Small airway function measured using forced expiratory flow between 25% and 75% of vital capacity and its relationship to airflow limitation in symptomatic ever-smokers: A cross-sectional study

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Supplementary Tables

Table E1. List of medications used in the included participants

Variable	Total n= 1458	Normal FEF_{25-75}/AL- *n = 316*	Low FEF_{25-75}/AL- *n = 335*	Low FEF_{25-75}/AL+ *n = 806*
SABA	891 (61.1)	128 (40.5)	186 (55.7)*	576 (71.4)*†
SAMA	51 (3.5)	2 (0.6)	10 (3)	39 (4.8)*
SABA/SAMA	1 (0.1)	0 (0)	0 (0)	1 (0.1)
ICS	85 (5.8)	17 (5.4)	22 (6.6)	45 (5.6)
LABA	24 (1.6)	1 (0.3)	3 (0.9)	20 (2.5)*
ICS/LABA	405 (27.8)	33 (10.4)	70 (21)*	302 (37.4)*†
LAMA	353 (24.2)	20 (6.3)	47 (14.1)*	286 (35.4)*†
LABA/LAMA	36 (2.5)	2 (0.6)	9 (2.7)	25 (3.1)
ICS/LABA/LAMA	7 (0.5)	0 (0)	0 (0)	7 (0.9)
Systematic CS	55 (3.8)	2 (0.6)†‡	15 (4.5)	38 (4.7)
Antibiotic	28 (1.9)	1 (0.3)	8 (2.4)	19 (2.4)
Montelukast	25 (1.7)	3 (0.9)	4 (1.2)	18 (2.2)
CV Medications	687 (47.1)	183 (57.9)†‡	160 (47.9)	343 (42.5)
GI Medications	381 (26.1)	97 (30.7)	96 (28.7)	187 (23.2)*
Domiciliary Oxygen	19 (1.3)	2 (0.6)	5 (1.5)	12 (1.5)
Mucolytic	101 (6.9)	3 (0.9)	14 (4.2)*	88 (10.9)*†
Theophylline	15 (1.0)	0 (0)	1 (0.3)	14 (1.7)

Legend: Data is presented in n (%); *Significantly different from group 1; †Significantly different from group 2; ‡Significantly different from group 3. Significance level was set at $P<0.05$

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; AL, airflow limitation; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; CS, corticosteroid; CV, Cardiovascular; GI, gastrointestinal.

Table E2. List of medications used across airflow limitation severity.

Variable	Mild *n = 178*	Moderate *n = 111*	Moderately severe *n = 120*	Severe *n = 263*	Very severe *n = 135*
Medications (n, %)					
SABA	103 (57.9)	77 (69.4)	83 (69.2)	197 (74.9)*	116 (85.9)*†‡
SAMA	5 (2.8)	4 (3.6)	7 (5.8)	15 (5.7)	8 (5.9)
SABA/SAMA	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)
ICS	10 (5.6)	5 (4.5)	6 (5)	17 (6.5)	8 (5.9)
LABA	4 (2.2)	2 (1.8)	2 (1.7)	9 (3.4)	3 (2.2)
ICS/LABA	43 (24.2)	29 (26.1)	41 (34.2)	112 (42.6)*†	77 (57)*†‡
LAMA	40 (22.5)	40 (36)	29 (24.2)	114 (43.3)	63 (46.7)*‡
LABA/LAMA	3 (1.7)	4 (3.6)	1 (0.8)	12 (4.6)	5 (3.7)
ICS/LABA/LAMA	1 (0.6)	1 (0.9)	1 (0.8)	1 (0.4)	3 (2.2)
Systematic CS	6 (3.4)	4 (3.6)	6 (5)	14 (5.3)	8 (5.9)
Mucolytic	10 (5.6)	8 (7.2)	8 (6.7)	36 (13.7)	26 (19.3)*‡
Antibiotic	1 (0.6)	2 (1.8)	3 (2.5)	7 (2.7)	6 (4.4)
Montelukast	1 (0.6)	0 (0)	2 (1.7)	9 (3.4)	6 (4.4)
CV Medications	89 (50)	44 (39.6)	60 (50)	109 (41.4)	41 (30.4)*‡
GI Medications	44 (24.7)	36 (32.4)	30 (25)	56 (21.3)	22 (16.3)†
Domiciliary Oxygen	0 (0)	4 (3.6)	1 (0.8)	4 (1.5)	3 (2.2)
Theophylline	0 (0)	1 (0.9)	1 (0.8)	7 (2.7)	5 (3.7)

Legend: Data is presented in n (%). *Significantly different from mild; †Significantly different from moderate; ‡Significantly different from moderately severe; §Significantly different from severe. Significance level was set at $p<0.05$.

Abbreviations: SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; CS, corticosteroid; CV, Cardiovascular; GI, gastrointestinal

Table E3. The relationship of FEF_{25-75} and FEF_{25-75}/FVC with spirometric measures (n=1458)

Spirometric measures	FEF_{25-75} % predicted		FEF_{25-75}/FVC	
	r^2	*P value*	r^2	*P value*
FEV_1 (% predicted)	0.71	<0.001	0.47	<0.001
FVC (% predicted)	0.13	<0.001	0.006	<0.001
FEV_1/FVC (%)	0.83	<0.001	0.92	<0.001
FEV_3/FVC (%)	0.70	<0.001	0.82	<0.001

Legend: This tables presents the relationship of FEF_{25-75} % predicted and FEF_{25-75}/FVC with other spirometric measures. The relationship was assessed using curvilinear regression analysis.

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_3, forced expiratory volume in three seconds.

Supplementary Figures

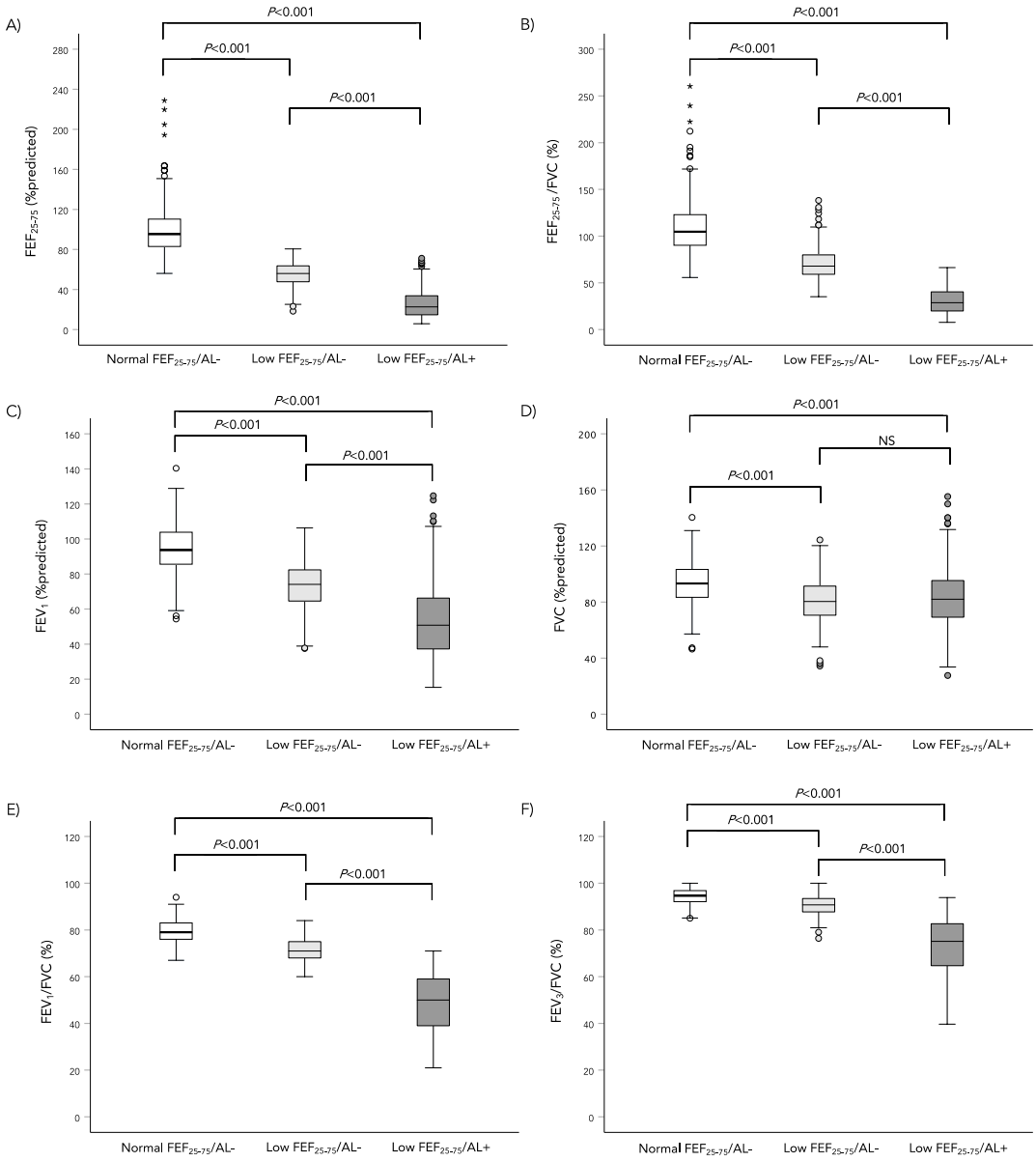


Figure E1. **Distribution of %predicted or ratio of spirometric measures across study groups**.

Legend: A box plot demonstrating the distribution of the % predicted or ratio of spirometric measures across study groups. The plot shows median, interquartile range, minimum and maximum. A) The distribution of

FEF_{25-75} % predicted across groups. B) The distribution of FEF_{25-75}/FVC ratio across groups. C) The distribution of FEV_1 % predicted across groups. D) The distribution of FVC % predicted across groups. E) The distribution of FEV_1/FVC ratio across groups. F) The distribution of FEV_3/FVC ratio across groups. For groups' comparisons, Kruskal-Wallis H test was performed, and for statistically significant test, a post-hoc Dunn's test was applied. The presented *P* values were adjusted using the Bonferroni method to account for multiple comparisons. For figures A and E, statistical test was only done for differences between groups where a definition did cause the variable to differ, and the reported p-values are for the Mann-Whitney U test. For figures B, C, D and F, the presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis tests p-values for all figures were <0.001.

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_3, forced expiratory volume in the first 3 seconds; AL, airflow limitation; NS, not significant.

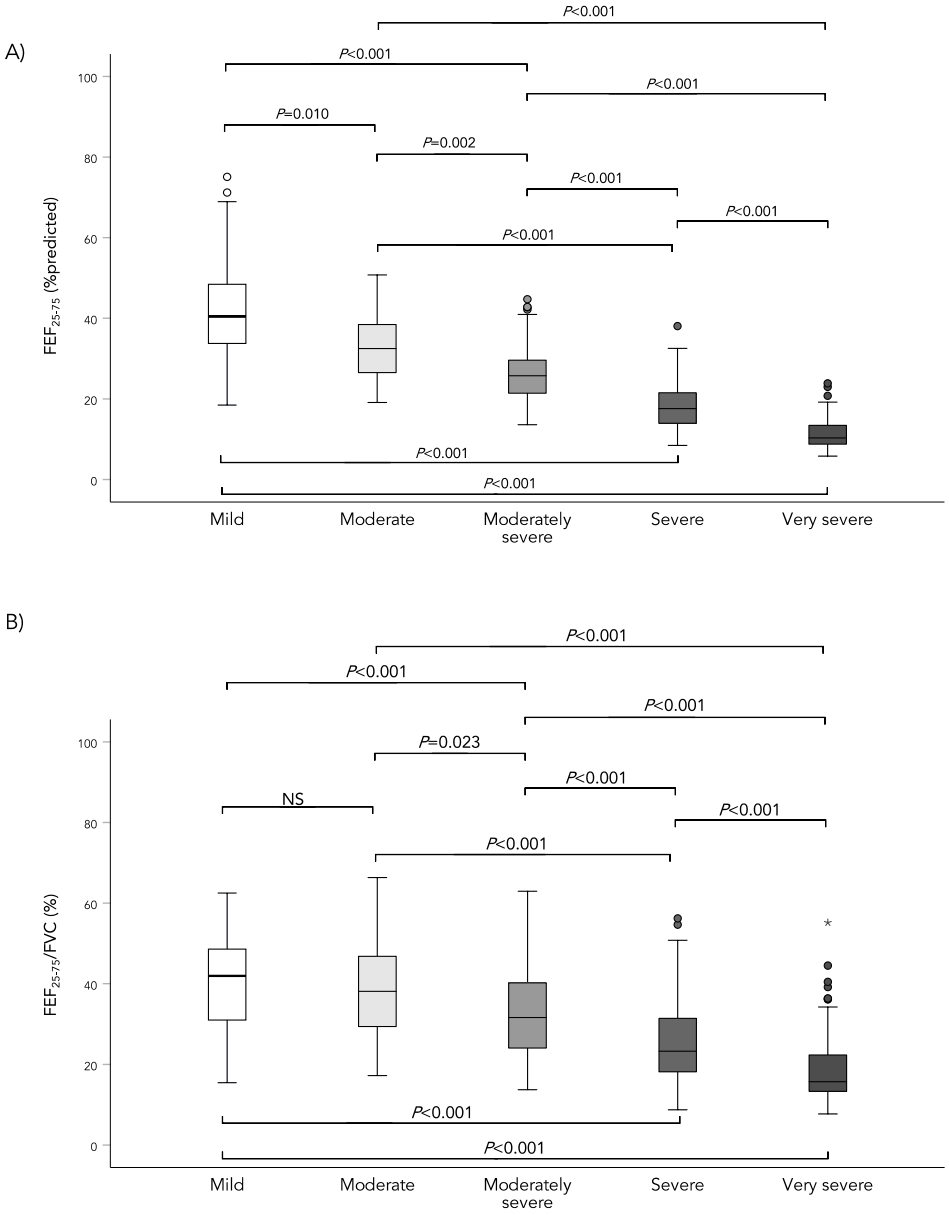
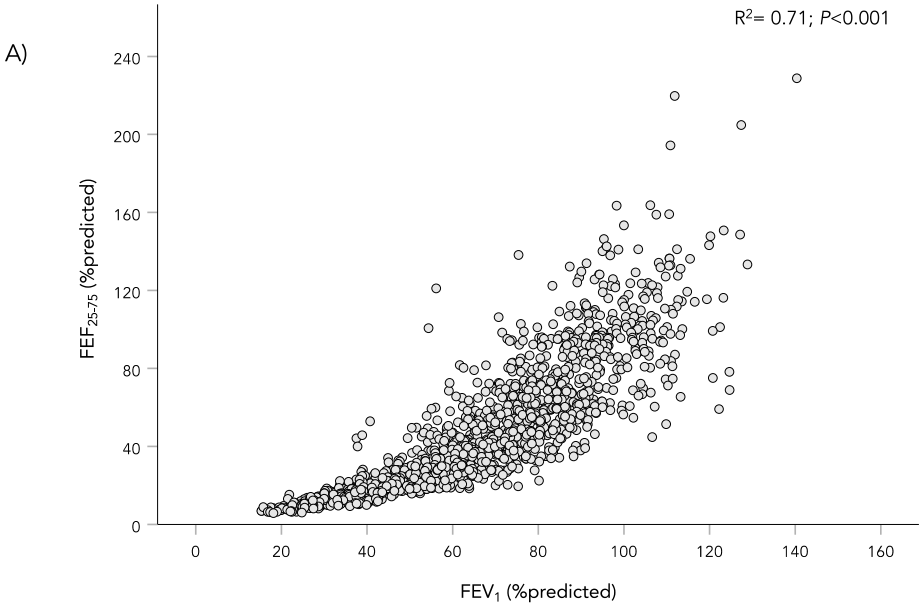


Figure E2. **Distribution of FEF_{25-75} and FEF_{25-75}/FVC across AL severity**.

Legend: A box plot demonstrating the distribution of FEF_{25-75} and FEF_{25-75}/FVC across AL severity. The plot shows median, interquartile range, minimum and maximum. A) The distribution of FEF_{25-75} % predicted across severity. B) The distribution of FEF_{25-75}/FVC ratio across severity. AL severity was assessed using FEV_1 z-score. For groups' comparisons, Kruskal-Wallis H tests was performed, and for statistically significant test, a

post-hoc Dunn's test was applied. The presented *P* values were adjusted using the Bonferroni method to account for multiple comparisons. The p-values for Kruskal-Wallis H tests for both figures were <0.001.

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FVC, forced vital capacity; NS, not significant; AL, airflow limitation.



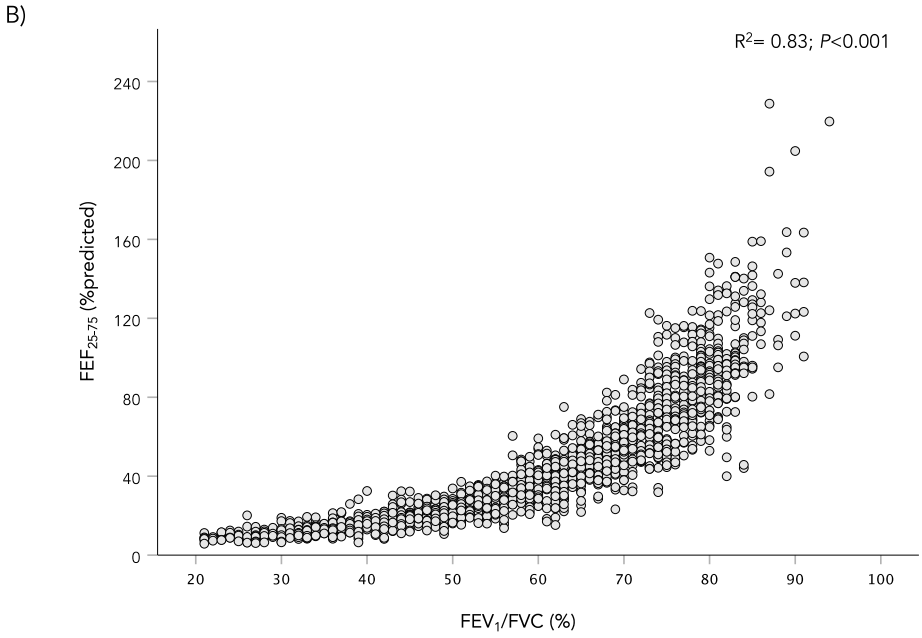


Figure E3. FEV_1 % predicted and FEV_1/FVC plotted against FEF_{25-75} % predicted.

Legend: A) A scatter plot showing the relationship between FEF_{25-75} % predicted and FEV_1 % predicted. B) A scatter plot showing the relationship between FEF_{25-75} % predicted and FEV_1/FVC %. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its *P* value.

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.

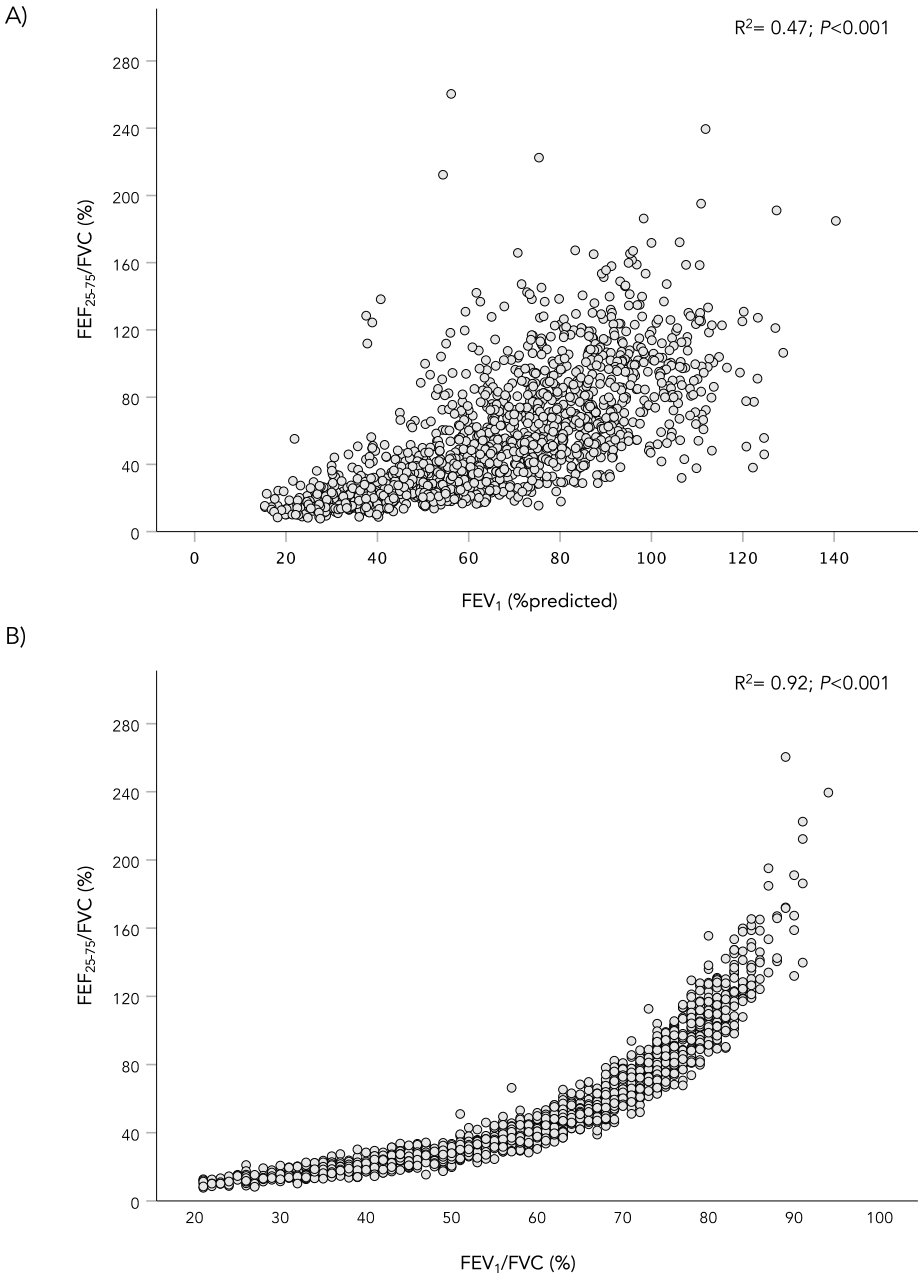


Figure E4. FEV_1 % predicted and FEV_1/FVC plotted against FEF_{25-75}/FVC.

Legend: A) A scatter plot showing the relationship between FEF_{25-75}/FVC and FEV_1 % predicted. B) A scatter plot showing the relationship between FEF_{25-75}/FVC and FEV_1/FVC. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its *P* value.

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.