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Atherosclerosis

Atherosclerotic calcification in major vessel beds in chronic obstructive pulmonary disease: The Rotterdam Study

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HIGHLIGHTS

- COPD is related to calcifications in the extracranial arteries.
- COPD may affect atherosclerosis in various vessel beds differently.
- COPD is related to arterial calcification independent of smoking.

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ABSTRACT

Background and aims: COPD is associated with an increased risk of cardiovascular morbidity and mortality, potentially by mechanisms of atherosclerosis. Insight into location-specific vulnerability to atherosclerosis in COPD, including intracranial arteries, is lacking. We aimed to investigate the relation between COPD and atherosclerosis in multiple vessel beds within a large population-based cohort study.
Methods: From 2003 to 2006, a random sample of 2187 elderly participants (mean age, 69.6 ± 6.8 years; 50.9% female; 11.7% COPD) from the population-based Rotterdam Study underwent computed tomography to quantify atherosclerotic coronary artery calcification (CAC), aortic arch calcification (AAC), extracranial carotid artery calcification (ECAC), and intracranial carotid artery calcification (ICAC). We investigated the association of COPD [ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) < 70%] with the presence of calcification and with calcification volumes in each vessel bed using logistic and linear regression, with adjustments for cardiovascular risk factors including smoking.
Results: The prevalence of CAC, AAC and ECAC was significantly higher in subjects with COPD compared to those without. After adjusting for age and smoking, COPD remained associated with the presence of ECAC (odds ratio 1.46 [95% confidence interval, 1.02–2.07, $p = 0.037$]). COPD was significantly associated with larger calcification volumes in all four vessel beds in people in whom calcification was present.
Conclusions: The results of this study suggest that COPD plays a role in extracranial carotid artery atherosclerosis initiation and systemic atherosclerosis aggravation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an important contributor to global morbidity and mortality [1,2]. In addition to its direct effect on mortality due to lung disease, COPD is also associated with an increased risk of cardiovascular morbidity and mortality [3–6]. From a clinical point-of-view, there is a need to identify as early as possible those persons with COPD that are at highest risk of

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cardiovascular events. Atherosclerosis may play a crucial role in the link between COPD and cardiovascular morbidity and mortality [3–5,7–9]. Studies have identified a high burden of atherosclerotic calcifications in multiple extracranial vessel beds in persons with COPD, independent of smoking [10–13]. Insight into whether COPD is also associated with aggravated atherosclerosis in intracranial vessels would be valuable. Previous longitudinal analyses showed higher cardiac risk estimates than stroke risk estimates for subjects with COPD compared to subjects without COPD [4,14]. We therefore hypothesized that persons with COPD present with a location-specific vulnerability to atherosclerosis, with smaller estimates of atherosclerosis in the intracranial vessel beds.

We aimed to examine the burden of atherosclerosis in persons with COPD in different vessel beds, including extracranial and intracranial vessels. To this end, we investigated the prevalence and volumes of atherosclerotic calcifications in subjects with COPD and subjects without COPD from a large, prospective population-based cohort study of middle-aged and elderly persons.

2. Patients and methods

2.1. Setting

This study is embedded within the prospective, population-based Rotterdam Study [15]. Between 2003 and 2006, all participants that visited the research center were invited to undergo multi-detector computed tomography (MDCT) to quantify the amount of atherosclerotic calcification in multiple vessel beds. In total, 2524 participants were scanned (Fig. 1). Due to the presence of image artefacts, coronary stent implantations or pacemakers, 111 CT examinations could not be graded for vascular calcification in at least one of the vessel beds, leaving 2413 participants with a complete CT-examination. Comparison of baseline characteristics between persons with complete CT examination and those with no or incomplete CT examination has been described previously [16,17]. In addition, these participants underwent spirometry to assess the presence of COPD.

The Rotterdam Study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants provided written informed consent.

2.2. COPD assessment

Spirometry was performed using a portable spirometer (SpiroPro; Erich Jaeger GmbH; Hoechberg, Germany) by trained paramedical personnel according to the ATS/ERS guidelines [18,19]. Reversibility tests were not performed in this population-based setting, however, participants with physician-diagnosed asthma were excluded [20]. The diagnosis and classification of COPD were based on the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria [proportion of the forced vital capacity exhaled in the first second (FEV_1/FVC) < 70%], with distinction of mild ($FEV1 \geq 80\%$), moderate ($FEV1 \geq 50$ and $FEV1 < 80\%$), and severe COPD ($FEV1 < 50\%$) [7,21]. In the absence of an interpretable spirometry within the Rotterdam Study, cases were defined as having COPD diagnosed by a physician on the basis of clinical presentation and obstructive lung function measured by the general practitioner or respiratory physician [22].

2.3. Assessment of atherosclerotic calcification

Non-contrast MDCT examinations were performed using a 16-slice (n = 785) or 64-slice (n = 1739) CT scanner (Somatom Sensation16 or 64; Siemens, Forchheim, Germany). The usage of the 16 slice CT *versus* 64 slice CT was not significantly differentially distributed between COPD and non-COPD subjects. Detailed imaging parameters can be found elsewhere [23]. In short, we acquired a cardiac scan and a scan that reached from the aortic arch to the intracranial vasculature (1 cm above the sella turcica) to obtain information on calcification in the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries (Fig. 2).

Coronary artery calcification (CAC), aortic arch calcification (AAC), and extracranial carotid artery calcification (ECAC) were quantified by calculating the volume using commercially available software (Syngo.via CalciumScoring; Siemens) [23,24]. For intracranial carotid artery calcification (ICAC), we used a semi-automated scoring method
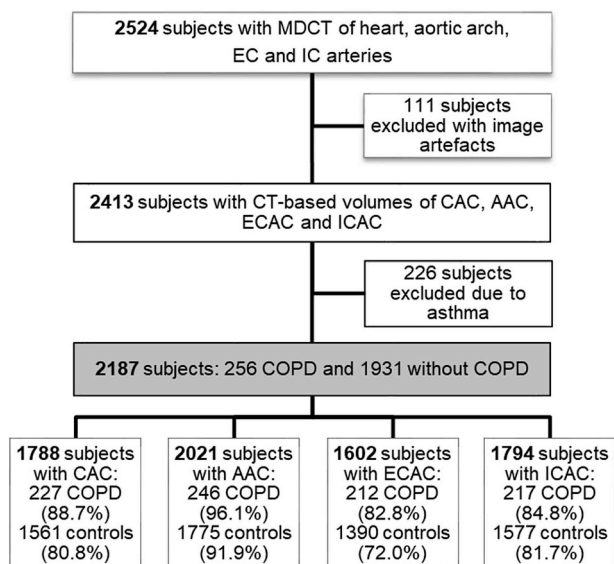

Fig. 1. Flowchart of the study population.
AAC: aortic arch calcification, CAC: coronary artery calcification, COPD: chronic obstructive pulmonary disease, ECAC: extracranial carotid (EC) artery calcification, ICAC: intracranial carotid (IC) artery calcification, MDCT: multi-detector computed tomography (CT).

Fig. 2. Arterial calcifications in different vessel beds visible on MDCT-images. AAC: aortic arch calcification, CAC: coronary artery calcification, ECAC: extracranial carotid (EC) artery calcification, ICAC: intracranial carotid (IC) artery calcification, MDCT: multi-detector computed tomography (CT).
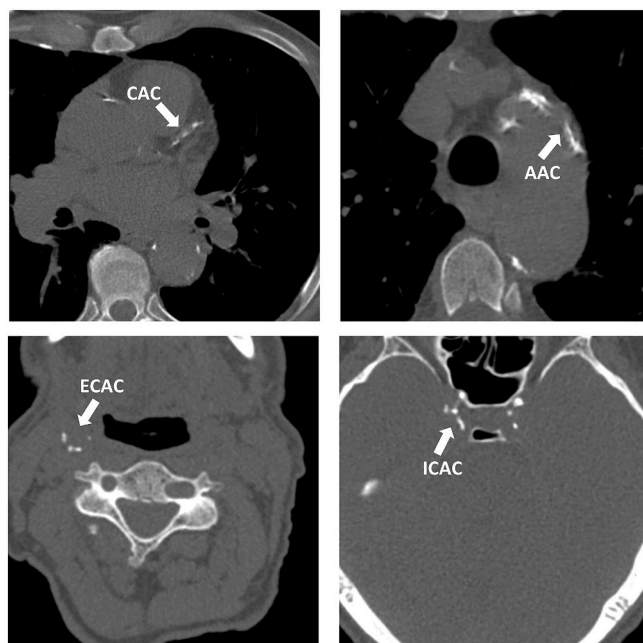
Table 1
Baseline characteristics of the study population (n = 2187).

	COPD (n = 256)	Controls (n = 1931)	*p*-value
Age (years)	69.8 (10.9)	67.8 (9.5)	0.00021
Males	146 (57.0)	928 (48.1)	0.007
Body mass index (kg/m^2)	26.5 (4.8)	27.1 (4.8)	0.008
Height (cm)	169.3 (13.3)	167.8 (13.8)	0.00047
Weight (kg)	77.2 (18.0)	77.0 (18.0)	0.844
Smoking status:			2.1 E − 14
Never smoking	44 (17.2)	662 (34.3)	
Past smoking	144 (56.3)	1056 (54.7)	
Current smoking	68 (26.6)	213 (11.0)	
Pack years	24.9 (37.9)	4.9 (23.0)	7.5 E − 20
Diabetes mellitus	48 (19.6)	218 (12.0)	0.001
Total cholesterol (serum, mmol/l)	5.5 (1.4)	5.7 (1.2)	0.00022
HDL-cholesterol (serum, mmol/l)	1.3 (0.5)	1.4 (0.5)	0.044
Systolic blood pressure (mmHg)	147.0 (29.5)	144.5 (25.0)	0.627
Diastolic blood pressure (mmHg)	78.5 (15.8)	80.5 (14.0)	0.028
Blood pressure lowering medication	111 (44.2)	724 (38.1)	0.060
Serum lipid reducing agents	60 (23.9)	429 (22.6)	0.632
FEV$_1$ (% predicted)	81.6 (27.5)	109.3 (24.1)	3.3 E − 48
FEV$_1$/FVC (%)	65.5 (7.7)	77.5 (7.1)	2.2 E − 35
CAC (%)	227 (88.7)	1561 (80.8)	0.002
AAC (%)	246 (96.1)	1775 (91.9)	0.018
ECAC (%)	212 (82.2)	1390 (72.0)	0.00024
ICAC (%)	217 (84.8)	1577 (81.7)	0.225

AAC: aortic arch calcification, CAC: coronary artery calcification, COPD: chronic obstructive pulmonary disease, ECAC: extracranial carotid (EC) artery calcification, FEV$_1$: forced expiratory volume in 1 s, FEV$_1$/FVC: proportion of the forced vital capacity exhaled in the first second, HDL: high-density lipoprotein, ICAC: intracranial carotid (IC) artery calcification. Categorical variables are expressed as numbers (percentage). Values of continuous variables are expressed as median (IQR). Pack years were missing in 15, diabetes status in 126, cholesterol in 35, blood pressure in 8, and drug use in 34 subjects. Spirometry was performed in 2031 subjects (246 with COPD and 1785 controls), results were comparable though only presented for interpretable measurements.

that is described in detail elsewhere [17,25]. All calcification volumes are expressed in mm^3.

2.4. Other covariables

Information on cardiovascular risk factors was obtained by interview, physical examination and blood sampling [15]. Body mass index (BMI) was calculated as weight/height in m^2. Systolic and diastolic blood pressures were measured twice at the right arm using a random zero sphygmomanometer and the mean of these measurements was used in the analyses. Arteriolar oxygen saturation was the average of the 2 measurements (with increments of 0.5% points) with a pulse oximeter (Oxycount; Andos, Hamburg, Germany) on the right index finger. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were determined in fasting blood samples using an automatic enzymatic procedure (Hitachi analyser, Roche Diagnostics). In addition, glucose was determined in blood samples obtained at the research center. Diabetes mellitus was defined as blood glucose-lowering medication use and/or a non-fasting serum glucose level of ≥11.1 mmol/L and/or fasting serum glucose levels ≥7 mmol/L. Information on smoking behaviour was collected using home interviews. Smoking status was self-reported and classified as current if subjects were still smoking at the time of the examination, past if they had quit smoking, or never. Cigarette pack years were computed as duration of smoking (years) multiplied by the number of smoked cigarettes, divided by 20. We assessed information on use of blood pressure-lowering medication, anti-diabetic medication and lipid-lowering medication by interview.

2.5. Statistical analyses

Differences in baseline characteristics between persons with and without COPD were studied using Student's t-test or Mann-Whitney *U* test for continuous variables and Chi-Square test for categorical

variables. Wilson score method for a binomial proportion was used to calculate prevalence plus 95% confidence intervals. We investigated the distribution of calcification in the four vessel beds in persons without and with COPD (by quartiles of calcification). We used logistic regression models to investigate the association between COPD and presence of calcification in the different vessel beds. Adjustments were made for all non-collinear potential confounders if they changed the risk estimate by more than 10%. Age, sex, body mass index (BMI), height, weight, smoking behaviour, systolic blood pressure, diastolic blood pressure, hypercholesterolemia [total serum cholesterol, high-density lipoprotein (HDL)-cholesterol], diabetes mellitus, and use of antihypertensives and lipid-lowering drugs were considered as potential confounders. An additional sex-stratified analysis was performed. Next, we used linear regression analyses to investigate associations of COPD and calcification volume per vessel bed in the persons with calcification. Because of the right-skewed distribution of calcification volume, values were natural log-transformed and 1.0 mm^3 was added to the non-transformed values to deal with calcium volumes of zero (Ln[calcificationvolume + 1.0 mm^3]). All non-collinear potential confounders were modelled in a linear regression model with stepwise backward selection. Statistical analyses were performed using SPSS, version 23.0 for Windows (IBM, North Castle, NY).

3. Results

3.1. Population for analysis

Of 2413 participants with a complete CT-examination, 226 subjects were excluded due to a confirmed or suspected diagnosis of asthma. Among the 2187 included subjects, 256 had COPD and 1931 subjects had no COPD at the time of the scan. Baseline characteristics of the study population are presented in Table 1. COPD subjects were slightly older, more often male and more frequently smokers.

Table 2

Logistic regression analyses of COPD on presence of calcification in the different vessel beds.

	Coronary artery calcification	Aortic arch calcification	Extracranial carotid artery calcification	Intracranial carotid artery calcification
	OR (95%CI) *p*-value	OR (95%CI) *p*-value	OR (95%CI) *p*-value	OR (95%CI) *p*-value
COPD				
Model 1[a]	1.59 (1.05; 2.40) 0.029	1.85 (0.95; 3.57) 0.069	1.63 (1.15; 2.32) 0.006	1.11 (0.77; 1.60) 0.592
Model 2[b]	1.57 (1.04; 2.39) 0.034	1.76 (0.91; 3.42) 0.094	1.61 (1.13; 2.29) 0.008	1.08 (0.75; 1.56) 0.690
Model 3[c]	1.39 (0.91; 2.12) 0.128	1.52 (0.78; 2.96) 0.222	1.46 (1.02; 2.07) 0.037	0.98 (0.66; 1.45) 0.978

CI: confidence interval, COPD: chronic obstructive pulmonary disease.

[a] Model 1 is adjusted for age and sex.

[b] Model 2 is adjusted for age, sex and presence of calcification in the other vessel beds.

[c] Model 3 is adjusted for all non-collinear confounders which changed the risk estimate by more than 10%, i.e. age and smoking status in all models and additionally sex and height in the CAC model; and sex, height, diastolic blood pressure, antihypertensives and antidiabetics in the ICAC model.
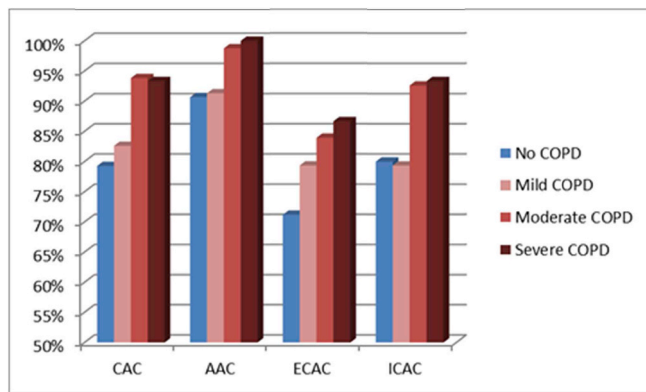

Fig. 3. Prevalence of atherosclerotic calcification according to the severity of lung function impairment.

COPD: chronic obstructive pulmonary disease, mild COPD: $FEV_1 \geq 80\%$, moderate COPD: $FEV_1 \geq 50$ and $FEV_1 < 80\%$, severe COPD: $FEV_1 < 50\%$.

3.2. Relation between COPD and prevalence of atherosclerotic calcification

Atherosclerotic calcification in the coronary arteries was present in 1788 subjects, in the aortic arch in 2021 subjects, in extracranial carotid arteries in 1602 subjects, and in intracranial carotid arteries in 1794 subjects (Fig. 1). The crude prevalence of CAC, AAC, and ECAC was significantly higher in subjects with COPD compared to those without COPD (88.7% *vs.* 80.8% (*p* = 0.002); 96.1% *vs.* 91.9% (*p* = 0.018), and 82.8% *vs.* 72.0% (*p* < 0.001), respectively). The prevalence of ICAC was also higher in subjects with COPD (84.8% *vs.* 81.7%), although not statistically significant (*p* = 0.225). Table 2 shows logistic regression analyses of COPD on the presence of calcification in the different vessel beds. After adjustment for potential

confounders, we observed that COPD was associated significantly with the presence of ECAC only [odds ratio (OR) 1.46 (95% confidence interval (CI): 1.02; 2.07, *p* = 0.037 adjusted for age and smoking)]. Sex-stratified analyses are presented in Supplementary Table 1. Fig. 3 shows the presence of atherosclerotic calcification according to the severity lung function impairment.

3.3. Relation between COPD and calcification volumes

Within subjects with presence of atherosclerotic calcification in the coronary arteries (n = 1788), aortic arch (n = 2021), extracranial carotid arteries (n = 1602) and intracranial carotid arteries (n = 1794), COPD was associated with larger volumes of atherosclerotic calcification in the respective vessel bed (unadjusted *p* = 0.006, *p* < 0.001, *p* < 0.001 and *p* < 0.001 respectively). Quartiles of calcification according to COPD status are presented in Supplementary Table 2. Table 3 demonstrates that in the final step of linear regression models, including all non-collinear potential confounders, COPD was significantly associated with larger volumes of atherosclerotic calcification in the different vessel beds (multi-adjusted *p* = 0.013, *p* < 0.001, *p* < 0.001 and *p* = 0.038 respectively). In line, the severity of airflow limitation (decreased FEV_1) was significantly associated with the atherosclerotic calcification volumes in the four vessel beds (*p* < 0.001 Pearson Correlation).

4. Discussion

In this large population-based cohort study, we demonstrated a high prevalence of atherosclerotic calcification in all four major vessel beds (CAC, AAC, ECAC and ICAC) in an elderly population. We showed that COPD is, independent of smoking, associated with the presence of atherosclerotic calcification in extracranial vessel beds, but not in the

Table 3

Linear regression analyses of COPD on calcification volumes in the different vessel beds.

	Coronary artery calcification	Aortic arch calcification	Extracranial carotid artery calcification	Intracranial carotid artery calcification
	β (95%CI) *p*-value	β (95%CI) *p*-value	β (95%CI) *p*-value	β (95%CI) *p*-value
COPD				
Model 1[a]	0.42 (0.16; 0.67) 0.001	0.61 (0.39; 0.84) 1.1E-7	0.58 (0.35; 0.81) 9.6 E−7	0.31 (0.13; 0.50) 0.001
Model 2[b]	0.08 (−0.14; 0.30) 0.493	0.33 (0.14; 0.53) 0.001	0.33 (0.13; 0.52) 0.001	0.02 (−0.14; 0.18) 0.851
Model 3[c]	0.33 (0.07; 0.59) 0.013	0.44 (0.21; 0.67) 0.00019	0.44 (0.21; 0.67) 0.00022	0.20 (0.01; 0.39) 0.038

Betas represent the difference in Ln[calcification volume + 1] in mm^3 for subjects with COPD compared to subjects without COPD.

CI: confidence interval, COPD: chronic obstructive pulmonary disease.

[a] Model 1 is adjusted for age and sex.

[b] Model 2 is adjusted for age, sex and calcification volumes in the other vessel beds.

[c] Model 3 is the final step from the linear regression model including all non-collinear potential confounders with stepwise backward selection, i.e. adjusted for age, sex, smoking status, diastolic blood pressure, blood pressure-lowering medication in all models and additionally height, diabetes, HDL cholesterol and lipid lowering drugs in the CAC model; systolic blood pressure, total and HDL cholesterol and lipid lowering drugs in the AAC model; systolic blood pressure and lipid lowering drugs in the ECAC model; and systolic blood pressure, diabetes, HDL cholesterol and lipid lowering drugs in the ICAC model.

intracranial carotid vessel beds. In a subset of individuals with calcifications, COPD was associated with larger volumes of atherosclerotic calcification in each respective vessel bed.

An important contribution of our study is that our results suggest a differential role of COPD in the initiation of atherosclerosis in the different vessel beds. COPD was significantly associated with ECAC (OR 1.5) after adjustment for potential confounders, but not with ICAC (OR 1.0). Estimates for AAC (OR 1.5) only reached borderline statistical significance, and estimates for CAC (OR 1.4) lost statistical significance after adjustment for potential confounders, likely due to a lack of power. Our study is the first to identify COPD as a risk factor specific for extracranial artery atherosclerosis, but not for intracranial carotid artery atherosclerosis, on a population-based level. A possible explanation for this finding may be due to the specific pathology of atherosclerosis in these vessel beds. Atherosclerosis in the extracranial carotid arteries is thought to be more susceptible to cigarette smoking and systemic inflammation, whereas atherosclerosis in the intracranial carotid arteries in other studies has been associated with female sex and metabolic syndrome [26–30]. The sex-stratified analysis did not support that mechanisms underlying intracranial artery atherosclerosis in women in general would be further aggravated in women with COPD. Given that, persons with COPD generally have higher levels of circulating leukocytes and inflammatory factors (e.g. C-reactive protein and fibrinogen), this might partially explain our findings. More evidence for this comes from a previous study of ours, in which we demonstrated a relation between COPD and plaques in the extracranial carotid arteries [7]. Yet, longitudinal research including markers of systemic inflammation is needed to shed further light on this association.

We also found that, when calcification is present, COPD related to larger calcification volumes or aggravation of atherosclerosis in each vessel bed. An interesting hypothesis is that different COPD-related mechanisms may play a role in plaque initiation compared to plaque aggravation. Indeed, this study shows that when atherosclerotic disease is already more advanced – i.e. when calcification is present –, the effect of COPD on atherosclerotic disease is no longer location-specific, but all vessel beds are affected.

Interestingly, in all our analyses we adjusted for smoking status (current, past or never smokers), and still found associations between COPD and atherosclerosis. In line with our results, others found an increased susceptibility for asymptomatic atherosclerosis in subjects with a higher degree of lung function impairment, which was also independent of smoking [10–13]. Prospectively, CAC was able to identify subjects at higher risk for COPD independent of smoking [13]. In our study, estimates for CAC lost statistical significance after adjustment for potential confounders, likely due to a lack of power. Within the etiological framework of both COPD and atherosclerosis, not only smoking and ageing, but also inflammation is an important risk factor. Indeed, differences in aortic calcium scores between subjects with normal and abnormal spirometry were lower after adjustment for inflammatory markers in a previous study, advocating a role of systemic inflammation [31].

From a clinical point of view, our results may be of particular importance in the early identification of COPD patients prone to the co-occurrence of atherosclerosis. Our results suggest that the screening for atherosclerosis in persons with COPD may additionally involve imaging of the extracranial carotid arteries. Especially if the screening for lung cancer in smokers or the diagnostic work-up of COPD already involves CT-chest imaging, it may be considered to extend the CT examination to the extracranial carotid arteries. Another valuable advantage of chest-CT is that CAC may be directly evaluated. Quantification of CAC has already proven to be useful in the decision making process for statin and aspirin therapy in primary prevention [32–35], and as a predictor of future cardiovascular events and deaths in subjects with COPD [36]. In combination with the assessment of ECAC, one may then estimate the risk of cardiovascular events more precisely using a single CT-examination (both for stroke and coronary heart disease) [37,38]. Yet,

although our results give thought to new possibilities for strategies as described above, the potential benefits, harms and costs should be carefully balanced, before implementation in current clinical practice. Prospective research in unselected populations is needed to elucidate the clinical implications of atherosclerotic calcification reported on CT-chest imaging ordered for other reasons [36].

A potential limitation of this study is that calcification represents only a part of the atherosclerotic plaque. Non-calcified plaques – which may be especially affected by COPD – cannot be visualized using non-enhanced CT, but requires MRI. Nonetheless, the amount of calcification has been established as a reliable marker of the total underlying plaque burden [39]. Second, although inflammation and oxidative stress are important risk factors for both COPD and atherosclerosis, we did not have information at the time of the scan on markers of systemic inflammation in these persons. Third, by means of cross-sectional analysis we were not able to investigate causality. Longitudinal studies are warranted to examine causality and to assess the association with clinical endpoints. Fourth, despite the relatively large sample size of population-based individuals with CT of all vessel beds in this study, we acknowledge the limited power with regards to the non-significant findings. Future research should validate our findings in other (larger) cohorts.

This study has several strengths. Our study is the first large study to comprehensively investigate the association of COPD with atherosclerotic calcification in different major vessel beds. Previous studies investigating multiple vessel beds in subjects with and without COPD were limited in sample (n = 1154, n = 234 and n = 235) size and did not measure intracranial carotid arteries [10,31,40]. Presence of significant associations in the population-based setting of this study implies a possible stronger link in clinical settings, where COPD is often more severe. Indeed, effect sizes for atherosclerotic risk markers are known to be larger in moderate-to-severe COPD [8]. Other strengths of our study include the standardized image-based assessment of atherosclerotic calcification as marker of atherosclerosis in multiple vessel beds and the detailed COPD assessment.

In conclusion, persons with COPD more often have CAC, AAC and ECAC, and larger volumes of atherosclerotic calcification in all four major vessel beds (i.e. CAC, AAC, ECAC and ICAC). The presence and extent of atherosclerosis in extracranial carotid arteries in patients with COPD might guide clinicians to add visualization of ECAC to CT-chest imaging to optimally screen vulnerable COPD patients for stroke and coronary heart disease.

Author contributions

Study design: A.L., B.H.S., G.G.B.; Data collection: L.L., D.B.; Data-analysis and writing: L.L., D.B.; Data-interpretation: L.L., D.B., B.H.S., G.G.B., S.R.A.W.; Critical review: B.H.S., A.L., G.G.B., S.R.A.W., M.K., M.W.V.

Declaration of competing interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.10.014.

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