Chronic Obstructive Pulmonary Disease is associated with an increased risk of peripheral artery disease and mortality

ABSTRACT

Introduction: Patients with COPD commonly present with multimorbidity. We aimed to investigate the association between COPD and the development of peripheral arterial disease (PAD) in the general population, and how this might affect mortality among individuals with COPD.

Methods: We included 3,123 participants of the population-based Rotterdam Study without PAD at baseline (mean age 65yr; 57.4% females). The association between COPD at baseline and PAD (Ankle Brachial Index ≤ 0.9) during follow-up at the research center, was studied using logistic regression. Cox regression was used for mortality analysis. Interaction terms were used to investigate mortality risk modification by PAD.

Results: Presence of COPD was associated with incident PAD, (Odds $Ratio_{adjusted}$ 1.9 (95% Confidence Interval 1.1-3.2)). Mortality rates per 100,000 PY were: 10.0 in individuals without COPD and PAD, 18.4 in those with only COPD, 16.1 in those with only PAD, and 30.1 in individuals with both COPD and PAD. No statistical interaction was found between PAD and COPD and risk of dying.

Conclusion: Individuals with COPD have an almost doubled risk of developing PAD. Although PAD does not modify the association between COPD and mortality, people suffering from both diseases have substantially higher mortality rates.

Key words: PAD, COPD, epidemiology, population-based, effect modification

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the third major cause of death worldwide (1). Beyond the airflow limitation and respiratory impairment, COPD patients often suffer from multi-morbidities, of which most prominently vascular diseases (2) (3).

Atherosclerosis is known as a major cause of symptomatic vascular disease. One of the manifestations of atherosclerosis is peripheral arterial disease (PAD), which refers to the occlusion of the arteries in the lower limbs. PAD is often asymptomatic but can be present in advanced stages in the form of intermittent claudication, leg pain at rest and rarely non-healing wounds, ulcerations and gangrene (4).

Patients with PAD have comparable – but not identical - risk factor profiles compared to patients with coronary heart disease, of which systemic inflammation, diabetes and smoking are most predominant in PAD (5-8).

The prevalence of PAD in individuals with COPD shows a wide range of variation depending on the COPD severity in the study population. Its prevalence was found to be 8% in Asian COPD patients, 8.8% in the German COSYCONET study of COPD patients followed in secondary care and 36.8% in COPD patients hospitalized for a severe exacerbation (9, 10 , 11).

A previous study by Pecci and colleagues (10) demonstrated that PAD was asymptomatic in a large proportion of COPD patients, and was associated with more severe lung disease than in COPD subjects without PAD. However, longitudinal studies investigating the association between COPD and incident PAD are lacking. In addition, although PAD is known to have a significant impact on mortality, it is unknown whether the risk of mortality is higher in patients with both COPD and PAD. Therefore, the objectives of our study were to investigate the association between COPD and incident PAD in a longitudinal cohort, and to elucidate the effect of PAD on mortality in subjects with COPD in a community-dwelling population of middle-aged and older subjects.

METHODS

Setting

The present study was embedded within the Rotterdam Study, an ongoing prospective population-based cohort which was enrolled to investigate the occurrence of, and risk factors for, chronic diseases in the general population. The aims and methods of the Rotterdam Study have been published in detail previously (12). In short, the Rotterdam Study started in 1990, where inhabitants of the Ommoord district in Rotterdam were invited every 3-4 years to the research centre for follow-up examination. Participants were additionally monitored continuously for morbidity and mortality through linkage

of general practitioners and municipality records to the study base. The present study was conducted using data from the first cohort of the Rotterdam Study (RS-I) and comprises of two parts; the first longitudinal analysis was performed in order to study the association between COPD (measured at baseline, between 1990-1993) and newly diagnosed PAD (measured between 1996-2000) (**Figure 1**). In short, there were 6,450 individuals with a measurement of the ankle-brachial index (ABI) at baseline as described below of whom 336 had prevalent PAD, 1,881 died, and 1,110 did not have a second measurement of the ABI. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Dutch Ministry of Health, Welfare and Sport. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

COPD diagnosis

We validated whether participants had COPD by reviewing the medical charts, including outpatient clinic reports and hospital discharge letters of all participants who used medication for obstructive lung disease for at least six months (Anatomical Therapeutic Chemical Classification codes: R03) or who stated to have COPD in the questionnaire. COPD cases were defined as having a medical COPD diagnosis supported by clinical presentation and/or obstructive lung function (13). The index date was defined as the date of diagnosis of COPD as described in the medical charts or the date of a first prescription of COPD medication in patients with COPD, whichever came first. In this study COPD data was used at baseline for the first objective and at follow-up for the second objective.

Assessment of Peripheral Artery Disease (PAD)

The method of measuring the Ankle Brachial Index (ABI) has been described previously (14). In short, blood pressure in the arm was obtained by calculating the mean of two successive measurements with a random-zero sphygmomanometer at the right brachial artery while the participant was in a sitting position (14). In addition, in both the left and the right leg, the systolic blood pressure level of the posterior tibial artery was measured using a random-zero sphygmomanometer and an 8-MHz continuous-wave Doppler probe (Huntleigh 500 D, Huntleigh Technology) while the participant was in the supine position. The ABI was defined as the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm and was calculated for each leg. The presence of PAD was defined as an ABI of ≤ 0.90 in at least one leg (5). Patients with prevalent PAD at baseline were excluded and only newly diagnosed (incident) PAD during follow-up was considered as outcome. Severe PAD was defined as ABI < 0.6 (11). Besides the ABI measurements, we used the criteria of the World Health

Organization/Rose questionnaire which was incorporated in the home interview (15) to investigate intermittent claudication to capture symptomatic PAD.

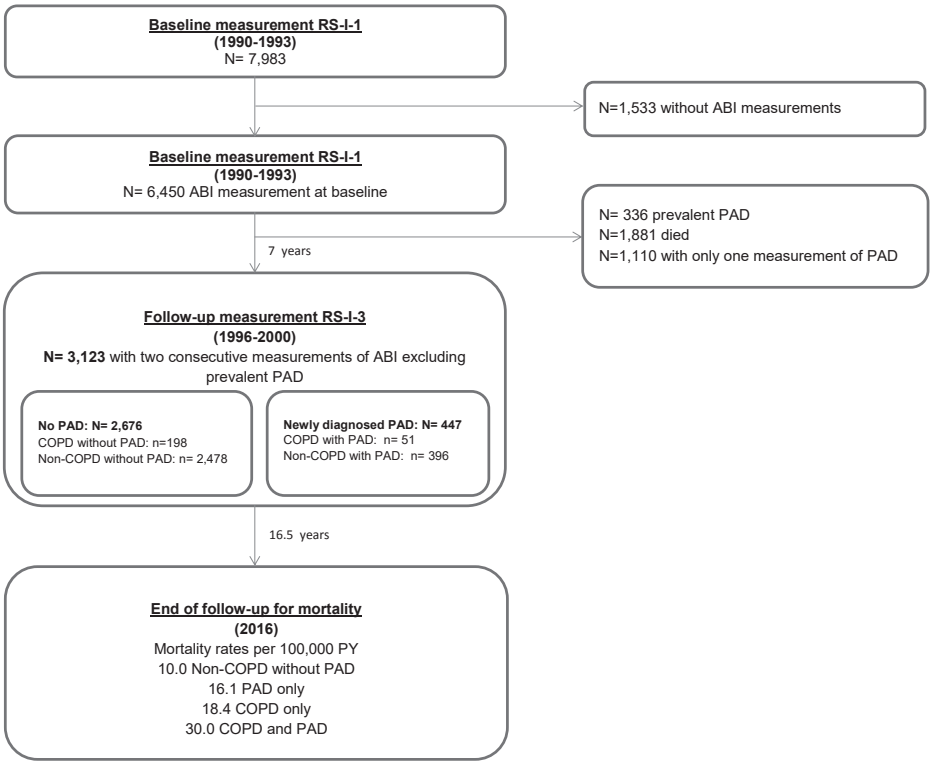

Figure 1: Flow chart to investigate the association between COPD and newly diagnosed PAD. ABI: Ankle Brachial Index; COPD: Chronic obstructive pulmonary disease; N: total sample size; PAD: Peripheral arterial disease; RS-I-1: The first visit of the first wave of the Rotterdam Study. RS-I-3: The third visit of the first wave of the Rotterdam Study.

Follow-up for mortality

To investigate whether PAD increases the risk of all-cause mortality in subjects with or without COPD, 3,123 individuals with 2 ABI measurements, were followed from the second PAD measurement on until mortality or the last visit to the study centre.

Information on mortality of study participants was obtained from the municipality of Rotterdam, and additionally validated with data from medical records kept by the general practitioner's, as described in detail previously (16). Mortality data was complete until August 2016. Cause specific mortality data was complete until January 2014.

Covariables

Relevant covariables at baseline of each analysis were obtained using interview, blood sampling, and physical examination (17). Smoking status was assessed by interview and categorized as never, former or current smoker, or as ever and never smoker. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or the use of blood pressure-lowering drugs. Subjects were classified as statin users if they had received at least one prescription for statins at baseline. Information on statin use was obtained from interview and from pharmacies. Type 2 diabetes mellitus was defined according to recent WHO guidelines, as a fasting blood glucose ≥ 7.0 mmol/L, a non-fasting blood glucose ≥ 11.1 mmol/L (in absence of fasting samples), or the use of blood glucose lowering medication (16). Concentrations of HDL cholesterol and total cholesterol were measured from the blood samples using an automated enzymatic method (18). HDL to total cholesterol ratio was calculated by dividing HDL blood concentrations by total cholesterol concentrations. Ethnicity was based on genetic ancestry data, or interview data in absence of genetic information. High sensitivity C-reactive protein (hs-CRP) was measured using Rate Near Infrared Particle Immunoassay (Immage Immunochemistry System, Beckman Coulter, Fullerton, CA).

Statistical analysis

To study population characteristics the chi-square test and the independent sample t-test were used to test differences between individuals with or without COPD. We determined the association between baseline COPD and the development of PAD (assessed during follow-up visit), using logistic regression after exclusion of individuals with prevalent PAD at baseline. For the association between COPD and newly diagnosed PAD, we adjusted for covariables that were considered risk factors for atherosclerosis and cardiovascular disease. The following potential confounders where considered: age, sex, smoking, pack years of smoking, BMI, hypertension, hs-CRP, statin use, HDL to cholesterol ratio, ethnicity and diabetes. Missing data on covariables were imputed using the Expectation Maximization (EM) method. Effect modification was tested with interaction terms. Additional sensitivity analyses were performed by adjusting for hs-CRP (as a marker for inflammation) and by excluding incident COPD or individuals with ABI > 1.4 (as a marker for arterial stiffening (14)) from the analysis.

As secondary objective, we aimed to study the impact of PAD on the risk of mortality among individuals with COPD. For this analysis four groups were defined. 1) individuals without COPD nor PAD, 2) individuals with COPD only, 3) individuals with PAD only and 4) individuals with both COPD and PAD all assessed at the second PAD round. Mortality rates were obtained by dividing the number of deaths by the total number of

person years (PY) of subjects at risk and were presented per 100,000 PY. Confidence intervals (CI) around these rates were calculated using a Poisson distribution. Follow-up time for all subjects was defined as the time period between the start of the second analysis (where incident PAD was measured) and death or the last visit to the study centre. Sensitivity analysis was performed by censoring for incident COPD during follow-up. Median follow-up time was estimated using the reverse Kaplan-Meier method. Crude survival curves were obtained using the Kaplan-Meier survival method. The Cox proportional hazard model was used to calculate mortality hazard ratios and was adjusted for age, sex, pack years of smoking, hypertension, HDL to cholesterol ratio and diabetes mellitus. We used SPSS version 21 (IBM Corp, Armonk, NY, USA) and R software for all analyses.

RESULTS

The characteristics of the population for follow-up (n=3,123) are presented in **Table 1**. The mean age was 65.1 (SD 6.6) years and 57.2% were women. The prevalence of ever smokers was 65% in the total population, and 67.1% in individuals with incident PAD (**Tables 1** and **2**). Within individuals with PAD, almost all men (89.1%) and 48.3% of the women were ever smoker. In total, 1.8% (56/3,123) had severe PAD based on an ABI < 0.6. Only 21.4% (12/56) of the subjects with severe PAD indicated to have intermittent claudication on questionnaire.

COPD and the association with newly diagnosed PAD

During a median follow-up of 7.4 years, 447 (12.9%) patients developed incident PAD. A statistically significant association was found between COPD and newly diagnosed PAD during follow-up. The age- and sex adjusted odds ratio (OR) was 1.89 (95% CI 1.13-3.17), and 1.87 (95% CI 1.10-3.18) after additional adjustment for pack years of smoking, hypertension, HDL to cholesterol ratio and diabetes mellitus (**Table 2**). This association remained significant upon additional adjustment for baseline hsCRP levels ($OR_{adjusted}$ 1.86 (95% CI 1.10-3.16), exclusion of individuals (n=186) who developed COPD during follow-up ($OR_{adjusted}$1.93 (95% CI 1.13-3.29)) and upon exclusion of individuals with ABI >1.40 (n=495) ($OR_{adjusted}$ 1.95 (95% CI 1.13-3.36)). The association between COPD and incident PAD was stronger in males ($OR_{adjusted}$ 2.59; 95% CI 1.04-5.16) than females (OR $1.22_{adjusted}$; 95% CI: 0.53-2.87). However, test for interaction between COPD and sex was not significant (p for interaction=0.18). Stratified analysis by smoking revealed that the overall association between COPD and newly developed PAD was driven by the group of individuals who had ever smoked (P for interaction = 0.41) (**Table 2**).

Table 1 Baseline characteristics of all subjects without PAD at baseline, stratified by COPD status.

	Overall	no COPD	COPD	p-value
N (%)	3,123 (100)	3,038 (97)	85 (3)	
Age (mean (sd))	65.14 (6.6)	65.12 (6.6)	65.69 (5.6)	0.43
Female, n (%)	1785 (57.2)	1745 (57.4)	40 (47.1)	0.07
BMI (mean (sd))	26.27 (3.5)	26.28 (3.5)	26.17 (3.1)	0.78
Pack years (mean (sd))	25.5 (21.3)	25.3 (21.2)	33.5 (24.1)	< 0.01
Smoking status,n (%)				< 0.01
Never	1069 (35.4)	1054 (35.8)	15 (18.5)	
Former	1394 (46.1)	1348 (45.8)	46 (56.8)	
Current	560 (18.5)	540 (18.4)	20 (24.7)	
Ever smoking, n (%)	1954 (64.6)	1888 (64.2)	66 (81.5)	< 0.01
Diabetes, n (%)	380 (12.6)	367 (12.5)	13 (15.9)	0.47
HDL/Chol ratio (mean (sd))	0.21 (0.1)	0.21 (0.1)	0.22 (0.1)	0.13
Cholesterol lowering drugs, n (%)	72 (2.3)	70 (2.3)	2 (2.4)	0.98
Hypertension, n (%)	1481 (47.4)	1446 (47.6)	35 (41.2)	0.29
BP lowering drugs, n (%)	770 (24.7)	743 (24.5)	27 (31.8)	0.12
hs-CRP (mean (sd))	2.44 (3.3)	2.42 (3.3)	3.02 (3.0)	0.11
Inhaled therapy (R03), n (%)	1.24 (4.0)	64 (2.1)	60 (70.6)	< 0.01

BP: Blood pressure; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; hs-CRP: High sensitivity C-reactive protein, HDL/Chol ratio: High density lipoprotein to cholesterol ratio; PAD: Peripheral arterial disease; SD: standard deviation
P-values represents the difference between COPD groups. Data represent original data without imputed values. In de total population, missing values were present for smoking (3.2%), pack years of smoking (7.1%), body mass index (0.2%), and diabetes mellitus (3.5%).
*Pack years are presented for former and current smokers only

Disease status and risk of all-cause mortality

We investigated the impact of PAD on mortality starting follow-up for all subjects from the time when the second PAD measurement was performed (n= 3,123). The general characteristics of the population which was followed-up for mortality are presented in **Table 3**. The prevalence of PAD in COPD was 20.5% (51/(198+51)) *versus* PAD in non-COPD 13.8% (396/(2,478+396)). We stratified the study population into the following four groups: 1) No COPD or PAD (N=2,478), 2) COPD only (N= 198) 3) PAD only (N= 396) and 4) comorbid COPD and PAD (N= 51). Median follow-up time for mortality was 16.5 years. At the end of follow-up, 1,805 individuals (58%) had died. The mortality rate in the group without COPD nor PAD was 10.0 per 100,000 PY (95% CI 9.47-10.62); subjects with COPD and subjects with PAD had comparable mortality rates: 18.4 (95% CI 15.49-21.58) and 16.1 (95% CI 14.17-18.16) per 100,000 PY,

Table 2 The association between COPD and the development of PAD additionally stratified by sex and smoking status

		N (%)						Model 1*		Model 2†		P int.‡
		Overall		No PAD		PAD case		OR	95% CI	OR	95% CI	
Overall		3,123	(100)	2,676	(100)	447	(100)					
non-COPD		3,038	(97.0)	2,611	(97.6)	427	(95.5)	**Ref.**	-	**-**	-	
COPD		85	(3.0)	65	(2.4)	20	(5.0)	**1.89**	1.13-3.18	**1.87**	1.10-3.18	
Stratified	***M***											0.18
non-COPD		1,293	(41.4)	1,122	(41.9)	171	(38.3)	**Ref.**	-	**-**	-	
COPD		45	(1.4)	32	(1.2)	13	(2.9)	**2.61**	1.33-5.12	**2.59**	1.04-5.16	
	F											
non-COPD		1,745	(55.9)	1,489	(55.6)	256	(57.3)	**Ref.**	-	-	-	
COPD		40	(1.3)	33	(1.2)	7	(1.6)	1.24	0.54-2.87	1.22	0.53-2.87	
	NS											0.41
non-COPD		1,066	(34.1)	921	(34.4)	145	(32.4)	**Ref.**	-	-	-	
COPD		15	(0.5)	13	(0.5)	2	(0.4)	1.00	0.21-4.47	1.20	0.26-5.57	
	ES											
non-COPD		1,972	(63.1)	1,690	(63.2)	282	(63.1)	**Ref.**	-	**-**	-	
COPD		70	(2.2)	52	(1.9)	18	(4.0)	**2.00**	1.14-3.50	**1.98**	1.12-3.49	

CI: Confidence interval; F: Female; M: male; N: total number; ES: Ever smoker; NS: Never smoker; OR: odds ratio; PAD: peripheral arterial disease
*Model1: adjusted for age and sex
†Model2: adjusted for age, sex, pack years of smoking, hypertension, HDL to cholesterol ratio and diabetes
#Excluding the covariate sex from the analysis
‡ P value for interaction, calculated by adding an interaction term to Model 2.
Data for smoking represent imputed values.

respectively. In subjects with both COPD and PAD, the mortality rate was the highest: 30.01 per 100,000 PY (95% CI 22.01-40.11). **Figure 2** represents the Kaplan-Meier survival curves in the different groups. Age and sex adjusted mortality hazard ratios compared to individuals without COPD nor PAD were, 1.41 (95% CI 1.24-1.61), 1.50 (95% CI 1.26-1.77) and 2.23 (95% CI 1.66-3.00) for subjects with PAD, COPD and subjects with both COPD with PAD, respectively. After additional adjustment for pack years of smoking, hypertension, HDL to cholesterol ratio and diabetes mellitus the mortality rates were 1.36 (95% CI 1.19-1.54), 1.52 (95% CI 1.28-1.80) and 2.30 (95% CI 1.71-2.09), for subjects with PAD, COPD and subjects with both COPD with PAD, respectively. We did not find effect modification by PAD on the multiplicative scale (p for interaction= 0.82). In addition, sensitivity analysis after censoring for incident COPD during follow-up did not materially change the results.

Table 3 Characteristics of all subjects at the second PAD assessment: individuals without COPD nor PAD, subjects with COPD only, subjects with PAD only and subjects with both COPD and PAD at the second PAD assessment . This table describes baseline characteristics of individuals who were followed for mortality.

	Overall	No COPD or PAD	COPD only#	PAD only	COPD and PAD#
N	3123	2478	198	396	51
Age (mean (SD))	71.73 (6.58)	71.13 (6.36)	72.79 (5.95)	74.58 (7.21)	74.84 (6.89)
Women (%)	1785 (57.20)	1435 (57.90)	87 (43.90)	246 (62.10)	17 (33.30)
BMI (mean (SD))	26.87 (3.89)	26.94 (3.86)	26.91 (3.78)	26.55 (4.08)	25.83 (3.72)
Ever smoker, (%)	2,049 (65.60)	1,580 (63.80)	163 (82.30)	261 (65.9)	45 (88.2)
Pack years (mean (SD))	25.47 (22.50)	23.99 (22.01)	34.13 (26.62)	26.49 (19.85)	39.78 (25.63)
Diabetes Mellitus (%)	816 (26.10)	608 (24.50)	63 (31.80)	130 (32.80)	15 (29.40)
HDL/Chol ratio (mean (SD))	0.24 (0.07)	0.25 (0.07)	0.25 (0.08)	0.23 (0.06)	0.25 (0.08)

Data represent imputed values

#The total number of individuals with COPD at follow-up as presented in this table (N=249, N=198 COPD only + N=51 COPD and PAD)) represent COPD at baseline (N=85, see Table 1) plus the individuals that acquired COPD during follow-up

*Pack years are presented for former and current smokers only

BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; HDL/Chol ratio: High density lipoprotein to cholesterol ratio; PAD: Peripheral arterial disease; SD: standard deviation.

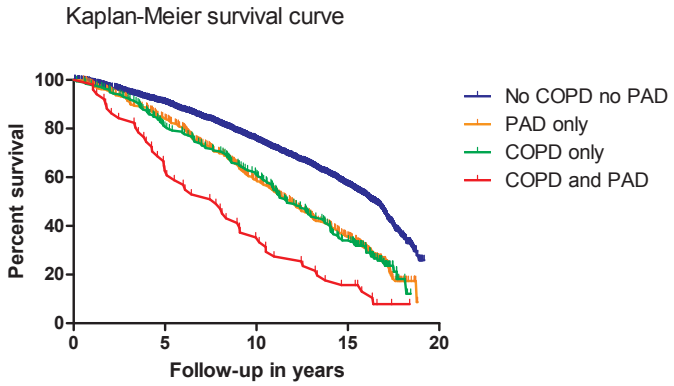

Figure 2: Kaplan-Meier curves of mortality in different groups according to the presence or absence of COPD and Peripheral Arterial Disease (PAD).
COPD: Chronic obstructive pulmonary disease; PAD: Peripheral arterial disease

DISCUSSION

To our knowledge, this is the first population based study that investigated longitudinally the association between COPD and incident PAD, and the influence of PAD on mortality rates in individuals with COPD. We observed that individuals with COPD have a higher risk of developing PAD, and that the risk of mortality was highest in people with both diseases.

Smoking is a well-known risk factor for both COPD and PAD. However in our study, the association between COPD and PAD remained statistically significant upon adjustment for cumulative smoking history (i.e. pack years). Additionally, increased CRP levels are known to be an important risk factor for PAD, and CRP is also elevated in a subgroup of patients with COPD (19). However, adjusting for baseline hsCRP levels did not change the overall association substantially. Despite the potential for residual confounding or other unmeasured mediators of systemic inflammation, such as Tumor Necrosis Factor-α(TNF-α, Interleukin-1β (IL-1β) or matrix metalloproteinases, we hypothesize that COPD-related mechanisms beyond smoking and systemic inflammation might contribute to the onset of PAD.

COPD and PAD have a well-known impact on mortality, however, no study in the literature has investigated the impact of PAD on the association between COPD and all cause-mortality. We observed a higher risk of mortality in individuals when COPD and PAD co-occur, although formally there was no statistical interaction between both diseases on a multiplicative scale. The observed mortality rates in individuals with PAD or with COPD are in line with literature reports. The ERS white book (https://www.erswhitebook.org) reported an age-standardised (to the European Standard Population) mortality rate for COPD of approximately 18 per 100,000 inhabitants per year. Also,

unstandardized all-cause mortality in the subgroup of individuals with only COPD was 18.4 per 100,000 PY. In addition, in a group of patients with asymptomatic PAD, Diehm *et. al.* (20) reported a mortality rate ratio of 1.4 after adjustment for known cardiovascular risk factors. We observed a similar adjusted hazard ratio of 1.4 in our population, which highlights the robustness of our data.

Our findings have important implications for disease management (21). As COPD is associated with PAD development and PAD is often asymptomatic, patients with COPD might benefit from routine ABI screening for the timely diagnosis of PAD. Apart from its cost-effectiveness, early targeted screening and treatment of asymptomatic PAD is likely to improve health by preventing future cardiovascular disease (22).

The strengths of this study are the prospective longitudinal design, and the standardised data collection. However, our study has also some limitations. First, information on PAD was only gathered at the study centre (during study visits), implying that actual dates of PAD onset were missing which prevented us to conduct time to PAD development analysis. Second, since spirometry measurements were not routinely performed in the early rounds of the Rotterdam Study data, the COPD incident date was based on a clinical diagnosis of COPD only, and not all clinically diagnosed COPD subjects were still alive to be confirmed by spirometry at the research centre later on. Third, although we have evaluated all available known potential confounders of the association between COPD and PAD development, residual confounding might still explain part of this association. Finally, including patients with two ABI measurements at two subsequent visits might lead to a selection towards healthier individuals.

Conclusion

Subjects with COPD have a higher risk of developing PAD. People with both COPD and PAD have a substantially increased risk of death. Consequently, early detection of PAD and preventive actions in people with COPD should receive more attention in clinical respiratory care.

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