LETTERS

Association between the *IL6*-174G/C SNP and maximally attained lung function

Recently, He *et al*[1] reported that the C allele of the interleukin 6 (*IL6*)-174G/C promoter polymorphism was associated with a rapid decline in forced expiratory volume in 1 s (FEV_1) (≥3% predicted/year) and susceptibility to chronic obstructive pulmonary disease (COPD) in middle-aged smokers derived from three different cohorts.[1] Alternatively, as also suggested by He *et al* in their discussion,[1] we hypothesised that the *IL6*-174G/C single nucleotide polymorphism (SNP) might not only affect the rate of lung function decline but also the maximally attainable value at around the age of 25. We investigated this hypothesis in young adults recruited from the East Flanders Prospective Twin Survey. Reproducible prebronchodilator lung function measurements according to international standards[2] and *IL6*-174G/C genotypes were available of 427 individuals (mean age 24.6±4.5 (SD), 232 women and 195 men). Mean FEV_1, forced vital capacity (FVC) and FEV_1/FVC ratio did not differ between current (n=131), former (n=33) and never smokers (n=263). The *IL6*-174G/C SNP was genotyped using pyrosequencing technology. PCR conditions and primer sequences are listed in online table 1. Genotype frequencies of the *IL6*-174G/C SNP were in accordance with Hardy–Weinberg equilibrium (p>0.05) (online Table 2). Data were analysed using the PROC MIXED method as previously described.[3]

In this sample of young adults, the *IL6*-174G/C SNP showed no association with the FEV_1, but the C allele of the *IL6*-174G/C SNP was significantly associated with a lower FVC (p=0.03) and a higher FEV_1/FVC ratio (p=0.003) under an additive mode of inheritance and independent of smoking status and birth weight (table 1).

Our results are in line with animal and in vitro studies consistently showing that IL-6 promotes lung morphogenesis, lung branching and surfactant protein A production during intrauterine lung development.[4] Local IL-6[4] and IL-6 receptor[5] expression has been described in the lungs during fetal development. Accordingly, our data suggest that the *IL6*-174G/C SNP may alter local IL-6 expression levels, potentially interfering with normal lung maturation. Collectively, the study by He *et al*[1] combined with these findings suggest that an interesting next step could be to investigate local IL-6 expression in the lungs in relation to the *IL6*-174G/C SNP during the course of life: during intrauterine development, at young adult age, and in middle-aged non-smokers versus smokers with and without COPD.

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Table 1 Descriptive data and associations between lung function and the *IL6*-174G/C single nucleotide polymorphism

	IL6-174G/C				
	GG	GC	CC	β (SE)	p Value adjusted for birth weight
n	143	197	87		
Age (years)	24.5 (0.4)	24.3 (0.3)	25.3 (0.5)		
Sex (M/F)	70/73	83/114	42/45		
Traits					
FEV_1 (% predicted)*	101.2 (1.1)	103.2 (1.0)	100.3 (1.1)	−0.19 (0.95)	0.839
FVC (% predicted)*	106.4 (1.1)	105.2 (1.0)	100.9 (1.3)	−2.18 (1.02)	**0.034**
FEV_1/FVC	82.2 (0.7)	84.8 (0.6)	86.1 (0.7)	1.83 (0.61)	**0.003**

Data are mean (SE).
*The percentage predicted values were calculated according to reference equations.[2]
F, female; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; M, male.

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Authors' reply

van den Borst and colleagues present interesting data regarding the role of the interleukin 6 (IL6)-74G/C promoter polymorphism (rs1800795) in determining the level of lung function.[1] We have shown that the C allele of the -174 polymorphism was associated with more rapid decline of lung function in the Lung Health Study (LHS) and with chronic obstructive pulmonary disease in the National Emphysema Treatment Trial (NETT).[2] However, there was no association of this polymorphism with baseline lung function in the LHS, and we hypothesised that this may have been due to the younger age of the participants of the LHS compared with the NETT group. Specifically, the baseline lung function in the LHS participants may have been strongly influenced by the maximal attained lung function, whereas lung function in the NETT group (on average two decades older) may be more reflective of the rate of decline of lung function. In this model, the -174G/C polymorphism primarily affects the rate of decline of lung function in response to cigarette smoke and not the maximal level attained during development.

The data from van den Borst *et al* show an association of the -174C allele with lower forced vital capacity in young adults who were on average 23 years younger than the LHS cohort which we studied. Thus, their results are more reflective of the effect of this polymorphism during lung development than ours, and this may partly explain the differences in results with regard to baseline lung function values. However, we agree with van den Borst and colleagues that further studies are warranted to clarify the mechanism underlying these observations.

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Health literacy and sleep apnoea

Determining which of our patients struggle with numeracy or literacy is difficult and clinicians overestimate the levels of patient literacy.[1] In a report in this journal, we demonstrate that 33% of new patients and 16% of serial users have difficulty completing the Epworth Sleepiness Scale (ESS).[2] To explore reasons for this we have assessed literacy in a further group of 122 patients attending either the Sleep Centre (Sleep group) or the Lung Function Laboratory (LF group). The level of functional literacy in medicine was assessed using the Rapid Estimate of Adult Literacy in Medicine (REALM) questionnaire.[3] A REALM score ≤60 suggests that the patient would struggle with patient education materials and prescription labels. In addition to REALM, information about educational attainments and use of the English language was collected.

Eighty-six (93.3%) of 92 Sleep group patients and 30/30 (100%) LF group patients completed the REALM questionnaire. Five (5.6%) in the Sleep group declined when shown the test. One did not complete due to time restrictions. Mean age was 51.2±11.8 years in the Sleep group and 56.1±17 years in the LF group. Mean age leaving formal education was 18.7±2.9 years in the Sleep group and 17.7±2.9 years in the LF group. In the Sleep group 38.4% (33/86) had a university education (24% graduate, 15% postgraduate degrees) versus 30% (9/30; 27% graduate and 3% postgraduate degrees) in the LF group. REALM scores are shown in table 1 grouped into the traditional four ranges. Seventy-eight per cent of the Sleep group patients and 83% of the LF group patients spoke English as their mother tongue; all patients used English as their everyday spoken language.

Table 1 REALM scores achieved by Sleep (n=86) and LF (n=30) group patients

REALM score ranges	Equivalent reading age		% Sleep group (n=86)	% LF group (n=30)
	US school grade	UK age equivalent		
0–18	Third grade or below	8 years or less	0.0	0.0
19–44*	Fourth/sixth grade	9–12 years	1.2	3.3
45–60*	Seventh/Eighth grade	12–14 years	15.1	6.7
61–66	High school	14–15+	83.7	90.0

*A score ≤60 suggests a literacy level that would struggle to cope with patient education materials and prescription labels. LF group, patients attending the Lung Function Laboratory; REALM, Rapid Estimate of Adult Literacy in Medicine; Sleep group, patients attending the Sleep Centre.

Assessing literacy in patients is not easy and completing tools such as REALM, while quick to administer, can be awkward for the patient. We have previously shown how patients struggle to complete the ESS. Indeed, some patients volunteered that they could not read or write but it is likely that others have developed coping mechanisms to hide their difficulties. Problems completing forms may occur for many reasons. In this study of 122 patients, we found evidence of impaired health literacy in 16.3% of the Sleep group and 10% of the LF group patients. Von Wagner *et al* estimate limited health literacy in 11.4% of their UK cohort and other studies in the UK and US report levels between 13% and 15% in patients attending secondary care.[4] That some Sleep group patients declined to be tested once shown the questionnaire might suggest that the 16.3% score is an underestimate. Why Sleep group patients should fare worse than LF group patients, if real, is unclear especially when educational attainments were higher and age was younger. All used English as their everyday language; however, fewer Sleep group patients had English as their mother tongue. Cognitive deficits associated with undiagnosed obstructive sleep apnoea syndrome (OSAS) and increased sleepiness could conceivably be a contributory factor.[5]

This study suggests that clinicians need to provide clinical material and information in a format that is comprehensible to a diverse population. A pictorial format would fulfil this need. Patients with OSAS may have particular need for such information.[2]

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