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Small airway dysfunction is associated with poorer asthma control

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Small Airways Dysfunction is Associated with Poorer Asthma Control

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36 **Take home message**
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39 In asthmatics with a preserved FEV₁, small airways dysfunction defined by FEF₂₅₋₇₅ and R5-
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41 R20 was associated with poorer long-term control.
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Small Airways Dysfunction is Associated with Poorer Asthma Control

The clinical relevance of the small airways in persistent asthma has been gaining greater recognition in recent years [1]. Studies have shown that a significant proportion of asthmatics on standard treatment fail to achieve satisfactory asthma control. For example, in one study of 3421 asthmatic subjects who underwent guideline driven dose titration with standard inhaled corticosteroids (ICS) / long-acting beta-agonist (LABA) combination therapy over 1 year, only 41% achieved total control of their asthma while 71% were well controlled [2].

Anderson et al [3] found a high prevalence of adult patients with persistent small airway dysfunction determined by impulse oscillometry (IOS, as R5-R20) and spirometry (as FEF₂₅₋₇₅) across British Thoracic Society (BTS) treatment steps for asthma, many of whom had a preserved FEV₁. This in turn suggests an unmet clinical need in terms of patients who may have a small airway asthma phenotype.

We therefore evaluated whether small airways dysfunction was associated with worse control in adult asthmatics with a preserved FEV₁ (FEV₁ > 80% predicted). Spirometry and IOS measurements from unselected asthmatics referred from primary care who attended for screening visits for clinical trials were linked to prescription data. The prescription data were obtained from the Tayside Health Informatics Centre which links all community dispensed prescriptions using a person's unique identifier, the Community Health Index. Spirometry and IOS measurements from asthmatics were linked to oral corticosteroid and short-acting beta-agonist (SABA) use. We evaluated if small airways dysfunction, defined as FEF₂₅₋₇₅ < 70%, or peripheral airway resistance as R5-R20 > 0.07 kPa·L⁻¹·s was associated with increased oral corticosteroid and SABA use. Oral steroid and SABA use 1 year prior and 1 year following the index measurements were determined i.e. whether or not patients had an oral steroid prescription for an asthma exacerbation or the use of > 4 or ≤ 4 SABA inhalers.

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3 Research ethics committee approval was obtained for all the studies the patients were being
4 screened into and Caldicott Guardian approval was obtained to transfer the data to the Health
5 Informatics Centre. IOS (Jaeger Masterscreen IOS, Hochberg, Germany) was performed in
6 triplicate in accordance with manufacturer's guidelines. A SuperSpiro spirometer (Micro
7 Medical Ltd., Chatham, Kent, United Kingdom) was used in triplicate in accordance with
8 European Society guidelines [4]. Logistic regression analysis was applied to calculate the
9 odds ratios (OR) for steroid and salbutamol use in the different groups. Age, gender, ICS,
10 LABA and leukotriene receptor antagonists (LTRA) use were all included as covariates to
11 calculate the adjusted OR and 95% confidence interval.
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14 302 out of 442 (68%) asthmatics had a preserved $FEV_1 > 80\%$, mean age: 40 years, FEV_1 :
15 97%, median ICS dose: 800 μ g, 42% taking LABA, 22% on LTRA and 5% on theophylline.
16
17 The proportion of patients at BTS treatment steps 1-4 were 6.3%, 37.7%, 27.8 % and 28.0 %
18 respectively. The results in Table 1 showed that persistent small airways dysfunction,
19 defined by FEF_{25-75} and R5-20, was associated with a significantly increased likelihood of
20 having worse long-term asthma control. The risk of having poorer control was greater when
21 measurements of FEF_{25-75} and R5-R20 were combined. However, adding in FEV_1/FVC to the
22 model did not appreciably improve the OR compared to the combined outcome of FEF_{25-75}
23 and R5-20 because FEV_1/FVC and FEF_{25-75} were both highly correlated ($r = 0.82$, $P < 0.001$).
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25 When our analysis was corrected for factors including age, gender, ICS, LABA and LTRA,
26 the adjusted OR for FEF_{25-75} and R5-20 were similar. R5% predicted (n=302) and resonant
27 frequency (n=268) however, did not have a significant impact in determining asthma control.
28
29 There were insufficient evaluable data to perform a meaningful analysis on reactance area
30 (AX) (n=75). During the study period, in those with a preserved FEV_1 , there were a total of
31 14 Emergency Department visits and 33 hospital admissions for asthma exacerbations.
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33 However, these numbers were too small to perform a meaningful analysis.
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3 Our results are similar to those of previously reported studies in asthmatic children by Shi et
4 al [5] who showed a significant difference between selected cohorts of controlled and
5 uncontrolled asthmatic children for both FEF_{25-75} and FEV_1/FVC , while peripheral resistance
6 ($R5-R20 > 0.15 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$) and reactance area ($AX > 0.95 \text{ kPa}\cdot\text{L}^{-1}$) were equally predictive
7 for detecting control. In a prospective follow up study [6] of initially controlled asthmatic
8 children, the same authors observed a significant difference in FEV_1/FVC but not FEF_{25-75} at
9 baseline, but for both FEV_1/FVC and FEF_{25-75} at follow up after 3 months, comparing those
10 who remained controlled to those who subsequently became uncontrolled. Rao et al [7] in a
11 similar design to the present study over 2 years using electronic prescribing linkage,
12 compared matched groups of asthmatic children who had a preserved $FEV_1 (> 80\%)$ with an
13 abnormal $FEV_1/FVC (< 0.85)$ and $FEF_{25-75} (< 60\%)$ versus those with normal values,
14 showing significantly increased OR for loss of control in terms of oral steroid use, asthma
15 exacerbations and controller use.
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32 We elected to use cut-off thresholds for small airways measurements which provided the best
33 compromise in terms of achieving balanced numbers of patients in each group from which to
34 make informative comparisons. Such cut-off values for normality are always going to be
35 rather arbitrary whether they are more or less severe in nature. We acknowledge our data has
36 some limitations in terms of it being a retrospective type health informatics study linked to a
37 single index measurement of pulmonary function. However, we feel that our data more
38 closely reflects real life practice where compliance is usually poor in the community. Our
39 unselected cohort of persistent asthmatics were referred from primary care and reflected a
40 wide spectrum of severity across BTS treatment steps.
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51 We feel that our study may have some important potential clinical implications. It appears
52 that effort independent (i.e. IOS) and effort dependent measurements (i.e. spirometry) may
53 provide distinct yet complimentary information on the small airways phenotype, as shown by
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3 the higher OR for the composite of FEF₂₅₋₇₅ and R5-R20 compared to either measurement
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5 alone.

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7 It remains unclear as to whether small airway markers may be improved by using extra fine
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9 particle inhaled therapy including currently available extra fine ICS and ICS/LABA
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11 formulations and how this relates to long-term asthma control. We also do not know if small
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13 airways dysfunction as reflected by abnormal FEF₂₅₋₇₅ or R5-20 is due to ongoing persistent
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15 inflammation or simply altered airways geometry. Several prospective randomised controlled
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17 trials have shown greater improvements in small airways outcomes in response to extra fine
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19 compared to coarse particle ICS formulations in unselected patient cohorts [8-12]. Other
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21 retrospective health informatics data comparing extra fine and coarse particle ICS
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23 formulations have revealed consistent results in terms of improved asthma control based on
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25 prescribing outcomes, but have not measured any small airway pulmonary function outcomes
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27 [13-15]. We believe the time has now come for designing prospective randomized controlled
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29 trials enrolling patients with an enriched small airways phenotype, perhaps powered on
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31 pragmatic outcomes such as the Asthma Control Questionnaire.
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36 In conclusion, we have shown that in adult asthmatics who have a preserved FEV₁, the
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38 presence of persistent small airways dysfunction was associated with poorer control, perhaps
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40 suggesting the presence of a defined small airway asthma phenotype.
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Table 1 Odds ratio (95% CI) for small airway indices in 302 patients with FEV₁ > 80% predicted

	Crude odds ratio	P value	Adjusted odds ratio	P value
FEF₂₅₋₇₅ < 70 % n=157 versus FEF₂₅₋₇₅ > 70% n=145				
Oral steroid use	1.67 (1.04-2.68)	0.04	1.50 (0.91-2.48)	0.11
SABA use	2.00 (1.27-3.16)	0.003	1.91 (1.19—3.07)	0.007
FEV₁/FVC < 0.80, n=167 versus FEV₁/FVC > 0.80, n=135				
Oral steroid use	2.06 (1.27-3.35)	0.004	1.85 (1.10-3.12)	0.02
SABA use	1.61 (1.02-2.54)	0.04	1.54 (0.95-2.51)	0.08
R5-R20 > 0.07 kPa·L⁻¹·s, n=135 versus R5-R20 < 0.07 kPa·L⁻¹·s, n =167				
Oral steroid use	1.99 (1.23-3.19)	0.005	1.80 (1.09-2.98)	0.02
SABA use	1.83 (1.16-2.89)	0.01	1.87 (1.15-3.01)	0.01
FEF₂₅₋₇₅ < 70 % & R5-R20 > 0.07 kPa·L⁻¹·s; n=83 versus FEF₂₅₋₇₅ > 70% & R5-R20 < 0.07 kPa·L⁻¹·s; n=93				
Oral steroid use	2.77 (1.48-5.18)	0.001	2.34 (1.20-4.58)	0.01
SABA use	3.07 (1.66-5.67)	<0.001	3.16 (1.64-6.07)	0.001
FEF₂₅₋₇₅ < 70 % , R5-R20 > 0.07 kPa·L⁻¹·s & FEV₁/FVC < 0.80; n=72 versus FEF₂₅₋₇₅ > 70% & R5-R20 < 0.07 kPa·L⁻¹·s & FEV₁/FVC > 0.80; n=75				
Oral steroid use	3.29 (1.64-6.61)	0.001	2.78 (1.28-6.04)	0.01
SABA use	3.16 (1.61-6.19)	0.001	2.96 (1.44-6.12)	0.003

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