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Characterising airway inflammation in Aboriginal and Torres Strait Islander and non-Aboriginal and Torres Strait Islander adults with asthma and COPD

Nick Young ,[1] Winnie Chen,[2] Shimul Chatterjee,[3] Scott Gelzinnis,[4] Aishath Lam'aan Latheef,[5] Jodie Simpson,[6,7] Peter A B Wark [8,9]

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JS and PABW are joint senior authors.

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For numbered affiliations see end of article.

Correspondence to
Dr Nick Young;
nick.young1@hotmail.com

ABSTRACT

Objective To examine airway inflammatory cell profiles in Indigenous Australian adults with asthma and chronic obstructive pulmonary disease (COPD).

Design/setting A retrospective, cross-sectional study on data from a tertiary referral respiratory outpatient clinic.

Participants Indigenous (n=23) and non-Indigenous (n=71) adults were matched according to diagnosis, gender and age to the ratio of 1:3.

Main outcome measures Participants were defined by self-determined identification as Indigenous (Aboriginal) or non-Indigenous. A relevant history was taken, and lung function was measured by spirometry. In those with a diagnosis of asthma, symptom control was assessed by the Asthma Control Questionnaire, six items (ACQ6). In those with a diagnosis of COPD, symptoms were assessed by the COPD assessment test (CAT). Airway cell counts were obtained in all groups from bronchial lavage (BL) cell count.

Results Lung function and inhaled corticosteroid dose were similar between groups. Current smoking was three times more common in Indigenous people (35%) compared with non-Indigenous people (12%, p=0.009). In participants with asthma, ACQ6 scores were similar between Indigenous and non-Indigenous participants with asthma. In those with COPD, Indigenous participants had significantly higher total CAT scores as well as scores for cough and sputum with a score indicating a high impact on quality of life (CAT score ≥14, 85%–25%, p=0.017). There was no difference in BL cell differential counts.

Conclusions Indigenous people with COPD had higher smoking rates, worsened CAT scores and more symptoms of cough and sputum production. There were no differences between the groups in airway inflammation, but neutrophilic inflammation was associated with poorly-controlled asthma.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic inflammatory airway diseases are more severe in Indigenous Australians, yet detailed characteristics on these conditions are limited.

WHAT THIS STUDY ADDS

⇒ Indigenous Australians with chronic obstructive pulmonary disease (COPD) were more likely to smoke, had higher COPD assessment test scores and experienced more severe symptoms of cough and sputum, suggesting a chronic bronchitis phenotype. No significant differences in inflammatory profiles were found.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This pilot study underscores the need for further research into airway disease phenotypes in Indigenous populations to allow for targeted treatment.

INTRODUCTION

Asthma is a common inflammatory airway disease in Australia and affects 11% of the total population.[1] However, the prevalence, hospitalisation rate and mortality from asthma in Indigenous populations are twice that seen in non-Indigenous populations.[2 3] One explanation of this may be an increased early exposure to tobacco smoke in Indigenous households. Indigenous children are twice as likely to live in smoking households (63%) compared with non-Indigenous children (32%) and frequent respiratory infections among Indigenous children correlate with significantly decreased forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC).[4–6] While asthma prevalence decreases in non-Indigenous individuals over the life course, asthma prevalence and severity increase with age in Indigenous adults. The reasons are uncertain but may be associated with comorbidities, lifestyle risk factors and socioeconomic disadvantage.[7 8]

Chronic obstructive pulmonary disease (COPD) affects 5% of Australians over the age of 45 years old, 30% of adults aged more than 75 years of age and in 2018 was the fifth-leading cause of death.[2] Indigenous Australians are 2.3 times more likely to have COPD,

5 times more likely to be hospitalised and 2.7 times more likely to die from COPD than non-Indigenous Australians.[9] Smoking is a major risk factor for COPD development and increased severity of COPD, and increased smoking rates in Indigenous populations have been associated with poorer disease outcomes.[4 6]

Asthma and COPD are complex airway diseases that are increasingly recognised to be characterised by heterogeneous inflammatory profiles which manifest in a range of clinical phenotypes, many of which are refractory to standard treatments.[10] Stratification of patients into subgroups based on the dominance of eosinophilic/neutrophilic inflammation in the airway has been demonstrated to greatly improve targeted treatment outcomes.[11 12] While inflammatory cell profiles in airway disease have been well characterised in the general population, little is known about patterns of airway inflammation and clinical severity in Indigenous Australians.[13 14] In addition to characterising clinical symptoms and airway inflammatory cell profiles in adult Indigenous Australians with asthma and COPD, our study sought to investigate the relationship between disease severity and functional impact.

METHODS

Participants

This study used a database of participants recruited from a respiratory outpatient clinic in the John Hunter Hospital, a tertiary referral centre and teaching hospital in Newcastle, New South Wales. Indigenous (n=23) and non-Indigenous participants (n=71) were identified using the Clinical Applications Portal. Participants with asthma (n=51) were defined by a physician's diagnosis along with evidence of variable airway obstruction or bronchial hyper-responsiveness. Variable airway obstruction was defined as a change in FEV_1 of ≥12% or 200 mL after 400 µg of salbutamol. Bronchial hyperresponsiveness was defined as at least a ≥15% decline in FEV_1 after bronchial provocation with 4.5% saline solution.[15] Those with COPD (n=49) had a physician's diagnosis in combination with a postbronchodilator FEV_1 of less than 80% of the predicted value and/or a postbronchodilator FEV_1/FVC less than 70%. Participants with both asthma and COPD diagnoses were also included in this study. No participants had a history of respiratory tract infection in the 4 weeks prior to bronchial lavage (BL) collection.

All participants who were undergoing bronchoscopy for clinical indications were approached to consent to have their BL collected and access to their clinical data provided for assessment. We included data from all Indigenous participants and then matched these with data from individuals who had consented to participate and had stated that they did not identify as Aboriginal or Torres Strait Islander. Matching was by age (to within 5 years), gender and respiratory condition.

Patient and public involvement

This study design and aim were discussed and formulated as part of Aboriginal outreach respiratory clinics in the Pius X Aboriginal Corporation in Moree, NSW and the Winanga-li Aboriginal Child and Family Centre in Narrabri, NSW.

Study design

This was a retrospective, cross-sectional exploratory study based on primary data collected from a tertiary respiratory centre. Data used for this study were age, gender, Indigenous identification, disease status (asthma, COPD and/or bronchiectasis), spirometry, smoking status, BL cell count, COPD Assessment Test (CAT) score and the six-item Asthma Control Questionnaire (ACQ) score.[16 17] Data collected, in particular BL results, CAT and ACQ scores, are varied dependent on data collected at that time. Indigenous and non-Indigenous participants were matched according to diagnosis, gender and age group to the ratio of 1:3.

Spirometry and bronchoscopy

Spirometry was performed according to American Thoracic Society guidelines,[18] without withholding usual medications on the day of the test. Percentage predicted for FEV_1 and FVC was calculated using The Third National Health and Nutrition Examination Survey.[19] Subjects were recruited at the time of clinical bronchoscopy. These patients had stable symptoms and respiratory disease, with no history of an acute worsening of their clinical condition and no history of acute infective symptoms within 6 weeks of their bronchoscopy. Flexible bronchoscopy was performed in stable participants to obtain BL by wedging into the bronchus of the right middle lobe or lingula and lavaging with 40 mL of sterile normal saline. Participants whose lung disease was not stable enough to undergo BL, or did not consent to BL, did not have cell counts collected, accounting for missing cell count data (n=5). BL was filtered and total cell count and viability were measured. BL was then centrifuged, and the cell pellet was resuspended in phosphate-buffered saline to the concentration of 1×10^6/mL and cellular cytospins prepared by adding 70 µL cell suspension into a cytospin bucket and centrifugation at 500× g. The cytospins were stained with May-Grünwald Giemsa (Beckman Coulter, Brea, California, USA) and differential cell count of 400 non-squamous cells was performed.

Asthma and COPD assessment

The ACQ6 was used to characterise the control, severity and frequency of exacerbation in participants, with an ACQ total of >1.5 indicating poorly controlled asthma.[20] The CAT was used to measure the impact of COPD symptoms (cough, sputum, chest tightness and dyspnoea) on health status.[16] Questions 1 and 2 of the CAT, comprising cough frequency and mucus presence, were compiled to

Table 1 Clinical characteristics of Indigenous and non-Indigenous participants with inflammatory airways disease

	Indigenous	Non-Indigenous	P value
	23	71	
Age, median (q1, q3)	61 (47, 68)	61 (50, 68)	0.898
COPD n (%)	12 (52.2)	37 (52.1)	0.593
Asthma n (%)	13 (56.5)	38 (53.5)	0.497
Males n (%)	10 (43.48)	35 (49.30)	0.404
Current smokers, n (%)	8 (34.8)	8 (11.7)	0.009
Never smokers n (%)	6 (26.1)	25 (35.2)	0.419
Ex-smokers n (%)	9 (39.1)	38 (53.5)	0.230
Pack-years median (q1, q3)	25 (0, 50)	12.5 (0, 37.5)	0.272
FEV_1% predicted	85 (56, 90)	79 (58, 87)	0.481
FEV_1/FVC median (variance)	69 (56, 74)	68 (57, 76)	0.902
Taking ICS n (%)	16 (69.6)	51 (71.83)	0.515
ICS dose, beclomethasone equivalent dose median	800 (0, 2000)	1000 (0, 2000)	0.542
Asthma only			
n	8	23	
ACQ6 mean score, median (q1, q3)	1.75 (0.94, 2.65)	1.33 (1.00, 2.10)	0.469
ACQ6>1.5 n (%)	5 (62.5)	10 (43.5)	0.303

ACQ6, Asthma Control Questionnaire, 6 items; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid.

represent the presence of chronic bronchitis.[21] Due to the retrospective nature of the study, some participants did not have CAT or ACQ data collected.

Statistical analysis

Data were analysed using Stata software V.11 (StataCorp) and subgroup analysis was performed using R V.1.4.1 (R Core Team, Vienna, Austria). Results are reported as mean (SD) or median (IQR), unless otherwise stated. Continuous measures were analysed with a two-sample Wilcoxon's rank-sum test or t-test. Categorical data were analysed using Fisher's exact test. Spearman correlation coefficients were calculated for the association between pack-years and eosinophil count, pack-years and CAT score, and CAT score and inflammatory cell count. A $p<0.05$ is taken as statistically significant.

RESULTS

Clinical characteristics

Both Indigenous and non-Indigenous participants were similar in age (median age 61, IQR 47–68 and 50–68 respectively), inhaled corticosteroid (ICS) dose, presence of COPD (table 1) Indigenous adults more likely to be current smokers in comparison to non-Indigenous adults, 34.78% and 11.27%, respectively (p=0.009). In those with a diagnosis of asthma, there was no difference in the mean asthma control score (table 1). However, there was a higher proportion of Indigenous patients whose ACQ scores indicated a greater risk of exacerbation (ACQ6>1.5, table 1).[20]

CAT scores in COPD

Indigenous participants with COPD had a significantly higher total CAT score and a higher proportion of participants with a total score of 14 or more, indicating a greater impact on daily quality of life and heightened risk of an exacerbation (table 2). Indigenous participants with COPD were significantly more likely to rate their mucus symptoms as worse on the CAT (2.7–1.25, respectively, p=0.014), while rating household activity limitation higher and daily energy level lower on the CAT than non-Indigenous participants; however, this did not achieve statistical significance. All Indigenous patients with COPD included in this study could be considered to have chronic bronchitis based on the CAT score questionnaire (table 2).[21]

BL inflammatory cell counts

Inflammatory cell counts were similar between Indigenous and non-Indigenous participants (table 3).

Associations between clinical and inflammatory outcome variables

There was a significant negative correlation between the number of pack-years and eosinophil proportion in the total cohort (p=0.0055, Spearman's r=−0.3662) (figure 1). No associations were found between pack-years and any other inflammatory cell count.

There was a significant negative correlation between CAT score and lymphocyte count in Indigenous participants (p=0.037, Spearman r=−0.90) (figure 2).

Table 2 COPD characteristics in Indigenous and non-Indigenous participants

	Indigenous	Non-Indigenous	P value
n	7	12	
Total score	21 (17, 22)	12.5 (10.5, 14.5)	0.025
Total score ≥14	6 (85.7)	3 (25.0)	0.017
Presence of chronic bronchitis*	6 (100%)	5 (55.6%)	0.162
Individual questions			
Q1 cough frequency	2.1 (0.69)	1.5 (1.24)	0.175
Q2 mucus presence	2.7 (1.11)	1.25 (1.13)	0.014
Q3 chest tightness	1.71 (1.11)	1.33 (1.44)	0.555
Q4 exercise limitation by breathlessness	3.29 (1.89)	2.92 (1.56)	0.651
Q5 household activity limitations from breathlessness	3.00 (1.41)	2.00 (0.41)	0.155
Q6 confidence leaving home	1.14 (1.21)	0.42 (0.90)	0.154
Q7 sleep quality	1.43 (1.40)	1.08 (1.24)	0.583
Q8 energy rating	3.14 (1.46)	2.5 (0.90)	0.250

*Chronic bronchitis: CAT Q1+Q2≥3.
CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease.

However, there was no significant correlation found in non-Indigenous participants (p=0.961, Spearman r=0.016). There were no significant correlations found between CAT score and any other inflammatory cell count.

Neutrophilic inflammation was associated with poorly controlled asthma (ACQ5 total >1.5) (z=2.717, p=0.007) in both Indigenous and non-Indigenous participants (z=1.938, p=0.053 and z=2.44, p=0.015, respectively). There was no significant association between eosinophilic inflammation and poorly controlled asthma (z=−1.475, p=0.14).

There was no significant difference in eosinophil count between patients taking ICSs between Indigenous participants and non-Indigenous participants (p=0.888).

DISCUSSION

In this observational cohort, Aboriginal adults with asthma or COPD were three times more likely to be current smokers, and if diagnosed with COPD, had more severe symptoms of cough and sputum production contributing to an overall significantly higher CAT score, with a greater proportion experiencing a high impact on quality of life than that of non-Indigenous Australians.

We found a significant difference in the CAT score ≥14, indicating that Indigenous people perceived the impact of their COPD to be worse and were three times more likely to have an exacerbation in the next 12 months than non-Indigenous people. Factors that can increase the chance of exacerbation of COPD are current smoking[22] and increased mucus production,[23] both of which were

Table 3 Inflammatory cell count in Indigenous and non-Indigenous participants with inflammatory airways disease

	Indigenous	Non-Indigenous	P value
n	**18**	**69**	
Total cells (×10^6/mL)	0.16 (0.09, 0.53)	0.23 (0.10, 0.73)	0.888
Viability, %	89.02 (56.00, 98.40)	81.82 (60.00, 92.00)	0.269
Neutrophils, %	64.00 (47.75, 86.00)	53.25 (28.75, 82.75)	0.222
Eosinophils, %	1.50 (0.60, 2.25)	1.50 (0.50, 3.75)	0.753
Eosinophil count ≥3%, %	4 (26.7%)	16 (31.4%)	0.941
Macrophages, %	23.63 (10.75, 38.25)	20.00 (9.50, 49.00)	0.846
Lymphocytes, %	1.00 (0.25,2.50)	0.25 (0.00, 1.25)	0.133
Columnar epithelial cells, %	1.88 (0.75, 5.75)	3.75 (0.75, 12.00)	0.434
Presence of pathogen, n (%)*	6 (40.0)	17 (36.2)	0.510

*Pathogens: *Haemophilus influenzae, Neisseria meningitidis, Acinetobacter baumannii, Staphylococcus aureus, Streptococcus pneumonia, Aspergillus fumigatus, Achromobacter, Candida species, Serratia marcescens.*

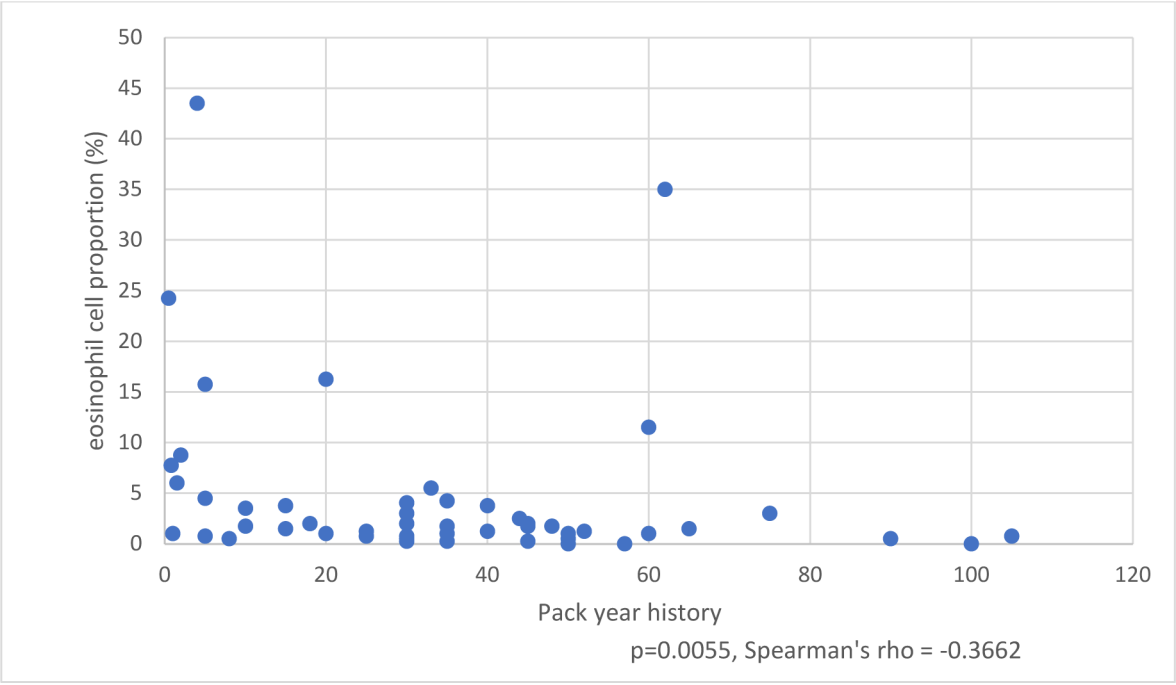

Figure 1 A correlation plot of smoking pack-years and bronchial lavage eosinophil proportion in the total cohort. The smoking pack-year history is marked on the x-axis and eosinophil proportion is marked on the y-axis. Each point represents one patient.

higher in Indigenous participants in this study. In the context of COPD, the presence of chronic bronchitis is closely associated with current smoking status and is also associated with worse quality of life and more frequent exacerbations.[24] These outcomes have also been linked in population studies to increased mortality associated with COPD.[25] Smoking is known to increase mucus production in airways in pulmonary disease,[26] which may account for more Indigenous participants reporting increased mucus production.

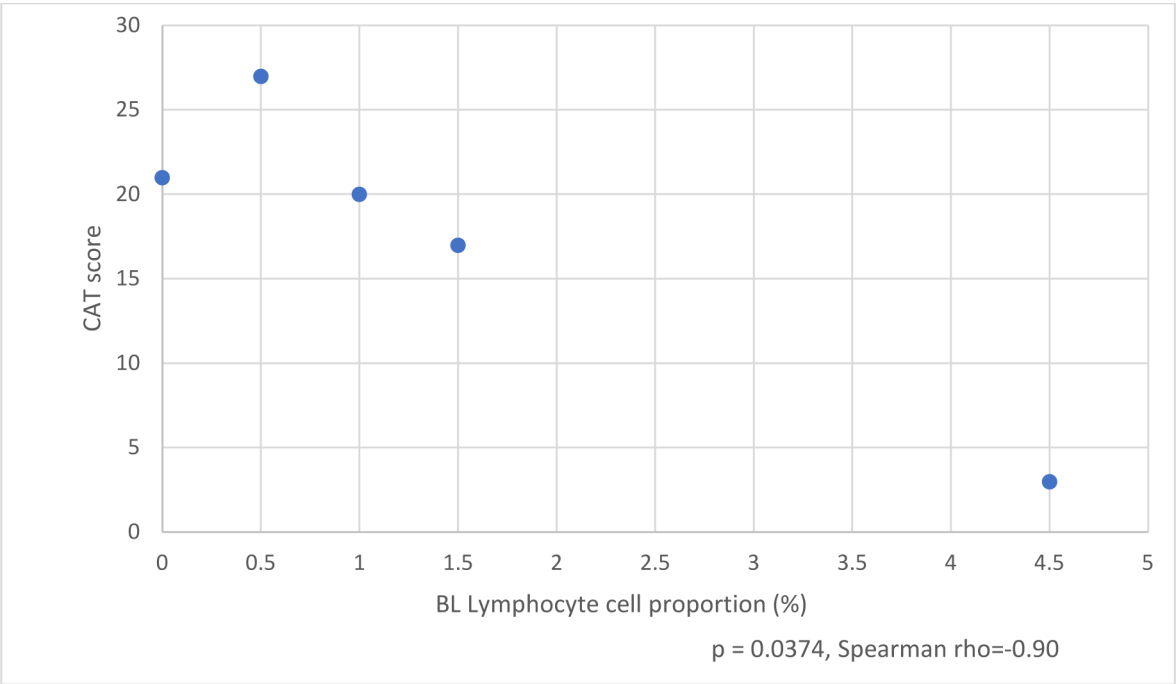

Figure 2 Total COPD Assessment Test (CAT) score and bronchial lavage cell proportion for Indigenous participants. CAT scores are represented on the y-axis and bronchial lavage cell proportion is marked on the x-axis. Each point represents one patient. COPD, chronic obstructive pulmonary disease.

While differences in current smoking status could contribute to the increased symptoms, there may be a more complex interplay of factors, including socioeconomic and genetic factors, that worsen symptoms in Indigenous participants, which was not within the scope of this study. These might include recurrent respiratory infections[26 27] and comorbidities such as cardiovascular diseases with similar symptoms of dyspnoea.[6 8] Socioeconomic factors such as rurality[6 28 29] and poor access to regular, culturally appropriate[29 30] healthcare may also have an impact. Our data supports previous studies which have observed increased first and secondhand smoking in Indigenous adults with asthma and COPD.[6 8] We also found that the number of pack-years was positively associated with CAT scores in Indigenous participants, linking the number of cigarettes smoked to worsened COPD symptom severity.

We found that all Indigenous participants in our study could be considered to have chronic bronchitis, based on symptomatic burden from cough and mucus production, whereas a reduced proportion of non-Indigenous participants appeared to have chronic bronchitis (6/6 compared with 5/12, p=0.163). While we have a small cohort, these findings are consistent with a disease phenotype of COPD that would be expected to lead to worse long-term disease outcomes in Indigenous Australians.[24 25]

In contrast to what we saw in COPD, there were no clear differences detected between Indigenous and non-Indigenous people with asthma as assessed by the ACQ6. There were relatively more Indigenous active smokers with asthma and a trend to poorer asthma control, but these differences were not significant. This may reflect our small numbers, and the ACQ does not focus as much on the presence of cough and sputum as the CAT does.

While there were no differences observed in BL cell counts, we observed that neutrophilic inflammation was associated with poorly controlled asthma in both Indigenous and non-Indigenous participants. We had hypothesised that neutrophilia may be more common in Indigenous Australians due to their increased exposure to recurring infection and cigarette smoke, but this was not the case in our study. One limitation was our relatively small sample size, restricted by the size of recruited Indigenous subjects who had undergone bronchoscopy. A strength was that participants were age and sex matched. Larger prospective studies are needed to examine this further. No differences in the prevalence of chronic infection with pathogenic microorganisms were observed between the groups. This is in keeping with there being no differences in airway neutrophils. However, our sample size was relatively small to draw any clear conclusion. Future studies with a larger sample size and using more sensitive non-culture-based approaches that assess the airway microbiome may assist in a greater understanding.

Previous research has demonstrated a possible link between eosinophilic inflammation in smokers with COPD.[31–34] Previous studies have suggested current smoking in COPD may decrease airway eosinophilic inflammation compared with former smokers with COPD;[32 33] however, the association between pack-year smoking history and eosinophilic inflammation has not been assessed. This possible association between pack-year history and eosinophilia would be a topic for further research to aid further in identifying patients at higher risk for eosinophilic inflammation to then target treatments.

This is the only study to look for differences in BL cell counts in adults with chronic inflammatory airways disease and who identify as Indigenous Australians and to compare these results with non-Indigenous Australians. There have been studies relating to inflammatory airways disease in rural and remote Aboriginal Australian settings,[6 28 35] while our study is one of the few conducted in regional NSW.

Limitations

There were fewer data available for Indigenous participants than non-Indigenous participants, and a larger sample size would allow for stratification into larger subgroups, allowing further comparison of inflammatory cells between Indigenous and non-Indigenous adults with different diagnoses of asthma and COPD. Our study did not include whether participants were involved in other non-pharmacological treatments such as cardiopulmonary rehabilitation, which has been shown to be effective in Aboriginal and Torres Strait Islander people with cardiopulmonary diseases.[36] It would be valuable to assess the role and nature of airway inflammation in younger populations, with larger sample sizes that could assess non-invasive biomarkers of airway inflammation that have now been established to clinically phenotype people with asthma, blood eosinophils and exhaled nitric oxide.

In addition, predictive values used for FEV1 and FVC were based on non-racially corrected values. This may have influenced an overestimation or underestimation of airway obstruction severity in Aboriginal and Torres Strait Islander adults in our cohort. However, there are no currently agreed on predicted values for Aboriginal and Torres Strait Islander people. Further research is required in this area; however, that is beyond the scope of this manuscript.

The design of the study also has limitations in the ability to draw conclusions of aetiology or pathogenesis of disease, and as such, it would be valuable to conduct further research designed to further examine inflammatory airways disease in Indigenous Australians.

CONCLUSIONS

Indigenous Australians with COPD were more likely to be smokers, had higher overall CAT scores and more severe symptoms of cough and sputum. These factors may relate

to a chronic bronchitis phenotype associated with worse long-term outcomes.

We were unable to detect any differences in those with a diagnosis but are likely to have been hampered by our small sample size. We did not find significant differences in the BL inflammatory profile between Indigenous and non-Indigenous participants, though it demonstrated that neutrophilic inflammation is associated with poorly controlled asthma, supporting the findings from previous studies.[37–39] This study, as a pilot study of airway inflammatory phenotypes in Indigenous adults with chronic airways disease, demonstrates there is still much to explore in future studies.

Author affiliations
[1]Hunter New England Local Health District, New Lambton, Newcastle, Australia
[2]Royal Australian College of General Practitioners, Sydney, New South Wales, Australia
[3]Central Coast Local Health District, Gosford, New South Wales, Australia
[4]Critical Care, Hunter New England Local Health District, New Lambton, New South Wales, Australia
[5]South Metro Local Health District, Perth, Western Australia, Australia
[6]School of Medicine and Public Health, School of Biomedical Sciences and Pharmacy, The University of Newcastle, Newcastle, New South Wales, Australia
[7]Priority Research Centre for Healthy Lungs, University of Newcastle Hunter Medical Research Institute, New Lambton, New South Wales, Australia
[8]Immunology, Respiratory Medicine, Monash University Faculty of Medicine Nursing and Health Sciences, Prahran, Victoria, Australia
[9]Allergy, Immunology and Respiratory Medicine, Alfred Health, Melbourne, Victoria, Australia

Contributors NY, WC, SC, ALL, JS and PABW worked in conception, design, analysis and interpretation of work, drafting of work. JS and PABW worked in acquisition of data and supervision of project. NY, WC, SG, JS and PABW worked in substantial revision of work. All authors agreed to be accountable for their contributions in this work and approved the submitted version of this work. Author NY is the guarantor of this work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Hunter New England Human Research Ethics Committee (Reference no. 15/03/18/3.04) and The University of Newcastle (H-2015-0147). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. Deidentified data will be made available on reasonable request to the corresponding author.

ORCID iDs
Nick Young http://orcid.org/0009-0002-7090-0453
Peter A B Wark http://orcid.org/0000-0001-5676-6126

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