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## **Smoking, telomere length and lung function decline: a longitudinal population-based study**

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### **Abstract**

Telomere shortening is associated with COPD and impaired lung function in cross-sectional studies, but there is no longitudinal study. We used data from 448 participants recruited as part of the French follow-up of the ECRHS. We found no relationship between telomere length at baseline and FEV1 decline after 11 years of follow-up. However, heavy smoking was associated with an accelerated FEV1 decline in individuals with short telomeres, but not in subjects with longer telomeres (p for interaction  $p=0.08$ ). Our findings suggest that short telomere length in peripheral leukocytes might be a marker for increased susceptibility to the effect of smoking.

**Words count: 1167**

## **Introduction**

Not all smokers will develop COPD but the reasons why some individuals are more susceptible to accelerated loss of lung function when exposed to tobacco smoke are still largely unexplained. Telomeres are structures at the chromosomal ends involved in chromosomal stability. COPD patients have been shown to have shorter telomeres compared to healthy smokers, and correlations between telomere shortening, premature senescence and lung inflammation have been reported (1-6). Experimental studies show that telomere dysfunction may result in replicative senescence and release of pro-inflammatory mediators (4, 7), leading to hypotheses that telomere shortening might contribute and maintain the inflammatory process causing airway remodelling and COPD. Consistent with this, mice with short telomeres secondary to knocking down telomerase *hTR*<sup>-/-</sup> were more likely to develop emphysema after cigarette smoke exposure than wild-type controls (5). Altogether, these data suggest that individuals with short telomere might be at increased risk of accelerated lung function decline when exposed to smoking. Telomere shortening has been associated with impaired lung function in cross-sectional studies of COPD patients and in cross-sectional analyses of large population-based samples (2,8,9). We are unaware of any longitudinal study that has examined this.

Using information from 448 middle-aged adults randomly selected from the general population and followed-up as part of the European Community Respiratory Health Survey (ECRHS) in 3 French centres (10), we assessed whether lung function decline after 11 years of follow-up was associated with telomere length at baseline (2000-2002), and whether the effect of smoking was modified by telomere length. Relative telomere length in peripheral leukocytes was measured by quantitative PCR (details in the Online Repository), and categorised into tertiles. The methods for ECRHS, statistical analysis, and participants' characteristics are described in the online supplement.

## **Results**

### ***Cross-sectional analysis at baseline.***

At baseline, relative telomere length was negatively associated with age, but was not associated with sex, pack-years smoked, body-mass index (BMI), physical activity, atopic sensitisation, asthma or other respiratory symptoms or comorbidities (Table E1). There was

no relationship between telomere length and FEV% or FVC%predicted. The percentage of subjects with pre-bronchodilator(BD) FEV1/FVC<lower limit of normal (LLN) at baseline was quite low (18/444) and did not vary with telomere length (Table E2).

### ***Telomere length at baseline and lung function at follow-up***

Participants with short and long telomeres showed similar patterns of smoking and BMI change over the follow-up (Table E1). At follow-up, there was a non-significant increased risk of pre-BD FEV1/FVC<LLN in individuals with telomere in the first tertile (short telomeres) as compared to those in the third tertile (Table E2), (odds-ratio adjusted for age, sex, centre, BMI, physical activity and smoking status: 2.18; 95%CI 0.85to5.57; p=0.10). When considering post-bronchodilator spirometry (only performed at follow-up), the percentage of subjects with fixed airflow obstruction was low (n=17/404) and did not vary with telomere length.

### ***Lung function decline by smoking and tertiles of telomere length***

There was no association of FEV1 decline with telomere length at baseline (Table E2). FEV1 decline was strongly associated with smoking. However, there was some evidence that this association was modified by telomere length. As shown in figure 1, the effect of smoking on lung function decline was highly significant in subjects with short telomeres (1<sup>st</sup> tertile), and largely reduced and non-significant in subjects with long telomeres (3<sup>rd</sup> tertile). In subjects with short telomeres, heavy-smokers had an accelerated decline of FEV1, with an additional loss of -20.1mL/yr (95%CI -32.7 to -7.5) as compared to never smokers (Table 1). In contrast, no effect of smoking was observed in subjects with long telomeres. Test for interaction showed significant interactions of short telomere length with both moderate (p=0.03) and heavy smoking (p=0.02) (Table E3). Similar patterns were seen in the sensitivity analyses (Table 1). Consistently, heavy-smoking was associated with a reduction in FEV1%predicted at follow-up of -14.9 (95%CI -22.3 to -7.4) in subjects with short telomere length, but no reduction (+2.3%) in those with long telomeres (Table E4).

## **Discussion**

We believe this is the first population-based longitudinal study investigating the relationships between telomere length and lung function decline. We found that smoking was associated with an accelerated loss in lung function in individuals with short telomeres and with little/no effect in those with longer telomeres.

In our cross-sectional analyses, we found no association of telomere length with FEV1%predicted or FVC%predicted. In a very large sample of the Danish population (comprising +20,000 participants aged over 60 years), there were significant associations of telomere length with FEV1 and FVC but these were largely attenuated after adjustment for age and other covariates (8). A meta-analysis of seven European studies unselected for lung disease showed cross-sectional associations of telomere length with FEV1, FVC and FEV1/FVC ratio, but that were significant only in women (9).

Epidemiological studies suggest that variability in telomere length is partly determined by genetic factors, but also by modifiable lifestyle factors such as smoking, obesity, physical activity or diet. However, to date, few prospective studies have investigated these relationships. In our sample of mostly healthy individuals, we did not find association between telomere length and lifestyle habits. Telomere length was lower in older participants, which supports the validity of measurements. Our study has some limitations including the relatively small sample size and the limited number of heavy-smokers. Because of the relatively young age of the sample, we used a low cut-off (>15 pack-years) to define heavy-smokers. Lung function was measured following international guidelines, but spirometers were changed between baseline and follow-up. However, the sensitivity analyses considering smokers with >20 pack-years as heavy-smokers, or using lung function corrected for change in spirometers yielded similar relationships.

While tobacco smoke may influence telomere dysfunction, our findings are consistent with the hypothesis that short telomere length might contribute to the differences in susceptibility to the deleterious effect of cigarette smoke in the lung (5). This is consistent with the large cross-sectional Danish study in which participants with COPD had shorter telomere length as compared to subjects with the same history of smoking but who had not developed COPD (8). It is also supported by Savale et al. showing shorter telomere length in COPD patients but no difference in telomere length between control smokers without COPD and control non-smokers (3).

To summarize, this population-based longitudinal study suggests that people with shorter telomere length are at increased risk of spirometrically defined COPD. Furthermore, smoking was associated with an accelerated loss of lung function only in individuals with shorter

telomeres, suggesting that telomere shortening might be a marker for increased susceptibility to the effect of smoking on lung function decline. Further prospective studies, with repeated measures of both telomere length and lung function, and including sufficient smokers, are warranted to further investigate the predictive value of this biomarker.

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## Figure legend

**Figure 1: Adjusted mean\* (95%CI) annual FEV<sub>1</sub> decline according to smoking status and tertile of telomere length.** Smoking status is defined according to smoking history at follow-up: Never smokers (NS); Ex-smokers (Ex); Current smokers or recent quitters with  $\leq 15$  pack-years smoked ( $<15$ PY); Current smokers or recent quitters with  $>15$  pack-years smoked ( $>15$ PY). Telomere length is assessed at baseline. \*Adjusted for age, gender, centre, BMI, physical activity and baseline FEV<sub>1</sub>.

**Table 1. Difference in annual decline in smokers as compared to never-smokers, stratified by tertiles of telomere length**

		Tertile of telomere length at baseline		
		Tertile1 (shortest)	Tertile2	Tertile3 (longest)
<b>Annual FEV<sub>1</sub> decline (ml/year)</b>				
Never smokers	n=164	(ref)	(ref)	(ref)
Ex-smokers	n=151	-8.1 (-17.8 to 1.5) §	-2.6 (-15.3 to 10.2)	-5.2 (-14.3 to 3.8)
Smokers ≤ 15 Pack-yrs	n=49	-16.6 (-29.8 to -3.4) †	-4.6 (-24.2 to 15.0)	6.0 (-5.7 to 17.7)
Smokers > 15 Pack-yrs	n=76	-20.1 (-32.7 to -7.5) ‡	-14.4 (-28.1 to -0.61) †	3.0 (-8.5 to 14.4)
<i>p for trend</i>		0.001	0.06	0.28
<b>Sensitivity Analysis</b>				
<b>Annual FEV<sub>1</sub> decline (ml/year) corrected as Gerbase</b>				
Never smokers	n=164	(ref)	(ref)	(ref)
Ex-smokers	n=151	-8.1 (-17.8 to 1.5) §	-2.6 (-15.3 to 10.1)	-5.2 (-14.3 to 3.8)
Smokers ≤ 15 Pack-yrs	n=49	-16.5 (-29.7 to -3.3) †	-4.7 (-24.3 to 14.9)	6.0 (-5.8 to 17.6)
Smokers > 15 Pack-yrs	n=76	-20.1 (-32.6 to -7.5) ‡	-14.3 (-28.1 to -0.58) †	3.0 (-8.4 to 14.4)
<i>p for trend</i>		0.001	0.06	0.28
<b>Annual FEV<sub>1</sub> decline (ml/year) corrected as Bridevaux</b>				
Never smokers	n=164	(ref)	(ref)	(ref)
Ex-smokers	n=151	-8.1 (-17.8 to 1.5) §	-2.6 (-15.3 to 10.1)	-5.2 (-14.2 to 3.9)
Smokers ≤ 15 Pack-yrs	n=49	-16.3 (-29.5 to -3.1) †	-4.7 (-24.3 to 14.8)	5.9 (-5.8 to 17.6)
Smokers > 15 Pack-yrs	n=76	-20.0 (-32.5 to -7.4) ‡	-14.3 (-28.0 to -0.54) †	3.0 (-8.4 to 14.4)
<i>p for trend</i>		0.001	0.06	0.28
<b>Annual FEV<sub>1</sub> decline – Using a cumulative history of &gt;20 pack-years as a cut-off to define heavy smoking</b>				
Never smokers	n=164	(ref)	(ref)	(ref)
Ex-smokers	n=151	-8.1 (-17.8 to 1.5) §	-2.6 (-15.3 to 10.2)	-5.2 (-14.3 to 3.8)
Smokers ≤ 20 Pack-yrs	n=59	-16.4 (-29.2 to -3.6) †	-7.8 (-25.3 to 9.8)	8.2 (-2.7 to 19.1)
Smokers > 20 Pack-yrs	n=66	-20.6 (-33.5 to -7.7) ‡	-14.0 (-28.6 to 0.50) †	-1.0 (-13.4 to 11.5)
<i>p for trend</i>		0.001	0.05	0.59
<b>Annual FEV<sub>1</sub> decline – considering tobacco consumption over the follow-up instead of cumulative history</b>				
Never smokers	n=164	(ref)	(ref)	(ref)
Ex-smokers	n=151	-7.6(-16.6 to 1.4)	-1.4 (-14.4 to 11.6)	-5.2 (-14.4 to 4.1)
ΔPack-yrs ≤ 5 Pack-yrs**	n=31	-6.9 (-21.0 to -7.2)	-9.5 (-37.9 to 18.9)	5.0 (-9.3 to 19.4)
ΔPack-yrs > 5 Pack-yrs**	n=49	-19.0 (-32.6 to -5.4) †	-21.5 (-37.7 to -5.2) †	2.7 (-10.5 to 15.8)
<i>p for trend</i>		0.01	0.01	0.40
<b>Decline in FEV<sub>1</sub>%predicted; 10yrs</b>				
Never smokers	n=164	(ref)	(ref)	(ref)
Ex-smokers	n=151	-2.8 (-6.1 to 0.6)	-0.3 (-4.2 to 3.5)	-1.9 (-4.9 to 1.02)
Smokers ≤ 15 Pack-yrs	n=49	-5.3 (-9.8 to -0.8) †	-0.7 (-6.6 to 5.2)	2.2 (-1.7 to 6.0)
Smokers > 15 Pack-yrs	n=76	-5.5 (-9.7 to -1.2) †	-3.2 (-7.3 to 0.8)	1.3 (-2.4 to 5.0)
<i>p for trend</i>		0.007	0.15	0.18

\*Data are regression coefficient (95%CI). Telomere length at baseline. All models adjusted for age, gender, centre, BMI and physical activity. Regression models for FEV<sub>1</sub> decline additionally adjusted for baseline FEV<sub>1</sub>. Smoking status is defined according to smoking status and cumulative pack-years smoked at ECRHS III. Details on correction used in sensitivity analysis are provided in the online supplement. \*\* change in pack-years smoking between baseline and follow-up, in current smokers at the end of follow-up. Smokers who quit smoking during the follow-up (n=45) were excluded from this analysis

† p<0.05 ‡ p<0.01 § p<0.10, as compared to never -smokers

