

## ORIGINAL ARTICLE

# Association between perinatal and early life exposures and lung function in Australian Indigenous young adults: The Aboriginal Birth Cohort study

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## Abstract

**Background and Objective:** Despite the high burden of respiratory disease amongst Indigenous populations, prevalence data on spirometric deficits and its determinants are limited. We estimated the prevalence of abnormal spirometry in young Indigenous adults and determined its relationship with perinatal and early life factors.

**Methods:** We used prospectively collected data from the Australian Aboriginal Birth Cohort, a birth cohort of 686 Indigenous Australian singletons. We calculated the proportion with abnormal spirometry (z-score <−1.64) and FEV<sub>1</sub> below the population mean (FEV<sub>1</sub>% predicted 0 to −2SD) measured in young adulthood. We evaluated the association between perinatal and early life exposures with spirometry indices using linear regression.

**Results:** Fifty-nine people (39.9%, 95%CI 31.9, 48.2) had abnormal spirometry; 72 (49.3%, 95%CI 40.9, 57.7) had a FEV<sub>1</sub> below the population mean. Pre-school hospitalisations for respiratory infections, younger maternal age, being overweight in early childhood and being born remotely were associated with reduced FEV<sub>1</sub> and FVC (absolute, %predicted and z-score). The association between maternal age and FEV<sub>1</sub> and FVC were stronger in women, as was hospitalization for respiratory infections before age 5. Being born remotely had a stronger association with reduced FEV<sub>1</sub> and FVC in men. Participants born in a remote community were over 6 times more likely to have a FEV<sub>1</sub> below the population mean (odds ratio [OR] 6.30, 95%CI 1.93, 20.59).

**Conclusion:** Young Indigenous adults have a high prevalence of impaired lung function associated with several perinatal and early life factors, some of which are modifiable with feasible interventions.

## KEYWORDS

aboriginal adults, Australian Aboriginal Birth Cohort, cross-sectional study, early life risk factors, Indigenous adults, lung function, perinatal risk factors, spirometry

## INTRODUCTION

Morbidity and mortality from respiratory diseases amongst Indigenous populations worldwide are recognized to be high.<sup>1–5</sup> Within Australia, respiratory morbidity and mortality in Indigenous people are considerably higher than the non-Indigenous population.<sup>6–12</sup> Data on chronic respiratory

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disease, prevalence of lung function abnormalities and their natural history amongst Indigenous adults in the community are limited. Current literature consist of older cohorts, describe chronic lung disease<sup>6,8,13–15</sup> and have not corrected for ethnicity differences when calculating predicted values.<sup>8,13</sup> These data have limited generalisability as lung function, spirometry references values<sup>12,16</sup> and outcomes are different in Indigenous people.<sup>12</sup>

There is an independent relationship between lung function impairment and future cardiovascular morbidity and mortality.<sup>17,18</sup> A large study demonstrated those with low lung function had increased risk of respiratory and cardiovascular abnormalities and higher all-cause mortality, independent of smoking exposure.<sup>17</sup> Another study showed FEV<sub>1</sub> was an independent predictor of cardio-respiratory morbidity and all-cause mortality, even in those with sub-clinical FEV<sub>1</sub> impairment.<sup>18</sup> Thus, estimating the prevalence of lung function impairment amongst Indigenous Australians is vital. There are limited data, with only one study investigating the association between perinatal and factors related to childhood environment and childhood lung function.<sup>19</sup>

Without any prospectively collected data from community-based Indigenous adults, we analysed data from a large birth cohort of Indigenous Australians. Our aims were to (i) describe spirometry patterns seen in young Indigenous adults, including estimating mean values for FEV<sub>1</sub>, forced vital capacity (FVC) and (ii) evaluate the association between perinatal and early life exposures with spirometric parameters.

## METHODS

### Study population

The Australian Aboriginal Birth Cohort (ABC) is a birth cohort of singleton babies born to mothers who self-identified as either Aboriginal or Torres Strait Islanders. Detailed information on recruitment and follow-up of this cohort is previously published.<sup>20</sup> The cohort consists of 686 live-born singleton Indigenous Australians (recruited 1981–1990) living in over 40 urban and remote communities across the Northern Territory (NT). Remote communities vary in size from approximately 200–2000 people, including outstations (<50 people). Follow-up has occurred every 5–7 years. Ethical approval was given by the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research, including the Aboriginal Ethical Sub-committee which has the power of veto (ABC Reference No: 2013-2022). Informed written consent was obtained from all participants.

### Data collection

Between 2014 and 2016, participants were seen at community centres, health centres and private homes. Follow-up information was conducted using standardized procedures,

## SUMMARY AT A GLANCE

Our study provides first estimates on the proportion of Indigenous Australians with abnormal spirometry and FEV<sub>1</sub> below the population mean. We also demonstrate maternal and early childhood factors associated with impaired lung function. The findings contribute to the evidence in support of optimization of respiratory health in early childhood.

using structured questionnaires via face-to-face interviews. Data collected included demographics, anthropometry, physical health assessment, spirometry, venous blood sampling and non-invasive ultrasound scans (thyroid, kidney and carotid intima-media artery thickness). Perinatal and birth data were recorded at initial recruitment by a neonatal paediatrician or an Indigenous research assistant. Details of maternal medical and/or obstetric history, birth measurements, childhood anthropometric measurements and hospital admissions were extracted from medical records.

Spirometry was undertaken using a portable spirometer (EasyOne™ ndd Medical Technologies, Andover, MA) in accordance with current guidelines.<sup>21</sup> All flow-volume loops were later independently reviewed and inspected by two respiratory physicians (DLF and VN) and only ones that were independently considered acceptable quality by both were included in the final analysis.

## Definition of outcomes

Using the Global Lung Initiative (GLI) reference equations for 'other/mixed' populations, we calculated the number of individuals with airflow obstruction (FEV<sub>1</sub>/FVC < lower limit of normal [LLN]), restrictive (FEV<sub>1</sub>/FVC ≥ LLN and FVC < LLN) or mixed spirometry (FEV<sub>1</sub>/FVC < LLN and FVC < LLN). This reference equation has been demonstrated to be the best fit for Indigenous ab Australian children and young adults.<sup>22</sup> We also calculated FEV<sub>1</sub>% predicted, FVC% predicted, FEV<sub>1</sub>/FVC ratio, FEV<sub>1</sub> z-score (zFEV<sub>1</sub>), FVC z-score (zFVC) and FEV<sub>1</sub>/FVC ratio z-score (zFEV<sub>1</sub>/FVC).

We stratified spirometry based on FEV<sub>1</sub>% predicted of between 0 and −2 standard deviations (SD) from the population mean. Although current practice only considers values of FEV<sub>1</sub>% predicted of greater than −2SD to be clinically abnormal,<sup>23</sup> FEV<sub>1</sub>% predicted in the clinically normal range (FEV<sub>1</sub>% predicted of 0 to −2SD), has been shown to be associated with worse morbidity and mortality.<sup>18</sup>

## Definition of exposures

Perinatal exposures examined were chosen a priori following literature review and included maternal body mass index

(BMI), smoking during pregnancy, maternal age, birth-weight, place of residence at birth, hospital admissions for respiratory infections under the ages of 2 and 5 and World Health Organization (WHO) weight-for-age z-scores for early childhood ( $\leq 5$  years).

BMI was calculated ( $\text{kg}/\text{m}^2$ ) and classified according to current guidelines.<sup>24</sup> The WHO provides child growth measures standardized by age and sex using z-scores. This describes where an observation falls within a number of standard deviations of the population mean.<sup>25,26</sup> The WHO weight-for-age z-scores were calculated using the formula outlined in the WHO database on child growth and malnutrition.<sup>27</sup> All recorded weights up to and including age 5 were included and in individuals with multiple records, the closest weight recorded to age 5 was used to calculate weight-for-age z-scores.

## Statistical analysis

We used linear regression to examine associations between perinatal and early life exposures with  $\text{FEV}_1$ , FVC,  $\text{FEV}_1\%$  predicted, FVC% predicted,  $\text{FEV}_1/\text{FVC}$  ratio,  $\text{zFEV}_1$ ,  $\text{zFVC}$  and  $\text{zFEV}_1/\text{FVC}$  ratio as individual outcomes in turn.

For  $\text{FEV}_1$  and FVC, age, sex, height and smoking were identified as a priori confounders. For  $\text{FEV}_1\%$  predicted, FVC% predicted,  $\text{FEV}_1/\text{FVC}$  ratio,  $\text{zFEV}_1$ ,  $\text{zFVC}$  and  $\text{zFEV}_1/\text{FVC}$  ratio, smoking status was an a priori confounder. We used Directed Acyclic Graphs to identify other possible confounders and establish minimally sufficient adjustment sets.<sup>28</sup> We repeated the analyses, stratifying by sex.

Maternal age, birthweight and weight-for-age-z-scores for early childhood weight were initially treated as continuous variables after confirming the linear term best fit the statistical model. We repeated the analyses with these exposures as tertiles, modelling them as categorical variables so that non-linear associations were not missed. All other exposure variables were categorized.

Likelihood ratio tests were used for all hypothesis testing. Analyses were conducted using Stata v15 (College Station, TX, USA). A  $p$ -value of  $<0.05$  was considered significant.

## RESULTS

### Study population

Four hundred and fifty-nine (70.7%) participants were followed up, of which spirometry was carried out on 312. Following review of the flow-volume loops, 148 spirometry traces were included in subsequent analyses (Figure 1). Fifty-nine out of 148 (39.9%, 95% CI 31.9–48.2) people had abnormal spirometry—38 restrictive ( $\text{FEV}_1/\text{FVC} \geq \text{LLN}$  and  $\text{FVC} < \text{LLN}$ ), 14 obstructive ( $\text{FEV}_1/\text{FVC} < \text{LLN}$ ) and 7 mixed ( $\text{FEV}_1/\text{FVC} < \text{LLN}$  and  $\text{FVC} < \text{LLN}$ ) (Table 1).

Mean age was 25.8 years (SD: 1.1) and 74 (50%) were male. Majority were current smokers (62.8%), lived in

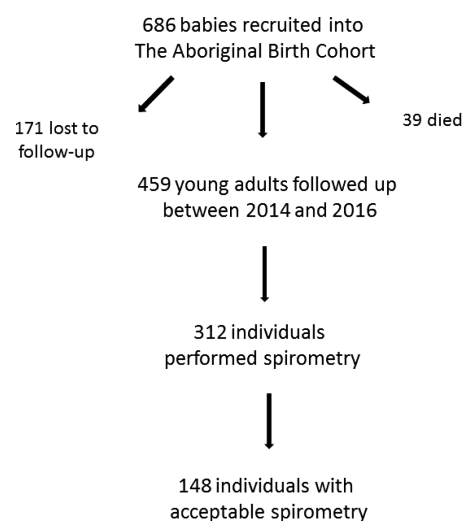


**FIGURE 1** Flow diagram of the Australian Aboriginal Birth Cohort (ABC) participants.

remote communities (68.9%) and dependent on benefits as their main income (58.8%) (Table 1). Participants without acceptable spirometry traces were more likely to be female, a current smoker, live in a remote location and dependent on benefits (Table 1).

After adjusting for age and height, mean  $\text{FEV}_1$  for men and women was 3.0 litres (95% CI 2.9–3.2) and 2.9 litres (95%CI 2.8–3.0), respectively. We found clinically abnormal  $\text{FEV}_1$  in 57 (38.5%, 95%CI 30.6–46.9) and FVC in 50 (33.8%, 95%CI 26.2–42.0) participants.

### Association between perinatal and early life exposures with lung function

Maternal age, respiratory hospitalisations in early childhood, and place of residence at birth was strongly associated with  $\text{FEV}_1$ ,  $\text{FEV}_1\%$  predicted, FVC and FVC% predicted, but not with  $\text{FEV}_1/\text{FVC}$  ratio (Table 2). Older maternal age was associated with better spirometry indices whilst respiratory hospitalisations (both for  $<2$  and  $<5$  years) and residing in a remote region were associated with reduced spirometry indices. When using the outcomes  $\text{zFEV}_1$  and  $\text{zFVC}$ , our findings were similar but additionally childhood weight z-scores were associated with  $\text{zFEV}_1/\text{FVC}$  (Table 2).

The highest tertile, maternal age between 26 and 42 years, was strongly associated with higher  $\text{FEV}_1$ ,  $\text{FEV}_1\%$  predicted, FVC and FVC% predicted (Table 3). We also found that obese or overweight children (WHO early childhood weight-for-age z-score 0.55–2.24) had lower  $\text{FEV}_1$ ,  $\text{FEV}_1\%$  predicted, FVC and FVC% predicted (see Table 3). Similar trends were seen with z-scores of  $\text{FEV}_1$ ,  $\text{zFVC}$  and  $\text{FEV}_1/\text{FVC}$  (Table S1 in the Supporting Information).

After stratifying for sex, we found the association between maternal age and  $\text{FEV}_1$ ,  $\text{zFEV}_1$ , FVC and  $\text{zFVC}$  were stronger in women, as was hospitalization for

**TABLE 1** Demographics of the Aboriginal Birth Cohort.

| Characteristic                                                                 |                                | Excluded from<br>final analyses<br>( <i>n</i> = 164) | Included in the<br>final ( <i>n</i> = 148) | Men ( <i>n</i> = 74) | Women ( <i>n</i> = 74) |
|--------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------|--------------------------------------------|----------------------|------------------------|
| Mean age (SD)                                                                  |                                | 25.7 (1.0)                                           | 25.8 (1.1)                                 | 25.9 (1.0)           | 25.6 (1.1)             |
| Gender (%)                                                                     |                                | 74 (45.1)                                            |                                            | 74 (5)               | 74 (50)                |
| Smoking habit (%)                                                              | Never smoked                   | 90 (54.9)                                            | 34 (23)                                    | 16 (21.6)            | 18 (24.3)              |
|                                                                                | Ex-smoker                      | 32 (19.5)                                            | 8 (5.4)                                    | 4 (5.4)              | 4 (5.4)                |
|                                                                                | Current smoker                 | 4 (2.4)                                              | 93 (62.8)                                  | 48 (64.9)            | 45 (60.8)              |
|                                                                                | Missing                        | 116 (70.7)                                           | 13 (8.8)                                   | 6 (8.1)              | 7 (9.5)                |
| Current place of residence (%)                                                 | Urban                          | 12 (7.3)                                             | 46 (31.1)                                  | 27 (36.5)            | 19 (25.7)              |
|                                                                                | Remote                         | 17 (10.4)                                            | 102 (68.9)                                 | 47 (63.5)            | 55 (74.3)              |
| Main source of income (%)                                                      | Employment                     | 147 (89.6)                                           | 56 (37.8)                                  | 34 (46.0)            | 22 (29.7)              |
|                                                                                | Family                         | 35 (21.3)                                            | 4 (2.7)                                    | 2 (2.7)              | 2 (2.7)                |
|                                                                                | Benefits                       | 2 (1.2)                                              | 87 (58.8)                                  | 38 (51.3)            | 49 (66.2)              |
|                                                                                | Missing                        | 123 (75.0)                                           | 1 (0.7)                                    | -                    | 1 (1.4)                |
| Mean FEV <sub>1</sub> (litres) (95% CI)                                        |                                | 1 (0.6)                                              | 2.9 (2.7–3.1)                              | 3.0 (2.9–3.2)        | 2.9 (2.7–3.0)          |
| Mean FEV <sub>1</sub> % predicted (SD)                                         |                                | 80 (48.8)                                            | 82.5 (14.5)                                | 81.6 (14.2)          | 83.3 (14.8)            |
| Mean FEV <sub>1</sub> z-score (SD)                                             |                                | 19 (11.6)                                            | −1.44 (1.19)                               | −1.51 (1.17)         | −1.37 (1.21)           |
| Mean FVC (litres) (95% CI)                                                     |                                | 15 (9.2)                                             | 3.6 (3.3–3.9)                              | 3.7 (3.6–3.9)        | 3.4 (3.3–3.6)          |
| Mean FVC% predicted (SD)                                                       |                                | 50 (30.5)                                            | 85.9 (14.0)                                | 85.1 (13.9)          | 86.6 (14.2)            |
| Mean FVC z-score (SD)                                                          |                                | 71 (43.2)                                            | −1.25 (1.24)                               | −1.35 (1.25)         | −1.16 (1.23)           |
| Mean FEV <sub>1</sub> /FVC (SD)                                                |                                | 68 (41.4)                                            | 0.80 (0.09)                                | 0.79 (0.09)          | 0.80 (0.09)            |
| Mean FEV <sub>1</sub> /FVC z-score (SD)                                        |                                | 25 (15.2)                                            | −0.57 (1.15)                               | −0.48 (1.14)         | −0.66 (1.16)           |
| Obstructive defect (FEV <sub>1</sub> /FVC < LLN) <i>n</i> (%)                  |                                | 22.9 (5.4)                                           | 14 (9.5)                                   | 6 (8.18)             | 8 (10.8)               |
| Restrictive defect<br>(FEV <sub>1</sub> /FVC ≥ LLN and FVC < LLN) <i>n</i> (%) |                                | 3059.8 (511.3)                                       | 38 (25.7)                                  | 24 (32.4)            | 14 (18.9)              |
| Mixed defect<br>(FEV <sub>1</sub> /FVC < LLN and FVC < LLN) <i>n</i> (%)       |                                | 118 (72.0)                                           | 7 (4.7)                                    | 2 (2.7)              | 5 (6.8)                |
| Maternal Body Mass Index (BMI) (%)                                             | Normal                         | 46 (28.0)                                            | 60 (40.5)                                  | 33 (44.6)            | 27 (36.5)              |
|                                                                                | Underweight (BMI < 18.5)       | 108 (65.9)                                           | 14 (9.5)                                   | 5 (6.8)              | 9 (12.2)               |
|                                                                                | Overweight or obese (BMI ≥ 25) | 56 (34.2)                                            | 23 (15.5)                                  | 12 (16.2)            | 11 (14.9)              |
|                                                                                | Missing                        | 135 (82.3)                                           | 51 (34.5)                                  | 24 (32.4)            | 27 (36.5)              |
| Maternal smoking during pregnancy (%)                                          | Never smoked                   | 8 (4.9)                                              | 57 (38.5)                                  | 29 (39.2)            | 28 (37.8)              |
|                                                                                | Smoked                         | 21 (12.8)                                            | 76 (51.4)                                  | 36 (48.7)            | 40 (54.1)              |
|                                                                                | Missing                        | −0.08 (0.87)                                         | 15 (10.1)                                  | 9 (12.2)             | 6 (8.1)                |
| Maternal age (SD)                                                              |                                |                                                      | 23.2 (6.6)                                 | 23.2 (6.9)           | 23.2 (6.4)             |
| Birthweight (grams) (SD)                                                       |                                |                                                      | 3011.7 (615.8)                             | 3108.0 (618.5)       | 2915.4 (602.0)         |
| Any respiratory hospitalizations ≤ 2 years                                     | None                           |                                                      | 106 (71.6)                                 | 50 (67.6)            | 56 (75.7)              |
|                                                                                | 1 or more                      |                                                      | 42 (28.4)                                  | 24 (32.4)            | 18 (24.3)              |
| Any respiratory hospitalizations ≤ 5 years                                     | None                           |                                                      | 99 (66.9)                                  | 48 (64.9)            | 51 (68.9)              |
|                                                                                | 1 or more                      |                                                      | 49 (33.1)                                  | 26 (35.1)            | 23 (31.1)              |
| Place of residence at birth                                                    | Remote                         |                                                      | 109 (73.7)                                 | 54 (73.0)            | 55 (74.3)              |
|                                                                                | Urban                          |                                                      | 27 (18.2)                                  | 13 (17.6)            | 14 (18.9)              |
|                                                                                | Missing                        |                                                      | 12 (8.1)                                   | 7 (9.5)              | 5 (6.8)                |
| WHO child weight z-scores <sup>a</sup> (SD)                                    |                                |                                                      | 0.12 (1.1)                                 | 0.07 (0.82)          | 0.18 (1.3)             |

Abbreviation: WHO, World Health Organization.

<sup>a</sup>The WHO child growth standards provides child growth measures (e.g., height, weight) standardized by age and sex using z-scores or standard deviation scores. This describes where an observation falls within a number of standard deviations of the population mean. z-scores are on a linear scale, with the same interval between values across the distribution.<sup>25,26</sup>

T A B L E 2 Effect of perinatal and early life exposures on FEV<sub>1</sub>, FEV<sub>1</sub>% predicted, FEV<sub>1</sub> z-scores, FVC, FVC% predicted, FVC z-score, FEV<sub>1</sub>/FVC ratio and FEV<sub>1</sub>/FVC z-score.

| Perinatal or early life exposure                        | FEV <sub>1</sub> (mLs) (95% CI) | FEV <sub>1</sub> % predicted (95% CI) | FEV <sub>1</sub> z-score (95% CI) | FVC (mLs) (95% CI)      | FVC% predicted (95% CI) | FVC z-score (95% CI)  | FEV <sub>1</sub> /FVC (95% CI) | FEV <sub>1</sub> /FVC z-score (95% CI) |
|---------------------------------------------------------|---------------------------------|---------------------------------------|-----------------------------------|-------------------------|-------------------------|-----------------------|--------------------------------|----------------------------------------|
| Maternal Body Mass Index <sup>c</sup>                   |                                 |                                       |                                   |                         |                         |                       |                                |                                        |
| Underweight (BMI < 18.5)                                | 187.8 (−109.6, 485.2)           | 6.1 (−2.2, 14.3)                      | 0.51 (−0.17, 1.18)                | 190.2 (−175.8, 556.2)   | 6.1 (−2.6, 14.7)        | 0.54 (−0.24, 1.31)    | 0.02 (−0.03, 0.06)             | 0.54 (−0.24, 1.32)                     |
| Overweight or obese (BMI ≥ 25)                          | 48.8 (−215.7, 313.3)            | 3.4 (−3.8, 10.7)                      | 0.27 (−0.33, 0.87)                | 107.4 (−181.6, 396.4)   | 4.2 (−2.5, 11.0)        | 0.30 (−0.31, 0.92)    | −0.02 (−0.06, 0.02)            | 0.30 (−0.32, 0.92)                     |
| Maternal smoking <sup>a</sup>                           |                                 |                                       |                                   |                         |                         |                       |                                |                                        |
| Smoked during pregnancy                                 | −49.6 (−233.0, 133.8)           | −1.9 (−7.0, 3.2)                      | 0.11 (−0.31, 0.53)                | −77.7 (−282.3, 126.8)   | −2.4 (−7.2, 2.4)        | 0.21 (−0.22, 0.64)    | −0.01 (−0.03, 0.02)            | 0.21 (−0.22, 0.64)                     |
| Maternal age <sup>a</sup>                               |                                 |                                       |                                   |                         |                         |                       |                                |                                        |
| 18.3 (5.4, 31.3)                                        |                                 | 0.6 (0.2, 0.9)                        | 0.04 (0.01, 0.07)                 | 22.1 (7.6, 36.7)        | 0.5 (0.3, 0.8)          | 0.05 (0.02, 0.08)     | −0.01 (−0.03, 0.02)            | −0.01 (0.04, 0.03)                     |
| Birthweight <sup>b</sup> (g)                            | 0.43 (−1.2, 2.0)                | 0.2 (−0.2, 0.6)                       | 0.002 (−0.001, 0.005)             | 0.51 (−1.4, 2.4)        | 0.1 (−0.1, 0.5)         | 0.005 (−0.003, 0.006) | −0.02 (−0.04, 0.02)            | −0.007 (−0.004, 0.003)                 |
| Any respiratory hospitalizations ≤ 5 years <sup>c</sup> | −185.5 (−377.2, −6.2)           | −5.2 (−10.4, −0.4)                    | −0.41 (−0.84, −0.03)              | −275.8 (−497.3, −54.2)  | −6.1 (−11.2, −0.98)     | −0.54 (−1.02, −0.07)  | 0.01 (−0.02, 0.04)             | 0.08 (−0.37, 0.53)                     |
| Any respiratory hospitalizations ≤ 5 years <sup>c</sup> | −216.0 (−396.7, −35.3)          | −5.5 (−10.5, −0.5)                    | −0.43 (−0.84, −0.02)              | −285.0 (−496.2, −73.8)  | −6.6 (−11.5, −1.6)      | −0.57 (−1.02, −0.12)  | 0.01 (−0.02, 0.04)             | 0.07 (−0.36, 0.49)                     |
| Place of residence at birth                             |                                 |                                       |                                   |                         |                         |                       |                                |                                        |
| Remote                                                  | −435.6 (−667.1, −203.9)         | −13.7 (−20.0, −7.5)                   | −1.12 (−1.63, −0.62)              | −577.1 (−842.1, −312.1) | −15.7 (−21.8, −9.7)     | −1.33 (−1.88, −0.77)  | −0.02 (−0.05, 0.02)            | 0.23 (−0.32, 0.79)                     |
| WHO childhood weight-for-age z-scores <sup>d,e</sup>    | −68.2 (−177.9, 41.7)            | −1.2 (−4.2, 1.7)                      | −0.15 (−0.39, 0.10)               | −9.7 (−142.0, 122.6)    | 0.5 (−0.1, 0.2)         | −0.02 (−0.30, 0.26)   | −0.02 (−0.03, 0.01)            | −0.27 (−0.53, −0.01)                   |

Note: FEV<sub>1</sub> and FVC were adjusted for age, sex, height and smoking status. FEV<sub>1</sub>, FVC% predicted and FEV<sub>1</sub>/FVC were adjusted for smoking status. Bolded text and values represent exposures and outcomes that are statistically significant.

<sup>a</sup>Adjusted for place of residence at birth.

<sup>b</sup>Adjusted for maternal BMI.

<sup>c</sup>Adjusted for birthweight.

<sup>d</sup>Adjusted for any respiratory hospitalizations ≤ 5 years.

<sup>e</sup>Maternal age, birthweight and WHO childhood weight-for-age z-scores analysed as continuous variable.

**TABLE 3** Effect of maternal age, birthweight and childhood weight Z-scores analysed as categorical variables (tertiles) on FEV<sub>1</sub>, FEV<sub>1</sub>% predicted, FVC, FVC% predicted and FEV<sub>1</sub>/FVC ratio.

| Perinatal or early life exposure                              | Category based on tertiles | FEV <sub>1</sub> (mLs) (95% CI) | FEV <sub>1</sub> % predicted (95% CI) | FVC (mLs) (95% CI)            | FVC% predicted (95% CI)  | FEV <sub>1</sub> /FVC (95% CI) |
|---------------------------------------------------------------|----------------------------|---------------------------------|---------------------------------------|-------------------------------|--------------------------|--------------------------------|
| <b>Maternal age<sup>a</sup> (years)</b>                       | 14–19                      | Baseline                        | Baseline                              | Baseline                      | Baseline                 | Baseline                       |
|                                                               | 20–25                      | 121.9 (–85.5, 329.3)            | 2.4 (–3.3, 8.2)                       | 232.6 (1.2, 464.0)            | 2.8 (–2.7, 8.3)          | –0.01 (–0.05, 0.02)            |
|                                                               | <b>26–42</b>               | <b>252.6 (52.3, 472.9)</b>      | <b>7.2 (1.4, 13.1)</b>                | <b>374.5 (134.4, 614.6)</b>   | <b>8.4 (2.7, 14.1)</b>   | <b>–0.01 (–0.04, 0.02)</b>     |
| Birthweight <sup>b</sup> (grams)                              | 1200–2860                  | Baseline                        | Baseline                              | Baseline                      | Baseline                 | Baseline                       |
|                                                               | 2870–3250                  | –134.2 (–349.0, 80.6)           | –3.0 (–9.0, 3.1)                      | –118.6 (–377.6, 140.5)        | –1.2 (–7.5, 5.1)         | –0.02 (–0.05, 0.02)            |
|                                                               | 3260–4930                  | 52.1 (–192.1, 296.3)            | 0.8 (–6.1, 7.6)                       | 92.2 (–195.0, 379.4)          | 1.8 (–5.1, 8.8)          | –0.01 (–0.04, 0.02)            |
| <b>WHO early childhood weight-for-age z-score<sup>c</sup></b> | –2.15 to –0.34             | Baseline                        | Baseline                              | Baseline                      | Baseline                 | Baseline                       |
|                                                               | –0.33 to 0.52              | –18.7 (–242.1, 204.8)           | –0.4 (–6.6, 5.9)                      | 101.6 (–161.6, 364.9)         | 3.7 (–2.6, 10.0)         | <b>–0.03 (–0.07, –0.01)</b>    |
|                                                               | <b>0.55 to 2.24</b>        | <b>–250.0 (–476.1, –19.8)</b>   | <b>–6.8 (–13.2, –0.4)</b>             | <b>–135.3 (–408.5, 137.8)</b> | <b>–3.6 (–10.1, 3.0)</b> | <b>–0.04 (–0.07, –0.01)</b>    |

Note: FEV<sub>1</sub> and FVC were adjusted for age, sex, height and smoking status. FEV<sub>1</sub>, FVC% predicted and FEV<sub>1</sub>/FVC were adjusted for smoking status. Bolded text and values represent exposures and outcomes that are statistically significant.

<sup>a</sup>Adjusted for place of residence at birth.

<sup>b</sup>Adjusted for maternal BMI.

<sup>c</sup>Adjusted for any respiratory hospitalizations ≤5 years.

respiratory infections before aged 5 years (see Table 4; Table S2). Birth in a remote area however had a stronger association with reduced FEV<sub>1</sub>, zFEV<sub>1</sub>, FVC and zFVC in men (Table 4; Table S2 in the Supporting Information).

## Lung function below the population mean

Seventy-two of the 148 participants (49.3%, 95%CI 40.9–57.7) had a FEV<sub>1</sub>% predicted below the population mean (FEV<sub>1</sub>% predicted 0 to –2SD) and 2 had clinically abnormal FEV<sub>1</sub> (FEV<sub>1</sub>% predicted < –2SD). Participants living in a remote community at birth were >6 times more likely to have FEV<sub>1</sub> below the population mean (odds ratio 6.30, 95%CI 1.93–20.59) compared to those with normal FEV<sub>1</sub>.

## DISCUSSION

To our knowledge, this is the first prospective longitudinal study to describe spirometry patterns and examine perinatal and early life factors amongst Indigenous young adults. Our study has three main findings: first, almost 40% of Indigenous adults had abnormal lung function based on current spirometry classifications.<sup>23</sup> Second, increasing maternal age was associated with higher lung function but pre-school hospitalisations for respiratory infections and living in a remote community were associated with lower lung function in early adulthood. The highest tertile of the WHO weight-for-age z-score in early childhood was also strongly associated with lower lung function. Additionally, we found effect modification by sex. Third, a substantial proportion had aFEV<sub>1</sub> below the population mean and were more than six times more likely to live in remote communities. On the basis of these findings, we estimate that two in five Indigenous adults will have abnormal spirometry and up to half

will have a FEV<sub>1</sub> below the population mean, which confers a higher risk of premature all-cause mortality and cardio-respiratory morbidity.<sup>18</sup>

There are limited data on lung function impairment in Indigenous populations. Existing evidence from cross-sectional studies describe lung function in older cohorts,<sup>6,8,13,15</sup> have included people with chronic respiratory disease,<sup>8,13</sup> and have used Caucasian reference equations.<sup>6,13</sup> The latter is important as a recent systematic review showed the use of reference values without correction for ethnicity does not accurately estimate lung function impairment in the Indigenous population.<sup>16</sup> Our findings are consistent with studies that demonstrate that restrictive spirometry patterns are more common in this population.<sup>8,13</sup>

The main strengths of our study are that data are from the largest and longest running birth cohort of Indigenous Australians and, in a mobile population, a high proportion (70.7%) were followed up.<sup>29</sup> The scope and detail of data collected enabled us to investigate the impact of multiple perinatal and early life exposures on lung function, minimize bias from confounding and explore effect modification. Furthermore, data were collected prospectively using structured questionnaires despite some of the cohort living in remote locations. In addition, all flow volume loops were reviewed by two respiratory physicians.

Despite this being the largest birth cohort of Indigenous Australians, the relatively small sample size is a limitation. It is likely that our study was underpowered to detect associations between some of the exposures investigated as only 47.4% of spirometry traces were deemed of acceptable quality to be included in our final analysis. However, this is a similar proportion to other studies investigating lung function abnormalities in rural Indigenous Australians in the NT, where between 42% and 55% of spirometry traces met ATS/ERS criteria.<sup>13,30</sup> The reasons for the difficulty in obtaining consistent, reproducible spirometry in the

T A B L E 4 Effect of perinatal and early life exposures with FEV<sub>1</sub>, FEV<sub>1</sub>% predicted, FVC, FVC% predicted and FEV<sub>1</sub>/FVC ratio, stratified by sex.

| Perinatal or early life exposure                               | Men (n = 74)                    |                                       |                         |                         |                                | Women (n = 74)                  |                                       |                        |                         |                                |
|----------------------------------------------------------------|---------------------------------|---------------------------------------|-------------------------|-------------------------|--------------------------------|---------------------------------|---------------------------------------|------------------------|-------------------------|--------------------------------|
|                                                                | FEV <sub>1</sub> (mLs) (95% CI) | FEV <sub>1</sub> % predicted (95% CI) | FVC (mLs) (95% CI)      | FVC% predicted (95% CI) | FEV <sub>1</sub> /FVC (95% CI) | FEV <sub>1</sub> (mLs) (95% CI) | FEV <sub>1</sub> % predicted (95% CI) | FVC (mLs) (95% CI)     | FVC% predicted (95% CI) | FEV <sub>1</sub> /FVC (95% CI) |
| Maternal Body Mass Index                                       |                                 |                                       |                         |                         |                                |                                 |                                       |                        |                         |                                |
| Underweight (BMI <18.5)                                        | 451.9 (−102.4, 1006.1)          | 12.1 (−1.3, 25.5)                     | 339.4 (−414.9, 1093.8)  | 7.1 (−7.7, 21.9)        | 0.05 (−0.02, 0.13)             | 38.8 (−275.5, 353.2)            | 2.1 (−8.3, 12.6)                      | 12.4 (−373.7, 398.5)   | 3.1 (−8.2, 14.5)        | 0.04 (−0.06, 0.07)             |
| Overweight or obese (BMI ≥25)                                  | 20.3 (−423.3, 463.9)            | 1.4 (−8.7, 11.5)                      | 181.3 (−313.2, 675.9)   | 4.4 (−5.2, 13.9)        | −0.05 (−0.02, 0.13)            | 168.9 (−148.2, 485.9)           | 6.2 (−4.2, 16.6)                      | 36.7 (−303.6, 398.5)   | 4.6 (−5.3, 14.5)        | 0.05 (−0.06, 0.07)             |
| Maternal smoking                                               |                                 |                                       |                         |                         |                                |                                 |                                       |                        |                         |                                |
| Smoked during pregnancy                                        | 56.1 (−240.1, 352.4)            | 1.0 (−6.2, 8.1)                       | 223.9 (−122.2, 570.0)   | 4.3 (−2.7, 11.2)        | −0.02 (−0.06, 0.02)            | 72.1 (−148.8, 293.0)            | 1.6 (−5.7, 9.0)                       | 120.0 (−361.9, 122.0)  | −2.5 (−6.4, 4.5)        | 0.02 (−0.02, 0.07)             |
| Maternal age <sup>a</sup>                                      |                                 |                                       |                         |                         |                                |                                 |                                       |                        |                         |                                |
| Birthweight (g)                                                | 19.8 (−2.1, 41.9)               | 0.4 (−0.1, 0.9)                       | 21.2 (−3.7, 46.0)       | 0.5 (−0.2, 0.9)         | −0.01 (−0.03, 0.02)            | 22.3 (6.0, 38.5)                | 0.7 (0.2, 1.2)                        | 26.7 (0.3, 44.2)       | 0.6 (0.1, 1.1)          | 0.03 (−0.03, 0.08)             |
| Respiratory hospitalization <sup>b</sup> ≤2 years <sup>c</sup> | 0.2 (−0.1, 0.4)                 | 0.04 (−0.01, 0.02)                    | 0.6 (−0.3, 0.4)         | 0.03 (−0.4, 0.1)        | 0.01 (−0.03, 0.05)             | −0.1 (−0.2, 0.1)                | −0.01 (−0.07, 0.05)                   | −0.2 (−0.3, 0.2)       | −0.03 (−0.6, 0.5)       | −0.03 (−0.05, 0.08)            |
| 1 or more                                                      | −250.4 (−549.4, 48.7)           | −5.8 (−13.2, 1.6)                     | −348.1 (−706.1, 9.9)    | −6.4 (−13.8, 1.0)       | −0.01 (−0.05, 0.03)            | −210.9 (−460.7, 39.0)           | −5.7 (−13.4, 1.9)                     | −321.6 (−603.4, −39.9) | −8.9 (−16.4, −1.4)      | 0.04 (−0.02, 0.08)             |
| Respiratory hospitalization <sup>b</sup> ≤5 years <sup>c</sup> |                                 |                                       |                         |                         |                                |                                 |                                       |                        |                         |                                |
| 1 or more                                                      | −251.5 (−558.3, 35.2)           | −5.9 (−13.2, 1.4)                     | −340.0 (−697.2, 16.3)   | −6.1 (−13.4, 1.2)       | −0.02 (−0.06, 0.03)            | −252.3 (−465.8, −38.9)          | −9.2 (−13.1, −0.8)                    | −324.6 (−569.2, −80.0) | −8.9 (−15.7, −2.0)      | 0.03 (−0.05, 0.07)             |
| Place of residence at birth                                    |                                 |                                       |                         |                         |                                |                                 |                                       |                        |                         |                                |
| Remote                                                         | −629.5 (−923.1, −236.1)         | −16.2 (−25.0, −7.4)                   | −738.6 (−918.6, −290.7) | −15.6 (−24.2, −7.1)     | −0.05 (−0.06, 0.05)            | −234.7 (−518.0, 48.5)           | −7.8 (−16.7, 1.1)                     | −413.1 (−732.9, −93.2) | −14.8 (−23.4, −6.2)     | 0.04 (−0.07, 0.09)             |
| WHO Childhood weight-for-age z-scores <sup>c</sup>             |                                 |                                       |                         |                         |                                |                                 |                                       |                        |                         |                                |
|                                                                | −68.3 (−265.9, 128.3)           | −0.5 (−5.4, 4.3)                      | 6.5 (−231.9, 244.8)     | 0.6 (−4.4, 5.5)         | −0.02 (−0.05, 0.03)            | −28.2 (−145.5, 89.1)            | −0.9 (−4.4, 2.7)                      | 10.0 (−132.8, 152.8)   | 0.2 (−4.8, 4.2)         | −0.01 (−0.03, 0.01)            |

Note: FEV<sub>1</sub> and FVC were adjusted for age, sex, height and smoking status. FEV<sub>1</sub>, FVC %predicted and FEV<sub>1</sub>/FVC were adjusted for smoking status. Bolded text and values represent exposures and outcomes that are statistically significant.  
<sup>a</sup>Adjusted for place of residence at birth.  
<sup>b</sup>Adjusted for maternal BMI.  
<sup>c</sup>Adjusted for any respiratory hospitalizations ≤5 years.

Indigenous population, especially those who live in remote communities are unclear. Participants without acceptable spirometry were more likely to be current smokers, live remotely and depend on benefits as their main source of income—all markers of deprivation. This raises the possibility that we have under-estimated the proportion of Indigenous adults who have abnormal lung function. There were also differences between individuals in the cohort who were followed up and participants lost to follow-up; with more men and those living in urban areas at time of birth being more likely to be lost to follow-up. Although this raises the possibility of selection bias, our final cohort is largely representative of Indigenous Australians.<sup>31</sup>

Some of the exposures are self-reported and may be subject to recall bias. This was minimized by babies being recruited into the cohort within 4 days of birth.<sup>20</sup> Additionally, information on exposures was collected from medical records, limiting this bias. Observer bias is unlikely as a wide range of data were collected during follow-up. Most Indigenous people in Australia live in urban settings, and are under-represented in this cohort.<sup>32</sup> The mean FEV<sub>1</sub> and FVC values in our cohort are similar to a cohort of remote-dwelling Indigenous adults in Western Australia,<sup>9</sup> suggesting that our findings are generalizable to the remote-dwelling Indigenous Australians.

We did not have information on diagnoses of chronic respiratory diseases or presence of respiratory symptoms in our cohort, therefore it is unclear if the large proportion of abnormal lung function in our cohort is due to undiagnosed lung disease. It is possible that our findings are a result of environmental injuries resulting in a lower baseline of respiratory reserve in our population. We were unable to calculate smoking-pack years in our cohort due to cultural practices of sharing cigarettes. Sixty-two percent of our cohort identified as current smokers, similar to reported smoking prevalence in the NT Indigenous population.<sup>33,34</sup>

There are little data on the association of perinatal or early life exposures and lung function in Indigenous populations, but our findings are consistent with previously published data from non-Indigenous cohorts. Data from the European Community Respiratory Health Survey found increased maternal age was associated with higher adult lung function and is more pronounced in women,<sup>35</sup> which is similar to the results of our study.<sup>36</sup> Recently, a systematic review found that early childhood lower respiratory tract infections (LRTIs) impaired future lung function<sup>37</sup> and a large UK birth cohort demonstrated that LRTIs during early childhood doubled the risk of premature adult deaths from respiratory disease.<sup>38</sup> Another Australian birth cohort reported that when childhood BMI increased into the obese range, a decline in young adult lung function was observed.<sup>39</sup>

Our study reports novel findings of an association between being born into a remote community and reduced lung function. We hypothesize that being born into a remote community has shared factors associated with socio-economic deprivation which impact lung function. Our

hypothesis is supported by the findings of the 2017 Australian Health Performance Framework that reported that hospitalizations for respiratory disease amongst remote living Indigenous Australians was almost three times higher compared to major cities, but rates for non-Indigenous Australians were similar across areas.<sup>40</sup>

Almost 50% of our cohort had aFEV<sub>1</sub> below the population mean which has implications for future cardiorespiratory morbidity and mortality.<sup>18</sup> This study reports that the population attributable risk of FEV<sub>1</sub> below the population mean for all-cause mortality (24.7%) was higher than that of tobacco smoking (19.7%), previous cardiovascular disease (5.5%) and hypertension (17.1%).<sup>18</sup> As cardiovascular disease is the largest cause of mortality in Indigenous Australians, interventions that promote attainment of normal lung function in adulthood is imperative.

In summary, we found that younger maternal age, pre-school hospitalizations for respiratory infections, being overweight in early childhood and being born into remote areas are strongly associated with reduced lung function in Indigenous adults. We also found that a large proportion of Indigenous adults have abnormal spirometry, particularly FEV<sub>1</sub> below the population mean, which is associated with increased risk of mortality and cardio-respiratory morbidity.<sup>18</sup> We hypothesize that our findings reflect possible impaired lung growth as a result of perinatal and early life exposures. These findings emphasize the need to increase awareness and promote public health interventions that optimize respiratory health in early childhood, especially given the growing evidence that early childhood LRTIs are associated with poorer lung function and premature adult deaths.

## AUTHOR CONTRIBUTIONS

**Vidya Navaratnam:** Conceptualization (lead); data curation (lead); formal analysis (lead); methodology (lead); writing – original draft (lead). **Douglas L. Forrester:** Conceptualization (supporting); data curation (equal); methodology (equal); project administration (equal); writing – review and editing (equal). **Anne B. Chang:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); writing – review and editing (equal). **Shyamali C. Dharmage:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); writing – review and editing (supporting). **Gurmeet R. Singh:** Conceptualization (equal); data curation (equal); funding acquisition (lead); methodology (supporting); writing – review and editing (supporting).

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## CONFLICT OF INTEREST STATEMENT

None declared.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## HUMAN ETHICS APPROVAL DECLARATION

This study was performed in accordance with the Declaration of Helsinki and approved by Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, including the Aboriginal Ethical Sub-committee which has the power of veto (ABC Reference No: 2013-2022). All adult participants provided written informed consent to participate in this study.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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