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## Airflow obstruction, atherosclerosis and cardiovascular risk factors in the AGES Reykjavik study

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### Abstract

**Background and aims**—Airflow limitation, i.e. reduced forced expiratory volume in one-second (FEV1) is associated with increased prevalence of atherosclerosis, however, causal mechanisms remain elusive. The objective of the study was to determine if the association between airflow obstruction and markers of atherosclerosis were mediated by systemic inflammation.

**Methods**—1154 subjects from the longitudinal AGES Reykjavik study were included. Population characteristics, systemic inflammation markers from blood (white blood cell counts (WBC) and level of C-reactive protein (CRP)) were compared between patients with and without airflow limitation defined by reduced FEV1 on spirometry. Atherosclerosis burden was quantified by measurements of coronary artery calcium, aortic arch and distal aortic calcification in addition to carotid intimal media thickness (CIMT).

**Results**—Subjects were split into four groups according to smoking status and if airflow limitation was present. There was a higher overall burden of atherosclerosis in ever-smokers compared to never-smokers, and in individuals with airflow obstruction compared to individuals without airflow obstruction. After adjusting for population characteristics, Framingham cardiovascular risk factors and markers of systemic inflammation (WBC and CRP), there was a significantly more aortic arch and distal aorta calcification and higher measurement of CIMT for individuals with airflow obstruction compared to individuals without airflow obstruction. After adjusting for population characteristics, Framingham cardiovascular risk factors and markers of systemic inflammation (WBC and CRP), there was a significantly more aortic arch and distal aorta calcification and higher measurement of CIMT for individuals with airflow obstruction compared to individuals without airflow obstruction.

**Conclusions**—Systemic inflammation (WBC and CRP) does not appear to mediate the association between airflow limitation and atherosclerosis. Only airflow limitation and not systemic inflammation (WBC and CRP) appears to be an independent predictor of atherosclerosis.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by expiratory airflow obstruction (reduced FEV<sub>1</sub> (forced expiratory volume in 1 sec)) that is not reversible by bronchodilators. The cardinal symptoms are longstanding cough and shortness of breath, and common clinical findings are hyperinflation of the lungs, gas trapping and gas exchange abnormalities. COPD is associated with significant morbidity and mortality (1,2).

Cardiovascular disease is a common comorbidity in patients with COPD and is a frequent cause of mortality (3). Although there is some heterogeneity in the results across different studies, several studies indicate that reduced FEV<sub>1</sub> is an important risk factor for cardiovascular mortality, independent of established cardiovascular risk factors such as cigarette smoking status, cholesterol, body mass index and systemic hypertension (3,4,5). It has been shown that for every 10% decrease in FEV<sub>1</sub> all-cause mortality increases by 14%, cardiovascular mortality increases by 28% and the frequency of non-fatal coronary events increases by 20% (3).

Chronic obstructive pulmonary disease is also associated with a systemic inflammatory response that is more pronounced with advanced disease and during exacerbations (3,4,5). Patients with COPD have elevation of markers of systemic inflammation, such as C-reactive protein (CRP) that also increases with severity of obstruction and in exacerbations (4,5,6). However, It is still unclear whether these associations between markers of systemic inflammation and airflow obstruction are a consequence of shared risk factors such as cigarette smoking or whether airflow limitation is truly causal factor.

The causal mechanisms linking airflow obstruction with atherosclerosis remain for most part unknown (7). It has been hypothesized that systemic inflammation mediates the association between airflow obstruction and atherosclerosis.

Here, we assessed expiratory airflow, systemic inflammation (WBC and CRP), and carotid/coronary/aortic atherosclerosis in a well phenotyped longitudinal cohort study from a subset of participants from the Reykjavik AGES study. We hypothesized that increased systemic inflammation would mediate the association between airflow obstruction and atherosclerosis so after adjusting for WBC and CRP as markers of systemic inflammation, the association between those two would be lost.

## Materials and methods

### Subject Population

Subjects were identified among subjects in the Age Gene/Environment Susceptibility (AGES)-Reykjavik study (8). The AGES-Reykjavik study is a longitudinal epidemiologic study with primary focus on the process of aging. It originates from the Reykjavik study (RS), a large longitudinal population based study primarily focusing on cardiovascular

disease. In 2002, 11,549 previously examined RS cohort members were still alive and invited for participation in the AGES-Reykjavik study. Recruitment took place from 2002 to 2006 with a total sample size of 5764 individuals. The mean age was 76.1 (SD 5.7) years with a range from 66 to 96 years. They were all Caucasians. The individuals answered detailed questionnaire and had an extensive laboratory measurements, physiological measurements (including spirometry) and imaging performed. Details of collected variables are provided elsewhere (8). The AGES-Reykjavik study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Icelandic Data Protection Authority and the Institutional Review Board of the Intramural Program of the National Institute for Aging. Written, informed consent was obtained from all participants.

### Identification of smokers

Smoking status was assessed by questionnaire. To be considered an ever smoker, the individuals either responded positively to smoking a cumulative number of 20 packs of cigarettes (more than 400 cigarettes over their lifetime) over their lifetime, or 1 cigarette/day for a whole year (more than 365 cigarettes over their lifetime). In the total population of 5764 individuals there were 12% current smokers, 43% previous smokers and 45% never smokers.

### Spirometry

Spirometry was performed with a Vitalograph Gold Standard Plus (Vitalograph Ltd., Buckingham, UK). The procedure was explained in details before starting and was done in a sitting position in a standardized manner. Three attempts were made for each individual. Inclusion criteria for acceptable spirometry was completion of at least two spirometry attempts, no more than 300 ml difference between the attempts and ability to exhale for at least six seconds. No bronchodilator was given, so airflow limitation was defined as FEV<sub>1</sub>/FVC ratio less than 0.7. Details of included individuals are in Figure 1.

### Cardiovascular risk factors

The presence of Framingham cardiac risk factors were evaluated in all individuals. These include: diabetes, hypertension, systolic blood pressure, cholesterol, HDL cholesterol and body mass index. Diabetes was defined as a history of diabetes, use of glucose-modifying medication, or fasting blood glucose of more than 7 mmol/L. Blood pressure was assessed from the mean value of two measurements using a large-cuff mercury sphygmomanometer. Hypertension was defined as measured systolic blood pressure of more than 140 mm Hg, diastolic blood pressure of more than 90 mm Hg, self-reported doctor's diagnosis of hypertension or usage of antihypertensive medications. High-density lipoprotein (HDL) cholesterol, and glucose were measured in fasting blood samples using reagents from RocheDiagnostics (Mannheim, Germany) on a Hitachi 912 analyzer (Hitachi Ltd., Tokyo, Japan) according to the manufacturer's instructions. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Body mass index (BMI) (weight(kg)/height (m)<sup>2</sup>) was calculated from measured height (cm) and weight (kg).

## Markers of systemic inflammation

Total white blood cell count (WBC) was measured in fasting whole blood samples using an automated cell counter, Coulter HmX AL Hematology Analyzer (Beckman Coulter, High Wycombe, England, UK). Level of C-reactive protein (CRP) was measured in plasma from fasting blood samples using reagents from Roche Diagnostics (Mannheim, Germany) on a Hitachi 912 analyzer (Hitachi Ltd., Tokyo, Japan) according to the manufacturer's instructions. Both within- and between-assay quality control procedures were used and the coefficient of variation of the method was 1.3% to 3.4%, respectively, through the period of data collection. All participants in this study had detectable CRP levels.

## Evaluation of atherosclerosis

**Carotid Intima-Media Thickness (CIMT)**—The CIMT, measured in millimeters (mm) were measured using high resolution ultrasonography (US) on all study subjects. The ultrasound protocol of the CIMT is described in more detail elsewhere (9,10). In brief, images of the right and left carotid artery (CCA), bifurcation, and internal carotid artery (ICA) were acquired with an Acuson Sequoia C256 with a two-dimensional 8 MHz linear array transducer. Images of the intima-media thickness were acquired from a predefined 10 mm segment (extending from 10 mm to 20 mm proximal to the tip of the flow divider) at defined interrogation angles using the Meijers Arc. Standard images were obtained from 4 angles at each side. The mean IMT of the near and far walls was determined from a single image at each interrogation angle for both the right and left CCA. The average of all these IMT values comprised the CCA-IMT outcome parameter. All IMT measurements were carried out using the Artery Measurement System (AMSII) software (v1.141)

**Coronary artery and aorta calcification**—Calcium was quantified by Agatston scores of coronary arteries, proximal aortic arch and distal aorta using computerized tomography (CT) images of the chest (10,11,12) Cerebral infarction: The scoring of cerebral infarcts has been described in detail elsewhere (13,14). In brief, infarcts were scored by trained radiographers and defined as defects of the brain parenchyma with a signal intensity isointense to cerebrospinal fluid on all MR images (FLAIR, PD/T2-weighted images), associated hyperintensity on T2-weighted and FLAIR images with a minimal diameter of 4 mm, except for infarcts in the cerebellum and brain stem which had no size criteria and did not require associated hyperintensity.

## Statistical Analysis

Stata 13.1 was used to perform the statistical analyses. Baseline characteristics for continuous variables were presented as mean values and standard deviations (SDs) or medians with 25th and 75th centiles and numbers and percentages were used for categorical variables. Logtrans formed outcomes for CRP were used. The overall comparison given in Table 1 is done with ANOVA except for the artery calcification variables where the Kruskal-Wallis test was used. We performed our analyses in three steps, one model for each step with outcome variable as given in Table 1. In the first step all the analyses were adjusted for age, airflow obstruction, smoking status (including interaction with airflow obstruction) and sex. In the second step, all analyses were adjusted for age, airflow obstruction, smoking status

(including interaction with airflow obstruction), sex, as well as Framingham cardiac risk factors. These include: diabetes, hypertension, systolic blood pressure, cholesterol, HDL cholesterol and body mass index. In the third step markers of systemic inflammation were added. They were CRP levels and WBC count. Relationship between the two variables was measured by the Pearson correlation coefficient ( $r$ ). Quantile regression was used for the outcome variables coronary calcium and aortic and distal calcium. Generalized linear model was used for CIMTmean and logit model was used for brain infarcts. Post estimation of adjusted differences was evaluated by the margins command in Stata and for covariates fixed at their means, see Table 2. Significance was defined as  $p < 0.05$ .

## Results

There were a total of 1154 individuals included in the analysis. Median age was 76 years and 47% were males. Smoking was more common in males. Average BMI was 26.7 kg/m<sup>2</sup> (SD 4.2). Subjects were divided into four groups according to smoking status and if airflow limitation was present or not. Comparisons between the four groups are shown in Table 1. Most of the subjects were ever smokers with normal spirometry and the group of never-smokers with abnormal spirometry had fewest individuals. There was no difference in blood pressure between the groups. WBC counts and CRP levels were higher in ever smokers than never smokers. Markers of atherosclerosis of coronaries/aorta/carotid arteries were highest in the smokers with airflow obstruction, especially compared with non-smokers.

### Airflow obstruction and atherosclerosis

Table 1 describes the measurements of atherosclerosis burden between the four groups. Individuals with airflow obstruction had significantly higher burden of atherosclerosis, indicated by either coronary calcium (171 Agatston units (log) vs 255 Agatston units (log) for never-smokers, 430 Agatston units (log) vs. 553 Agatston units (log) for ever-smokers), aortic arch calcium (1145 vs 2276 for never-smokers, 1614 Agatston units (log) vs. 2481 Agatston units (log) for ever-smokers) distal aorta calcium (98 Agatston units (log) vs 562 Agatston units (log) for never-smokers, 157 Agatston units (log) vs. 454 Agatston units (log) for ever-smokers) and CIMT (0.93 mm vs 0.98 mm for never-smokers, 0.98 mm vs. 0.99 mm for ever-smokers). In general we found that neither CRP levels nor WBC counts showed significant association with any of the calcium variables. However, WBC counts was found to be associated with aortic arch calcium score ( $p=0.038$ ) if CRP levels were not in the model. Correlation between  $\log(\text{CRP})$  and WBC was  $r=0.25$  ( $p < 0.0001$ ).

In multivariable analysis for all individuals after adjusting for age, sex and smoking history, airflow obstruction was associated with a higher burden of atherosclerosis as measured by the difference in both aortic arch (511, 95% CI 167–854 Agatston units (log)), distal aorta (203, 95% CI 102–304 Agatston units (log)) calcification and CIMT (0.017, 95% CI 0.0–0.034), This relationship was further strengthened after additional adjustment for Framingham risk factors and markers of inflammation (Table 2, model 2 and 3).

## Discussion

In this study we confirmed the previously known association between reduced airflow and atherosclerosis in a large prospectively collected cohort. Furthermore, we showed that association holds even after correcting the association for markers of systemic inflammation (WBC and CRP). Thus, it seems unlikely that markers of systemic inflammation (WBC and CRP) mediates the association between airflow limitation and atherosclerosis. Rather, both airflow limitation and markers of systemic inflammation (WBC and CRP) appear to be independent predictors of atherosclerosis.

Although cigarette smoking is widely accepted as the most important risk factor for COPD, it is now recognized that never-smokers may account for between one fourth and one third of all COPD patients (15). Several studies have demonstrated that risk factors for airflow limitation differ in smokers and never-smokers (15,16). In addition studies have shown that in older individuals definition of airflow obstruction as a ratio of FEV<sub>1</sub>/FVC lower than 0.7 may overestimate the incidence of airflow obstruction compared with using lower limits of normal in elderly subjects (17). Thus it is important to study the observation in both ever- and never-smokers. We compared subjects both according to airflow limitation and smoking status by splitting them up into four groups as others have done previously (18). We found that the relationship between airflow obstruction and atherosclerosis after correcting for markers of systemic inflammation (WBC and CRP) is similar in both never- and ever-smokers.

Our findings that both coronary calcium, aortic arch calcification, distal aorta calcification and CIMT are worse in patients with airflow obstruction, both in ever-smokers and never-smokers, can be compared to several previous studies. In the National Health and Nutrition Examination Survey (NHANES) database the estimated self-reported cardiovascular disease prevalence was 20.0% and 7.4% in COPD and non-COPD groups, respectively (19). In multivariable analysis, COPD was an independent risk factor for self-reported cardiovascular disease. A study from Japan found that mean CIMT was greater in smokers with airflow limitation compared to either control smokers without airflow limitation or control never-smokers (20). Multivariable analyses showed significant associations between both thickened CIMT and decreased percent FEV<sub>1</sub> independent of age, pack-years of smoking, body mass index, peripheral mean arterial pressure, heart rate, glucose, and low density lipoprotein cholesterol. Another study from Japan categorized 234 patients with coronary artery disease into four groups: never-smokers with normal pulmonary function (group A), never-smokers with airflow limitation (group B), ever-smokers with normal pulmonary function (group C), and ever-smokers with airflow limitation (group D)(18). They found the prevalence of airflow limitation was 23.1%. The prevalence of carotid atherosclerosis was 28.2, 29.4, 41.3, and 45.9%, respectively, in the four groups (group D vs. group A,  $p=0.035$ ). Even after multivariable adjusting for confounding factors, ever-smokers with airflow limitation were independently associated with carotid atherosclerosis (odds ratio 2.89, 95% confidence interval, 1.19–7.00,  $p=0.019$ ). The Mesa study also found that FEV<sub>1</sub> was associated with the extent of distal aortic calcification (0.76; 95% CI 0.60–0.97,  $p=0.02$ ) but not proximal aortic calcification (21). A study by Chae et al found that the amount of vascular calcification was associated with the extent of emphysema on computed

tomography and airflow limitation (22). This is in contrast with a recent study from China on elderly smokers with airflow limitation that found no evidence that the association of pulmonary function with CIMT varied by smoking status (23).

Similarly, our findings that markers of systemic inflammation are correlated with atherosclerosis are supported by a vast literature on the association between markers of systemic inflammation and atherosclerosis. An example is the recent study by Rein et al, showing that both peripheral vascular disease and coronary artery disease are associated with higher levels of CRP compared to controls (24). Secondly, the study by Cushman and colleagues in which 3,971 men and women aged  $\geq 65$  years were followed for 10 years, found that patients with a CRP level  $>3.0$  mg/L had a 1.45-fold increased risk of myocardial infarction or death due to coronary heart disease after adjustment for traditional CAD risk factors (25). There is also vast information available on the relationship between systemic inflammation and FEV1. In a recent study spirometry was measured in a population-based cohort at ages 32 and 38 years. CRP, fibrinogen, and WBC were measured at the same ages. There were no longitudinal associations between WBC and lung function. Higher CRP and fibrinogen at age 32 were associated with higher FEV1 and FEV<sub>1</sub>/FVC at age 38. The authors concluded that there was no evidence that systemic inflammation causes a decline in lung function (26). Metaanalysis has shown association between systemic inflammation and airway obstruction (5). Studies have also shown that markers of systemic inflammation are associated with rapid decline in FEV1 in individuals with COPD (27). As shown systemic inflammation has been linked to both atherosclerosis and airflow limitation. Possible pathways include complex interrelationships between chronic low-grade systemic inflammation and oxidative stress as well as shared risk factors such as age, cigarette smoking, and environmental pollutants.

The strength of the study is the well defined population of both males and females. They represent a sample of older individuals from the Reykjavik metropolitan area that have all lived within a 30 km radius and been exposed to rather similar amount of air pollution. The AGES-Reykjavik study has a very rigid data collection protocols. To our knowledge, none of the available studies has simultaneously available data on airflow obstruction, markers of systemic inflammation and atherosclerosis. We were in a unique position to contrast the three and test the association between airflow obstruction and atherosclerosis after correcting for the most common indicators of systemic inflammation and cardiovascular risk factors.

Our study has several limitations. One is the lack of perform postbronchodilator pulmonary function tests, so the study might overestimate the prevalence of subjects with non-reversible airflow limitation. This deficiency is partially mediated since we excluded the diagnosis of other respiratory diseases through self-reported diagnoses. Therefore it is most likely that these individuals had COPD. Another limitation is that we only use two markers of systemic inflammation, ie WBC and CRP. Most previous studies use one or two markers to represent systemic inflammation. It might be interesting to measure other markers of systemic inflammation. The third limitation is that there were only Caucasians in the study and results can possibly not directly be applied to other races. This was a study of elderly people and similarly results can therefore also not be applied to other age populations.

In summary our study shows that two markers of systemic inflammation (WBC and CRP) do not mediate the association between airflow limitation and atherosclerosis. Only airflow limitation and not markers of systemic inflammation (WBC and CRP) appear to be independent predictor of atherosclerosis.

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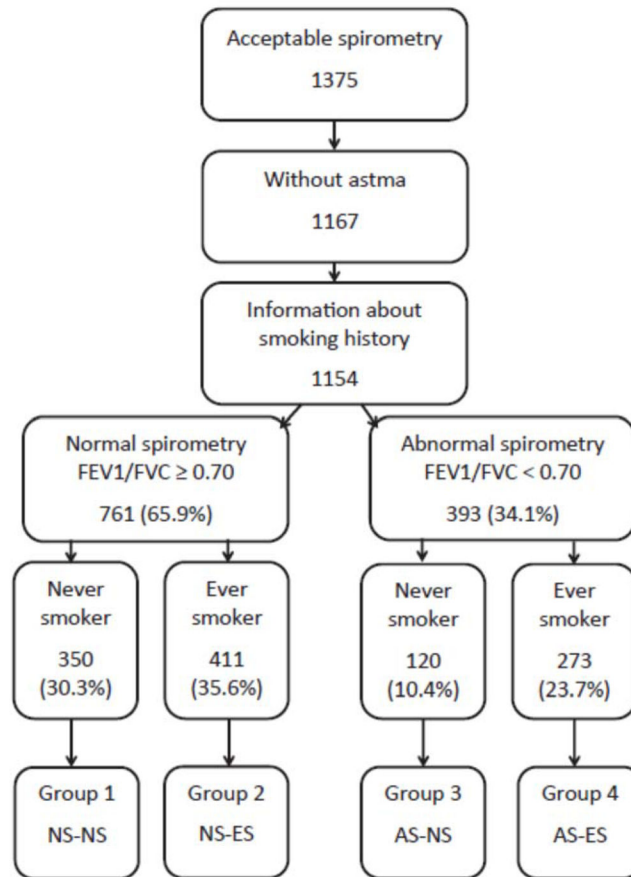
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**Fig. 1. Classification of individuals based on smoking and spirometry results**

Flowchart of inclusion of individuals into the study after applying exclusion criteria, and their categorization into four groups based on spirometry (normal spirometry(NS) or abnormal spirometry (AS)) and smoking status (never smoker (NS) or ever smoker ES)). The final four groups used in analysis are Group 1: NS-NS. Normal spirometry and never-smokers; Group 2: NS-ES. Normal spirometry and ever-smokers; Group 3: AS-NS: Normal spirometry and never-smokers and Group 4: AS-ES: Abnormal spirometry and never-smokers.

**Table 1**

Comparison between four groups according to smoking status and spirometry

d	Normal spirometry and never smoker			Normal spirometry and ever smoker			Abnormal spirometry and never smoker			Abnormal spirometry and ever smoker			Total	p
	n	mean	sd	n	mean	sd	n	mean	sd	n	mean	sd		
Age	350	76.0	5.5	411	74.9	5.5	120	79.4	5.4	273	76.6	5.6	1154	<0.0001
BMI <sup>a</sup>	350	27.0	4.4	411	27.6	3.9	120	25.3	3.7	273	25.7	4.1	1154	<0.0001
FVC <sup>b</sup> L	350	2.99	0.78	411	3.29	0.80	120	2.84	0.83	273	2.92	0.85	1154	<0.0001
FEV <sub>1</sub> <sup>c</sup> L	350	2.28	0.62	411	2.50	0.64	120	1.75	0.57	273	1.81	0.57	1154	<0.0001
FEV <sub>1</sub> /FVC Ratio	350	0.76	0.04	411	0.76	0.04	120	0.62	0.09	273	0.62	0.08	1154	
Smoking	350			411	0.16		120			273	0.30		1154	
Packyears	350			367	21.34		120			256	28.9		1093	
Systolic BP <sup>d</sup>	350	142	20	411	141	20	120	146	24	273	141	21	1154	0.099
Diastolic BP <sup>d</sup>	350	74	9	411	74	9	120	72	10	273	73	9	1154	0.063
LDL <sup>e</sup>	350	3.68	1.01	411	3.47	1.01	120	3.66	1.05	273	3.40	0.97	1154	0.001
WBC <sup>f</sup>	349	5.79	1.84	411	5.99	1.59	120	5.72	1.60	273	6.36	1.83	1153	0.0002
				centiles			centiles			centiles				
		median	25th-75th		median	25th-75th		median	25th-75th		median	25th-75th		
CRP <sup>g</sup> mg/l	350	1.6	1-1.3	411	2.1	1.1-4.3	119	1.7	1.0-2.8	273	2.0	1.1-4.3	1153	0.011
Coronary calcium <sup>h</sup>	346	171	14-622	410	430	69-1174	120	255	66-775	269	553	128-1288	1145	<0.0001
Aortic arch calcification <sup>i</sup>	347	1145	343-3023	410	1614	575-3621	120	2276	1076-4910	267	2481	1072-5547	1144	<0.0001
Distal aorta calcification <sup>i</sup>	346	98	5-720	410	157	16-876	120	562	62-1166	269	454	95-1397	1145	<0.0001
CIMT mm	344	0.93	0.85-1.03	401	0.98	0.88-1.08	119	0.98	0.87-1.09	270	0.99	0.90-1.09	1134	<0.0001

<sup>a</sup>BMI: body mass index (kg/m<sup>2</sup>)

<sup>b</sup>FVC: forced vital capacity in liters

<sup>c</sup>FEV<sub>1</sub>: Forced expiratory volume in one second in liters

<sup>d</sup>BP: blood pressure in mmHg

LDL: low density cholesterol in mmol/l<sub>e</sub>  
WBC: white blood cell count x 10E9/L<sub>f</sub>  
CRP: C-reactive protein<sub>g</sub>  
CIMT: Carotid Intima media thickness<sub>h</sub>  
I (Agatston units)<sub>i</sub>

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**Table 2** Multivariable analysis of cardiovascular outcomes using three models for different adjustments

Outcome	Adjusted difference between normal and abnormal spirometry										
	N	Model 1 <sup>a</sup>			Model 2 <sup>b</sup>			Model 3 <sup>c</sup>			p
		Adjusted difference	95% CI	p	Adjusted difference	95% CI	p	Adjusted difference	95% CI	p	
Coronary calcium	1142	69.9	-23.9, 163.6	=0.144	84.2	-15.7, 184.2	=0.099	97.0	-0.982, 195.0	=0.052	
Aortic arch calcification	1141	510.7	167.4, 853.9	<0.004	504.2	148.2, 860.3	<0.006	481.9	112.1, 851.8	<0.011	
Distal aorta calcification	1142	202.8	102.0, 303.6	<0.0001	158.3	52.2, 264.5	<0.004	146.4	37.8, 255.1	=0.008	
CIMTmean	1131	0.017	0.000, 0.034	=0.054	0.019	0.002, 0.036	=0.027	0.019	0.002, 0.036	=0.029	
Brain Infarcts+	1013	0.013	-0.051, 0.076	=0.694	0.017	-0.048, 0.083	=0.600	0.016	-0.050, 0.081	=0.636	
<b>Adjusted difference between normal and abnormal spirometry for ever-smokers</b>											
Coronary Calcium	1142	122.5	8.2, 236.9	=0.036	87.1	-34.4, 208.5	=0.160	105.4	-13.9, 224.7	=0.083	
Aortic arch calcification	1141	706.5	287.5, 1125.6	<0.001	575.5	142.6, 1008.4	<0.009	540.9	90.3, 991.5	<0.019	
Distal aorta calcification	1142	203.5	80.6, 326.5	<0.001	138.0	9.1, 267.0	=0.036	117.6	-14.7, 249.9	=0.081	
CIMTmean	1131	0.013	-0.008, 0.034	=0.219	0.017	-0.004, 0.038	=0.105	0.017	-0.004, 0.037	=0.118	
Brain Infarcts <sup>d</sup>	1013	0.018	-0.060, 0.096	=0.657	0.024	-0.056, 0.104	=0.557	0.020	-0.059, 0.100	=0.616	

<sup>a</sup>Model 1 is adjusted for age, sex and contains main effects and interaction between smoking history and airflow obstruction

<sup>b</sup>Model 2 is model 1 extended by adjusting for the Framingham risk factors.

<sup>c</sup>Model 3 is model 2 extended by adjusting for CRP and WBC.

<sup>d</sup>absolute difference between proportions