⁻⁵⁶ and associations between low (even within the normal range) adult lung function with future cardiovascular morbidity and mortality,^{47,114} investigation and

prevention of factors that could impact on lung function growth such as early childhood pneumonia, particularly in disproportionately affected populations such as First Nations Australians, is critically important. Reductions in spirometry values, both within the First Nations Australian population and in populations internationally, were statistically significant but small, and may be important in changing population risk rather than individual risk. Currently, there is a paucity of data relating to minimally clinically important differences in FEV₁ and FVC adults,¹⁵⁴ and no data for children. Perhaps the most consequential finding from my systematic review is the need for additional data from populations most affected, including data from developing nations, and disadvantaged populations of affluent countries such as First Nations Australians. These populations are known to be disproportionately affected by early childhood pneumonia,⁶³ yet there is insufficient data to determine the impact to lung function within these populations.

Evaluation of the paediatric IROC service in Chapters 3 and 4 were the first evaluation of a respiratory specialist outreach service in any setting to examine the change in lung function of children tested at outreach and compare to an associated tertiary hospital respiratory service. Similarities in improvements to lung function observed at both clinic types suggests that effective high-quality clinical care is achievable with an appropriate model of care embedded within primary healthcare. Analysis of the equivalent adult service suggests specialist care may halt, and in some cases reverse, the gradual lung function decline associated with chronic respiratory disease in this clinical population. Overall, these data show culturally appropriate outreach services modelled to the needs and resources available to target communities may provide effective care comparable to services delivered within tertiary centres. This knowledge of the effectiveness of outreach services has global health implications, including informing evaluation of respiratory-based health services and guiding recommendations and policy decisions relating to the provision of outreach services that can reduce inequity in health service delivery.

Analysis of outcomes using clinical data from the adult IROC service supports and extends existing data on associations between spirometry values and the D_{LCO} with all-cause mortality and cardiopulmonary disease.¹¹⁴⁻¹¹⁶ Before this analysis, spirometry values as a predictor of these outcomes had been previously described in a large-scale, international study,¹¹⁴ however, this was the first analysis of its kind in the First Nations Australian population. Analysis of K_{CO} and V_A values and associations with cardiovascular disease incidence all-mortality risk is the first of its kind in any population. Including when spirometry values are clinically normal, abnormal D_{LCO} continues to be related to adverse outcomes in adulthood, emphasising the importance of gas diffusing capacity testing alongside routine spirometry testing. These findings stress the

importance of lung function optimisation in the First Nations Australian population, who like other global Indigenous populations, are at increased risk of chronic respiratory and cardiovascular diseases, and early mortality.

Analysis of normative FeNO data in First Nations Australians within my thesis is directly translatable to clinical care. In analysis of FeNO values from healthy children and adults, I elected not to propose a cut-off value (or separate child and adult cut-off values), as is currently done in interpretive guidelines for FeNO testing.^{21,25-27} Consistent with previous reports, FeNO values scaled with increasing age and height of healthy participants.^{35,36} Therefore, cut-off values that do not account for these factors are inherently limited and could be misleading. GAMLSS modelling that accounted for age and height was used to develop look-up tables that provide height-for-age predicted and ULN values for First Nations Australians aged 4-76 years. To aid the roll-out of these normative data to Australian lung function laboratories, I developed a calculator in Microsoft Excel that allows clinicians to enter the date of birth and height of the individual being tested, to effortlessly calculate a predicted and ULN value. These normative data should be used in place of current interpretive guidelines for FeNO, which (1) do not account for age and height as modifiers of FeNO values, and (2) were developed using Caucasian data and it is now known that FeNO values may also differ between ethnic groups.³⁷ These normative data have the capacity to change FeNO testing of First Nations Australians in Australian lung function laboratories.

Analysis of normative spirometry data in First Nations Australians is important in the context of previous research^{18,88,96,227,229,230} which suggests normative spirometry data in this population may be up to 20-30% lower than for Caucasians. In a previous analysis²⁰ this was shown to be closer to 7-8% lower in children and young adults aged 5-25 years, consistent with the GLI-2012 'Other/mixed' ethnic category. This has not prevented more recent studies²²⁷ continuing to suggest that the gap may be as high as 20%. Common to all studies that suggest such a large deficit are severe methodological flaws, including inadequate, or entirely absent exclusion of participants with respiratory disease, or ever smokers, and insufficient numbers (300 healthy participants as per GLI⁹ criteria).¹⁸ Analysis of 1444 healthy, non-symptomatic, non-smoking, non-obese First Nations Australian children and adults aged 5-91 confirms that the FEV₁ and FVC values are 8% lower than Caucasians, and that the GLI-2012 'Other/mixed' reference category should be used when testing First Nations Australians, consistent with current GLI recommendations.¹⁹⁹ This thesis makes extensive use of the term 'Caucasian', as this is the language used by the GLI to describe the equation from which other ethnic equations are based. It is important to note that this

is an obsolete, dated term that does not properly describe an ethnicity but is instead often used to describe phenotypic features.

Long-term benefits of these studies on normative data for First Nations Australians include earlier diagnosis leading to treatment of lung disease can improve severity and reduce disease process.^{197,242} This data may lead to improved accuracy in interpretation and subsequent respiratory clinical care, an area of significant chronic illness and inequality for First Nations. Predicted and ULN values for FeNO, derived using methods consistent with GLI criteria,⁹ may have significant long-term implications nationally if they are used for future lung function testing for First Nations Australians.

13.3 RESEARCH STRENGTHS AND LIMITATIONS

Study-specific strengths and limitations are discussed within the relevant chapters, however there are several strengths and limitations common to multiple studies completed in the formulation of this thesis.

13.3.1 Research Strengths

Consistent with current guidelines for research within Australia,²⁴³ there was First Nations consultation and involvement in the published works where relevant. Data involving the IROC service was aided and co-authored by First Nations IROC Project Officers, who played an important role in the collection of demographic and medical history data at the IROC clinics, and in facilitating data collation of normative spirometry and gas diffusing capacity data. For collection of data relating to the IRRV and HILTA databases (see Chapter 2), there was extensive First Nations involvement in community consultation, study recruitment, spirometry and FeNO testing, and reviewing of manuscripts. Community elders were consulted during the planning phase of the HILTA study. These discussions were facilitated and led by First Nations research team members. Elders offered feedback on study questionnaires, offered advice on recruitment strategies, and were eager to learn of the potential benefit to their communities. Local First Nations community members were hired to facilitate recruitment within regional and remote communities. Their extensive knowledge of the community and its members were used to great effect and allowed us to achieve many successful recruitment trips within Queensland and the Northern Territory. Finally, First Nations research team members were involved in the recruitment and testing within these communities, and the review of the manuscripts produced for Chapters 10 and 11.

Ensuring high quality lung function data is important to ensure these data may be safely incorporated into future guidelines or international studies, and to achieve the best possible signal-

to-noise ratio for data analysis. All spirometry testing in the early childhood pneumonia cohort study, paediatric and adult IROC analysis, and collection of normative data were performed by trained respiratory scientists according to ATS/ERS criteria for acceptability and repeatability.^{8,10} Similarly, all FeNO testing done in the collection of normative data were also done in accordance with ATS/ERS guidelines.²⁸ In the formulation of normative spirometry and FeNO data, participants with chronic respiratory disease, smoking history, atopy (FeNO only), obesity (spirometry only), or whose results did not meet acceptability or repeatability criteria were excluded from the final analysis. Participant questionnaires were used to obtain this data, and where possible medical records housed within local hospitals of communities were used to verify questionnaire data.

13.3.2 Research Limitations

The limitations of each study are mentioned within the papers generated. Overall, the most significant limitation of data within my PhD is that the lung function featuring throughout was primarily sourced from Queensland, with data from the Northern Territory and Western Australia also contributing to normative data analysis. Further, most data were from remote communities where poverty and social disadvantage is higher, aspects known to influence lung function.^{217,218} Descriptions of data from clinical services, and our analysis of lung function and associations with all-cause mortality risk and cardiopulmonary disease, were completed using data of patients seen in regional and remote Queensland. Thus, there is a degree of uncertainty about the generalisability of these findings to other First Nations communities around Australia, and whether these findings are broadly applicable to urban-based First Nations Australians. Furthermore, mortality data was generated using electronic medical records, and in most instances discharge summaries (created at the time of death) were utilised to discern the cause of death. In some cases, discharge summaries were not available and so cause of death was impossible to determine. Furthermore, it is possible that deaths occurring outside health facilities are not always accounted for. Thus, there are several important limitations for each of our mortality analyses. The studies included in this thesis make use multivariable modelling where the study sample sizes allow. It is important to note that in some cases, categorical variables included have multiple levels, some of which have smaller sample sizes. These are usually reflected in widened confidence intervals and therefore less certainty surrounding the estimates provided by the model but are important to acknowledge.

The use of ethnic correction in clinical algorithms has been the subject of growing debate within the literature, and there are now calls to remove racial classification from spirometry reference values^{213,214} and algorithms used in other fields of medicine.^{215,216} Central to these

arguments are practical issues inherent with ethnic correction, including (i) the inability to account for mixed parentage, ancestry, and genetic diversity more generally, and (ii) that little consideration has been given to determinants of health when surveying racial or ethnic groups to produce ethnic adjustments, possibly normalising abnormal results in disadvantaged populations. There is now evidence to suggest that socioeconomic determinants impact lung function even within racial and ethnic groups.^{217,218} Participants with known factors that influence lung function (e.g., respiratory disease or symptomology) were excluded from these analyses of normative FeNO and spirometry data, though this analysis did not account for socioeconomic determinants of health. In analysis of normative spirometry data, urban and rural participants were separated in a sub-analysis to indirectly measure some of this effect, as it is now known that Australians living in rural and remote areas are at substantially higher disease-associated morbidity and mortality.¹⁷⁰ Nevertheless, this sub-analysis was unlikely to fully capture the effect of socioeconomic burden on the lung function of First Nations Australians, even in the absence of respiratory disease and symptomology, and ever smokers.

13.4 IMPACT OF RESEARCH TO DATE

Research conducted in the formulation of this thesis has led to the publication of 10 peer-reviewed journal articles, and nine presentations delivered to Australian and international audiences. Analysis of longitudinal lung function of paediatric patients seen at IROC was the first evidence that the lung function decline of children with bronchiectasis can not only be halted, but reversed, with appropriate specialist care.^{173,174} These studies were referenced in the bronchiectasis clinical management plan randomised control trial protocol,²⁴⁴ an international roadmap for clinical and research priorities for children and adolescents with bronchiectasis,²⁴⁵ in the first report from the newly established Australian Bronchiectasis Registry,²⁴⁶ and in the first reports from the Children's Bronchiectasis Research, Education, and Advocacy Network ERS clinical research collaboration.^{247,248} Comparison of paediatric lung function at outreach and tertiary hospitals gained international recognition in an editorial in CHEST which highlighted the need for paediatric outreach services to deliver care to disadvantaged children (particularly First Nations children globally), to reduce the burden of COPD and other morbidities in adulthood.¹⁶⁹

Throughout recruitment of healthy participants to establish normative spirometry and FeNO data, basic respiratory education was provided to community members assisting with recruitment, and to participants tested. This was a great opportunity to increase awareness of respiratory disease, and increase awareness of IROC, who frequently visit communities where recruitment occurred. Participants were also notified email of their test results, with an attached finalised

report. Articles published on normative spirometry and FeNO data were only very recently published, however, I intend to use upcoming conferences and other presentation opportunities to disseminate our findings, particularly to encourage uptake of our novel normative data for FeNO testing.

Normative spirometry and FeNO data for First Nations Australians will be submitted to the GLI for inclusion in future reference equations and guidelines, which will help to ensure the correct reference equations for this population are used in clinical practice. Until the GLI published this data, my supervisory team and I will continue to disseminate these data to ensure respiratory laboratories use the GLI-2012 ‘Other/mixed’ reference equation for spirometry, and the novel FeNO predicted and ULN values generated in Chapter 10.

13.5 FUTURE RESEARCH

While my PhD work has several novel findings and implications, there is more still to be done in my field as a respiratory scientist with dedication to First Nations Australians and other aspects of lung function. These questions include but not limited to:

1. Does the disproportionate burden of early childhood pneumonia in First Nations Australians and other disadvantaged populations worldwide modify the impact to spirometry values?
2. What socioeconomic determinants of health are contributing to the lower spirometry values of healthy, rural based First Nations Australians, compared to their urban counterparts?
3. In addition to differences in the Cormic Index, what other factors explain the 9% gap in spirometry values between healthy First Nations Australians and Caucasians?

Future research in this area should use the data presented in this thesis to develop targeted research questions utilising a casual framework.

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Appendices

Appendix A – Search Strategy for Early Childhood Pneumonia Systematic Review

PubMed (searched October 27, 2021 and May 12, 2022)

(humans<=5yo AND pneumonia) AND (humans>=5yo AND (lung function OR spirometry)) AND observational studies AND human research AND English language		
Search Number	Query	Step
1	"Infant, Newborn"[Mesh]	
2	"Infant"[Mesh]	
3	"Child, Preschool"[Mesh]	
4	"child"[Title/Abstract]	
5	"childhood"[Title/Abstract]	
6	"children*"[Title/Abstract]	
7	"infant"[Title/Abstract]	
8	"infants"[Title/Abstract]	
9	"early life"[Title/Abstract]	
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	Age <=5
11	"Pneumonia"[MeSH]	
12	"Respiratory Tract Infections"[MeSH]	
13	"pneumonia"[Title/Abstract]	
14	"respiratory tract infection*"[Title/Abstract]	
15	"respiratory infection*"[Title/Abstract]	
16	"LRI"[Title/Abstract]	

17	"LRTI"[Title/Abstract]	
18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	pneumonia
19	#10 AND #18	Age <=5 AND pneumonia
20	"Child"[Mesh]	
21	"Adolescent"[Mesh]	
22	"Adult"[Mesh]	
23	"Middle Aged"[Mesh]	
24	"Aged"[Mesh]	
25	"Aged, 80 and over"[Mesh]	
26	#4 OR #5 OR #6 OR #9	
27	"adolescen*"[Title/Abstract]	
28	"adult*"[Title/Abstract]	
29	"aged"[Title/Abstract]	
30	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	Age >=5
31	"Respiratory Function Tests"[Mesh]	
32	"Spirometry"[Mesh]	
33	"Lung Volume Measurements"[Mesh]	
34	"spirometry"[Title/Abstract]	
35	"Forced Expiratory Volume"[Mesh]	
36	"FEV1"[Title/Abstract]	
37	"forced expiratory volume"[Title/Abstract]	
38	"Vital Capacity"[Mesh]	
39	"FVC"[Title/Abstract]	

40	"forced vital capacity"[Title/Abstract]	
41	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	lung function
42	#30 AND #41	Age >=5 AND lung function
43	"Epidemiologic studies"[Mesh:NoExp]	
44	"Epidemiologic Methods"[Mesh:NoExp]	
45	"Case-Control Studies"[Mesh]	
46	"Cohort Studies"[Mesh]	
47	"Cross-sectional Studies"[Mesh:NoExp]	
48	"cohort study"[Title/Abstract]	
49	"cohort studies"[Title/Abstract]	
50	"cohort analy*"[Title/Abstract]	
51	"follow-up study"[Title/Abstract]	
52	"follow-up studies"[Title/Abstract]	
53	"observational study"[Title/Abstract]	
54	"observational studies"[Title/Abstract]	
55	"longitudinal study"[Title/Abstract]	
56	"longitudinal studies"[Title/Abstract]	
57	"retrospective study"[Title/Abstract]	
58	"retrospective studies"[Title/Abstract]	
59	"prospective study"[Title/Abstract]	
60	"prospective studies"[Title/Abstract]	
61	"case-control study"[Title/Abstract]	
62	"case-control studies"[Title/Abstract]	
63	"cross-sectional study"[Title/Abstract]	

64	"cross-sectional studies"[Title/Abstract]	
65	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64	Observational study types
66	#19 AND #42 AND #65	(Age <=5 AND pneumonia) AND (Age >=5 AND lung function) AND observational study types
67	"Animals"[Mesh] NOT "Humans"[Mesh]	
68	#66 NOT #67	limit to human research
69	#68 AND english[Filter]	limit to English language

Embase (searched October 27, 2021 and May 12, 2022)

(humans<=5yo AND pneumonia) AND (humans>=5yo AND (lung function OR spirometry)) AND observational studies AND human research AND English language		
Search Number	Query	Step
1	'newborn'/exp	
2	'infant'/exp	
3	'preschool child'/exp	
4	'child'/exp	
5	'infant':ti,ab	
6	'child':ti,ab	
7	'childhood':ti,ab	
8	'children*':ti,ab	

9	'early life':ti,ab	
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	Age <=5
11	'pneumonia'/exp	
12	'respiratory tract infection'/exp	
13	'pneumonia':ti,ab	
14	'respiratory tract infection*':ti,ab	
15	'respiratory infection*':ti,ab	
16	'lri':ti,ab	
17	'lrti':ti,ab	
18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	pneumonia
19	#10 AND #18	Age <=5 AND pneumonia
20	'school child'/exp	
21	'adolescent'/exp	
22	'adult'/exp	
23	'aged'/exp	
24	#6 OR #7 OR #8 OR #9	
25	'adolescen*':ti,ab	
26	'adult':ti,ab	
27	'aged':ti,ab	
28	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	Age >=5
29	'lung function test'/exp	
30	'spirometry'/exp	

31	'lung volume'/exp	
32	'forced expiratory volume'/exp	
33	'vital capacity'/exp	
34	'lung volume':ti,ab	
35	'spirometry':ti,ab	
36	'fev1':ti,ab	
37	'forced expiratory volume':ti,ab	
38	'fvc':ti,ab	
39	'forced vital capacity':ti,ab	
40	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	lung function
41	#28 AND #40	Age >=5 AND lung function
42	'clinical study'/de	
43	'epidemiology'/de	
44	'case control study'/exp	
45	'cohort analysis'/exp	
46	'cross-sectional study'/de	
47	'observational study'/de	
48	'retrospective study'/de	
49	'prospective study'/de	
50	'longitudinal study'/de	
51	'controlled study'/de	
52	(controlled NEXT/1 (study OR studies)):ti,ab	
53	(longitudinal NEXT/1 (study OR studies)):ti,ab	
54	(retrospective NEXT/1 (study OR studies)):ti,ab	

55	(prospective NEXT/1 (study OR studies)):ti,ab	
56	('cross-sectional' NEXT/1 (study OR studies)):ti,ab	
57	(cohort NEXT/1 (study OR studies)):ti,ab	
58	('follow-up' NEXT/1 (study OR studies)):ti,ab	
59	(observational NEXT/1 (study OR studies)):ti,ab	
60	(epidemiologic* NEXT/1 (study OR studies)):ti,ab	
61	('case-control' NEXT/1 (study OR studies)):ti,ab	
62	#42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61	Observational study types
63	#19 AND #41 AND #62	(Age <=5 AND pneumonia) AND (Age >=5 AND lung function) AND observational study type
64	'animal'/exp NOT 'human'/exp	
65	#63 NOT #64	limit to human research
66	#65 AND [english]/lim	limit to English language

Web of Science (searched October 27, 2021 and May 12, 2022)

(humans<=5yo AND pneumonia) AND (humans>=5yo AND (lung function OR spirometry)) AND observational studies AND human research AND English language		
Search Number	Query	Step
1	TS=(child*)	
2	TS=(infant\$)	

3	TS=("early life")	
4	#1 OR #2 OR #3	Age <=5
5	TS=(pneumonia)	
6	TS=("respiratory tract infection\$")	
7	TS=("respiratory infection\$")	
8	TS=(LRI)	
9	TS=(LRTI)	
10	#5 OR #6 OR #7 OR #8 OR #9	pneumonia
11	#4 AND #10	Age <=5 AND pneumonia
12	TS=(adolescen*)	
13	TS=(adult*)	
14	TS=(aged)	
15	#1 OR #12 OR #13 OR #14	Age >=5
16	TS=("lung volume")	
17	TS=("spiromet*")	
18	TS=("forced expiratory volume")	
19	TS=(fev1)	
20	TS=("forced vital capacity")	
21	TS=(fvc)	
22	#16 OR #17 OR #18 OR #19 OR #20 OR #21	lung function
23	#15 AND #22	Age >=5 AND lung function
24	#11 AND #23	(Age <=5 AND pneumonia) AND (Age >=5 AND lung function)

25	#24 AND LA=(English)	limit to English language
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Appendix B – HILTA Participant Questionnaire

PARTICIPANT QUESTIONNAIRE Healthy Indigenous Lung Testing in Adults
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COVID-19 Screening Questionnaire		
Have you been diagnosed with COVID-19?	☐ YES	☐ NO
Have you had direct contact with someone diagnosed with COVID-19?	☐ YES	☐ NO
Have you returned from overseas/interstate in the last 14 days?	☐ YES	☐ NO
Do you have any fever or have recorded a temperature greater than 38 degrees?	☐ YES	☐ NO

Lung Function Safety	
In the last 4-6 weeks have you had any of the following? • heart attack blot clot in the lung • collapsed lung • surgery to your chest, abdomen, brain, eyes, ears, nose or throat?	☐ YES ☐ NO
Have you ever had either • very high blood pressure (200/120 mmHg) • or aortic aneurysm?	☐ YES ☐ NO

If answering YES to any of the above, please alert a researcher.

Please complete this questionnaire before doing the lung function tests. If you require assistance please ask one of the researchers. When completed please give to researchers.

Participant details

First Name/Names:	Surname:	
If applicable - other first names I use:	If applicable - other surnames I use:	
Address:	Phone: H:	Mob:
	Email:	
Date of Birth:	Sex: ☐ Male ☐ Female	
Do you identify as Aboriginal, Torres Strait Islander or both? ☐ YES ☐ NO	If YES then please specify ☐ Aboriginal ☐ Torres Strait Islander ☐ Both If NO what is your racial background, eg Caucasian, SE Asian?	
Is your Aboriginal or Torres Strait Islander heritage from your mother's side (1 or 2 grandparents) or father's side (1 or 2 grandparents)?	Mother's side ☐ 1 grandparent ☐ both grandparents	Father's side ☐ 1 grandparent ☐ both grandparents

	☐ don't know	☐ don't know
--	-------------------------------------	-------------------------------------

Medical history

1. Have you ever been told that you have a respiratory illness? *(tick all that apply)*

- ☐ Asthma
 ☐ Pneumonia
 ☐ Bronchiectasis
☐ Neonatal lung disease
 ☐ Lung cancer
 ☐ COPD (Chronic Obstructed Pulmonary Disease)
☐ Others (give details) _____

2. Have you ever been hospitalised or referred to a specialist doctor to treat any of the above? Give details of approximate dates if known.

3. Do you usually have a cough that brings up phlegm/sputum even when you don't have a cold or chest infection?

- ☐ No, only when I have a cold or chest infection
 ☐ Yes. How long for? _____

4. Do you currently have a chest infection?

- ☐ No
 ☐ Yes, how long for? _____

5. Are you currently on any medication?

- ☐ No
 ☐ Yes, please list

6. Have you ever smoked tobacco cigarettes?

- ☐ No, *Skip to question 9*
☐ Yes. In approximately what year did you start? _____

How many cigarettes per day did you smoke? _____

7. Are you currently smoking?

- ☐ No, in what year did you quit _____
 ☐ Yes, how many in the last 48 hours _____

8. Have you ever quit smoking?

- ☐ No
 ☐ Yes, for how long _____

9. Does anybody at your house usually smoke inside?

☐ No

☐ Yes, how many people _____

10. Have you ever worked in a job that you think may have affected your lung, e.g. mining?

☐ No

☐ Yes, Give details below

What

industry?

.....

How

long

did

you

work

there

for?

.....

Appendix C – HILTA Medical Chart Review Form

Medical Chart Review of Participants: Healthy Indigenous Lung Testing in Adults (HILTA) Study

Participant name			
Date of Birth			
Patient ID			
Location of Chart	☐ Hospital ☐ Community Medical/Health Centre ☐ Electronic record		
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				
COPD				
Pneumonia				
Chronic Bronchitis Wet productive cough >1 month				

Neonatal Lung Disease				
Lung Cancer				
Tuberculosis				
Other lung disease e.g. interstitial lung disease				
Other hospitalised Respiratory illness as a child (not captured above)				
Any other illness? ☐ Scabies ☐ Hayfever ☐ Eczema ☐ Tonsillitis ☐ Auto-immune disease ☐ Neuromuscular disease ☐ Hypertension ☐ Myocardial infarction ☐ Other cardiovascular ☐ Diabetes ☐ Obesity (BMI >30) ☐ Renal disease (if yes, type ____) ☐ Other (list below) _____ _____ _____ ☐ NONE				

2. Tobacco smoke exposure?

In-utero	No / Yes	Mother? Or Other family member?
Current smoker	No / Yes	Since when Pack years?
Other exposure (to family members)	No / Yes	Who?

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

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

4. Birth weight? _____(kg)

PARTICIPANT ASTHMA & ALLERGY QUESTIONNAIRE
Healthy Indigenous Lung Testing in adults

SECTION 1

1. Do you ever have trouble with your breathing? (Tick one box only)

never

☐

only rarely

☐

repeatedly, but it always gets completely better

☐

continuously, so that your breathing is never quite right

☐

2. Have you had wheezing or whistling in your chest at any time
in the past 12 months?

Yes

☐

No

☐

IF YOU HAVE ANSWERED “NO”, PLEASE SKIP TO SECTION 2

3. How many attacks of wheezing have you had **in the past 12 months?**

None

☐

1-3

☐

4-12

☐

more than 12

☐

4. **In the past 12 months,** how often, on average, has your sleep been disturbed
due to wheezing?

Never woken with wheezing

☐

Less than one night per week

☐

One or more nights per week

☐

5. Have you ever been breathless when the wheezing noise was present?

Yes

☐

- No ☐
6. **In the past 12 months**, how often, on average, has your sleep been disturbed due to shortness of breath?
- Never ☐
- Less than one night per week ☐
- One or more nights per week ☐
7. **In the past 12 months**, how often, on average, has your sleep been disturbed due to coughing?
- Never ☐
- Less than one night per week ☐
- One or more nights per week ☐
8. **In the past 12 months**, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?
- Yes ☐
- No ☐

SECTION 2

9. Have you ever had asthma?
- Yes ☐
- No ☐

IF YOU HAVE ANSWERED "NO", PLEASE SKIP TO SECTION 3

-
10. Was your asthma confirmed by a doctor?
- Yes ☐
- No ☐
11. Do you have a written plan which tells you how to look after your asthma?
- Yes ☐
- No ☐
12. How old were you when you had your first attack of asthma?

Years ☐

13. Have you had an attack of asthma **in the past 12 months?**

Yes ☐

No ☐

14. Have you used any inhaled medicines e.g. puffers to help your breathing at any time **in the past 12 months?** (when you did not have a cold)

Yes ☐

No ☐

If yes:

Please indicate how often you used each of the **inhaled** medicines listed below **in the past 12 months:**

only when needed / in short courses / every day

<i>Ventolin or Asmol</i>	☐	☐	☐
<i>Serevent or Onbrez</i>	☐	☐	☐
<i>Flixotide or Pulmicort</i>	☐	☐	☐
<i>Seretide or Symbicort</i>	☐	☐	☐

15. Have you used any tablets, capsules, liquids or other medicines e.g. pills that you swallowed to help your breathing at any time **in the past 12 months?** (when you didn't have a cold)

Yes ☐

No ☐

If yes:

Please indicate how often you used each of the tablets, capsules, liquids or other medicines e.g. pills (*use local terminology*) listed below **in the past 12 months:**

only when needed / in short courses / every day

<i>Montelukast</i>	☐	☐	☐
<i>Salbutamol (tablets)</i>	☐	☐	☐
<i>Nuelin</i>	☐	☐	☐
	☐	☐	☐

Prednisolone

16. **In the past 12 months**, how many times have you **urgently** been to a doctor because of your breathing problems?

None	1-3	4-12	more than 12
☐	☐	☐	☐

17. **In the past 12 months**, how many times have you **urgently** been to an Emergency Department without being admitted to hospital because of breathing problems?

None	1-3	4-12	more than 12
☐	☐	☐	☐

18. **In the past 12 months** how many times have you been admitted to hospital because of your breathing problems?

None	1	2	more than 2
☐	☐	☐	☐

19. **In the past 12 months**, how many days was your usual activity (at work or in the home) limited because you had breathing problems?

None	1-3	4-12	more than 12
☐	☐	☐	☐

SECTION 3

20. Have you ever worked in any job that caused wheezing or whistling in your chest?

Yes	☐
No	☐

If yes:

20a. Have you had to leave any of these jobs because they affected your breathing?

Yes ☐
No ☐

21. Have you ever had hay fever?

Yes ☐
No ☐

IF YOU HAVE ANSWERED “NO”, PLEASE SKIP TO QUESTION 23

22. Was your hay fever confirmed by a doctor?

Yes ☐
No ☐

If yes:

Have you ever had eczema?

Yes ☐
No ☐

23. Was your eczema confirmed by a doctor?

Yes ☐
No ☐

Appendix E – CHEST editorial accompanying Chapter Six

Kasi AS, Lesnick BL. Can We Prevent COPD by Reaching Out to Children at Risk? *Chest*. 2020;158(4):1327-8.

COPD is thought to arise from an accelerated decline in lung function with age, a failure to attain normal lung function at the conclusion of childhood growth, or a combination of these two factors. Childhood asthma, pulmonary infections, and maternal smoking increase the risk of suboptimal lung function in early adulthood.⁵⁴ The key to preventing a significant portion of adult COPD lies in normalizing lung development in children.

Perhaps nowhere are disparities in child health more evident than between indigenous and nonindigenous people living in affluent countries.⁹¹ Acute and chronic respiratory diseases are both more prevalent and severe in indigenous populations of Australia, the United States, and New Zealand. This results in more frequent hospitalizations and early mortality for those adversely affected.^{91,249-251} Redding et al²⁴⁹ have previously reported a prevalence of chronic suppurative lung disease/bronchiectasis in indigenous children in Australia and Alaska >100 times greater than that of European children. Such outcomes are likely functions of recurrent acute lower respiratory tract infections, overcrowding, indoor air pollution, poverty, and lack of access to high-quality specialist care.^{91,252} Although considerable resources would be required to correct the poverty, overcrowding, and indoor air pollution, a more directed approach might be to focus on access to high-quality specialist care. Remote locations, poverty, and cost of travel are all barriers to health-care access in these communities.^{91,250} A program designed to overcome these barriers might reduce the risk of poor pulmonary outcomes in disadvantaged children. Previous studies have demonstrated that early identification and prompt institution of therapies to reduce complications can prevent rapid decline in lung function.^{249,253} However, there have not been longitudinal data to demonstrate that access to specialty care can normalize pulmonary outcomes compared with those less disadvantaged. Indeed, a study demonstrating that a change in the trajectory of lung development can be accomplished with access to specialist care alone, without changing other social determinants of health, would be highly impactful. It would provide a path for a feasible and effective COPD prevention program.

In this issue of CHEST, Collaro et al¹⁷⁴ demonstrate precisely such a path. The authors report on the successful integration between pediatric respiratory specialist outreach services and local clinical teams in remote Australian communities with large populations of indigenous children. Their collaboration and longitudinal clinical care of children in remote communities led to lung function improvements comparable with children treated in tertiary hospital respiratory clinics.

Comparison of the change in spirometry Z-scores showed that both FEV₁ and FVC significantly improved in children with asthma and bronchiectasis managed at tertiary hospital and outreach clinics. In fact, the authors found no significant difference in spirometric improvements between children treated at outreach and tertiary hospital clinics during the study period.

The authors quantified the impact of their improvement by referencing work done in the adult setting. The Prospective Urban Rural Epidemiology (PURE) study, a large prospective multinational cohort study in adults, revealed that even mild reduction in FEV₁ that is in the clinically normal range is a predictor of morbidity and mortality.¹¹⁴ Collaro et al¹⁷⁴ compared the FEV₁ results of their cohort using the PURE study criteria and found that with longitudinal specialist care, there was a significant improvement in the number of children with no FEV₁ impairment (Z-score for FEV₁ ≥ 0) in both outreach and tertiary hospital clinics. In the outreach setting, 29 of 252 participants went from impairment to no impairment. Among the 134 participants who remained with some impairment on follow-up, 29 had improved their degree of severity, with 22 of those leaving the severe category and moving up to moderate, mild, or no impairment. Similar results were seen in the 2,249 participants treated in the tertiary hospital clinics. Although there remain children at both sites at risk for COPD and other morbidities, these improvements were substantial. The results were achieved by integrating the visiting specialty team with the local treating team and reviewing every child's clinical care after each clinic with the community doctor, nurse, and indigenous health worker. The bronchiectasis treatment was aligned with Australian guidelines, including airway clearance taught by a chest physiotherapist, long-term use of azithromycin, and prompt treatment of exacerbations including IV antibiotics when patients failed to improve with 4 weeks of oral antibiotics.

One limitation of the study is the retrospective design. We must also consider the generalizability of this intervention to other populations. Although the lung function results are limited to remote indigenous communities in Australia, previous studies in multinational cohorts of indigenous children have also reported on the benefits of comprehensive outreach care to improve respiratory outcomes.^{249,253} In the United States, a large pediatric study showed that access to health care improved between 2000 and 2014, including the vulnerable population groups that showed greater gains. Although improved, the unmet health-care needs of children (5.8% in 2014) is still a substantial number.²⁵⁴ These gains may be at risk with current deteriorating economic conditions. It is tempting to speculate that culturally sensitive outreach programs for children in the United States might reduce the subsequent burden of lung disease in adults.

Correcting all the social determinants of health in children would be a Herculean effort. Collaro et al¹⁷⁴ have shown us that a more directed approach, just providing high-quality specialty care, can have a huge impact. The maxim of an ounce of prevention being worth a pound of cure is apt. For COPD, investing in the health of disadvantaged children can save pounds, dollars, and euros.

Appendix F – Pediatric Pulmonology editorial accompanying Chapter 12

Mozun R, Berger F, Singer F. One size does not fit all-Why do pediatric spirometry estimates vary across populations "down under"? *Pediatr Pulmonol.* 2022;57(2):345-6.

Spirometry is the reference standard technique to estimate airflow and lung volumes, which may be reduced in individuals with obstructive or restrictive lung diseases. To classify spirometry indices, we need to define upper and lower limits of normal usually set at ± 1.645 Z-score. The Global Lung Function Initiative (GLI) developed reference equations that allow standardized interpretation of spirometry results.⁹ GLI references account for known drivers of physiological lung function variability: age, sex, height, and ethnicity including White, Black, North East Asian, South East Asian, and other or mixed ethnicities.⁹ Main reason for ethnic differences in lung function includes genetic and anthropometric factors such as height, sitting-height standing-height ratio (Cormic index), weight, and body composition.^{15,218,255} However, not all ethnic groups were included in the GLI population and it is recommended to validate the equations locally.²⁵⁶ If GLI equations do not appropriately fit a given population, over- or underestimation of predicted spirometry values may occur and individuals may be misclassified as either having falsely normal or abnormal lung function.

In this issue, Collaro et al.²³² studied if the Cormic index differed between 619 First Nations Australian children and 907 White North American children and whether this difference was associated with lower lung function in First Nations than in White children. This study sheds further light on possible ethnicity-driven differences in lung function between First Nations and White children. They found an 8%–10% predicted lower forced expiratory volume in 1s (FEV₁) and forced vital capacity (FVC) in First Nations than in White children. First Nations children also had a lower Cormic index than White children, which explained differences in FEV₁ and FVC among 8–11-year-old children by 14% and 15%, respectively, and among 12–16-year-old adolescents by 26% and 31%. Predicted GLI reference values for other or mixed ethnicities are lower than those for Whites, and Blake et al.²⁰ showed that they provided a good fit to the lung function of contemporary First Nations children. The results of Collaro et al. suggest that reasons for the lower lung function in First Nations children compared to White children must include other intrinsic or extrinsic determinants besides anthropometric factors like height and Cormic index. This has potentially relevant implications for clinical care and public health programs, as it may affect spirometry interpretation.

Intrinsic factors like pubertal status and anthropometric measurements other than Cormic index were not assessed in participants of the study by Collaro et al., as is the case in many other

epidemiological studies. During puberty, there is a dysanaptic growth of the lungs and airways, and the timing of puberty may vary between ethnic groups.^{15,257} This can affect spirometry outcomes, although part of the differences in lung function between ethnic groups due to pubertal status may be partially explained by changes in the upper segment of the body, which is included in the Cormic index.¹⁵ Other anthropometric factors like weight or body composition such as fat mass may also systematically differ between ethnic groups. Some studies indicate that body composition can influence lung function in children and adults^{218,258,259} while others suggest that this effect is negligible.²²⁷ Collaro et al. frankly acknowledged that samples of White and First Nations children were collected 20 years apart, and secular time trends are known to affect the timing of puberty, anthropometric characteristics, and lung function.²⁴¹

Extrinsic conditions like socioeconomic deprivation and environmental exposures such as pollution can lead to reduced lung function and lung growth in children. Some populations may be exposed to unfavourable living conditions more often.²⁵⁹ Children exposed to socioeconomic disadvantage and environmental risk factors may have lower lung function than those unexposed.⁴ For example, Sonnappa et al.²¹⁸ found that lung function of healthy urban children living in India was comparable to that of healthy Indian children living in the United Kingdom but higher than that of healthy rural and semiurban children living in India. Those living in rural and semiurban areas were exposed to tobacco and biomass smoke more often than those living in urban areas. In addition, muco-obstructive lung diseases such as protracted bacterial bronchitis or bronchiectasis are more prevalent in First Nations children, than in White children and adults.^{3,227} Both questionnaires on symptoms and spirometry may underestimate the presence of muco-obstructive lung disease. This could contribute to systematically lower lung function in First Nations children at the population level, although at the individual level some children with muco-obstructive lung diseases may still have normal spirometry values. Yet, multi-slice chest imaging to rule out subclinical muco-obstructive lung disease is rarely done,²²⁷ and may not be feasible in pediatric epidemiological studies.

We would like spirometry reference values to account as good as possible for intrinsic variability between ethnic groups. This is, however, complex, since ethnicity is a social construct that is difficult to measure, populations often are ethnically mixed, and different ethnic groups may be exposed to extrinsic factors in diverse ways. In addition, there is no uniform consensus on how to select healthy participants in studies done to create or assess fit of reference equations.²⁶⁰ Heterogeneity in health status across studies hampers comparability between studies and collation of data.²⁶¹ Furthermore, disentangling sources of differences in physiological estimates between

ethnic groups is a challenge not only for pediatric spirometry but also for echocardiography, since the growth of the lungs and heart progresses nonlinearly through time.²⁶²

In conclusion, we need to be cautious when collecting, interpreting, and collating normative physiological data across diverse populations. Investigating determinants and potential confounders of physiological estimates across diverse populations will ensure appropriate interpretation of the dynamic physiology in children.