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## Impaired lung function is associated with systemic inflammation and macrophage activation

To the Editor:

Lung function impairment, as assessed by a reduction in the forced expiratory volume measured in the first second of exhalation (FEV<sub>1</sub>) and forced vital capacity (FVC), contributes significantly to several major health issues, such as all-cause mortality [1, 2], chronic lung disease prevalence (chronic obstructive pulmonary disease (COPD) and asthma) [3, 4], and death from cardiovascular disease [5]. Preservation of lung health during ageing [6] through identification of modifiable risk factors is a key research priority.

Low-grade chronic systemic inflammation, determined by elevation of C-reactive protein (CRP) and interleukin (IL)-6 is a common mechanistic pathway contributing to reduced lung function [4, 5, 7] and increased cardiovascular events [8, 9]. Systemic inflammation is also a feature of chronic respiratory conditions including asthma and COPD [10]. However, the influence of systemic inflammation on lung function across different populations needs further investigation if targeting this inflammation is to be developed as a strategy in preventing lung function decline. Circulating soluble (s) CD163 is a biomarker of macrophage activation and is elevated in many inflammatory and infectious disease states [11]. While macrophage activation has been associated with chronic lung disease, it has not previously been assessed in relation to lung health at a population level.

The Inuit indigenous population of Greenland provides a unique and important opportunity to assess the relationships between systemic inflammation and macrophage activation on lung function impairment in a genetically homogenous population. We hypothesised that lung function impairment would be associated with systemic inflammation and macrophage activation. This study investigates systemic inflammation and macrophage activation as predictors of lung function in an Inuit indigenous population residing in the Arctic (Greenland) or Western Europe (Denmark).

TABLE 1 Association between inflammatory markers and lung function adjusted for age, sex, smoking and height

	FEV <sub>1</sub> n=1068		FVC n=1048	
	$\beta$	p-value	$\beta$	p-value
lnIL6	−0.032±0.022	0.144		>0.2
lnCRP	−0.060±0.013	<b>&lt;0.0001</b>	−0.078±0.013	<b>&lt;0.0001</b>
lnCD163	−0.057±0.027	<b>0.034</b>	−0.080±0.031	<b>0.011</b>

Data are presented as  $\beta \pm \text{SE}$ . Bold indicates significance. FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity.

A random sample of first generation Inuit immigrants living in urban areas of Denmark was accessed by the civil registration list, and a random sample of Inuits from the main city of Greenland (Nuuk) as well as a population sample from an isolated area of four small settlements on the northwest coast (Uummanaq) were accessed *via* the Greenland population register [12]. In total, 1104 Inuits had questionnaire-based interviews, clinical examination including lung function measurement and blood collection for assessment of serum inflammatory biomarkers. Systemic inflammation was measured by detecting serum CRP (Quickread go; Orion Diagnostic Oy, Espoo, Finland) and serum IL-6 (Human IL-6 Quantikine high sensitivity ELISA; R&D Systems, Minneapolis, MN, USA). Systemic macrophage activation was measured by detecting serum sCD163 (Macro163 sCD163 ELISA; Trillium Diagnostics LLC, Brewer, ME, USA). Multiple stepwise linear regressions were performed for FEV<sub>1</sub> and FVC as dependent variables, adjusted for age, sex, smoking status and height. To assess the effect systemic inflammation and macrophage activation on respiratory function, both FEV<sub>1</sub> and FVC multiple regressions included natural log transformed CRP, IL-6 and sCD163 as independent variables with backward elimination for parameters  $p > 0.2$ .

The study included 1104 Inuit people, of whom 51% (n=565) lived in Greenland, and 49% (n=539) lived in Denmark. The Inuit in Denmark had spent 55% of their lifetime there. The majority were female: 75% in Denmark and 62% in Greenland, with a median age of 43 years. The median body mass index (BMI) was 25 with 36% (n=387) who were overweight (BMI 25–30), 15% (n=158) who were obese (BMI >30), and 7% (n=76) who were underweight (BMI <20). The majority were current smokers (60%), with a median smoking history of 12 pack-years. Lung function was similar for those living in Denmark and Greenland (median FEV<sub>1</sub> 3.05 L and FVC 3.7 L).

The influence of systemic inflammation and macrophage activation on lung function was assessed using regression modelling. As expected, advancing age, smoking and female sex had negative effects on FEV<sub>1</sub> and FVC, and regression models were adjusted for these variables. Both CRP and sCD163 had a significant negative effect on FEV<sub>1</sub> and FVC. The association between the inflammatory markers and lung function are expressed as linear regression coefficients ( $\beta$ ) and are shown in table 1. Due to the log-transformation of the inflammatory markers,  $\beta$  represents the change in lung function for a 100% increase in the non-transformed inflammatory marker.

CRP and sCD163 were both associated with a significant reduction in lung function: (FEV<sub>1</sub> $\beta$ =−0.060,  $p < 0.0001$ ; FVC $\beta$ =−0.078,  $p < 0.0001$ ), (FEV<sub>1</sub> $\beta$ =−0.057,  $p = 0.034$ ; FVC $\beta$ =−0.080,  $p = 0.011$ ). Therefore, an increase in CRP from the median value of 1.1 mg·mL<sup>−1</sup> to the upper quartile value of 2.7 mg·mL<sup>−1</sup> was associated with lower FEV<sub>1</sub> and FVC (147 mL and 191 mL, respectively). An increase in sCD163 from the median value of 1558 ng·mL<sup>−1</sup> to the upper quartile of 2341 ng·mL<sup>−1</sup> was associated with lower FEV<sub>1</sub> and FVC (86 mL and 120 mL, respectively) after adjustment for covariates. There was no significant association between IL-6 and lung function.

In addition to the known adverse effects of CRP on lung function, we found that elevated levels of the macrophage activation marker sCD163 in the circulation were associated with reduced lung function, in this young–middle-aged population with a high smoking prevalence. The mechanisms of the adverse effect of sCD163 could be due to other factors driving systemic inflammation, such as microbial colonisation, other environmental exposures or reverse causation.

We report a significant association between systemic inflammation and lung function. Systemic inflammation is assessed by the measurement of inflammatory biomarkers CRP which is produced by hepatocytes under the control of IL-6. A previous study conducted in Iceland reported that higher CRP and IL-6 were independently associated with lower FEV<sub>1</sub> and FVC [4]. The London (UK) based Whitehall II prospective study showed that higher CRP and IL-6 and their change over 12 years was associated with slightly poorer lung function [7]. Our results confirm these observations, but in a younger age group with a high smoking prevalence. In this setting, we observed that each 10% increase in CRP was associated with a 6.0–7.8 mL lung function decrement.

We made the novel observation that elevated sCD163 decreased in FEV<sub>1</sub> and FVC. Each 10% increase in sCD163 was associated with a 5.7–8.0 mL decrement in lung function. This demonstrates a novel relationship between macrophage activation and lung function impairment. CD163 is a haemoglobin scavenger receptor specifically present on cells of the monocyte–macrophage lineage [11]. The soluble form of CD163 is a serum/plasma biomarker that indicates macrophage activation and is elevated in many acute and chronic inflammatory and infectious conditions, as well as some malignancies [11]. It is formed through shedding of the membrane receptor stimulated by tumour necrosis factor (TNF)- $\alpha$  cleaving enzyme (TACE) and is released into the circulation following enzymatic cleavage by ADAM17 [13]. sCD163 is not altered in asthma after allergen challenge [14]; however, it is increased in COPD [15].

A limitation of this study is its cross-sectional design and, therefore, longitudinal studies will be required to follow up these findings and their long-term effects. However, the same relationships have been observed between systemic inflammation and lung function in the other longitudinal studies [7], with differing populations. In contrast, our study population is predominantly female, younger and with high rates of smoking.

This study demonstrates that systemic inflammation and macrophage activation play a role in modulating lung function. In particular, elevated CRP and sCD163 are associated with poorer lung function. These factors likely play an important role in preserving lung health in this population. Targeting a reduction systemic inflammation and macrophage activation may slow lung function decline that occurs during ageing.



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**Systemic inflammation and macrophage activation play a role in modulating lung function**

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