Title:

Markers of cardiovascular autonomic dysfunction predict COPD in middle-aged subjects

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Summary: Clinical markers of cardiovascular autonomic dysfunction strongly predict incident COPD in a middle-aged population.

Conflicts of interest:

None.

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ABSTRACT

Autonomic dysfunction is commonly observed in chronic obstructive pulmonary disease (COPD) and may relate to the comorbidity that exists with coronary artery disease (CAD). We hypothesized that clinical markers of cardiovascular autonomic dysfunction predict COPD in the population, independently of CAD.

In population-based cohort of 24 768 subjects (mean age 45 years) without baseline airflow obstruction, we analysed the cross-sectional relationship of one-minute orthostatic systolic (delta-SBP) and diastolic (delta-DBP) blood pressure changes, and resting heart rate with forced vital capacity (FVC) and forced expiratory volume (FEV_1). Next, we used Cox-regression-models to analyse the association of delta-SBP, delta-DBP, and resting heart rate with incident COPD over 32-year follow-up.

Baseline delta-SBP (p=0.020) and delta-DBP (p=0.001) were associated with reduced FVC, whereas resting heart rate associated with reduced FVC and FEV_1 (both p<0.001). After adjustment for smoking and baseline lung function, delta-SBP predicted COPD (Hazard ratio [HR] 1.10 per 10mmHg decrease; 95% confidence interval [CI]:1.03-1.18). Resting heart rate predicted COPD among smokers (HR 1.11 per 10 beats-per-minute increase; 95%CI:1.05-1.18). Results were similar in subjects without CAD.

Subtle signs of cardiovascular autonomic dysfunction may precede development of COPD in middle-aged subjects. This association is independent of the relationship between cardiovascular autonomic dysfunction and CAD.

Keywords: autonomic nervous system; autonomic dysfunction; orthostatic hypotension; heart rate, chronic obstructive pulmonary disease; prognosis.

Introduction

There is a strong association between chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) in the general population, especially between COPD and coronary artery disease (CAD) (1-4). The link between COPD and CAD is only partially explained by known common risk factors, such as tobacco smoking (5-8) or other airborne pollutants (9-13). A number of conditions, including systemic inflammation (14,15) and common genetic variants (16) have been proposed as possible mediators, however a significant proportion of the relationship between COPD and CAD still remains elusive (3), especially in non-smokers, who represent approximately one-fourth of the COPD population (17).

In recent years, manifestations of cardiovascular autonomic dysfunction, including increased resting heart rate (18) and orthostatic hypotension (OH) (19), have been shown to predict CVD and CAD. Furthermore, OH has been shown to predict mortality due to respiratory disease (20). Given the direct involvement of the autonomic nervous system in the respiratory system and the presence of autonomic dysfunction in COPD (21), we hypothesized that markers of cardiovascular autonomic dysfunction may predict development of COPD in the general population.

Accordingly, we aimed to test whether markers of cardiovascular autonomic dysfunction - i.e. orthostatic blood pressure instability and elevated resting heart rate - predict incident COPD in the middle-aged population without signs of airflow obstruction at baseline.

Methods

Study population

The study population consisted of 33 346 inhabitants of the city of Malmö in Sweden, recruited between 1974 and 1992 for the Malmö Preventive Project (MPP). At baseline, participants were screened for hypertension, diabetes, obesity, hyperlipidaemia, smoking status, history of cardiovascular and lung disease. Those who confirmed regular or occasional smoking in the preceding three months were defined as smokers. The consumption of more than 20 cigarettes per day was recorded as heavy smoking. Physical activity in men was assessed using a question "Are you mostly engaged in sedentary activity in your spare time?". Some questions were changed during the screening period. In women, physical activity was therefore assessed using the questions, "Are you engaged in physical activity (e.g., swimming, gymnastics, badminton, tennis, folk dance, running, etc.) 1–2 hours per week?" or "Do you usually get to do light physical exercise like walking or cycling (or other activities with similar effort) on a regularly weekly basis?". All subjects fasted overnight prior to the baseline investigations but were allowed to drink water. All examinations were performed in the morning. Among numerous variables, previously described in detail (22), anthropometric measurements, blood pressure (BP), resting heart rate and pulmonary function test (PFT) data were recorded and the subjects provided fasting blood samples. The health service authority of Malmö approved and funded the screening programme. All participants provided informed consent.

For the current study, subjects with prevalent COPD (n=126; 0.4 %) were excluded. PFT data were available in 28 834 subjects without overt COPD (see below). In order

to further eliminate subjects with airflow obstruction at baseline, we excluded 4066 subjects (14.1%) with one-second forced expiratory volume ratio (FEV_1) and forced vital capacity (FVC) below lower limit of normal (LLN) according to the Global Lung Function Initiative Equations (23). Ultimately, 24 768 subjects were eligible for the study and haemodynamic data of orthostatic systolic (SBP)-response, diastolic (DBP)-response and resting heart rate were available in 24 702, 24 694, and 24 641 subjects, respectively.

Definitions of baseline characteristics

OH was defined according to the international consensus as a decrease in SBP ≥20 mmHg and/or a decrease in DBP ≥10 mmHg (24). Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L, current pharmacological treatment of diabetes, or self-reported history of diabetes (25).

Haemodynamic measurements

Blood pressure was measured by specially trained nurses using the auscultatory method, a mercury sphygmomanometer and an appropriately-sized cuff placed around the right arm supported at the heart level. The first BP and heart rate reading were taken twice after 10-min rest in the supine position. Then, participants were asked to stand up and the second BP measurement was taken twice after 1 min in the standing position. The average values of both supine and standing hemodynamic parameters were calculated.

Orthostatic blood pressure-decrease was defined as the average BP values in the supine position minus the average values in the standing position i.e. a positive value

meant BP decrease on standing. Resting heart rate was measured in the supine position only and was recorded as beats-per-minute (bpm).

Pulmonary function tests

Pulmonary function at baseline was assessed as forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) using a Spirotron apparatus (Drägerwerk AG, Lübeck, Germany) carried out by trained nursing staff. The procedure was done without the use of a bronchodilator. One acceptable manoeuvre was required. FVC and FEV_1 were standardized for age and height using the Global Lung Function Initiative Equations (23).

Definition and retrieval of endpoints

The endpoints were identified through linkage of the 10-digit personal identification number of each Swedish citizen with specific registers. The subjects were followed from the baseline examination until admission to hospital for COPD, death, emigration from Sweden or 31 December 2013, whichever came first.

The Swedish Patient Register was used for case retrieval of COPD, as previously described (26) and the register has been validated for COPD (27). This register has been operating in the south of Sweden during the entire follow-up period, and has covered the whole of Sweden since 1987. Admissions to hospital with COPD were defined as cases with a discharge diagnosis of COPD according to the International Classification of Diseases 9th and 10th Revisions (ICD9 and ICD10) 490–492, 496 (ICD-9) or J40–J44 (ICD-10) as one of the first three listed diagnoses.

CAD was defined as fatal or non-fatal myocardial infarction (MI), death from ischemic heart disease, coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). In addition to the Swedish Patient Register, the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and the Swedish Cause of Death Register were used. MI was defined on the basis of codes 410 and I21, respectively. Death due to ischemic heart disease was defined on the basis of codes 412 and 414 (ICD9) or I22–I23 and I25 (ICD10) a. CABG was identified from the national Swedish classification registers of surgical procedures: the KKÅ System from 1963 until 1989, and the Op6 System since then. CABG was defined as a procedure code of 3065, 3066, 3068, 3080, 3092, 3105, 3127, 3158 (Op6) or FN (KKÅ97). PCI was defined based on the operation codes FNG05 and FNG02.

We also retrieved data on hospitalizations for OH and syncope, though only available through 31 December 2011. This combined endpoint was based on primary or main secondary discharge diagnoses (OH: ICD-9=458 and ICD-10=I951; syncope: ICD-9=780.2 and ICD-10=R55.9), excluding cases with concurrent CVD diagnoses identified as the primary cause of admission.

Statistical analysis

The cross-sectional relationship between the hemodynamic parameters, and FVC and FEV_1 at baseline was assessed by linear regression models, adjusted for age, sex, current smoking and predicted FVC or FEV_1 from the reference equations.

The associations between the hemodynamic parameters at baseline and incident COPD during follow-up were tested using Cox regression models. The hemodynamic parameters were entered as continuous variables; SBP was also dichotomized

according to the consensus definition of OH (20 mmHg decrease) and according to cohort-specific tertiles of SBP-decrease. We used minimally (age and sex) adjusted models, as well as multivariable-adjusted models including BMI, current smoking, diabetes, total cholesterol, supine BP, antihypertensive therapy, FVC and FEV_1 in percent of predicted. In addition, among smokers, the dichotomous variable denoting heavy smoking (n=2331; 20.6 %) was added as a covariate.

Analyses were stratified according to four baseline factors with potential influence on the association between the hemodynamic factors and COPD: sex, smoking status (current versus no smoking; smoking quantity) and physical inactivity. Moreover, formal interaction analyses between smoking and the hemodynamic parameters on incident COPD during follow-up were performed using Cox regression models including age, sex, smoking and FVC and FEV_1 in percent of predicted in addition to the interaction term of smoking x hemodynamic parameter. In addition to baseline factors analyses were stratified according to incident CAD during follow-up. Finally, as cardiovascular autonomic dysfunction may be associated with episodes of syncope and symptomatic OH, we explored the incidence of COPD according to hospitalization for syncope or symptomatic OH during follow-up.

The proportional hazard assumption for Cox regression analyses was tested by visual inspection of survival curves of tertiles of the hemodynamic parameters. All analyses were performed using IBM SPSS Statistics version 24 (SPSS Inc., Chicago, IL, USA). All tests were two-sided whereby $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of the 24 768 subjects free of airflow obstruction at baseline are shown in Table 1. The subjects were followed for a median time of 32 years, during which COPD was diagnosed in 1576 subjects (6.4 %), rendering an incidence rate of 2.2 per 1000 person-years. The median time from baseline to the COPD diagnosis was 25 years.

There was a linear relationship between FVC at baseline and changes in orthostatic SBP (ß -0.014 L per 10 mmHg; p=0.020) and DBP (ß -0.034 L per 10 mmHg; p=0.001), but not for FEV_1 (p=0.69 and p=0.20, respectively). Resting heart rate showed a linear correlation with both baseline FVC (ß -0.056 L per 10 bpm; p<0.001) and FEV_1 (ß -0.030 L per 10 bpm; p<0.001).

Orthostatic blood pressure response in relation to incident COPD

Orthostatic SBP-decrease, but not orthostatic DBP-decrease, predicted incident COPD in the minimally and in the multivariable adjusted model. Orthostatic SBP-decrease according to the OH definition (>20 mmHg) did not predict COPD (Table 2). In contrast, a SBP-decrease>5 mmHg, corresponding to the upper tertile of the study population, was associated with incident COPD in multivariable adjusted model (HR 1.142 in relation to first tertile; 95 % CI 1.007-1.295; p=0.039; Figure 1).

Stratification according to current smoking status at baseline revealed that delta-SBP significantly predicted COPD in current smokers, but not in non-smokers (Table 2). There was however no significant interaction between current smoking and orthostatic SBP change on incident COPD (P-interaction=0.226). Further adjusting

for heavy smoking did not change the overall results among smokers. Stratification according to smoking heavy smoking revealed that delta-SBP significantly predicted COPD only among the larger group of non-heavy smokers (Table XXX). However, there was no interaction between heavy smoking and orthostatic SBP change on incident COPD among smokers (P-interaction=0.156).

Sex-specific analyses revealed that orthostatic SBP decrease predicted COPD only among the considerably larger group of men (Supplementary Table 1).

Adding physical inactivity to the multivariable adjusted model did not change the overall association between orthostatic SBP-decrease and incident COPD (HR 1.101 per 10 mmHg SBP decrease; 95 % CI 1.026-1.180; p =0.007). However, stratification according to physical inactivity revealed that orthostatic SBP decrease predicted COPD among physically inactive subjects only (Supplementary table 2). Subjects reporting physical inactivity showed larger orthostatic SBP-decrease (1.7 vs 1.5 mmHg; p = 0.016), lower FEV_1 (88% vs 92 % of predicted), FVC (87% vs 91 % of predicted) and were more likely to be smokers (42% vs 50 %; p <0.001) and men (68 % vs 76 %; p <0.001).

Resting heart rate in relation to incident COPD

Resting heart rate predicted incident COPD in the multivariable-adjusted models, but not in the minimally adjusted model. This was explained by the confounding effect of smoking on resting heart rate, which was found to be higher in non-smokers (69.2 bpm) compared with smokers (68.7 bpm; p<0.001). Moreover, interaction analysis revealed a significant interaction between resting heart rate and smoking on incident COPD (p-interaction = 0.045). Accordingly, resting heart rate predicted incident

COPD only in smokers, whereas adjustment for smoking quantity did not change the results (Table 3). In similar to delta-SBP, stratification resting heart rate predicted COPD only among the non-heavy smokers (Table XXX?) and there was no interaction between smoking quantity and heart rate on incident COPD among smokers (P-interaction=0.117).

Among smokers, resting heart rate was associated with lower FVC (beta, -0.066 L per 10 bpm; p<0.001) and FEV_1 (beta, -0.038 L per 10 bpm; p<0.001) in models adjusted for age, sex and individually predicted absolute values of FVC or FEV_1.

Sex-specific analyses revealed that orthostatic SBP decrease predicted COPD only among the larger group of men (Supplementary Table 1).

Adding physical inactivity to the multivariable adjusted model did not change the association between resting heart rate and incident COPD (HR 1.062 per 10 bpm; 95 % CI 1.006-1.210; p=0.029). In analyses stratified for physical inactivity, resting heart rate did not significantly predict COPD in neither physically inactive nor physically active subjects (Supplementary table 2).

Analyses stratified according to CAD

A total of 89 subjects (0.4%) had CAD at baseline. During follow-up, 5,000 (20.3%) additional subjects developed CAD. In the 19 679 subjects without overt CAD during follow-up, orthostatic SBP decrease predicted incident COPD, whereas resting heart rate predicted incident COPD among smokers only (Table 4).

Incident COPD in relation to episodes of OH or syncope

A total of 707 subjects were hospitalized due to OH/syncope. During follow-up 107 (15.1%) of them were also hospitalized due to COPD, as compared to 6.1% in those without OH/syncope. Excluding the subjects with episodes of OH/syncope did not change the main results of SBP-decrease or resting heart rate in relation to incident COPD (data not shown).

Discussion

We observed that subtle manifestations of cardiovascular autonomic dysfunction, i.e. orthostatic blood pressure decrease and elevated resting heart rate, are significantly associated with impaired lung function and predict development of COPD in the middle-aged population. Moreover, we have shown that the relationship between orthostatic blood pressure instability and incidence of COPD is maintained also in subjects without overt CAD during follow-up.

The autonomic nervous system is directly involved in the homeostasis of the respiratory system. There is also evidence of an “inflammatory reflex” in which the nervous system is involved in the regulation of inflammation (28), which in turn is considered a hallmark of COPD. Thus, the relationship between malfunction of the autonomic nervous system and COPD is indeed quite plausible from a pathophysiological perspective. Previous research has focused on the occurrence of autonomic dysfunction in manifest COPD, for which patients demonstrate autonomic dysfunction in terms of elevated resting heart rate, reduced heart rate variability, reduced baroreflex sensitivity (21) and pathologic responses to the Valsalva manoeuvre (29,30).

In the MPP cohort, OH was reported to be associated with increased mortality from respiratory diseases, which could not be fully explained by death from COPD (20). Furthermore, in other cohorts, COPD has been identified as a risk factor for traumatic falls (31,32), while in elderly patients OH has been found to coexist to a large extent with COPD (33). Our study is the first to show that subtle signs of cardiovascular autonomic dysfunction may predict incident COPD many years in advance in

relatively young and apparently healthy subjects without airflow obstruction at baseline.

Remarkably, orthostatic BP decrease was cross-sectionally associated with reduced FVC, whereas elevated heart rate was associated with both reduced FVC and FEV_1. At baseline, orthostatic BP decrease may be related with loss of lung capacity rather than obstruction. This can be observed in a number of conditions, including COPD, restrictive lung diseases, heart failure and diabetes (34,35). These conditions, as well as subclinical phenotypes of such diseases, may well coexist with subtle signs of cardiovascular autonomic dysfunction. Conversely, FEV_1, especially in relation to FVC, is more specific of airflow obstruction (36). A possible explanation for the lack of association between orthostatic BP decrease and baseline FEV_1 may be that the subtle signs of cardiovascular dysfunction may precede decrease in FEV_1 first after many years of exposure.

Orthostatic SBP changes, on a continuous scale and dichotomized as detectable decrease of 5 mmHg predicted incident COPD, whereas the cut-off criterion applied to diagnose orthostatic hypotension (37) did not. This may be due to the fact that the prevalence OH at baseline (2.5 %) was rather low. However, previous studies have documented that orthostatic SBP decrease less than 5 mmHg is representative for normal controls(38) with preserved orthostatic homeostasis. This is identical with the cut-off limit for the highest tertile of SBP change on standing, suggesting that individuals in the third tertile demonstrated signs of subtle to overt autonomic dysfunction. Thus, the finding of a positive relationship between smaller magnitudes of systolic blood pressure decrease and incident COPD emphasize that subtle and subclinical cardiovascular autonomic dysfunction may be an early predictor of

increased COPD risk, especially in the presence of concomitant exposure to cigarette smoking, a well-known major aetiological factor in the development of COPD and COPD-related peripheral neuropathy(39). The fact that the associations were seen among non-heavy smokers only is likely a result of lack of power, since only 20 % of the smokers in MPP reported heavy smoking. Moreover, the median time from baseline to first COPD event was long (25 years), hence supporting the hypothesis that changes in cardiovascular autonomic dysfunction may precede the development of manifest COPD many years in advance. On the other hand, COPD was much more common in subjects that were also hospitalized due to OH or syncope during follow-up, which further support a strong comorbidity and parallel development of both manifest autonomic dysfunction and COPD.

In addition to orthostatic blood pressure instability, the impact of elevated resting heart rate as a marker of cardiovascular autonomic dysfunction deserves special consideration. Patients with COPD demonstrate higher resting heart rate as a central feature of autonomic dysfunction (21). Elevated heart rate is also a hallmark of COPD exacerbations and a common side effect of bronchodilators (40). In this study, we found a strong association between an elevated resting heart rate and both lung function at baseline and incidence of COPD during follow-up. Unexpectedly, resting heart rate was lower among smokers compared with non-smokers at baseline. Furthermore, there was an interaction between resting heart rate and smoking on the incidence of COPD during follow-up, meaning that an elevated resting heart rate predicted COPD only among smokers. In addition, higher resting heart rate among smokers was also associated with reduced lung function at baseline. Whereas we cannot exclude residual confounding, an elevated heart rate predicted COPD also

after adjustment for baseline lung function. Thus, the effect of resting heart rate on incident COPD may go beyond the potential relationship of autonomic dysfunction with a subtle lung function impairment that was already present at baseline.

Physical activity is thought to be inversely related with autonomic function. In our study orthostatic blood pressure decrease, but not resting heart rate, seem to relate to the risk of future COPD only among physically inactive subjects. Most likely this is based on a heavier risk factor burden for both autonomic dysfunction and COPD in this group, however future studies should examine whether physical activity that improve autonomic function also lead to a correspondingly decreased risk of COPD.

Our results were to a large extent consistent when comparing all subjects with those without overt CAD during follow-up. The slight attenuation of significance for resting heart rate most likely reflects the reduced statistical power in the subgroup analysis. Thus, the associations between markers of cardiovascular dysfunction and COPD incidence seem to be independent from the development of CAD. Even though we cannot exclude a sequential pathway through development of subclinical atherosclerosis, we believe that our findings support the role of the autonomic nervous system as a plausible mechanism underlying the association between COPD and CAD, however with no distinct overlap. Further studies should investigate the specific role of signs of cardiovascular autonomic dysfunction in relation to both COPD and CAD.

Subclinical parasympathetic dysfunction has been found to be positively correlated with the severity of hypoxaemia in a cohort of 96 patients with COPD and further confirmed by the acetylcholine sweat-spot test(39,41). Nowadays, grading of

autonomic impairment can be quantitated through the composite autonomic severity score (CASS), using cardiovascular reflex tests and quantitative sudomotor axonal reflex test in three domains (cardiovagal, adrenergic and sudomotor) or, alternatively, through the quantitative autonomic reflex and small fibers tests (QASAT), including 3 main modules: cardiovascular, cerebral blood flow and small fiber neuropathy(42,43). Further research should be fostered to test the importance in the disease process and the incremental prognostic value of presence, site and severity of dysautonomia, - as assessed by different tests and scores, ie. CASS or QASAT – both in patients with overt COPD and in those without airflow obstruction but with risk factors for COPD.

Some limitations should be addressed. Firstly, the baseline examinations in MPP did not include standing heart rate measurement. Secondly, even though the PFT data in MPP used in previous studies have confirmed the expected association between lung function, smoking and outcomes (26,44), PFT in MPP was performed before the time of international standardisation, meaning that the procedure included only one acceptable maneuverer. Moreover, spirometry was performed without a bronchodilator, meaning that we probably excluded a number of subjects with reversible airflow obstruction that do not meet the criteria for COPD. Whereas such subjects may not be considered completely healthy in terms of lung function, their exclusion may have underestimated our findings. Moreover, pre-bronchodilator PFT may explain the slightly reduced mean values of FEV1 and FVC in relation to GLI predicted values. Thirdly, although the COPD endpoint used in the current study has been validated (27), a hospital diagnosis of COPD does not necessarily indicate a confirmed diagnosis on PFT, which is the gold standard. Fourthly, whereas markers

of cardiovascular autonomic dysfunction predicted COPD in subjects that were free from manifest CAD during follow-up, we were not able to test the relationship in subjects with subclinical atherosclerosis. Fifthly, the baseline exam in MPP did not include data on medications with influence on autonomic function, such as opioids or sympathomimetics. Finally, women were highly underrepresented in MPP, meaning that we were underpowered for studying sex-specific relations.

In conclusion, we have observed that subtle and in most cases probably subclinical signs of cardiovascular autonomic dysfunction are associated with impaired lung function and may predict development of COPD in middle-aged subjects without airflow obstruction. This association is independent of the relationship between cardiovascular autonomic dysfunction and CAD. We propose that cardiovascular autonomic dysfunction may be taken into account when evaluating risk of future COPD, in addition to the currently known risk factors.

Tables

Table 1. Baseline characteristics of the study population.

	All (n=24 768)	Non-smokers (n=13 448)	Smokers (n=11 320)
Age, years	44.5 (7.3)	44.6 (7.2)	44.3 (7.4)
Women, %	28.0	29.4	26.4
BMI, kg/m²	24.5 (3.5)	24.7 (3.5)	24.1 (3.5)
Supine SBP, mmHg	128.6 (15.4)	130.0 (15.3)	126.8 (15.2)
Supine DBP, mmHg	84.9 (9.4)	86.0 (9.2)	83.6 (9.5)
Postural SBP decrease, mmHg	1.6 (7.2)	1.5 (7.1)	1.7 (7.3)
Postural DBP decrease, mmHg	-2.4 (4.4)	-2.5 (4.4)	-2.2 (4.5)
Orthostatic hypotension, %	2.5	2.2	2.8
SBP-decrease ≥20 mmHg, %	1.9	1.7	2.1
Resting heart rate, bpm	69.0 (10.0)	69.2 (10.1)	68.7 (9.8)
FVC, mL	4169 (996)	4265 (993)	4054 (988)
FVC in percent of predicted	89 (15)	92 (15)	86 (15)
FEV_1, mL	3359 (796)	3451 (791)	3250 (788)
FEV_1 in percent of predicted	90 (15)	93 (15)	86 (15)
FEV_1/FVC ratio	0.81 (0.07)	0.81 (0.07)	0.81 (0.07)
Physical inactivity, %	49.6	45.8	54.2
Antihypertensive treatment, %	4.8	5.6	4.7
Diabetes, %	4.5	4.4	4.7
CAD, %	0.4	0.3	0.4

Displayed as mean (SD) or % of total. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; CAD, coronary artery disease; FVC,

forced vital capacity; FEV_1,forced expiratory volume in one second.

Table 2. The relationship between baseline orthostatic blood pressure response and incident COPD.

	Sample size (events)	HR per 10 mmHg	95 % CI	P-value
All subjects				
ΔSBP Model 1*	24697 (1569)	1.123	1.049-1.202	0.001
ΔSBP Model 2**	24647 (1564)	1.101	1.026-1.180	0.007
ΔSBP > 20 mmHg**	24647 (1564)	1.216	0.886-1.669	0.227
ΔDBP Model 1*	24689 (1569)	1.052	0.940-1.178	0.378
ΔDBP Model 2**	24639 (1564)	0.989	0.886-1.104	0.841
Smokers				
ΔSBP Model 1*	11280 (1228)	1.119	1.036-1.208	0.004
ΔSBP Model 2**	11259 (1224)	1.112	1.028-1.202	0.008
ΔSBP Model 3***	11259 (1224)	1.112	1.029-1.201	0.007
ΔSBP >20 mmHg**	11259 (1224)	1.268	0.898-1.790	0.177
ΔDBP Model 1*	11276 (1228)	1.004	0.885-1.138	0.954
ΔDBP Model 2**	11255 (1224)	1.001	0.9882-1.136	0.983
ΔDBP Model 3***	12255 (1224)	1.008	0.889-1.143	0.901
Non-smokers				
ΔSBP Model 1*	13413 (341)	1.032	0.890-1.198	0.673
ΔSBP Model 2**	13384 (340)	1.056	0.906-1.231	0.485
ΔSBP >20 mmHg**	13384 (340)	0.972	0.430-2.197	0.946
ΔDBP Model 1*	13409 (341)	0.932	0.732-1.187	0.570
ΔDBP Model 2**	13380 (340)	0.934	0.728-1.198	0.589

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, hazard ratio, reported per 10 mmHg SBP/DBP-decrease, except for the dichotomous variable denoting SBP >20 mmHg. *

Model adjusted for age and sex. ** Model adjusted for age, sex, BMI, (current smoking), diabetes, total cholesterol, supine SBP or supine DBP, antihypertensive therapy, FVC in percent of predicted, FEV_1 in percent of predicted. *** As Model 2 but additionally adjusted for smoking quantity ≥ 20 cigarettes per day

Table 3. The relationship between baseline resting heart rate and incident COPD.

	Sample size (events)	HR per 10 bpm	95 % CI	P-value
All subjects				
Model 1*	24636 (1561)	1.028	0.978-1.081	0.274
Model 2**	24582 (1556)	1.064	1.009-1.123	0.023
Over median 68 bpm**	24582 (1556)	1.121	1.011-1.244	0.030
Smokers				
Model 1*	11244 (1220)	1.120	1.059-1.185	<0.001
Model 2**	11223 (1216)	1.111	1.045-1.181	0.001
Model 3***	11223 (1216)	1.112	1.046-1.182	0.001
Over median 67 bpm**	11223 (1216)	1.219	1.084-1.371	0.001
Non-smokers				
Model 1*	13388 (341)	0.983	0.883-1.095	0.754
Model 2**	13355 (340)	0.944	0.842-1.060	0.331
Over median 68 bpm**	13355 (340)	0.864	0.692-1.079	0.197

Bpm, beats per minute; HR, hazard ratio. HRs are reported per 10 bpm except for the dichotomous variable denoting median resting heart rate. * Model adjusted for age and sex. ** Model adjusted for age, sex, BMI, (current smoking), diabetes, total cholesterol, supine SBP, antihypertensive therapy, FVC in percent of predicted, FEV_1 in percent of predicted.

*** As Model 2 but additionally adjusted for smoking quantity ≥ 20 cigarettes per day

Table 4. The relation between baseline hemodynamic parameters and incident COPD stratified according to CAD.

	Sample size (events)	HR per 10 mmHg or bpm	95 % CI	P-value
No CAD				
ΔSBP in all	19579 (1094)	1.106	1.016-1.204	0.020
ΔSBP in smokers	8471 (861)	1.118	1.017-1.229	0.021
RHR all	19526 (1086)	1.063	0.996-1.134	0.064
RHR smokers	8443 (853)	1.097	1.020-1.179	0.013
CAD				
ΔSBP in all	5068 (470)	1.081	0.957-1.221	0.209
ΔSBP in smokers	2787 (363)	1.102	0.959-1.267	0.169
RHR in all	5056 (470)	1.086	0.983-1.199	0.105
RHR in smokers	2779 (363)	1.149	1.026-1.285	0.016

CAD, coronary artery disease; bpm, beats per minute; HR, hazard ratio; RHR, resting heart rate.

All analyses adjusted for age, sex, BMI, diabetes, total cholesterol, supine SBP, antihypertensive therapy, FVC in percent of predicted, FEV_1 in percent of predicted.

Table 5. The relation between baseline hemodynamic parameters and incident COPD stratified according to smoking quantity in smokers.

	Sample size (events)	HR per 10 mmHg or bpm	95 % CI	P-value
< 20 cigarettes per day				
ΔSBP	8777 (893)	1.157	1.054-1.270	0.002
RHR	8749 (886)	1.106	1.028-1.190	0.007
≥ 20 cigarettes per day				
ΔSBP	2319 (312)	1.013	0.858-1.196	0.880
RHR	2311 (311)	1.084	0.966-1.216	0.173

P-interaction for [smoking quantity x ΔSBP] on incident COPD = 0.156

P-interaction for [smoking quantity x heart rate] on incident COPD = 0.117

CAD, coronary artery disease; bpm, beats per minute; HR, hazard ratio. RHR = resting heart rate

All analyses adjusted for age, sex, BMI, diabetes, total cholesterol, supine SBP, antihypertensive therapy, FVC in percent of predicted, FEV_1 in percent of predicted.

Supplementary Table 1. The relation between baseline hemodynamic parameters and incident COPD stratified according to sex.

	Sample size (events)	HR per 10 mmHg or bpm	95 % CI	P-value
Men				
ΔSBP	17762 (1023)	1.104	1.007-1.210	0.034
RHR	17709 (1016)	1.079	1.010-1.152	0.023
Women				
ΔSBP	6883 (541)	1.089	0.980-1.211	0.114
RHR	6871 (540)	1.080	0.979-1.190	0.125

P-interaction for [sex x ΔSBP] on incident COPD = 0.337

P-interaction for [sex x heart rate] on incident COPD = 0.119

CAD, coronary artery disease; bpm, beats per minute; HR, hazard ratio.

All analyses adjusted for age, BMI, diabetes, total cholesterol, supine SBP, antihypertensive therapy, FVC in percent of predicted, FEV_1 in percent of predicted.

Supplementary Table 2. The relation between baseline hemodynamic parameters and incident COPD stratified according to physical inactivity.

	Sample size (events)	HR per 10 mmHg or bpm	95 % CI	P-value
Physically active				
ΔSBP	12412 (690)	1.059	0.951-1.179	0.297
RHR	12378 (686)	1.082	0.997-1.175	0.059
Physically inactive				
ΔSBP	12229 (874)	1.133	1.034-1.242	0.007
RHR	12198 (870)	1.050	0.977-1.128	0.186

P-interaction for [physical inactivity x ΔSBP] on incident COPD = 0.293

P-interaction for [physical inactivity x heart rate] on incident COPD = 0.974

CAD, coronary artery disease; bpm, beats per minute; HR, hazard ratio.

All analyses adjusted for age, sex, BMI, diabetes, total cholesterol, supine SBP, antihypertensive therapy, FVC in percent of predicted, FEV_1 in percent of predicted.

Figure captions and legends:

Figure 1

Caption: Incident COPD by tertiles of orthostatic systolic blood pressure decrease

Legend: Incident chronic obstructive pulmonary disease (COPD) during follow-up by tertiles of orthostatic systolic blood pressure (SBP) response at baseline.

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