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Association of the transfer coefficient (Kco) with emphysema progression in male smokers

Running head: **Kco and emphysema progression in heavy smokers**

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ABSTRACT

RATIONALE A decreased Kco is associated with emphysema. We evaluated whether in heavy smokers, baseline Kco was associated with progression of CT-detected emphysema, and progression of airflow limitation.

METHODS Heavy smokers, mean (SD) 41.3 (18.7) pack years, participating in a lung cancer screening trial underwent diffusion testing and CT-scanning of the lungs. CT-scanning was repeated after median (25^{th} – 75^{th} percentile) 2.8 (2.7-3.0) years and emphysema was assessed by lung densitometry using the 15^{th} percentile (Perc15). The association between Kco at baseline with progression of emphysema and lung function decline was assessed by multiple linear regression, correcting for baseline CT-quantified emphysema severity and FEV_1/FVC, age, height, BMI, pack years and smoking status (current / former smoker).

RESULTS 522 participants were included with a mean (SD) age of 60.1 (5.4) years. Mean) Perc15 was -938 (19), absolute FEV_1/FVC was 71.6 % (9) and Kco was 1.23 (0.25), which is 81.8% (16.5) of predicted. By interpolation: a one standard deviation (0.25) lower Kco value at baseline, predicted a 1.6 HU lower Perc15 and a 0.78% lower FEV_1/FVC after follow-up ($p<0.001$).

CONCLUSION A lower baseline Kco value is independently associated with a more rapid progression of emphysema and airflow limitation in heavy smokers.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the only chronic disease with increasing mortality rates and is supposed to be the third leading cause of death by 2020. [1] Since prevention of COPD appears to be more promising than treatment, early recognition of COPD susceptible subjects therefore is pivotal to reduce the increasing burden of this disease. COPD is characterized by progressive airflow limitation and consists of chronic bronchitis and emphysema. Chronic bronchitis leads to e.g. increased mucus production in the (smaller) airways causing airway obstruction, while emphysema induces airflow obstruction by loss of elastic recoil of lung tissue. Both can coincide, and contribute to a greater degree of airflow obstruction. Currently, in the living subject, emphysema can only be assessed by means of computed tomography (CT)-scans and lung densitometry measurements to quantify the extent of it. However, there are some disadvantages to CT-scanning, most importantly the radiation exposure, the costs and the availability of the equipment. [2]

The diffusion capacity of carbon monoxide is an easy to perform tool to assess the functionality of the alveolar-capillary membrane and is reported as the Kco, the carbon monoxide transfer coefficient. [3] The Kco can be considered as the rate constant for alveolar CO uptake and is lowered in the presence of emphysema. Holme et al. showed that a large proportion of subjects with a lowered Kco, but with normal FEV_1/FVC values, show radiological evidence of emphysema. [4]A decreased Kco therefore supports a diagnosis of emphysema in patients with or without airflow obstruction and may add to spirometry to establish the diagnosis of COPD.[5]

However, little is known about the association between Kco and the natural course of CT-quantified emphysema and FEV_1/FVC in heavy, but relatively healthy smokers. We hypothesized that lower baseline Kco values were associated with a more rapid progression of CT-quantified emphysema and decline in FEV_1/FVC. Therefore, the aim of the present

study was to assess the relationship between the Kco at baseline and the progression of CT-quantified emphysema and, secondly the progression of airflow obstruction.

METHODS

Participants

The study was conducted among participants of the Dutch-Belgian Lung Cancer Screening Trial (NELSON) who were recruited by the University Medical Center Utrecht, the Netherlands, as only this center included diffusion capacity measurements. The NELSON is a population based CT-screening trial for lung cancer and inclusion criteria have been published before. [6 7] In short, participants meeting the inclusion criteria of having smoked a minimum 20 pack years and fit enough to undergo potential thoracic surgery were invited to participate. Only males were included based on the high risk to develop lung cancer/ COPD as fewer women in the Dutch population have accumulated a long-term exposure to cigarettes compared to men. [5] Baseline details on smoking habits were gathered through questionnaires which included questions about duration of smoking, number of packyears smoked and smoking status at enrolment (current or former smoker). At the start of the study it was decided that this study provided the unique opportunity to also assess lung function and to investigate this in relation to CT measures. Therefore spirometry was assessed in all individuals.

The NELSON trial was approved by the Dutch Ministry of Health on December 23, 2003 and by the institutional review board of the University Medical Center Utrecht, the Netherlands (approval number 03/040) The NELSON trial is registered at www.trialregister.nl with trial number ISRCTN63545820. Informed consent was obtained from all participants.

Pulmonary Function Testing

Pulmonary function tests (PFT) included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), alveolar volume (Va), and transfer coefficient for carbon monoxide (Kco), which all were carried out according to current European Respiratory Society guidelines. [8] [9] Reversibility was of airflow obstruction not assessed. PFT was performed on the same day as the CT-scan. Airflow obstruction was defined as an FEV_1/FVC below the lower limit of normal (LL) at baseline. [10]

Kco measurements were performed with a MasterLab Pro (Erich Jaeger GmbH, Wurzburg, Germany), with the single breath maneuver method; the test gas contained CO 0.25%, He 9.17% with balance air. Kco was expressed as mmol/min/kPa/l. A breath holding period of 10 seconds (Jonas and Meade method) and discard / sample volumes 750 mL were adopted[11]. Smokers refrained smoking from 24 hours before the measurement; no correction for hemoglobin levels was made since this only has a very limited effect. [12] Predicted values and the lower limits of normal were calculated by using appropriate reference values. [10] [13] Kco values below the lower limit of normal (LLN) were considered abnormal.

CT Scanning

All participants received low-dose CT, with 16-detector MDCT scanners (Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH), at baseline and after follow-up. Scan data were obtained in spiral mode, with 16 x 0.75mm collimation and in full inspiration. No spirometric gating was applied since this does not improve repeatability of lung density measurements. [14;15] Axial images were reconstructed with 1.0mm thickness at 0.7mm increment. All scans were reconstructed with a soft reconstruction filter (Philips B, Siemens B30f) at a 512x512 matrix. Exposure settings were 30mAs at 120kVp or 140kVp, depending on participant's weight. This low-dose CT protocol has previously been used to quantify

emphysema in COPD patients and heavy smokers [16;17]. All CT scans were automatically analyzed by in-house developed soft-ware. [18] Airways were excluded to ensure that only lung parenchyma was analyzed. [19]

Emphysema quantification

Severity of emphysema was based on the 15th percentile (Perc15) technique. This technique provides the Hounsfield Units (HU) point below which 15% of the voxels are distributed. The lower the Perc15 values are, i.e. closer to -1000 HU, the more emphysema is present. This method of emphysema quantification has been validated against pathology [20] and has been applied in multiple studies [21]. The Perc15 was preferred to the % 950 HU measurement,. [22] However, a secondary analysis was done using the % 950 HU as emphysema severity measure, which is defined as the proportion of low density voxels below -950 HU, and is reported in the supplementary files.

Statistical evaluation

Mean and standard deviation (SD) values were calculated for normally distributed data and median and 25^{th} – 75^{th} percentile (Q_1-Q_3) values for non-normally distributed data. Student's t-tests and chi-square tests were used to test differences between groups as appropriate. Pearson's correlations were used to establish associations between variables at baseline. Emphysema severity (Perc15) and FEV_1/FVC at the end of the observation period were the primary endpoints and were analyzed by multiple linear regression analyses. Kco at baseline was the main explanatory factor. Adjustments were made for baseline Perc15 and FEV_1/FVC, age, height, BMI, pack years, and smoking status (current / former smoker). Perc15 progression and FEV_1/FVC decline were calculated by subtracting follow-up values adjusted by multiple linear regression analyses from observed baseline values. P-values <0.05 were considered significant. All statistical analyses were performed using SPSS 18 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline demographics, lung function and CT-quantified emphysema

A number of 609 participants underwent follow-up CT-scanning and spirometry. Of these 609 participants, 87 participants were excluded due to missing or incomplete baseline Kco values, resulting in 522 participants being included in the current study. There were no significant differences in baseline age, height, BMI, packyears, smoking status, spirometry results or CT-quantified emphysema severity between included participants and excluded due to missing or incomplete Kco values.

Mean (SD) age was 60.1 (5.4) years and 256 (49.2%) were current smokers. Mean (SD) FEV_1/FVC was 71.6 % (9) of predicted and mean (SD) Kco was 1.23 (0.25) which is 81.8% (16.5) of predicted. Further baseline demographics and lung function parameters for the total study population are provided in Table 1. More than half of the participants, 272 (52.3%), had an abnormal Kco at baseline and the baseline Kco was significantly correlated with baseline FEV_1/FVC (r = 0.46, p<0.001). Demographics and lung function parameters stratified by normal and a Kco<LLN are presented in Table 2. The majority of participants, 424 (81.2%), had no airflow obstruction (FEV_1/FVC >LLN). Of the participants with no airflow obstruction, 213 (50.2%) had a lowered Kco. Figure 1 illustrates the baseline FEV_1/FVC stratified by Kco >LLN and <LLN.

The mean (SD) Perc15 was -937.7 HU (18.5). Baseline Kco was significantly correlated with Perc15 at baseline (r = 0.23, p<0.001). Participants with an abnormal Kco (<LLN) had significantly (p=0.002) more CT-quantified emphysema as compared to subjects with a normal Kco, -940.1 HU (19.0) and -935.1 HU (17.6), respectively.

Association of Kco with progression of CT-quantified emphysema

Median (interquartile range) follow-up time was 2.8 (2.7 - 3.0) years. The mean Perc15 HU after follow-up was -944.4 HU (17.9) and the mean (SD) progression of emphysema was 6.3 HU (5). The statistical model explained 68% of the variance in the Perc15 after follow-up (R^2 = 0.68). Baseline values of FEV_1/FVC, Perc15 and Kco and smoking status (current or former smoker) proved to be significant predictive factors for the progression of Perc15, see Table 3. A 0.25 lower baseline Kco (being the standard deviation of Kco in this sample) predicted an additional 1.6 HU lower Perc15 after follow-up ($p<0.001$). The effect of Kco is illustrated in Figure 3. The effects of the other significant covariates in the model are listed in Table 3. Age, height, BMI and pack years smoked were not significantly associated with Perc15 progression.

An additional analysis was performed to test whether the association of Kco with Perc15 progression was independent of the baseline level of FEV_1/FVC. An interaction term between baseline FEV_1/FVC and baseline Kco was inserted in the statistical model. The baseline FEV_1/FVC value was significantly ($p<0.001$) associated with progression of Perc15; a 1% lower baseline Kco value predicted an additional 0.3 HU lower Perc15. However, the interaction term was not significant ($p=0.099$) indicating that the association of baseline Kco was similar in participants with different levels of airflow obstruction.

Using the % 950 HU approach as measure of emphysema severity yielded similar results as using the Perc15 (see supplemental files).

Association of Kco with decline in FEV_1/FVC

Mean absolute (SD) FEV_1/FVC after follow-up was 70.2% (9.4). The statistical model explained 80% of the variance in FEV_1/FVC after follow-up (R^2 = 0.80). Baseline values of FEV_1/FVC and Kco proved to be significant predictive factors for FEV_1/FVC decline as

shown in Table 3. Adjusted mean (SD) decline was 1.44 % (0.92) during 3-year follow-up. To put this decline in perspective, the expected 3-year decline in FEV_1/FVC according to appropriate reference values is 0.5%. [10] When a subject showed a 0.25 lower Kco (being one standard deviation) compared to another subject, that subject suffered from an additional 0.78% lower FEV_1/FVC after follow-up ($p<0.001$), see Table 3 and Figure 2.

The analysis with insertion of an interaction term between baseline FEV_1/FVC and baseline Kco showed that the association of Kco with FEV_1/FVC decline was independent of the baseline FEV_1/FVC value as the interaction term was not significant ($p=0.133$).

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DISCUSSION

In the present study we showed that a lower Kco value is associated with an increase of CT-quantified emphysema and a larger decline in FEV_1/FVC during a three year follow-up of heavy male smokers. This association proved to be independent of the level of FEV_1/FVC. Kco, a simple and patient friendly measurement, therefore may help to detect current and former smokers who are susceptible for a more rapid progression of CT-quantified emphysema and decline in lung function independently of their FEV_1/FVC level.

Parameters like the FEV_1/FVC do not reflect the presence or the severity of emphysema accurately. [23] Mild emphysema does not always lead to a FEV_1/FVC <70% (or <LLN), and thus COPD can be missed if only spirometry is performed. However, in daily practice the evaluation of subjects at risk for (or with established) COPD is usually based on spirometry. [10] Unfortunately, spirometry fails to discriminate between chronic bronchitis and emphysema, the latter may be assessed by CT-scanning. A disadvantage of CT-scanning is that it exposes subjects to radiation and is relatively expensive and therefore CT-scanning is not performed on a regular basis, which is also true for repeatedly performed low-dose CT-scans. An advantage of CT-scanning is the additional information which is obtained on the distribution of emphysema, but it is questionable whether this information is clinically relevant. [24] On the other hand, diffusion testing is harmless, less expensive, and thus can be applied routinely and more frequently than CT-scanning. This is strengthened by the finding that of the 272 participants with a Kco below the LLN only 71 had an FEV_1/FVC below the LLN. This finding again illustrates that in an at-risk population with high smoking history only performing spirometry may miss a large degree of subjects with abnormal diffusion tests results.

The association of a lower baseline Kco with progression of emphysema and decline of FEV_1/FVC was independent of the level of baseline FEV_1/FVC as there were no significant interactions between them. This is an important finding because it illustrates that it is useful to perform Kco measurements in heavy smokers, independently of their FEV_1/FVC. Only taking in account the FEV_1/FVC, and not the Kco, in the evaluation of heavy smokers may result in missing subjects who will suffer from a stronger progression of Perc15. The assessment of Kco thus may have important prognostic implications.

To our knowledge, there are no longitudinal studies examining the predictive value of Kco on FEV_1/FVC decline. One study did examine the predictive value of DLco on FEV_1-decline and showed that DLco differentiates smokers who will experience a rapid FEV_1-decline. [25] The included subjects were comparable to our population. They were also relatively healthy, but slightly younger. Although these authors measured the DLco instead of the Kco, their results support our findings that the Kco may help to identify subjects with a more rapid lung function decline.

As for the association between Kco and lung function decline, literature evaluating the predictive value on emphysema progression is scarce. Cross-sectional studies have shown that the Kco is lower in subjects with pathologically defined as well as with CT-detected emphysema [26] [27] [28]. We confirm these findings by showing that there was a significant correlation between Kco and Perc15 at baseline (r = 0.23). The correlation however was not as strong as previously reported, which is most probably due to the fact that the included subjects were relatively healthy and without severe emphysema.

There are a number of strengths to our study. Firstly, emphysema scores were automatically quantified which eliminates interobserver variability known to be present in the visual assessment of emphysema. Secondly, the study was performed in one center and only one type of CT-scanner was used, excluding possible scanner bias due to different algorithms

used by different types of CT-scanners. Thirdly the same diffusion testing equipment was used. This is especially important since it is known that large variability may exist in Kco measurements between different lung function laboratories. [29] Fourthly, only heavy smoking, but relatively healthy participants were included. This makes the results especially applicable to subjects who are at risk for progression of emphysema and airflow obstruction. The earlier mentioned cross-sectional studies were almost all restricted to (severe) COPD subjects. Finally, because of the large sample size we could extensively correct for potential confounding factors like age, packyears smoked and smoking status. This makes our reported results more precise.

This study also has some limitations. Firstly, only pre-bronchodilator spirometry was obtained, which could have resulted in lower measured FEV_1/FVC values in our study. As a result, the percentage of participants without airflow obstruction could actually be lower. However, because we treated FEV_1/FVC as a quantitative treat we do not expects that this has affected our results. Secondly, no females were included, due to the inclusion criteria of the study. This is unfortunate because the prevalence of COPD is increasing in women. Previous studies showed that emphysema scores in females are lower than in men, and that females also show lesser progression of emphysema after follow-up. [30] [31] [32] Lastly, we performed analyses with both the Perc15 as the %950 HU, the results of the latter are described in the supplemental files. The outcomes of the analyses with %950 as emphysema measurement are in the similar direction as by using Perc15 and underscore our conclusions. It should however be realized that the Perc15 takes in account, not only the regions with markedly reduced density, but the whole lung, while the %950 HU is less sensitive for lung density changes of the whole lung.

In conclusion, we have shown that current and former heavy smokers with lower baseline Kco values show a significantly greater progression of CT-quantified emphysema and decline in FEV_1/FVC. These results show that the Kco may be a useful measurement in the evaluation and follow-up of heavy smoking subjects, with or without airflow obstruction yet.

Author's contribution

F.A.A. Mohamed Hoesein and Dr. P. Zanen were responsible for the concept and design of the study and performed the statistical analysis and drafted the manuscript. Both are guarantor of the paper. Dr. B. van Ginneken was responsible for the software development which allowed for the CT-quantification of emphysema. Dr. R.J. van Klaveren is a primary investigator in the NELSON trial. Prof. J.W.J. Lammers assisted in the concept and design of the study. All authors contributed to writing and approved the final version of the manuscript.

Table 1. Baseline demographics. Means and standard deviations (SD) are provided. * Median (Q_1-Q_3)

N= 522	Mean (SD)
Age [years]	60.1 (5.4)
Height [meters]	1.78 (0.07)
BMI (kilograms*meter^{-2})	26.8 (3.3)
Follow-up* [years]	2.75 (2.7 - 3.0)
Pack years smoking	41.3 (18.7)
Current smokers [%]	48.7
FEV_1 [L]	3.35 (0.72)
FEV_1 % predicted	97.6 (18.2)
FEV_1/FVC absolute [%]	71.6 (9)
Participants with airflow obstruction (FEV_1/FVC <LLN) (%)	98 (18.8%)
Kco [mmol/min/kPa/l]	1.23 (0.25)
Kco %predicted	81.8 (16.5)
Perc15 emphysema score on CT scan [HU]	-937.8 (18.5)

Table 2. Baseline demographics stratified by normal and Kco <LLN. Means and standard deviations (SD) are provided. * Median (Q_1-Q_3)

	Normal Kco (n= 250)	Kco < LLN (n=272)	P-value
Age [years]	60.6 (5.4)	59.7 (5.3)	0.067
Height [meters]	1.78 (0.06)	1.78 (0.06)	0.155
BMI (kilograms*meter^{-2})	26.8 (3.3)	26.8 (3.3)	0.256
Follow-up* [years]	2.75 (2.7 - 3.0)	2.75 (2.7 - 3.0)	0.325
Pack years smoking	40.4 (19.1)	42.1 (18.3)	0.326
Current smokers [%]	91 (36.4)	170 (59.4%)	**<0.001**
FEV_1 [L]	3.40 (0.68)	3.30 (0.75)	0.142
FEV_1 %predicted	99.6 (16.6)	95.8 (19.3)	**0.015**
FEV_1/FVC absolute [%]	74.4 (7.4)	69.2 (9.6)	**<0.001**
Participants with airflow obstruction (FEV_1/FVC < LLN) (%)	27 (10.8%)	71 (26.1%)	**<0.001**
Kco [mmol/min/kPa/l]	1.43 (0.15)	1.05 (0.17)	**<0.001**
Kco %predicted	95.6 (9.6)	69.7 (10.8)	**<0.001**
Perc15 emphysema score on CT scan [HU]	-935.1 (17.6)	-940.1 (19.0)	**0.002**

Table 3. Results from the multiple linear regression analyses showing the estimated effects of baseline Kco and the other significant covariates on A) FEV_1/FVC% after follow-up and B) Perc15 HU after follow-up. A) A 0.25 lower Kco at baseline predicts an additionally 0.78% lower FEV_1/FVC after 3-year follow-up. B) A 0.25 lower Kco at baseline predicts an additionally 1.6 HU lower Perc15 after 3-year of follow-up.

A.

Estimated effects of changes in parameters on FEV_1/FVC in % after follow-up				
Covariate	**Change**	**Change in FEV_1/FVC [%]**	**CI95%**	**p-value**
Kco	0.25 lower	-0.78%	0.31 – 1.14	<0.001
Baseline FEV_1/FVC absolute [%]	1% lower	-0.90%	0.85 – 0.94	<0.001

B.

Estimated effects of changes in parameters on Perc15 in HU after follow-up				
Covariate	**Change**	**Change in Perc15 [HU]**	**CI95%**	**p-value**
Kco	0.25 lower	-1.6 HU	0.59 – 2.60	0.002
Baseline FEV_1/FVC absolute [%]	1% lower	-0.3 HU	0.19 – 0.43	<0.001
Smoking status	Current versus ex-smoker	+3.2 HU	1.30 – 5.1	<0.001
Baseline Perc15 HU	1 HU lower	-0.67 HU	-0.61– -0.72	<0.001

Figure 1. Histograms of absolute FEV_1/FVC values for participants stratified by Kco >LLN and <LLN.

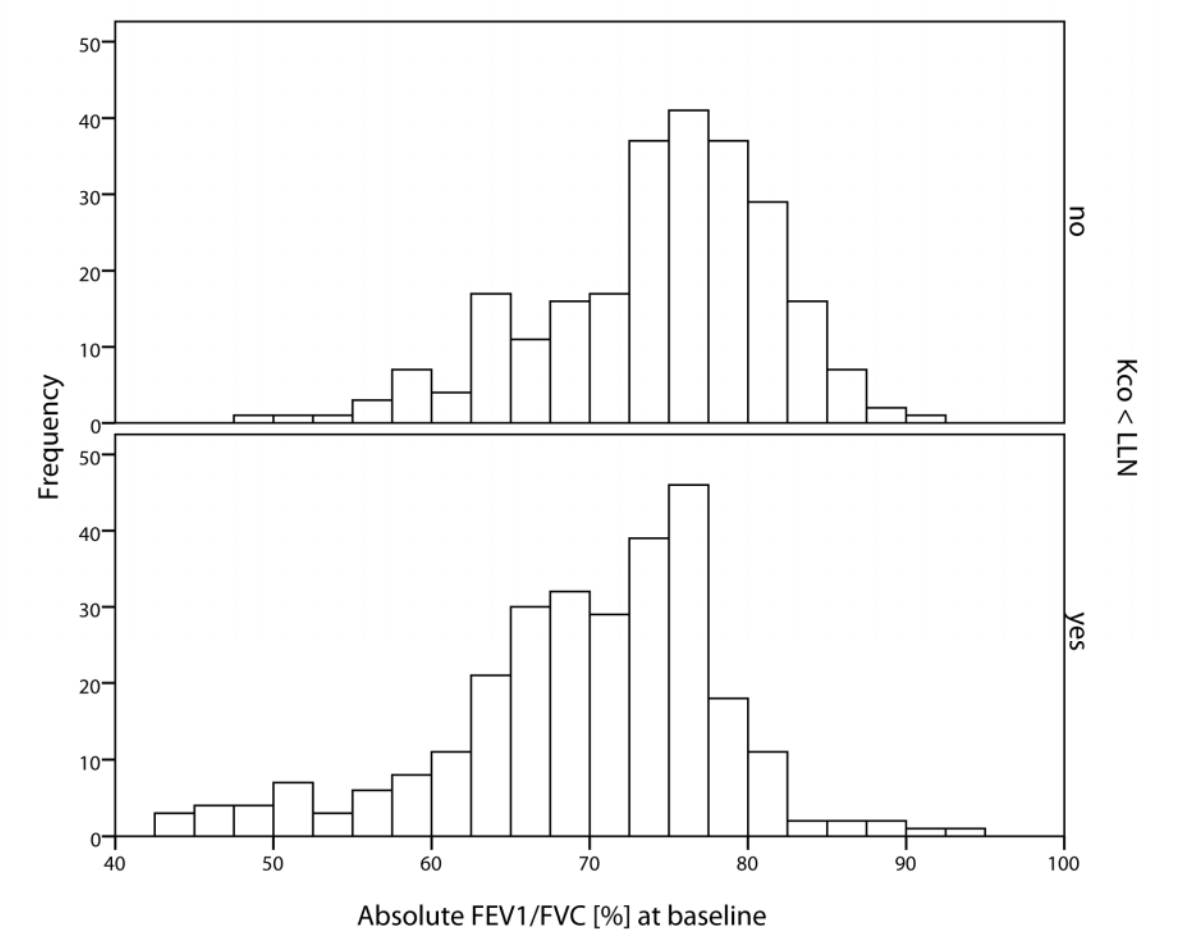


Figure 2. Relation of baseline Kco and FEV_1/FVC after follow-up. This situation represents participants with a baseline age of 60.1 years, packyears of 41.3, height of 1.75 meters, FEV_1/FVC of 71.6% and a Perc15 of 937.8 HU, which are the mean values of the study population at baseline. It can be seen that a lower Kco at baseline predicts a larger decline in FEV_1/FVC. As an illustration: a Kco value of 1.2 at baseline associates with a follow-up FEV_1/FVC of 70.07%, while a Kco value of 1.4 at baseline associates with a follow-up FEV_1/FVC of 70.69%, despite similar age, height, packyears smoking and Perc15 levels of these individuals at baseline.

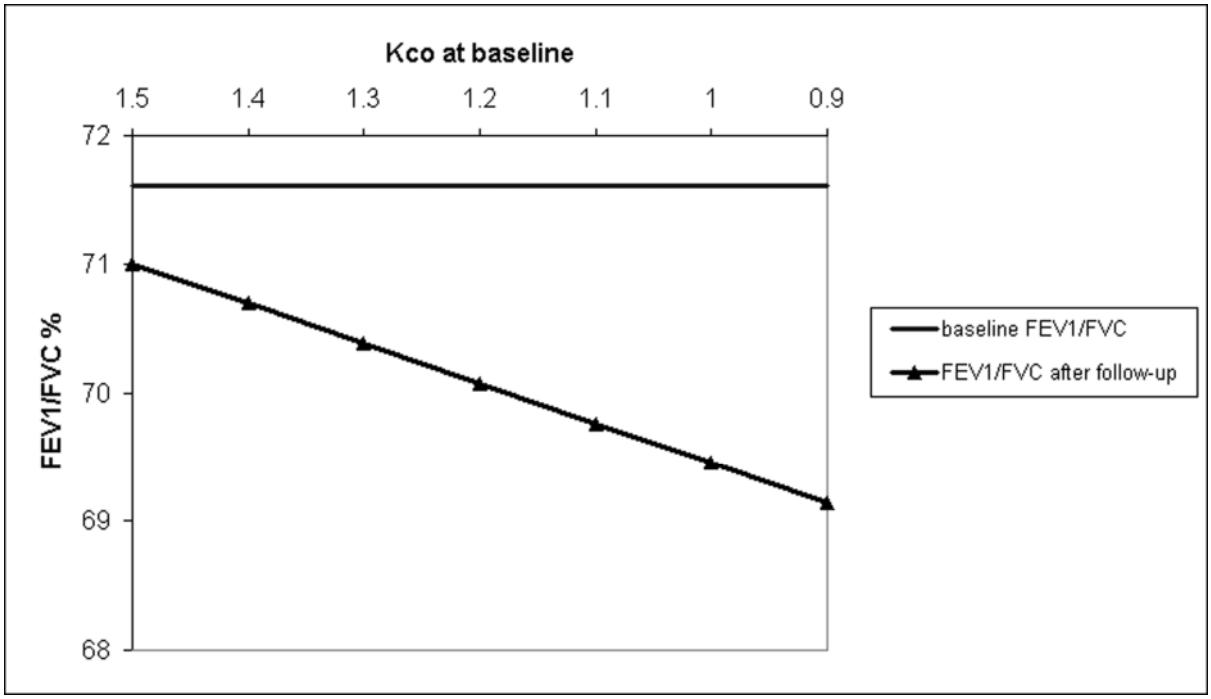
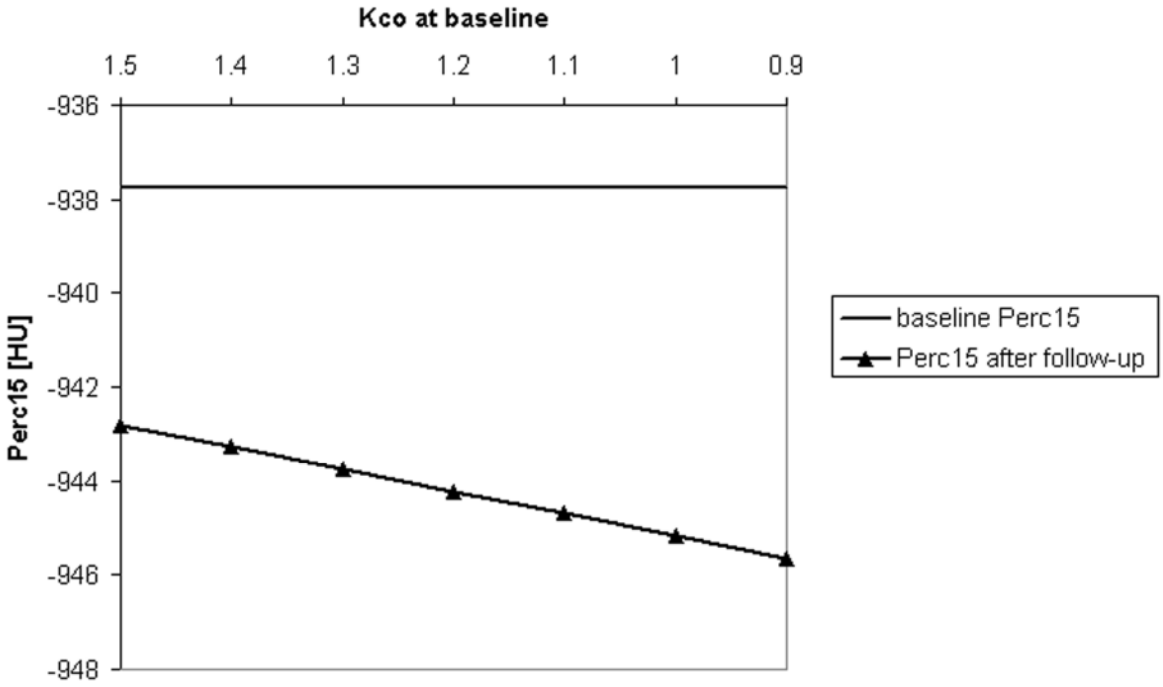


Figure 3. Relation of baseline Kco and Perc15 after follow-up. This situation represents participants with a baseline age of 60.1 years, packyears of 41.3, height of 1.75 meters, FEV_1/FVC of 71.6% and a Perc15 of 937.8 HU, which are the mean values of the study population at baseline. It can be seen that a lower Kco at baseline predicts a more rapid decline of Perc15, e.g. worsening of CT-quantified emphysema. As an illustration: a Kco value of 1.2 at baseline associates with a follow-up Perc15 of -944.2 HU, while a Kco value of 1.4 at baseline associates with a follow-up Perc15 of -943.3 HU, despite similar age, height, packyears smoking and Perc15 levels of these individuals at baseline.


Kco at baseline
1.5
1.4
1.3
1.2
1.1
1
0.9
-936
-938
-940
-942
-944
-946
-948
Perc15 [HU]
baseline Perc15
Perc15 after follow-up

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