is known to be related to the age, the sex and the size of the subject [4, 5]. For size, the subject's height is often used, but for the equation used by the authors alveolar volume (V_A) is used in the prediction [6]. In the paper the subjects' V_A values are not stated so the reader also does not know how much size differences might affect the authors' results.

For these reasons we believe the paper and editorial are potentially misleading. If authors wish to publish using fixed thresholds to make clinical judgements they must undertake a comprehensive and unbiased analysis that includes a comparison with true population lower limits of normal, a methodology that adheres to conventional statistical principles. The field of COPD research requires publications that offer clarification on these and other issues so clinicians are then best able to improve the management of this condition.

@ERSpublications
The subsequent development of COPD has not yet been proven to relate to a particular threshold value of T_{LCO} http://ow.ly/XAlx1

Martin R. Miller[1] and Vito Brusasco[2]
[1]Institute of Occupational and Environmental Medicine, University of Birmingham, Birmingham, UK. [2]Dipartimento di Medicina Interna e Specialità Mediche, Università di Genova, Genoa, Italy.

Correspondence: Martin R. Miller, Institute of Occupational and Environmental Medicine, University of Birmingham, Birmingham, B15 2TT, UK. E-mail: martin@millermr.com

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To the Editor:

In a recent issue of the *European Respiratory Journal*, Harvey *et al.* [1] measured spirometry and transfer factor on two occasions in 105 smokers (74% African-Americans). Throughout the study, there was no evidence of respiratory disease. Whilst all had a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio >0.7, in 46, the measured transfer factor of the lung for carbon monoxide (T_{LCO}) was <80% predicted. In 15 out of 59 subjects with normal values, T_{LCO} fell below 80% predicted during follow-up; in two, the FEV_1/FVC ratio declined slightly below 0.7. Of the 46 subjects with T_{LCO} <80% predicted, the FEV_1/FVC ratio declined to <0.7. The authors conclude that a normal-spirometry, low-T_{LCO} phenotype is a risk factor for developing chronic obstructive pulmonary disease. However, there are several flaws in this study that invalidate the conclusion.

An FEV_1/FVC ratio <0.7 but above the lower limit of normal (LLN) (fifth centile) is not associated with respiratory disease [2]. Curiously, whereas the 95% reference range for biochemical entities in healthy subjects, which are homeostatically controlled, is universally accepted as a normal range, reference ranges are still not generally used in respiratory medicine. Thus, many regard a fixed FEV_1/FVC ratio of 0.7 as the LLN. However, this index is not homeostatically controlled but varies with age, height and sex; it is above this threshold in subjects <45 years of age and below it in elderly subjects. In a male and female of average height, the ratio declines from 0.7 to 0.65 between ages 40 and 65 years [3]. In a healthy population, 5% of spirometric indices fall below the LLN. Judging from the age range and illustrations, it

TABLE 1 Age-related decline in the lower limit of normal for the transfer factor of the lung for carbon monoxide as a function of age according to several authors

First author [ref.]	Age years				
	30	40	50	60	70
Miller [7]	77	75	74	71	69
Paoletti [8]	76	75	74	72	70
Roca [9]	80	79	78	76	75
Roberts [10]	73	71	69	66	64
Quanjer [11]	80	78	77	75	74
Cotes [12]	75	73	71	69	67
Thompson [13]	80	80	79	78	76

Data are presented as %.

is likely that in the study by Harvey *et al.* [1], <5% developed an FEV1/FVC ratio below the LLN. Hence, there is no evidence for the development of airway obstruction.

It has often been shown that 80% predicted does not represent the LLN for respiratory indices over the entire age range [3–5]. Between age 40 and 65 years, the LLN for FEV1 and FVC falls from about 77% to 72% in African-American males and females. The authors base their assessment of the *T*LCO on a very old study [6] that provided no information about subject selection, inclusion or exclusion criteria, smoking habits, numbers involved, or ethnicity, and the reference equation does not allow estimation of the LLN. Again, the authors adopted 80% predicted as the LLN. Between age 30 and 70 years, the LLN of the *T*LCO, averaged over seven prediction equations, drops from an average of 77% to 71% (table 1).

Three studies [14–16] found that the *T*LCO in African-Americans was appreciably lower than in European-Americans, yet the authors used predicted values for white subjects.

Any study with one repeated measurement is prone to being affected by regression to the mean: an extreme variable on its first measurement will tend to be closer to the average on its second measurement and *vice versa*. This may both obscure and exaggerate the age-related decline in *T*LCO.

The authors showed that these carefully selected smokers, who were free of symptoms and any other conditions that might affect their lung function, had no airflow limitation but that about half of them had a lower *T*LCO. The evidence for the development of airway obstruction is unconvincing, and the prevalence of functional abnormalities overestimated due to the use of old prediction equations, inappropriate cut-off values and not taking into account ethnic differences in *T*LCO.

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The proposal of a normal-spirometry, high-*T*LCO phenotype that predisposes to airway obstruction has several flaws http://ow.ly/XRmz2

Philip H. Quanjer
Depts of Pulmonary Diseases and Paediatrics–Pulmonary Diseases, Erasmus Medical Centre, Erasmus University, Rotterdam, The Netherlands.

Correspondence: Philip H. Quanjer, Kervel 19, 7443 GT, Nijverdal, The Netherlands. E-mail: pquanjer@xs4all.nl

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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 (FEV_1), forced vital capacity (FVC) and total lung capacity (TLC) ⩾80% predicted and FEV_1/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 (FEV_1/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 (FEV_1/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 FEV_1 and FVC % pred and FEV_1/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 FEV_1, FVC and FEV_1/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 FEV_1/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