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From the authors:

We thank Drs Quanjer and Miller for their commentaries to our recently published manuscript in the *European Respiratory Journal* [1]. Our manuscript describes a follow-up study of pulmonary function tests (PFTs) in two groups of healthy smokers with normal post-bronchodilator spirometry and total lung capacity (forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and total lung capacity (TLC) ⩾80% predicted and FEV1/FVC >0.7, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) initiative) [2–5]. The smokers in one group had normal spirometry and normal diffusion capacity of the lung for CO (D_{LCO}) defined as ⩾ 80% pred ("normal spirometry/normal D_{LCO}", n=59) and the smokers in the other group had normal spirometry but low D_{LCO} (<80% pred, "normal spirometry/low D_{LCO}", n=46). The groups were similar in age, sex and ethnicity, with no difference in exposure to risk factors (*i.e.*, smoking history, pack-year history, packs per day or age of smoking initiation), cough or sputum scores or emphysema score. At the end of the follow-up period (<4 years, on average, for both groups), 2 (3%) out of 59 of the normal spirometry/normal D_{LCO} smokers developed GOLD-defined COPD (FEV1/FVC <0.7) *versus* 10 (22%) out of 46 of the normal spirometry/low D_{LCO} smokers (p<0.009). We concluded that despite appearing "normal" by GOLD, smokers with normal spirometry but low D_{LCO} are at significantly higher risk for developing COPD with obstruction to airflow.

The authors of both commentaries raised concerns about the use of a set cutoff for the definition of COPD (FEV1/FVC <0.7), and for the definition of low D_{LCO} (<80% pred) rather than using cutoff values based on a lower limit of normal (LLN) calculated for each individual based on their demographics. These arguments have been previously raised by different researchers in the field, and are referred to in our published manuscript. In addition to using set values for the definitions of COPD and low D_{LCO} we calculated a sex and ethnicity-based LLN for both parameters using spirometry and D_{LCO} data from an internal database of 405 healthy nonsmokers recruited from the general population, comprised of similar sexes and ethnicities as in our study groups. The results were summarised in the original manuscript and are detailed in table 1. However, to answer the concerns raised in the commentaries and to further strengthen our results, we have re-analysed our data using a calculating tool created by QUANJER *et al.* [6] based on spirometry data obtained from 73 centres worldwide and more than 160 000 individuals to calculate the LLN for FEV1 and FVC % pred and FEV1/FVC ratio for each individual based on sex, ethnicity, height and age. For calculating D_{LCO} % pred based on ethnicities other than Caucasians, we used the recalculated FEV1, FVC and FEV1/FVC values in combination with either the set cut off of D_{LCO} <80% or the LLN of D_{LCO} % pred calculated based on or internal database to re-evaluate our results. The results are detailed in table 1.

To summarise the results of all analyses, using either cutoff of the FEV1/FVC ratio to define COPD and/or either cutoff of D_{LCO} % predicted to define normal/low D_{LCO} yielded similar results. This supports our findings that smokers with low D_{LCO} are significantly at higher risk for developing COPD.

In addition, we would like to emphasise that: 1) the study population of both groups was randomly chosen from a large cohort of individuals recruited from the general population of New York (NY, USA), answering advertisement calling for assessment of lung health; 2) PFTs were performed according to American Thoracic Society/European Respiratory Society standards [7, 8] and spirometry and D_{LCO} curves

TABLE 1 Progression to chronic obstructive pulmonary disease (COPD) in smokers with normal spirometry/low diffusing capacity of the lung for CO (D_{LCO}) *versus* smokers with normal spirometry/normal D_{LCO} using different methods to determine normal levels

Parameters	D_{LCO} % predicted level cutoff used to define low D_{LCO}					
	<80%			Below LLN calculated based on internal database		
	Developed COPD		p-value	Developed COPD		p-value
	Normal D_{LCO}	Low D_{LCO}		Normal D_{LCO}	Low D_{LCO}	
FEV1/FVC ratio used to define COPD						
GOLD defined (< 0.7)[#]	3 (2/59)	22 (10/46)	<0.009	5 (4/74)	26 (8/31)	<0.008
Below LLN calculated for each individual based on internal database[¶]	2 (1/58)	22 (10/46)	<0.003	4 (3/73)	26 (8/31)	<0.004
Below LLN calculated for each individual using the Quanjer tool[+]	2 (1/59)	16 (7/45)	<0.03	1 (1/74)	23 (7/30)	<0.0007

Data are presented as % (n/N), unless otherwise stated. [#]: results detailed or summarised in [1]; [¶]: one normal spirometry/normal D_{LCO} excluded from the study due to baseline forced expiratory volume in 1 s/forced vital capacity ratio (FEV1/FVC) ratio below the lower limit of normal (LLN); [+]: one normal spirometry/low D_{LCO} excluded from the study due to baseline FEV1 % predicted below the LLN.

of all PFTs were validated based on ATS/ERS guidelines [7], as detailed in our manuscript [1]; 3) all individuals with low D_{LCO} at baseline, except for one, continuously demonstrated low DLCO at each PFT; 4) COPD was validated at several time points; [4] all individuals in both groups were periodically contacted at the same time intervals for PFT follow-up and all available PFT data has been used in this study and presented. Further details of the methods and results of our study can be found in our published manuscript [1].

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Smokers with normal spirometry/low D_{LCO} are at higher risk of COPD *versus* those with normal D_{LCO} http://ow.ly/4mQBwZ

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