



Emphysema Severity Index: a new spirometric parameter in epidemiology

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ESI represents a potentially valuable indicator in epidemiological surveys on the general population, as it reflects current respiratory health status and demonstrates predictive capacity for future hospitalisations <https://bit.ly/4u2ynbN>

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Abstract

Background The Emphysema Severity Index (ESI) is a recently developed parameter describing the curvilinear shape of the expiratory flow/volume curve to evaluate the emphysema contribution to airflow obstruction (AO), as observed in COPD patients and geriatric populations. The aim of the present study was to assess ESI usefulness in respiratory epidemiology studies where spirometry is typically the only available objective tool.

Methods An adult population sample of Pisa (Central Italy) (n=685, 47.3% male, mean age 53.3 years) participated in an epidemiological survey through standardised questionnaire and spirometry (2009–2011); information on hospital admissions was available up to 2017. The input variables for the ESI computing algorithm are peak expiratory flow, forced vital capacity (FVC) and the forced expiratory flows at 25%, 50% and 75% of FVC. ESI is a numerical value ranging from 0 (no emphysema) to 10 (very severe emphysema). Statistics included descriptive analyses, Kruskal–Wallis nonparametric test and logistic regression models.

Results The ESI mean±SD value was: 1.16±0.78; median (IQR) 0.98 (0.39). The ESI was significantly higher in males, ex-smokers, the elderly, subjects with asthma/COPD, and in those with limited daily activities, higher number of doctor visits and hospital admission for respiratory disease. For each increment of an ESI IQR, higher odds of respiratory outcomes, daily activity limitations and use of health services emerged in the total sample, but also in subjects without AO.

Conclusions ESI represents a potentially valuable indicator in epidemiological surveys on the general population and allows early changes in lung function to be identified also in subjects without AO, which is valuable for secondary prevention.

Introduction

Morphology of the maximal expiratory flow/volume (MEFV) curve exhibits characteristic configurations corresponding to various patterns of airway pathological changes [1–3]. Beyond its utility in identifying significantly altered airway dynamics, detailed analysis of the MEFV curve shape can detect a slowing of flow at low lung expiratory volumes, even in individuals whose forced expiratory volume in 1 s (FEV₁) after a deep inhalation remains within normal limits. Low resistance to airflow in the large cross-sectional area of small airways at high lung volumes can increase significantly at lower lung volumes [4]. Accordingly, a more detailed analysis of the downslope of flow–volume curve for its whole length might be appropriate to detect morphological changes compatible with early obstructive alterations.



Spirometry is widely employed in epidemiological studies, and it is based on analyses of numerical values, often overlooking MEFV curve morphology. However, detecting the earliest changes in airflow dynamics through detailed curve analysis might be crucial for revealing potential effects of harmful external factors in general population studies.

A parametric biomechanical model was recently developed to approximate the shape of the MEFV curve descending portion and to estimate presence and severity of emphysema, as assessed by computed tomography (CT), in patients with COPD [5–6]. The novel parameter, called the Emphysema Severity Index (ESI), is calculated based on the assumption that pressure loss in a fluid flowing through a cylindrical duct (the airways) at a given time is inversely related to the duct's diameter and directly related to the fluid (air) density, velocity and specific friction factor, as described in the circular ducts theory [5]. Spirometric input parameters required for ESI mathematical computation do not rely on retrospective statistical inference or standardisation using % predicted reference values, as ESI is directly determined by the curve shape for each individual undergoing spirometry [5–6]. Prior efforts to quantify these alterations in COPD patients using geometric parameters (*e.g.*, slopes, integrals, flow ratios) have shown limited sensitivity and specificity in distinguishing emphysema from airway disease [7–13].

In addition to detecting emphysema-related changes in the MEFV curve of COPD patients, ESI has been shown to specifically predict respiratory mortality in a large sample of the geriatric Swedish population. In such a population, age, male sex, current smoking and FEV₁ were associated with both respiratory and nonrespiratory mortality [14].

The aim of the current study was to assess whether ESI might be useful in epidemiological studies, where spirometry and specific questionnaires are the only available tools to evaluate the effects of risk factors on respiratory health. To this end, we measured ESI in an Italian general population sample and investigated whether ESI might provide additional valuable information in respiratory epidemiological research.

Methods

The study population included 685 subjects participating in an observational analytical study aimed at investigating allergic and respiratory conditions in a general population sample living in the urban/suburban area of Pisa (Tuscany, Italy) between 2009 and 2011. Detailed information on inclusion/exclusion criteria are reported in the supplementary material, while population characteristics and methods are available elsewhere [15–18].

Information on symptoms/diseases and risk factors was obtained through a standardised interviewer-administered questionnaire [18].

Data on hospitalisation causes for 1997–2017 and on all-cause deaths for 2019 were available through the civil registry office.

All subjects agreed to perform pre-bronchodilator spirometry (forced vital capacity (FVC) manoeuvre) according to the American Thoracic Society/European Respiratory Society recommendations [19], through a hand-held ultrasonic spirometer (EasyOne Model 2001 Spirometer; NDD Medical Technologies), under the guidance of trained technicians. Each spirogram underwent a *post hoc* review by two independent reviewers. ESI was calculated on curves that passed this validation.

The study protocol, patient information sheet and consent form were approved by the Pisa University Hospital Ethics Committee (Prot. no. 23887, 16 April 2008; Prot. no. 24567, 8 May 2018).

ESI computation

The ESI computing algorithm only uses five input variables obtained from standard spirometry: peak expiratory flow, FVC and forced expiratory flows at 25%, 50% and 75% of FVC. All input variables are expressed in absolute values. ESI is a continuous positive numerical value ranging from 0 (no emphysema) to 10 (very severe emphysema), calibrated against the extent of emphysema detected *via* CT [5–6]. A detailed description of the method has been previously published [5].

Respiratory outcomes

The following cross-sectional respiratory outcomes reported from questionnaire were considered and categorised as yes/no: 1) asthma, COPD, emphysema, chronic bronchitis; 2) asthma attacks in the last 12 months, chronic phlegm, chronic cough, dyspnoea grade I+; 3) drug consumption (inhaled corticosteroids (ICS) or long-acting β -adrenoceptor agonists (LABA) or short-acting β -adrenoceptor

agonists or ICS+LABA or anticholinergics or chromones); 4) emergency department visits/hospitalisations, physician visits and daily activity limitations for respiratory causes in the last 12 months.

Data from routine administrative and health archives permitted retrospective and prospective information to be accessed: 1) all-cause deaths in 2019 (yes/no); 2) hospitalisations for respiratory diseases and for other causes until the field study (at baseline) (1997–2011) (yes/no) and after the field study (post-baseline) (2012–2017) (yes/no).

Airflow obstruction (AO) was detected using either the European Respiratory Society (ERS)/American Thoracic Society (ATS) criterion (FEV_1/FVC % predicted <lower limit of normal (AO_{LLN})) [20] (the LLN was derived from population-specific prediction equations [21]) or the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion (FEV_1/FVC <70% (AO_{GOLD})) [22].

Statistical analyses

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS version 28.0). Comparisons were carried out using the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables.

The association among respiratory outcomes and one interquartile range (IQR) increase of the ESI score was assessed through multiple logistic regression models, adjusting for age, sex and smoking habits (current, ex- and nonsmokers). Stratified analyses by sex and by AO were run to analyse possible different associations in males and females and in subjects having or not having AO_{LLN} or AO_{GOLD} . Additionally, sensitivity analyses were performed by adjusting multiple logistic regression models for FEV_1 observed value. Moreover, an analysis using, as dependent variable, the FEV_1/FVC % instead of ESI was performed.

Odds ratio and 95% confidence interval were calculated. Significance level was set at 0.05. A p-value $0.05 < p < 0.1$ was considered borderline statistically significant.

Results

Distribution of ESI in the study population

Among 685 participants (47.3% male; mean±SD age 53.5±16.6 years), age distribution spanned from 18 to 89 years. 21.8% of subjects were current smokers, 33.7% ex-smokers (table 1). Subjects with AO tended to be older and more frequently ex-smokers; they showed lower spirometric values and a higher ESI value (table 1).

	Total	Without AO_{LLN}	With AO_{LLN}	p-value
Subjects, n	685	575	110	
Sex %				0.408
Males (n=324)	47.3	46.6	50.9	
Females (n=361)	52.7	53.4	49.1	
Age years, mean±SD	53.5±16.6	51.5±16.4	63.9±13.5	<0.001
Range years	18–89	18–88	19–89	
Smoking habits %				0.001
Smokers (n=149)	21.8	21.7	21.8	
Ex-smokers (n=231)	33.7	31.0	48.2	
Nonsmokers (n=305)	44.5	47.3	30.0	
FEV_1 L, mean±SD	3.0±1.0	3.1±0.9	2.2±0.8	<0.001
Range L	0.5–6.0	0.5–6.0	0.5–4.1	
FVC L, mean±SD	3.9±1.2	4.0±1.2	3.8±1.2	0.087
Range L	0.6–7.5	0.6–7.5	0.9–6.5	
FEV_1/FVC%, mean±SD	74.8±10.4	78.1±6.9	57.7±9.2	<0.001
Range %	17.0–98.0	62.0–98.0	17.0–71.0	
ESI, median (IQR)	0.9 (0.4)	0.9 (0.3)	1.6 (1.1)	<0.001
AO_{LLN} : airflow obstruction detected using lower limit of normal criterion; FEV_1 : forced expiratory volume in 1 s; FVC: forced vital capacity; ESI: Emphysema Severity Index. Statistically significant or borderline results are reported in bold.				

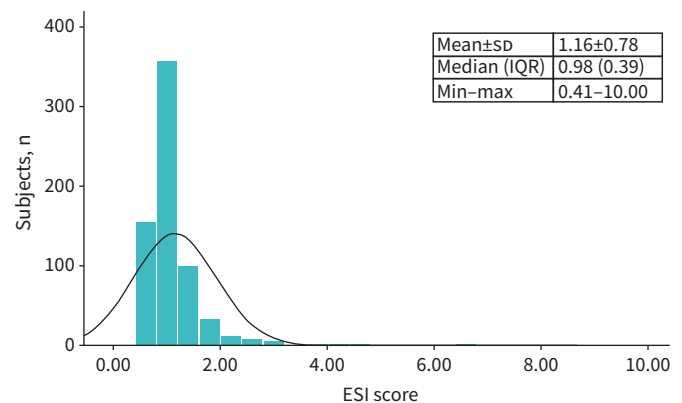


FIGURE 1 Emphysema Severity Index (ESI) value distribution. IQR: interquartile range; min: minimum; max: maximum.

ESI value distribution had a right-skewed pattern with most values clustered in the lower value group (about 50% of sample had ESI values between 0.80 and 1.20) (figure 1). ESI values increased progressively with age (regression coefficient and standard error 0.006, 0.002; $p<0.001$). Ex-smokers showed higher ESI values than nonsmokers (median (IQR) 1.04 (0.50) *versus* median 0.96 (0.39); $p=0.081$) (data not shown).

The highest prevalence values of respiratory conditions were shown for dyspnoea (32.7%) and for AO (19.7% AO_{GOLD} and 16.1% AO_{LLN}). About 10% of the subjects reported consumption of inhaled drugs, asthma diagnosis and chronic phlegm (figure 2).

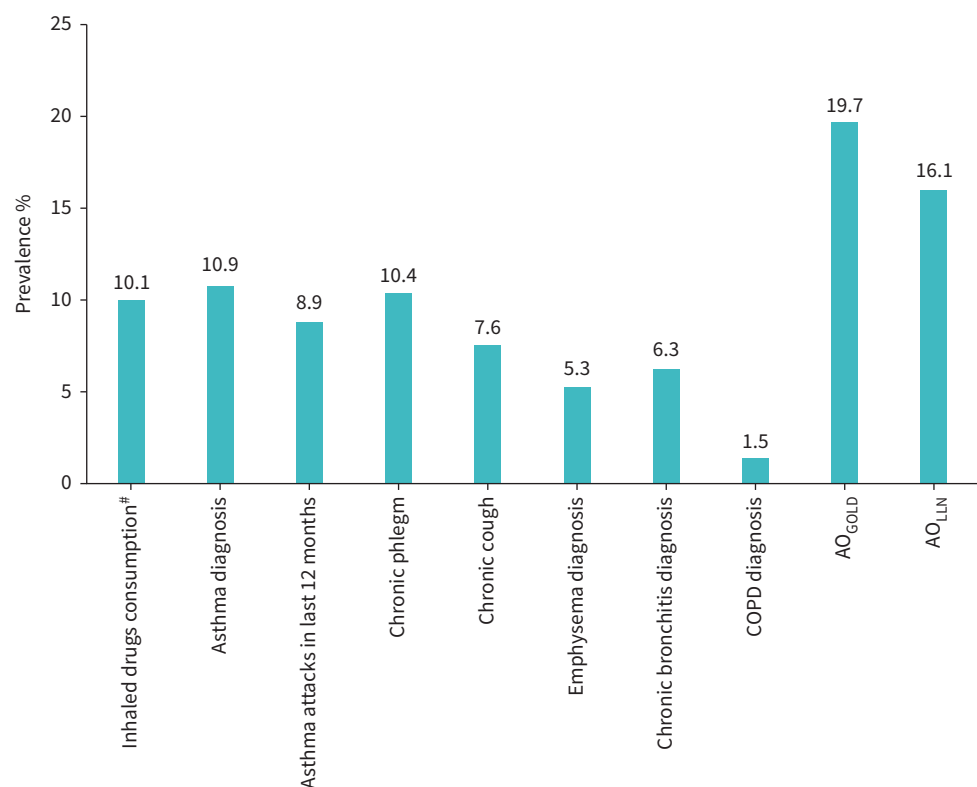


FIGURE 2 Respiratory outcomes prevalence. LABA: long-acting β -adrenoceptor agonists; SABA: short-acting β -adrenoceptor agonists; AO_{GOLD}: airflow obstruction detected using Global Initiative for Chronic Obstructive Lung Disease criterion; AO_{LLN}: airflow obstruction detected using lower limit of normal criterion. [#]: inhaled steroids (ICS), ICS+LABA, LABA, SABA, anticholinergics and chromones.

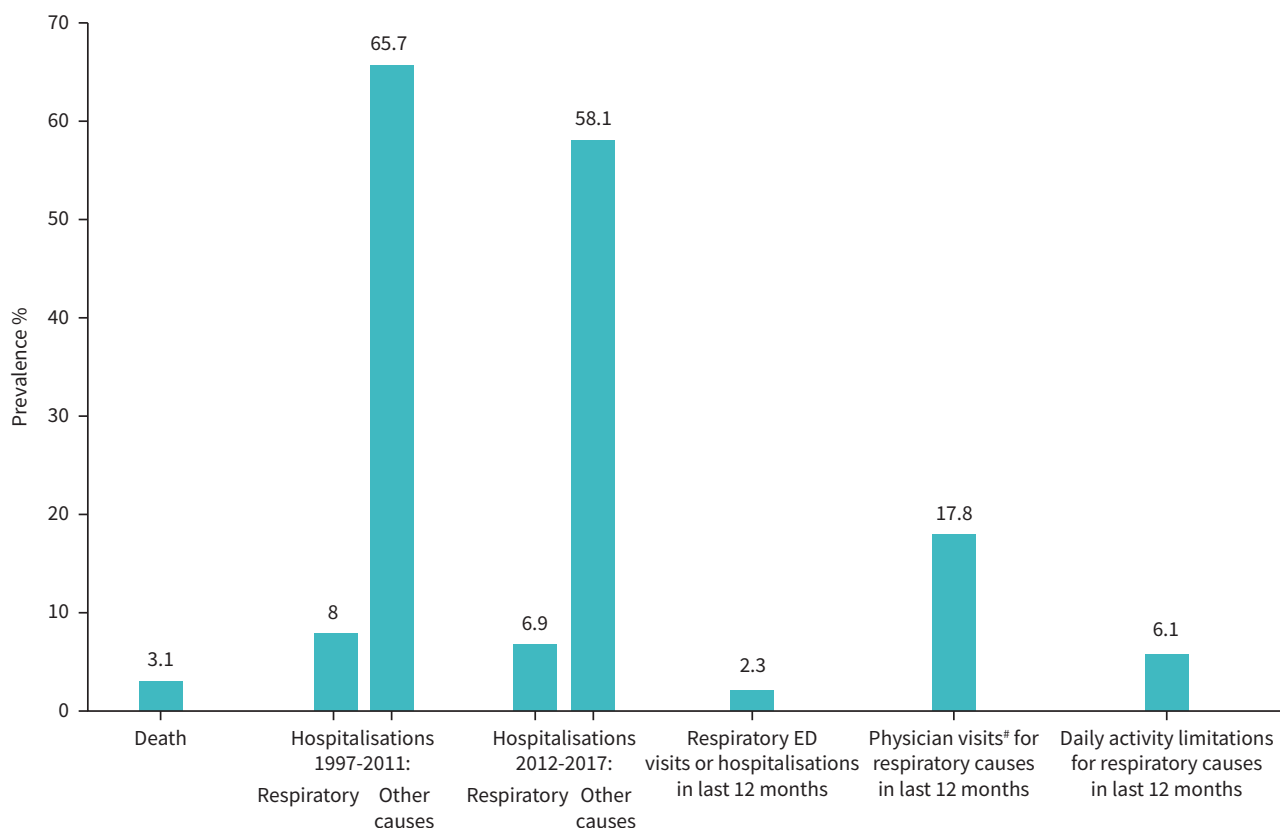


FIGURE 3 Mortality, use of health services and daily activity limitations prevalence. ED: emergency department. [#]: general practitioners, specialists and control visits.

About 8% of participants had respiratory-related hospitalisations over their lifetime, while a much higher percentage (about 60%) were hospitalised for other causes. In the previous 12 months, about 20% consulted general practitioners or specialists for respiratory conditions, while daily activities were limited by respiratory causes in 6.1% (figure 3).

ESI values and analysed outcomes

ESI values were significantly higher in subjects who reported respiratory symptoms, respiratory diagnosis and inhaled drugs use compared to those who did not (table 2: total sample).

An association between higher ESI values and respiratory outcomes was observed also in subjects without AO (table 2: without AO_{LLN}).

ESI values were significantly higher in subjects with daily activity limitations and in those with lifetime respiratory hospitalisations at baseline evaluation, respiratory ED or respiratory-related physician visits (table 3).

ESI values were higher also in subjects having respiratory hospitalisations post-baseline evaluation (table 3).

The same results for hospitalisations post-baseline and activity limitations emerged in the subgroup of subjects without AO_{LLN} (table 3).

Associations among health outcomes and a 1-IQR increase in ESI

Through logistic regression analyses, adjusted for sex, age and smoking habits, a 1-IQR increase in ESI value was associated with a higher probability of having all the investigated respiratory conditions, except for chronic phlegm and chronic cough (table 4).

TABLE 2 Emphysema Severity Index (ESI) score by respiratory outcomes in the total sample and by AO_{LLN}

	Total		Without AO _{LLN}		With AO _{LLN}	
	Median (IQR)	p-value [#]	Median (IQR)	p-value [#]	Median (IQR)	p-value [#]
Subjects, n	685		575		110	
Inhaled drugs consumption						
Yes	1.26 (1.44)	<0.001	1.08 (0.30)	<0.001	2.76 (2.34)	<0.001
No	0.96 (0.37)		0.92 (0.33)		1.48 (0.50)	
Asthma diagnosis						
Yes	1.15 (0.78)	<0.001	1.07 (0.35)	<0.001	2.50 (1.60)	0.002
No	0.97 (0.37)		0.91 (0.33)		1.53 (0.74)	
Asthma attacks in last 12 months						
Yes	1.17 (0.84)	<0.001	1.08 (0.32)	<0.001	2.51 (2.75)	<0.001
No	0.97 (0.38)		0.91 (0.33)		1.52 (0.73)	
Chronic phlegm						
Yes	1.07 (0.51)	0.056	0.96 (0.34)	0.319	2.12 (1.53)	0.166
No	0.98 (0.38)		0.92 (0.33)		1.55 (0.92)	
Chronic cough						
Yes	1.08 (0.46)	0.035	0.95 (0.35)	0.384	1.67 (1.59)	0.328
No	0.98 (0.38)		0.92 (0.33)		1.55 (1.14)	
Emphysema diagnosis						
Yes	1.57 (1.73)	<0.001	0.96 (0.43)	0.590	2.56 (3.09)	<0.001
No	0.97 (0.37)		0.92 (0.33)		1.52 (0.75)	
Chronic bronchitis diagnosis						
Yes	1.24 (1.59)	<0.001	1.02 (0.41)	0.042	2.69 (2.59)	0.009
No	0.97 (0.37)		0.92 (0.33)		1.53 (0.72)	
COPD diagnosis						
Yes	2.56 (2.02)	<0.001	1.22 (0.09)	0.012	2.97 (2.86)	0.001
No	0.98 (0.38)		0.92 (0.33)		1.54 (0.91)	
COPD/CB/emphysema						
Yes	1.26 (1.34)	<0.001	0.99 (0.43)	0.064	2.48 (2.00)	<0.001
No	0.97 (0.37)		0.92 (0.33)		1.50 (0.50)	
Dyspnoea (grade I+)						
Yes	1.03 (0.42)	0.022	0.94 (0.31)	1.000	1.91 (1.54)	0.012
No	0.97 (0.39)		0.92 (0.34)		1.52 (0.48)	

AO_{LLN}: airflow obstruction according to lower limit of normal of American Thoracic Society (ATS) and European Respiratory Society (ERS) (FEV₁/FVC <5th percentile of predicted value); CB: chronic bronchitis. #: Kruskal–Wallis test for independent samples. The p-values refer to total, without AO and with AO subsamples. Statistically significant or borderline results are reported in bold.

The same trends were confirmed in the analyses stratified by AO_{LLN}, with the highest ORs in subjects without AO_{LLN} (table 4). This finding might be due to the stronger effect of 1-IQR increase in subjects with a lower baseline value of ESI (ESI median value 0.92 in subjects without AO_{LLN} versus 1.61 in subjects with AO_{LLN}). These results were confirmed also when considering AO_{GOLD} (supplementary table S1).

A 1-IQR ESI increase was also significantly associated with respiratory hospitalisations at baseline (OR 1.23, 95% CI 1.06–1.42) (table 5). Similar patterns were found for ED visits or hospitalisations and physician visits in the last 12 months. ESI was related to daily activity limitations in the last 12 months (OR 1.12, 95% CI 1.01–1.24) (table 5). The same trends were confirmed in subjects with AO_{LLN}, except for daily activity limitations. Highest ORs were found in subjects without AO_{LLN}, except for hospitalisations at baseline (table 5). These results were confirmed when also considering AO_{GOLD} (supplementary table S2).

A 1-IQR ESI increase was significantly related to respiratory hospitalisations post-baseline (OR 1.27, 95% CI 1.09–1.48); this result was confirmed in subjects with and without AO_{LLN} (table 5). No significant association emerged for all-cause death and an ESI IQR increase (data not shown).

Stratifying the analyses by sex, females were found to be less likely to smoke, with lower FEV₁ and FVC values but a higher FEV₁/FVC ratio and a lower ESI value (supplementary table S3). The associations

TABLE 3 Emphysema Severity Index (ESI) score by mortality, use of health services and daily activity limitations in the total sample and by AO_{LLN}

	Total		Without AO _{LLN}		With AO _{LLN}	
	Median (IQR)	p-value [#]	Median (IQR)	p-value [#]	Median (IQR)	p-value [#]
Subjects, n	685		575		110	
Death (2019)						
Yes	1.11 (0.63)	0.190	0.89 (0.36)	0.869	1.76 (5.08)	0.205
No	0.98 (0.38)		0.93 (0.33)		1.59 (1.05)	
Lifetime hospitalisations (primary cause) at baseline (1997–2011)						
Respiratory	1.06 (0.70)	0.064	0.99 (0.27)	0.220	2.97 (2.08)	0.001
Other causes	0.97 (0.40)		0.91 (0.34)		1.63 (0.81)	
No hospitalisation	0.98 (0.41)		0.94 (0.33)		1.36 (0.65)	
Lifetime hospitalisations (primary cause) post baseline (2012–2017)						
Respiratory	1.30 (2.01)	<0.001	1.04 (0.40)	0.011	3.98 (3.94)	0.015
Other causes	0.95 (0.36)		0.90 (0.31)		1.54 (0.86)	
No hospitalisation	0.98 (0.41)		0.94 (0.33)		1.36 (0.65)	
Respiratory ED visits or hospitalisations in last 12 months						
Yes	1.16 (0.72)	0.056	0.95 (0.31)	0.370	3.98 (3.81)	0.054
No	0.98 (0.39)		0.92 (0.33)		1.55 (1.00)	
Physician visits for respiratory causes in last 12 months						
Yes	1.06 (0.63)	0.001	0.96 (0.28)	0.206	2.12 (2.40)	0.003
No	0.97 (0.38)		0.92 (0.34)		1.52 (0.67)	
Daily activity limitations for respiratory causes in last 12 months						
Yes	1.09 (0.67)	0.009	1.03 (0.29)	0.015	1.98 (2.84)	0.232
No	0.97 (0.39)		0.92 (0.33)		1.55 (0.99)	

AO_{LLN}: airflow obstruction according to lower limit of normal of American Thoracic Society and European Respiratory Society (forced expiratory volume in 1 s/forced vital capacity ratio <5th percentile of predicted value); ED: emergency department. [#]: Kruskal–Wallis test for independent samples. The p-values refer to total, without AO and with AO subsamples. Statistically significant or borderline results are reported in bold.

with ESI persisted with the highest OR in females, except for emphysema diagnosis (not significant in females), and daily activity limitations (not significant in males) (supplementary table S4–S5).

Sensitivity analyses

The analyses performed also adjusting for FEV₁ values confirmed the main results in the subsample of subjects without AO. As expected, some results differed in the total sample and in the subsample with AO, since this group by definition has a reduced FEV₁ (supplementary table S6–S7).

TABLE 4 Association between Emphysema Severity Index (ESI) score interquartile range and respiratory outcomes

	Total, OR (95% CI)	Without AO _{LLN} , OR (95% CI)	With AO _{LLN} , OR (95% CI)
Inhaled drugs consumption	1.56 (1.35–1.80)	1.63 (1.17–2.28)	1.72 (1.30–2.27)
Asthma diagnosis	1.24 (1.13–1.37)	1.40 (1.03–1.89)	1.18 (1.03–1.35)
Asthma attacks in last 12 months	1.30 (1.17–1.45)	1.67 (1.17–2.38)	1.26 (1.09–1.46)
Chronic phlegm	1.05 (0.96–1.15)	1.27 (0.94–1.73)	1.02 (0.89–1.16)
Chronic cough	1.05 (0.95–1.16)	1.24 (0.87–1.76)	1.04 (0.90–1.20)
Emphysema diagnosis	1.28 (1.13–1.44)	1.36 (0.79–2.34)	1.21 (1.03–1.43)
Chronic bronchitis diagnosis	1.24 (1.12–1.38)	1.67 (1.17–2.39)	1.19 (1.05–1.37)
COPD diagnosis	1.28 (1.08–1.50)	3.15 (1.06–9.39) [#]	1.22 (1.02–1.46)
COPD/CB/emphysema	1.37 (1.21–1.56)	1.59 (1.15–2.21)	1.28 (1.09–1.50)
Dyspnoea (grade I+)	1.24 (1.11–1.39)	1.16 (0.92–1.47)	1.33 (1.09–1.63)

Model adjusted for sex, age and smoking habits. AO_{LLN}: airflow obstruction according to lower limit of normal of American Thoracic Society and European Respiratory Society (forced expiratory volume in 1 s/forced vital capacity ratio <5th percentile of predicted value); CB: chronic bronchitis. [#]: only four subjects with COPD diagnosis. Statistically significant or borderline results are reported in bold.

TABLE 5 Association between Emphysema Severity Index (ESI) score interquartile range, use of health services and daily activity limitations

	Total, OR (95% CI)	Without AO_{LLN}, OR (95% CI)	With AO_{LLN}, OR (95% CI)
Lifetime hospitalisations (primary cause) at baseline (1997–2011)			
Respiratory	1.23 (1.06–1.42)	1.14 (0.67–1.96)	1.33 (1.03–1.72)
Other causes	0.99 (0.88–1.13)	0.98 (0.71–1.34)	0.99 (0.81–1.21)
Lifetime hospitalisations (primary cause) post-baseline (2012–2017)			
Respiratory	1.27 (1.09–1.48)	2.08 (1.14–3.81)	1.26 (1.00–1.59)
Other causes	0.97 (0.84–1.12)	0.90 (0.63–1.27)	0.97 (0.78–1.20)
Respiratory ED visits or hospitalisations in last 12 months	1.16 (1.02–1.32)	1.36 (0.66–2.83)	1.28 (1.04–1.58)
Physician visits for respiratory causes in last 12 months	1.22 (1.11–1.35)	1.29 (0.99–1.69)	1.27 (1.08–1.48)
Daily activity limitations for respiratory causes in last 12 months	1.12 (1.01–1.24)	1.47 (1.04–2.07)	1.13 (0.97–1.31)
Model adjusted for sex, age and smoking habits. AO _{LLN} : airflow obstruction according to lower limit of normal of American Thoracic Society and European Respiratory Society (forced expiratory volume in 1 s/forced vital capacity ratio <5th percentile of predicted value); ED: emergency department. Statistically significant or borderline results are reported in bold.			

Discussion

In our general population sample, an increased ESI value was linked to a higher probability of having respiratory outcomes, use of health services and daily activity limitations. Associations with daily activity limitations and post-baseline respiratory hospitalisations were confirmed also in those without AO, suggesting ESI as a useful indicator of early identification of subjects most likely to use health services in respiratory epidemiology.

Despite a right-skewed pattern, with most values concentrated at the lower end of the scale, ESI was significantly associated with key demographic and clinical characteristics. Notably, ESI values were higher in males, increased with age and were elevated in ex-smokers compared to never-smokers. These findings are consistent with the expected cumulative burden of airway structural and functional alterations due to age and smoking history.

ESI demonstrated robust associations with several respiratory health indicators. Higher ESI values were consistently observed in individuals with physician-diagnosed COPD, asthma or emphysema, as well as among those with either AO_{LLN} or AO_{GOLD}. The higher ESI values among subjects diagnosed with COPD suggest that ESI may be especially useful in detecting emphysema-like changes not captured by standard spirometric thresholds [5, 6, 23, 24]. A recent study [25] suggests that ESI values, comparable to those observed in our emphysema subgroup, may not adequately capture the loss of alveolar septal vessels, a feature more accurately reflected by measurements of lung capillary blood volume derived from diffusing capacity. It has been hypothesised that ESI values indicative of mild-to-moderate emphysema primarily reflect reduced alveolar tethering of the small airways, contributing to expiratory airflow limitation [25].

Furthermore, ESI showed significant associations with respiratory-related hospitalisations (both at baseline and post baseline), emergency department visits and physician consultations. In addition, increased ESI was linked to daily activity limitations.

The regression analyses further underscored the association of ESI with the current health status and the predictive value in terms of hospitalisations. An interquartile range increase in ESI was associated with significantly higher odds of reporting asthma attacks, respiratory drug use, diagnoses of COPD, chronic bronchitis or emphysema, dyspnoea and use of health services, independent of sex, age and smoking status. Stratified analyses showed that these associations were particularly strong in individuals without AO, indicating that ESI may detect early or subclinical alterations in lung function not yet reflected in conventional obstruction thresholds. The analyses adjusted for FEV₁ reinforced the results in the subsample of subjects without AO.

Furthermore, we have evaluated the predictive performance of ESI *versus* FEV₁% pred in subjects without AO: similar relationships for ESI and FEV₁ were found cross-sectionally; ESI (but not FEV₁) was significantly associated with a higher probability of post-baseline hospitalisations longitudinally (data not shown). At last, a sensitivity analysis was performed using FEV₁/FVC% as dependent variable in place of ESI: ESI value shows larger strengths of associations with respiratory outcomes than FEV₁/FVC% (supplementary tables S8 and S9). These findings align with the theoretical basis of ESI, which quantifies the expiratory flow–volume curve's shape and may reflect early small airways disease [5–6].

The lack of significant association between ESI and overall mortality, previously observed in a larger geriatric general population sample [14], may reflect the relatively young mean age of the cohort, limited follow-up time for mortality data or the multifactorial nature of general mortality in population samples.

Sex-stratified analyses revealed stronger associations in females for most outcomes, suggesting potential sex-related differences in the structural or physiological changes captured by ESI. Conversely, emphysema diagnosis was not significantly associated with ESI in females, and daily activity limitations were not associated with ESI in males, indicating that the clinical expression and functional impact of ESI-detectable changes may vary by sex.

Limitations and strengths

These findings highlight ESI as a promising metric in respiratory epidemiology. It offers the advantage of being derived from observed values of standard spirometry data, making it feasible for large-scale use without additional data collection burden [14]. Its independence from anthropometric factors and its calibration against CT-based emphysema further supports its potential clinical and epidemiological value. Indeed, ESI was developed to compare CT and spirometry assessment of emphysema in patients with COPD. Assessing emphysematous destruction of lung parenchyma in a general population study might therefore seem somewhat inappropriate. However, measurable amounts of emphysema have been detected by CT scan even among healthy never-smokers in a large multiethnic general population sample [24]. Another general population study has shown that 11% of subjects older than 40 years who never smoked and 30% of smokers with normal lung function have evidence of emphysema on CT scans [26]. Thus, it seemed appropriate to evaluate whether in our general population sample ESI could detect the small percentages of emphysema-like changes as observed in CT studies obtained in normal subjects in different populations.

Nonetheless, several limitations should be acknowledged. First, the cross-sectional nature of the study limits causal inference. Second, despite the robustness of associations, the relatively low prevalence of certain outcomes (*e.g.*, COPD diagnosis) may have limited the statistical power for subgroup analyses. Third, while ESI was developed and validated against emphysema on imaging, this study lacked direct imaging data to assess concordance in this population. Fourth, the use of a questionnaire for gathering information on symptoms/diseases could be influenced by a reporting bias, dependent on personal recall. Nevertheless, the standardised questionnaire stands out as a primary tool for research in respiratory epidemiology [27, 28]. Moreover, we also applied an objective respiratory outcome (lung function), not affected by this potential bias.

A strength of our study is the application of standardised study protocols and questions derived from validated international questionnaires, which had passed the scrutiny of independent reviewers. In addition, ESI was not conceived or calculated at the time of data collection and, therefore, spirometry was not performed with the specific intent of optimising ESI estimation. This implies that the procedures were completely independent of ESI, resembling real-life scenarios, and thereby reducing the risk of selection biases related to the index itself. Another strength comes from the analysis of a general population sample that ranged from early to late adulthood (elderly people), using both qualitative and quantitative individual data. Moreover, the sample size permitted us to analyse data stratified by sex, showing a stronger effect of ESI increase on daily activity limitations and use of health services in females. These results can have important implications, especially in gender-specific healthcare.

The ESI score was measured cross-sectionally for each individual, leading to uncertainty as it is based on only one point in time. A longitudinal analysis on the health outcomes and use of health services could further strengthen our evidence. However, we had the opportunity to analyse the relationship between ESI and post-baseline respiratory hospital admissions (2012–2017), highlighting how an increase in ESI value is linked to a higher probability of hospital admissions, even in subjects without baseline AO.

Finally, we believe that the ESI value relies on its ability to reflect more accurately than other standard spirometry parameters the shape of the flow–volume curve. The routine evaluation of the shape of the flow–volume curve is subjectively made by the pulmonologist at every spirometry test. Morphological changes, with particular reference to the descending limb of the curve, are indeed considered relevant for the clinical assessment of each patient. ESI confers objectivity to this evaluation and expands the information obtained from spirometry beyond the first second of expiration indicating early airflow limitation at low expiratory lung volume that may not be detected by FEV₁.

Conclusions

ESI is a novel indicator of expiratory airflow limitation that reflects current respiratory health status and also demonstrates predictive value for future outcomes, particularly hospitalisations. ESI holds promise as

a valuable tool in both epidemiological research and clinical practice, with potential predictive utility. Its integration into population-based studies may improve the identification and characterisation of airway disease burden, particularly among individuals who do not meet conventional criteria for AO. To secure widespread use of ESI in the future, it is desirable to define reference values for ESI in the general population and perform longitudinal investigations on different and larger samples to further validate these findings and explore its prognostic capabilities.

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References

- 1 Saltzman HP, Ciulla EM, Kuperman AS. The spirographic “kink”: a sign of emphysema. *Chest* 1976; 69: 51–55.
- 2 Pellegrino R, Crimi C, Gobbi A, et al. Severity grading of chronic obstructive pulmonary disease: the confounding effect of phenotype and thoracic gas compression. *J Appl Physiol* 2015; 118: 796–802.
- 3 Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretative strategies for routine lung function tests. *Eur Respir J* 2022; 60: 2101499.
- 4 Macklem PT, Mead J. Resistance of central and peripheral airways measured by a retrograde catheter. *J Appl Physiol* 1967; 22: 395–401.
- 5 Occhipinti M, Paoletti M, Bartholmai BJ, et al. Spirometric assessment of emphysema presence and severity as measured by quantitative CT and CT-based radiomics in COPD. *Respir Res* 2019; 20: 101.
- 6 Occhipinti M, Paoletti M, Crapo JD, et al. Validation of a method to assess emphysema severity by spirometry in the COPDGene study. *Respir Res* 2020; 21: 103.
- 7 Topalovic M, Exadaktilos V, Peeters A, et al. Computer quantification of airway collapse on forced expiration to predict the presence of emphysema. *Respir Res* 2013; 14: 131.
- 8 Dominelli PB, Foster GE, Guenette JA, et al. Quantifying the shape of the maximal expiratory flow-volume curve in mild COPD. *Respir Physiol Neurobiol* 2015; 219: 30–35.
- 9 Wang W, Xie M, Dou S, et al. Computer quantification of “angle of collapse” on maximum expiratory flow volume curve for diagnosing asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 3015–3022.
- 10 Bhatt SP, Bhakta NR, Wilson CG, et al. New spirometry indices for detecting mild airflow obstruction. *Sci Rep* 2018; 8: 17484.
- 11 Mochizuki F, Iijima H, Watanabe A, et al. The concavity of the maximal expiratory flow-volume curve reflects the extent of emphysema in obstructive lung diseases. *Sci Rep* 2019; 9: 13159.
- 12 Das N, Topalovic M, Aerts JM, et al. Area under the forced expiratory flow-volume loop in spirometry indicates severe hyperinflation in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 409–418.
- 13 Ronish BE, Couper DJ, Barjaktarevic IZ, et al. Forced expiratory flow at 25%–75% links COPD physiology to emphysema and disease severity in the SPIROMICS cohort. *Chronic Obstr Pulm Dis* 2022; 9: 111–121.
- 14 Luoto J, Pihlsgard M, Pistolesi M, et al. Emphysema severity index (ESI) associated with respiratory death in a large Swedish general population. *Respir Med* 2022; 200: 106899.
- 15 Viegi G, Paoletti P, Prediletto R, et al. Prevalence of respiratory symptoms in an unpolluted area of northern Italy. *Eur Respir J* 1988; 1: 311–318.
- 16 Carrozzi L, Giuliano G, Viegi G, et al. The Po River Delta epidemiological study of obstructive lung disease: sampling methods, environmental and population characteristics. *Eur J Epidemiol* 1990; 6: 191–200.
- 17 Viegi G, Pedreschi M, Baldacci S, et al. Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. *Int J Tuberc Lung Dis* 1999; 3: 1034–1042.
- 18 Maio S, Baldacci S, Carrozzi L, et al. Respiratory symptoms/diseases prevalence is still increasing: a 25-yr population study. *Respir Med* 2016; 110: 58–65.
- 19 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
- 20 Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
- 21 Pistelli F, Bottai M, Carrozzi L, et al. Reference equations for spirometry from a general population sample in central Italy. *Respir Med* 2007; 101: 814–825.

- 22 Global initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis and Management of COPD: 2025 Report. <https://goldcopd.org/2025-gold-report/>
- 23 Dal Negro R, Paoletti M, Pistolesi M. Standard spirometry to assess emphysema in patients with chronic obstructive pulmonary disease: the Emphysema Severity Index (ESI). *Multidisc Respir Med* 2021; 16: 805.
- 24 Hoffman EA, Ahmed FS, Baumhauer H, et al. Variation in the percent of emphysema-like lung in a healthy, nonsmoking multiethnic sample. *Ann Am Thorac Soc* 2014; 11: 898–907.
- 25 Dal Negro RW, Turco P, Povero M. Sensitivity and specificity of various lung function parameters recommended for phenotyping COPD in clinical practice. *Respir Med* 2025; 246: 108256.
- 26 Tan WC, Hague CJ, Leipsic J, et al. Findings on thoracic computed tomography scans and respiratory outcomes in persons with and without chronic obstructive pulmonary disease: a population-based cohort study. *PLoS ONE* 2016; 11: e0166745.
- 27 Bakke PS, Rönmark E, Eagan T, et al. Recommendations for epidemiological studies on COPD. *Eur Respir J* 2011; 38: 1261–1277.
- 28 Pistelli F, Maio S. Questionnaires and lung function. In: Annesi-Maesano I, Lundback B, Viegi G, eds. *Respiratory Epidemiology (ERS Monograph)*. Sheffield, European Respiratory Society, 2014; 65; pp. 257–272.