SUPPLEMENTAL MATERIAL

Phenotyping asthma with airflow obstruction in middle-aged and older adults: a CADSET Clinical Research Collaboration

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Table S1. Inclusion and exclusion criteria and ethics committee of cohorts.

Study:	COSYCONET
Type of study:	COPD-based cohort
Number of sites:	31 study centers in Germany
Population:	2,741 COPD patients
Inclusion Criteria:	- Aged 40 years and older, - Diagnosis of COPD (according to GOLD criteria) or chronic bronchitis, - Availability for repeated study visits over at least 18 months.
Exclusion Criteria:	- Having undergone major lung surgery (e.g., lung volume reduction, lung transplant), - Moderate or severe exacerbation within the last 4 weeks, - Having a lung tumor, - Physical or cognitive impairment resulting in an inability to walk or to understand the intention of the project.
Ethics committees	The study protocol was approved by the central ethical committee in Marburg (Ethikkommission FB Medizin Marburg) and the respective local ethical committees: Bad Reichenhall (Ethikkommission Bayerische Landesärztekammer); Berlin (Ethikkommission Ärztekammer Berlin); Bochum (Ethikkommission Medizinische Fakultät der RUB); Borstel (Ethikkommission Universität Lübeck); Coswig (Ethikkommission TU Dresden); Donaustauf (Ethikkommission Universitätsklinikum Regensburg); Essen (Ethikkommission Medizinische Fakultät Duisburg-Essen); Gießen (Ethikkommission Fachbereich Medizin); Greifswald (Ethikkommission Universitätsmedizin Greifswald); Großhansdorf (Ethikkommission Ärztekammer Schleswig-Holstein); Hamburg (Ethikkommission Ärztekammer Hamburg); MHH Hannover/Coppenbrügge (MHH Ethikkommission); Heidelberg Thorax/Uniklinik (Ethikkommission Universität Heidelberg); Homburg (Ethikkommission Saarbrücken); Immenhausen (Ethikkommission Landesärztekammer Hessen); Kiel (Ethikkommission Christian-Albrechts-Universität zu Kiel); Leipzig (Ethikkommission Universität Leipzig); Löwenstein (Ethikkommission Landesärztekammer Baden-Württemberg); Mainz (Ethikkommission Landesärztekammer Rheinland-Pfalz); München LMU/Gauting (Ethikkommission Klinikum Universität München); Nürnberg (Ethikkommission Friedrich-Alexander-Universität Erlangen Nürnberg); Rostock (Ethikkommission Universität Rostock); Berchtesgadener Land (Ethikkommission Land Salzburg); Schmallenberg (Ethikkommission Ärztekammer Westfalen-Lippe); Solingen (Ethikkommission Universität Witten-Herdecke); Ulm (Ethikkommission Universität Ulm); Würzburg (Ethikkommission Universität Würzburg). The study was performed in accordance with the declaration of Helsinki, and all participants gave their written informed consent.

Study:	ECLIPSE
Type of study:	COPD-based cohort
Number of sites:	44 study centers in 12 countries worldwide
Population:	- 2,164 COPD subjects - 337 smoking controls - 245 nonsmoking controls
Inclusion Criteria:	COPD - Male/female subjects aged 40–75 years - Baseline post-bronchodilator FEV_1 of <80% pred and FEV_1/FVC of ≤0.7 - Current or ex-smokers with a smoking history of ≥10 pack-years consent obtained prior to participation - Ability to comply with the requirements of the protocol and be available for study visits over 3 years CONTROLS - Male/female subjects aged 40–75 years, who are free from significant disease as determined by history, physical examination, and screening investigations - Baseline post-bronchodilator FEV_1 of >85% pred and FEV_1/FVC of >0.7 - Signed and dated written informed consent obtained prior to participation - Ability to comply with the requirements of the protocol and be available for study visits over 3 years - Current or ex-smokers with a smoking history ≥10 pack-years, or nonsmokers with a smoking history of <1 pack-years
Exclusion Criteria:	- Known respiratory disorders other than COPD and severe α1-antitrypsin deficiency - Prior medical history (known history of significant inflammatory disease other than COPD - COPD exacerbation within 4 weeks of enrolment - Lung surgery

	- Recent diagnosis of cancer - Blood transfusion in the 4 weeks prior to study start - Inability to walk - Taking part in a blinded drug study - Therapy with oral corticosteroids at inclusion - Participation in studies with radiation exposure.
Ethics committee	ECLIPSE complies with the Declaration of Helsinki and Good Clinical Practice Guidelines, and has been approved by the ethics committees of the participating centres. All participants provided written informed consent (ClinicaltTrials.gov identifier: NCT00292552). The members of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) Steering Committee are: (University of British Columbia, Vancouver, BC, Canada); (University of Cambridge, Cambridge, UK); (University of Edinburgh, Edinburgh, UK); (Brigham and Women's Hospital, Boston, MA, USA);; (Co-Chair; Hvidovre Hospital, Hvidovre, Denmark); (Son Dureta Hospital and Cimera, Palma, Spain); (University Hospital Aintree, Liverpool, UK); (Caritas St. Elizabeth's Medical Center, Boston, MA, USA); (University of Nebraska, Omaha, NE, USA); (University of Maastricht, Maastricht, the Netherlands)

Study:	PAC-COPD
Type of study:	COPD-based cohort
Number of sites:	9 tertiary hospital centers in Spain
Population:	329 COPD patients
Inclusion Criteria:	- Patient admitted for the first time for an exacerbation of COPD to any of the 9 participating hospitals between January 2004 and March 2006 (27 months) - The diagnosis of COPD is confirmed using spirometric criteria (post-bronchodilation FEV_1/FVC ratio of 0.7) at least 3 months after admission and with the patient in stable condition.
Exclusion Criteria:	- Age under 45 years, - Severe comorbidity, such as terminal or advanced cancer, pulmonary tuberculosis with involvement of more than one-third of the total lung parenchyma, pneumectomy, or pneumoconiosis, - Old age or general fragility (eg, difficulty walking, lack of autonomy) that can make it substantially difficult for the patient to participate in the study, regardless of the patient's desire to participate, - Mental disability diagnosed by the attending physician or determined using the Folstein Mini-Mental State Exam,16 better known as the MiniMental Test in its adapted version validated for Spain17, - Not being a resident of the province where the hospital is located, - Not being able to understand Spanish.
Ethics committee	The study was approved by the Ethics Committee of all participating hospitals and the coordinating centre, as detailed below: • Comitè Ètic d'Investigació Clínica IMAS: 2004/1762/I, 2002/1346/I • Hospital Clínic i Provincial de Barcelona; project approval number: 1215 • Hospital de la Santa Creu i Sant Pau, Barcelona; project approval number: 19/06/2002 • Hospital General Universitari Vall d'Hebron, Barcelona; project approval number: 2002/13461/1 • Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat; project approval number: 150/02 • Hospital Universitari Germans Trias i Pujol, Badalona; project approval number: 21/06/2002 • Hospital de Sabadell, Corporació Parc Taulí, Sabadell; project approval number: 03/141 • Hospital Son Dureta, Palma de Mallorca; project approval number: 19/06/2002 • Hospital de Cruces, Baracaldo, Vizcaya; project approval number: E03/2

Study:	Urban Training
Type of study:	COPD-based cohort
Number of sites:	5 centers in Spain
Population:	407 COPD patients
Inclusion Criteria:	All subjects with a diagnosis of COPD according to the American Thoracic Society/European Respiratory Society recommendations (post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio <0.70) who were seen in any of the participating 33 primary care and five hospital health centers from five Catalan seaside municipalities.
Exclusion Criteria:	Patients with severe or life-threatening comorbidities, or those clinically unstable.

Ethics committee	The Urban Training trial was approved by the Ethics Committees of all participating institutions (Comitè Ètic d'Investigació Clínica Parc de Salut MAR 2011/4291/I, Comitè Ètic d'Investigació Clínica de l'IDIAP Jordi Gol i Gurina P11/116, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge PR197/11, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Germans Trias i Pujol AC-12-004, Comitè Ètic d'Investigació Clínica de l'Hospital Clínic de Barcelona 2011/7061, Comitè Ètic d'Investigació Clínica de l'Hospital de Mataró November 23rd, 2011) and all participants provided written informed consent.

Study:	OLIN
Type of study:	asthma-based cohort
Number of sites:	single-center
Population:	2,055 asthma adults from Northern Sweden recruited by postal questionnaire since 1986
Inclusion Criteria:	- Self-reported asthma - Highly suspected asthma
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	Regional Ethical Review Board at Umeå University

Study:	U-BIOPRED
Type of study:	asthma-based cohort
Number of sites:	16 clinical centers in 11 European countries
Population:	610 adults with asthma and healthy controls
Inclusion Criteria:	- Severe nonsmoking asthmatics, - Smokers and ex-smokers with severe asthma, - Mild/moderate non-smoking asthmatics, - Healthy non-smoking controls
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	Approved by the ethics committee for each participating clinical institution (ClinicalTrials.gov identifier: NCT01982162)

Study:	Rotterdam Study
Type of study:	population-based cohort
Number of sites:	single-center
Population:	14,926 participants
Inclusion Criteria:	Inhabitants of the Ommoord district, Rotterdam, Netherlands, aged 45 years or over.
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	Medical ethics committee of the Erasmus Medical Centre (Rotterdam, the Netherlands), and the review board of the Netherlands Ministry of Health, Welfare and Sports (1068889-159521-PG)

Study:	LifeLines
Type of study:	population-based cohort
Number of sites:	multi-center
Population:	167,729 participants
Inclusion Criteria:	All inhabitants in the Netherlands between 25-50 years of age at recruitment, registered with a GP, and their relatives (parents, partners, children).
Exclusion Criteria:	- Severe psychiatric or physical illness, limited life expectancy (<5 years) - Insufficient knowledge of the Dutch language to complete a Dutch questionnaire.
Ethics committee	Ethics Committee of University Medical Center Groningen (The Netherlands)

Study:	Danish Twin Registry
Type of study:	population-based cohort
Number of sites:	nationwide registry
Population:	136,684 twin pairs (in addition: 775 triplets and 22 quadruplets)
Inclusion Criteria:	Twin cohorts in Denmark including twin pairs born between 1870-2006.
Exclusion Criteria:	No prespecified exclusion criteria.
Ethics committee	The Regional Committees on Health Research Ethics for Southern Denmark (De Videnskabsetiske Komitéer for Region Syddanmark); Journal number S-VF-19980072.

Data collection, definitions and missing data handling.

An *ad-hoc* data collection form was designed to collect the summary statistics used in this analysis. All data were collected at the index date defined by the first spirometry measurement in the respective cohorts. Comorbidities included hypertension, coronary artery disease (CAD), heart failure, diabetes, depression, gastro-esophageal reflux disease (GERD), osteoporosis, history of stroke, and history of myocardial infarction. Comorbidities were defined based on self-reported doctor diagnosis, validation in medical files, questionnaire-based, or by examination (cfr. below). Underweight = BMI < 18.5, normal weight = BMI ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 30. Smoking behavior was self-reported and categorized as current, former, or never smokers. Dyspnea was considered clinically relevant when the mMRC (modified Medical Research Council dyspnea) score ≥2. Emphysema was defined as per-cohort definition (cfr. below). Chronic bronchitis was defined as daily sputum production lasting for at least three months during two consecutive years. Exacerbations in the year prior to the index data were analyzed and categorized into severe (hospitalization or emergency room visit) and moderate exacerbations (ambulant use of oral corticosteroids and/or antibiotics). Missing data were considered missing at random and were not imputed.

Asthma

- **Lifelines:** self-reported physician diagnosis
- **Rotterdam Study:** physician diagnosis in medical files (De Roos EW et al. Respir Med. 2018;139:6-12)
- **DTR:** self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** physician diagnosis
- **Urban Training:** physician diagnosis
- **PAC-COPD:** physician diagnosis
- **U-BIOPRED: "**Participants with asthma had either airflow reversibility (increase in forced expiratory volume in 1s (FEV_1) >12% predicted or 200 mL following inhalation of 400 µg salbutamol), airway hyperresponsiveness (methacholine provocative concentration causing a 20% fall in FEV_1 <8 mg·mL−1, or diurnal peak expiratory flow amplitude >8% of mean), or a decrease in FEV_1 of 12% predicted or 200 mL within 4 weeks after tapering maintenance treatment." (Shaw DE, et al. European Respiratory Journal. 2015;46(5):1308-21)
- **OLIN:** physician diagnosis or a medical history of asthma together with a) physiologically verified bronchial variability and/or b) asthma medication.

Emphysema

- **COSYCONET**: self-reported physician-diagnosis
- **ECLIPSE**: > 5% low attenuation areas (LAA)
- **PAC-COPD:** density < -950 Hounsfield units in at least one are (supracarinal, carinal or infracarinal, in right or left lung)

Hypertension

- **Lifelines:** self-reported
- **Rotterdam Study:** use of antihypertensive medication, systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg
- **DTR:** self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported
- **Urban Training:** physician diagnosis
- **PAC-COPD:** physician diagnosis

Coronary artery disease

- **Lifelines:** self-reported
- **Rotterdam Study:** coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), verified in medical files
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported

Myocardial infarction

- **Lifelines:** self-reported
- **DTR:** self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported

Heart failure

- **Lifelines:** self-reported
- **Rotterdam Study:** typical symptoms/signs confirmed by radiographic evidence of cardiac dysfunction
- **DTR:** self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported
- **Urban Training:** physician diagnosis
- **PAC-COPD:** physician diagnosis

Stroke

- **Lifelines:** self-reported
- **Rotterdam Study:** self-reported and verified in medical files
- **DTR:** self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported
- **PAC-COPD:** physician diagnosis

Gastro-esophageal reflux disease

- **DTR:** self-reported physician diagnosis
- **COSYCONET**: self-reported physician diagnosis
- **ECLIPSE:** self-reported

Diabetes

- **Lifelines:** self-reported
- **Rotterdam Study:** use of blood glucose-lowering medication
- **DTR:** self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported
- **Urban Training:** physician diagnosis
- **PAC-COPD:** physician diagnosis

Depression

- **Lifelines:** self-reported (ever)
- **Rotterdam Study:** CES-D(20) questionnaire score of 16 or higher
- **DTR:** self-reported physician diagnosis
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported

Osteoporosis

- **DTR:** self-reported
- **COSYCONET:** self-reported physician diagnosis
- **ECLIPSE:** self-reported

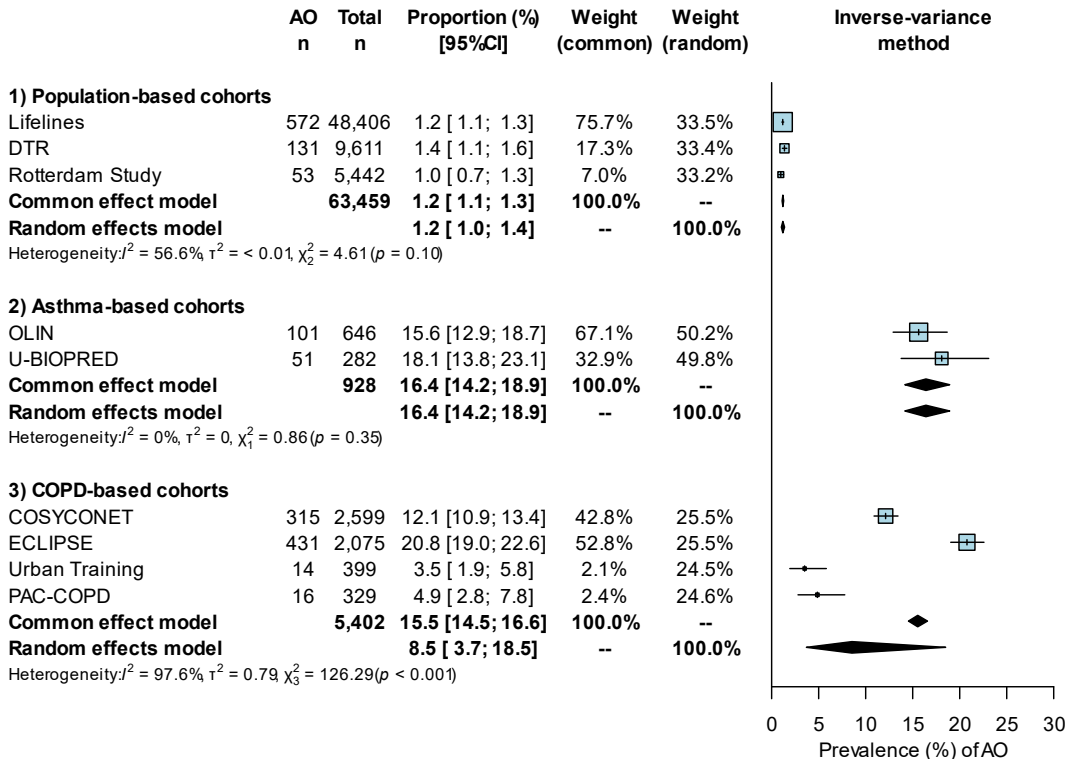

Figure S1. Meta-analyzed prevalence of asthma with LLN-defined airflow obstruction.

Table S2. Cohort-specific AO prevalence and severity of airflow obstruction.

	AO n (%)	FEV_1% pred mean (95%CI)	FVC% pred mean (95%CI)	FEV_1/FVC % mean (95%CI)
Population cohorts				
LifeLines	931 (1.9)	88.0 (78.5-97.5)	103.1 (100.7-105.5)	67.5 (58.5-76.5)
RS	106 (1.9)	82.7 (69.2-96.3)	90.1 (84.1-96.0)	68.1 (58.9-77.4)
DTR	261 (2.7)	81.1 (68.9-93.4)	88.9 (84.1-93.8)	66.9 (56.9-76.9)
Asthma cohorts				
OLIN	128 (19.8)	72.9 (45.4-100.3)	81.0 (70.9-91.2)	69.9 (51.1-88.8)
U-BIOPRED	67 (23.8)	59.2 (36.0-82.4)	85.6 (73.6-97.6)	54.8 (37.0-72.5)
COPD cohorts				
Urban Training	15 (3.8)	56.4 (53.0-59.9)	77.3 (75.6-79.0)	53.7 (50.8-56.6)
PAC-COPD	23 (7.0)	51.9 (50.1-53.7)	71.9 (67.9-75.9)	52.8 (51.4-54.2)
COSYCONET	371 (14.3)	52.5 (51.8-53.3)	78.1 (77.3-78.9)	51.8 (50.8-52.8)
ECLIPSE	448 (21.6)	44.5 (43.9-45.1)	79.8 (79.0-80.6)	44.4 (43.8-44.9)

Table S3. Sample sizes and p-values accompanying Table 1 in the manuscript.

	Population cohorts			**Asthma cohorts**		**COPD cohorts**	
	AO	Asthma-only	COPD-only	AO	Asthma-only	AO	COPD-only
Age (years)							
N	1298	1985	9760	195	733	857	4088
P-value	REF	0.199	**0.016**	REF	**0.011**	REF	**0.006**
Female							
N	1298	1985	9760	195	733	857	4088
P-value	REF	**<0.001**	0.053	REF	**<0.001**	REF	0.121
BMI (kg/m^2)							
N	1298	1983	9755	186	708	857	4086
P-value	REF	**<0.001**	**<0.001**	REF	**<0.001**	REF	0.376
BMI category							
N	1298	1982	9755	186	708	857	4086
Underweight *P*-value	REF	0.060	0.277	REF	0.691	REF	0.801
Normal weight *P*-value	REF	**0.022**	0.634	REF	**0.017**	REF	0.574
Overweight *P*-value	REF	0.902	0.556	REF	0.898	REF	0.929
Obese *P*-value	REF	**<0.001**	**0.001**	REF	**<0.001**	REF	0.932
Smoking status							
N	1283	1971	8430	195	733	856	4085
Never smoker *P*-value	REF	**0.025**	**0.047**	REF	0.289	REF	0.206
Former smoker *P*-value	REF	0.733	0.318	REF	0.454	REF	0.263

Current smoker P-value	REF	**0.001**	**<0.001**	REF	**0.039**	REF	**0.023**
Pack-years							
N	1285	1971	9286	25	90	851	4078
P-value	REF	**<0.001**	**0.050**	REF	0.872	REF	**0.004**
mMRC score ≥2							
N	359	793	2393	128	518	851	4075
P-value	REF	**<0.001**	**<0.001**	REF	**0.003**	REF	**0.033**
Allergic disease history							
N	931	1161	7296	195	733	393	2104
P-value	REF	0.644	**<0.001**	REF	0.588	REF	0.365
Chronic bronchitis							
N	366	820	2445	195	733	842	3731
P-value	REF	**0.017**	0.177	REF	**0.015**	REF	0.446
Emphysema							
N	-	-	-	-	-	828	3523
P-value	REF	NA	NA	REF	NA	REF	0.534
FEV_1 (%) predicted							
N	1197	1840	8627	195	730	857	4088
P-value	REF	**<0.001**	**<0.001**	REF	**<0.001**	REF	0.675
FVC (%) predicted							
N	1197	1840	8627	195	730	857	4088
P-value	REF	0.228	**<0.001**	REF	**<0.001**	REF	0.987
FEV_1/FVC (%)							
N	1298	1985	9760	195	733	857	4088
P-value	REF	**<0.001**	0.057	REF	**<0.001**	REF	0.061
Peripheral blood WBC (10^9 cells/L)							
N	1018	1546	7988	66	209	471	1864
P-value	REF	0.065	0.515	REF	**0.024**	REF	0.867
BEC above 300 cells/µL							
N	895	1124	7055	66	209	459	1864
P-value	REF	**<0.001**	**<0.001**	REF	0.112	REF	0.347
Serum CRP (mg/dL)							
N	-	-	-	67	211	21	281
P-value	REF	NA	NA	REF	0.814	REF	0.397
Serum IgE (IE/mL)							
N	REF	NA	NA	66	209	21	275
P-value	REF	NA	NA	REF	0.760	REF	0.479

AO = asthma with airflow obstruction, BEC = blood eosinophil count, CRP = C-reactive protein, IgE = immunoglobulin E, mMRC = modified Medical Research Council Dyspnea, NA = not applicable, WBC = white blood cell count. AO was defined as ever asthma with airflow obstruction (pre/post BD FEV_1/FVC<0.70) in population- and clinic-based cohorts, respectively. Asthma-only was defined as ever asthma without airflow obstruction and COPD-only was defined as airflow obstruction without a history of asthma. Underweight = BMI < 18.5, normal weight = BMI ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 30. Missing variables per cohort: RS and DTR: allergic disease, emphysema, BEC, CRP, IgE; LifeLines: chronic bronchitis, emphysema, mMRC, WBC, CRP, IgE; OLIN: pack-years, chronic bronchitis, WBC, CRP, BEC, IgE; U-BIOPRED: emphysema; COSYCONET: WBC, CRP, BEC, IgE; ECLIPSE: allergic disease history, IgE; PAC-COPD: no missing variables; Urban Training: chronic bronchitis, emphysema, allergic disease history; WBC, CRP, BEC, IgE. Significant differences (P<0.05) with AO are indicated in bold.

Table S4. Meta-analyzed characteristics of LLN-defined AO.

	Population-based cohorts			Asthma-based cohorts		COPD-based cohorts	
	AO	**Asthma-only**	**COPD-only**	**AO**	**Asthma-only**	**AO**	**COPD-only**
Characteristics							
Age (years), mean (95% CI)	62.7 (58.7-66.7)	63.2 (57.3-69.2)	63.6 (57.8-69.4)	60.3 (57.6-63.0)	59.1 (56.9-61.4)	64.7 (62.9-66.6)	**66.8 (64.5-69.1)**
Female, prop (95% CI)	60.4 (52.4-68.4)	60.8 (54.6-66.9)	51.5 (45.3-57.8)	48.0 (40.1-55.9)	**58.2 (54.7-61.6)**	30.7 (8.1-53.3)	**22.9 (9.0-36.7)**
BMI (kg/m^2), mean (95% CI)	26.5 (26.2-26.8)	27.6 (25.9-29.3)	**25.9 (25.6-26.2)**	26.2 (23.7-28.8)	**28.2 (26.1-30.3)**	27.4 (25.6-29.2)	27.2 (26.2-28.2)
Underweight, prop (95% CI)	0.9 (0.2-1.6)	0.3 (0.0-0.7)	1.6 (0.1-3.1)	0.7 (0.0-2.3)	1.1 (0.0-2.6)	3.6 (1.4-5.8)	2.9 (1.1-4.7)
Normal weight, prop (95% CI)	38.1 (29.5-46.7)	32.2 (21.2-43.1)	42.1 (36.8-47.5)	47.0 (24.9-69.2)	**27.6 (21.7-33.6)**	30.5 (15.2-45.8)	31.1 (22.6-39.7)
Overweight, prop (95% CI)	42.9 (33.1-52.6)	42.9 (40.2-45.6)	42.0 (35.0-49.0)	36.3 (28.5-44.1)	41.2 (31.4-51.1)	36.8 (33.5-40.2)	37.2 (35.5-38.9)
Obese, prop (95% CI)	17.1 (14.4-19.7)	25.0 (11.2-38.7)	**13.5 (12.3-14.6)**	15.6 (0.0-37.3)	**30.3 (13.0-47.7)**	22.4 (17.3-27.4)	27.4 (19.5-35.3)
Never smoker, prop (95% CI)	26.7 (17.6-35.8)	31.1 (20.4-41.9)	**15.2 (9.3-21.2)**	11.5 (4.6-18.3)	25.1 (0.0-58.2)	6.3 (0.0-14.8)	1.5 (0.0-3.3)
Former smoker, prop (95% CI)	51.7 (48.2-55.3)	52.9 (47.0-58.9)	45.7 (35.5-55.9)	34.8 (13.2-56.4)	36.8 (33.4-40.2)	65.4 (62.0-68.7)	68.5 (64.7-72.3)
Current smoker, prop (95% CI)	22.8 (11.7-34.0)	15.7 (3.6-27.9)	**39.1 (25.6-52.6)**	53.8 (25.4-82.2)	**38.6 (2.5-74.7)**	23.5 (5.4-41.6)	29.9 (24.6-35.1)
Pack-years, mean (95% CI)	23.1 (16.6-29.6)	19.7 (13.0-26.3)	**29.9 (25.6-34.2)**	13.9 (7.9-20.0)	18.3 (14.4-22.2)	46.3 (34.0-58.5)	**57.1 (47.5-66.8)**
mMRC score ≥2, prop (95% CI)	41.9 (34.7-49.1)	**25.2 (4.4-46.0)**	**22.1 (5.3-39.0)**	60.4 (50.9-69.9)	**39.8 (35.7-43.9)**	63.2 (36.0-90.4)	59.9 (34.0-85.7)
Allergic disease history, prop (95% CI)	78.9	**40.7**	**40.8**	67.8	73.7	34.4	29.7

	(75.5-82.2)	**(38.0-43.4)**	**(39.1-42.5)**	(43.3-92.2)	(62.2-85.1)	(0.0-75.8)	(23.6-35.8)
Chronic bronchitis, prop (95% CI)	28.1 (11.5-44.6)	**13.9 (10.1-17.7)**	16.7 (14.1-19.3)	30.6 (0.0-63.7)	24.0 (0.7-47.3)	54.4 (30.2-78.5)	53.4 (35.1-71.6)
Emphysema, prop (95% CI)	-	-	-	-	-	52.1 (2.5-100.0)	47.3 (6.2-88.3)
Spirometry							
FEV_1 (%) predicted, mean (95% CI)	67.5 (58.1-76.8)	**88.7 (81.5-95.9)**	**71.8 (61.7-82.0)**	53.0 (41.7-64.2)	**78.9 (63.4-94.5)**	49.6 (43.0-56.3)	49.3 (45.4-53.2)
FVC (%) predicted, mean (95% CI)	90.1 (79.7-100.6)	**97.6 (90.8-104.4)**	**94.1 (84.1-104.2)**	77.2 (73.7-80.8)	**88.7 (83.2-94.1)**	77.6 (72.4-82.8)	76.9 (73.9-79.8)
FEV_1/FVC (%), mean (95% CI)	57.6 (54.1-61.0)	**70.6 (61.4-79.8)**	58.2 (55.0-61.4)	53.0 (38.7-67.3)	**71.7 (56.3-87.1)**	49.3 (44.5-54.1)	48.7 (44.7-52.8)
Biomarkers							
Peripheral blood WBC (10^9 cells/L), mean (95% CI)	6.7 (5.8-7.7)	6.7 (5.8-7.7)	7.3 (5.3-9.3)	8.3 (7.6-9.0)	7.7 (7.3-8.0)	7.9 (7.7-8.1)	7.7 (7.3-8.2)
BEC above 300 cells/μL, prop (95% CI)	28.2 (24.4-31.9)	**16.0 (14.0-18.1)**	**16.0 (14.7-17.3)**	52.9 (39.2-66.6)	**35.3 (29.0-41.5)**	23.7 (19.7-27.7)	18.8 (13.0-24.7)
Serum CRP (mg/dL), median (IQR)*	-	-	-	2.2 (3.5)	2.1 (3.8)	4.3 (5.3)	3.7 (5.2)
Serum IgE (IE/mL), median (IQR)*	-	-	-	116 (292)	110 (221)	83 (208)	54 (119)

AO = asthma with airflow obstruction, BEC = blood eosinophil counts, CRP = C-reactive protein, IgE = immunoglobulin E, mMRC = modified Medical Research Council Dyspnea, WBC = white blood cell count. AO was defined as a physician-diagnosis of asthma (ever) with airflow obstruction (pre/post BD FEV_1/FVC<LLN) in population- and clinic-based cohorts, respectively. Asthma-only was defined as ever asthma without airflow obstruction and COPD-only was defined as airflow obstruction without a history of asthma. Underweight = BMI < 18.5, normal weight = BMI ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 30. *Summary statistics of individual cohorts were meta-analyzed, except for IgE and CRP for which only single-study data was available. Missing variables per cohort: Rotterdam Study and DTR: allergic disease, emphysema, BEC, CRP, IgE; LifeLines: chronic bronchitis, emphysema, mMRC, WBC, CRP, IgE; OLIN: pack-years, chronic bronchitis, WBC, CRP, BEC, IgE, emphysema; U-BIOPRED: emphysema; COSYCONET: WBC, CRP, BEC, IgE; ECLIPSE: allergic disease history, CRP, IgE; PAC-COPD: no missing variables; Urban Training: chronic bronchitis, emphysema, allergic disease history; WBC, CRP, BEC, IgE. Significant differences (P<0.05) with AO are indicated in bold.

Table S5. Characteristics of AO compared to normal group in the Rotterdam Study.

	FR-based obstruction		LLN-based obstruction	
	Normal (n = 4132)	**AO (n = 106)**	**Normal (n = 4613)**	**AO (n = 53)**
Age (years), mean (SD)	68.8 (8.8)	67.8 (8.0)	69.2 (8.9)	**65.7 (8.1)**
Female, n (%)	2352 (56.9)	63 (59.4)	2540 (55.1)	**38 (71.7)**
BMI (kg/m^2), mean (SD)	27.7 (4.3)	26.9 (5.1)	27.5 (4.3)	**26.2 (4.6)**
Underweight, n (%)	13 (0.3)	1 (0.9)	16 (0.3)	1 (1.9)
Normal weight, n (%)	1102 (26.7)	**46 (43.4)**	1268 (27.5)	**27 (50.9)**
Overweight, n (%)	2025 (49.0)	**37 (34.9)**	2257 (48.9)	**16 (30.2)**
Obese, n (%)	991 (24.0)	**22 (20.8)**	1071 (23.2)	9 (17.0)
Never smoker, n (%)	1521 (36.8)	**34 (32.1)**	1626 (35.2)	**16 (30.2)**
Former smoker, n (%)	2209 (53.5)	**59 (55.7)**	2487 (53.9)	**26 (49.1)**
Current smoker, n ()	401 (9.7)	**13 (12.3)**	500 (10.8)	**11 (20.8)**
Pack-years, mean (SD)	12.1 (18.0)	**18.0 (23.4)**	13.3 (19.1)	18.7 (25.9)
mMRC score ≥2, n (%)	340 (8.9)	**47 (48.0)**	415 (9.8)	**22 (45.8)**
Chronic bronchitis, n (%)	151 (3.7)	**16 (15.2)**	196 (4.3)	**10 (19.2)**
FEV_1 (%) predicted, mean (SD)	101.7 (15.7)	**74.2 (16.7)**	99.9 (16.5)	**66.0 (14.1)**
FVC (%) predicted, mean (SD)	99.5 (15.1)	**89.6 (16.0)**	99.1 (15.4)	**85.5 (14.4)**
FEV_1/FVC (%), mean (SD)	78.7 (4.8)	**63.5 (6.1)**	77.5 (5.8)	**59.6 (6.4)**
Peripheral blood WBC (10^9 cells/L), mean (SD)	7.0 (1.9)	**7.3 (1.5)**	7.0 (1.9)	**7.2 (1.4)**

AO = asthma with airflow obstruction; FR = fixed ratio (FEV_1/FVC < 0.7); LLN = lower limit of normal (FEV_1/FVC < LLN); normal = no asthma nor COPD. Underweight = BMI < 18.5, normal weight = BMI ≥ 18.5 and < 25, overweight = BMI ≥ 25 and < 30, obese = BMI ≥ 30. Significant differences (P<0.05) indicated in bold.

Table S6. Exacerbation rate in last year of AO in clinic-based cohorts.

ECLIPSE	**FR-based obstruction**		**LLN-based obstruction**	
	AO vs COPD-only OR (95%CI)	P-value	AO vs COPD-only OR (95%CI)	P-value
1 or more moderate exacerbations	1.76 (1.44-2.15)	**<0.01**	1.71 (1.34-2.18)	**<0.01**

U-BIOPRED	**FR-based obstruction**		**LLN-based obstruction**	
	AO vs asthma-only OR (95%CI)	P-value	AO vs asthma-only OR (95%CI)	P-value
1 or more moderate exacerbations	2.05 (1.01-4.17)	**0.05**	1.60 (0.75-3.42)	0.23

COSYCONET	**FR-based obstruction**			**LLN-based obstruction**		
	AO n (%)	COPD-only n (%)	P-value	AO n (%)	COPD-only n (%)	P-value
1 or more moderate exacerbations	148 (39.9%)	495 (27.3%)	**<0.01**	130 (41.3%)	441 (28.4%)	**<0.01**
1 or more severe exacerbations	85 (22.9%)	357 (19.7%)	**<0.01**	78 (24.8%)	326 (21.0%)	0.16

AO = asthma with airflow obstruction; FR = fixed ratio (FEV1/FVC < 0.7); LLN = lower limit of normal (FEV1/FVC < LLN); OR = odds ratio. Odds ratios were adjusted for age, sex, smoking status, and BMI.

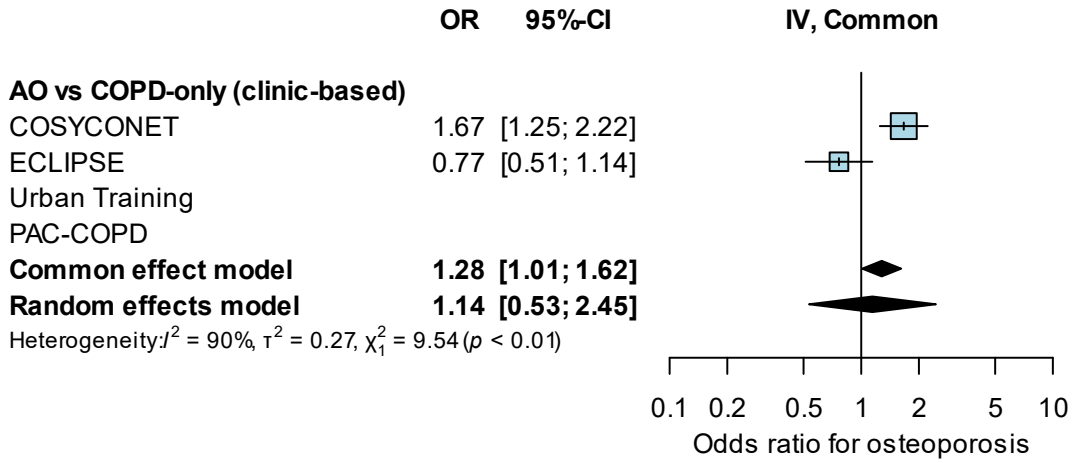

Figure S2.1. Meta-analyzed (adjusted odds) of osteoporosis.

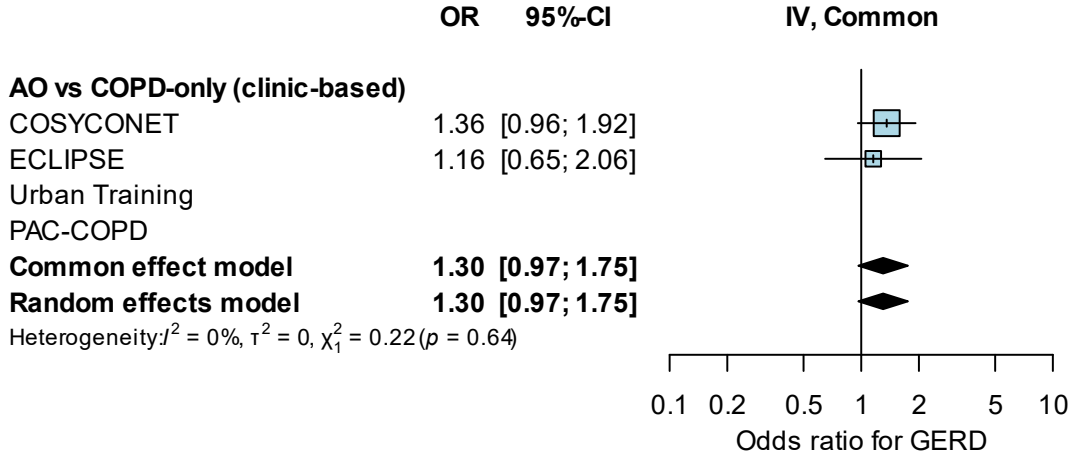

Figure S2.2. Meta-analyzed (adjusted odds) of gastro-esophageal reflux disease.

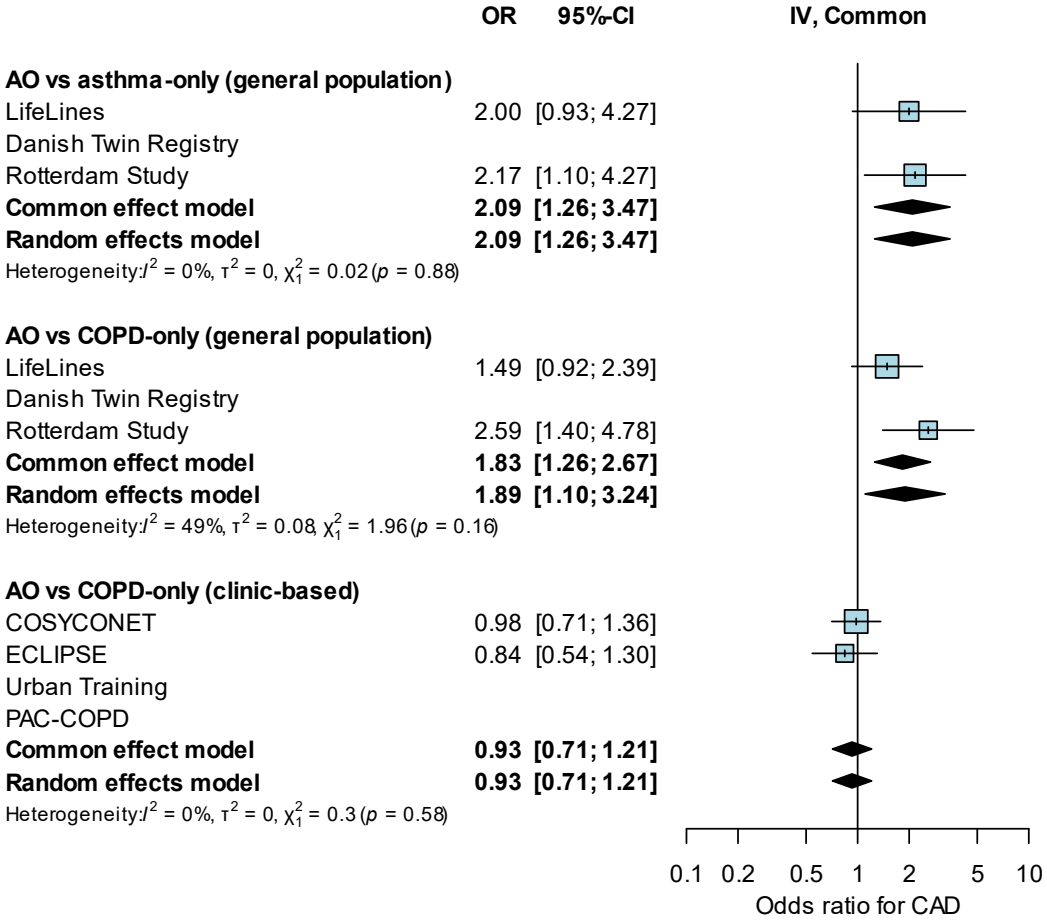

Figure S2.3. Meta-analyzed (adjusted odds) of coronary artery disease.

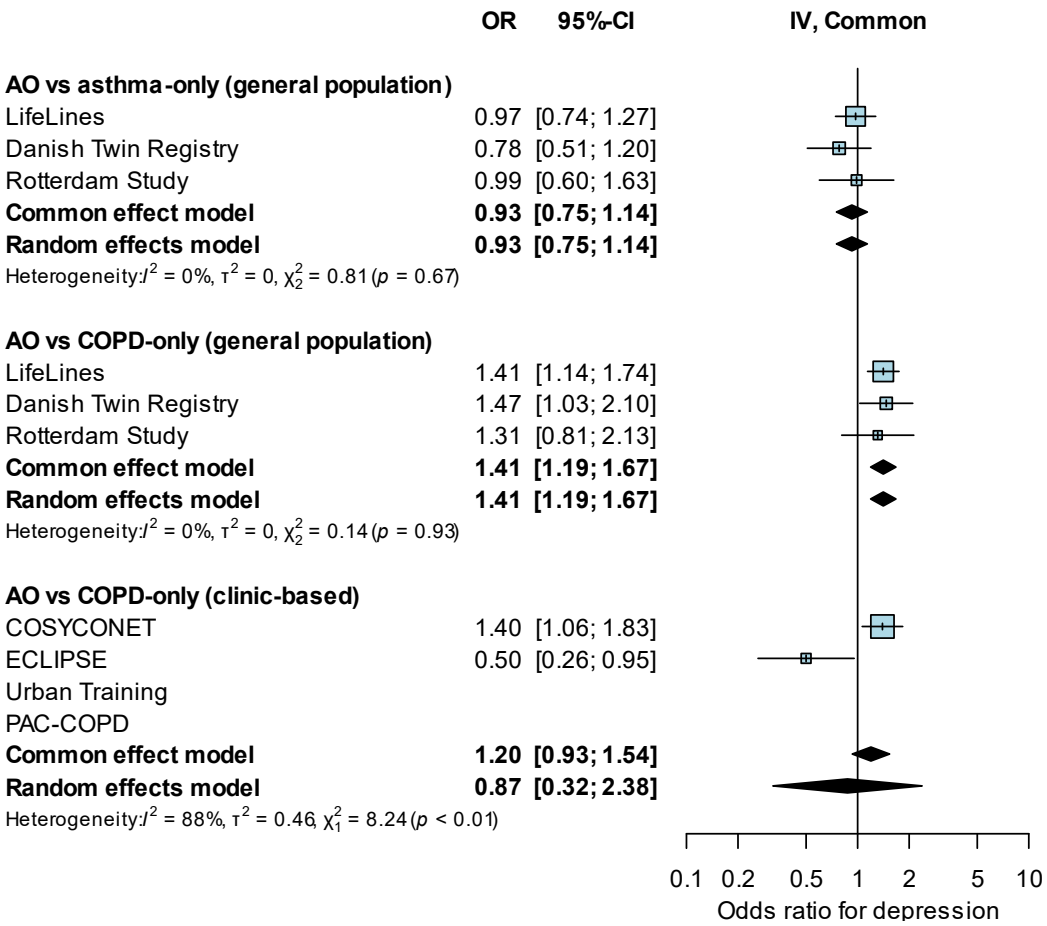

Figure S2.4. Meta-analyzed (adjusted odds) of depression.

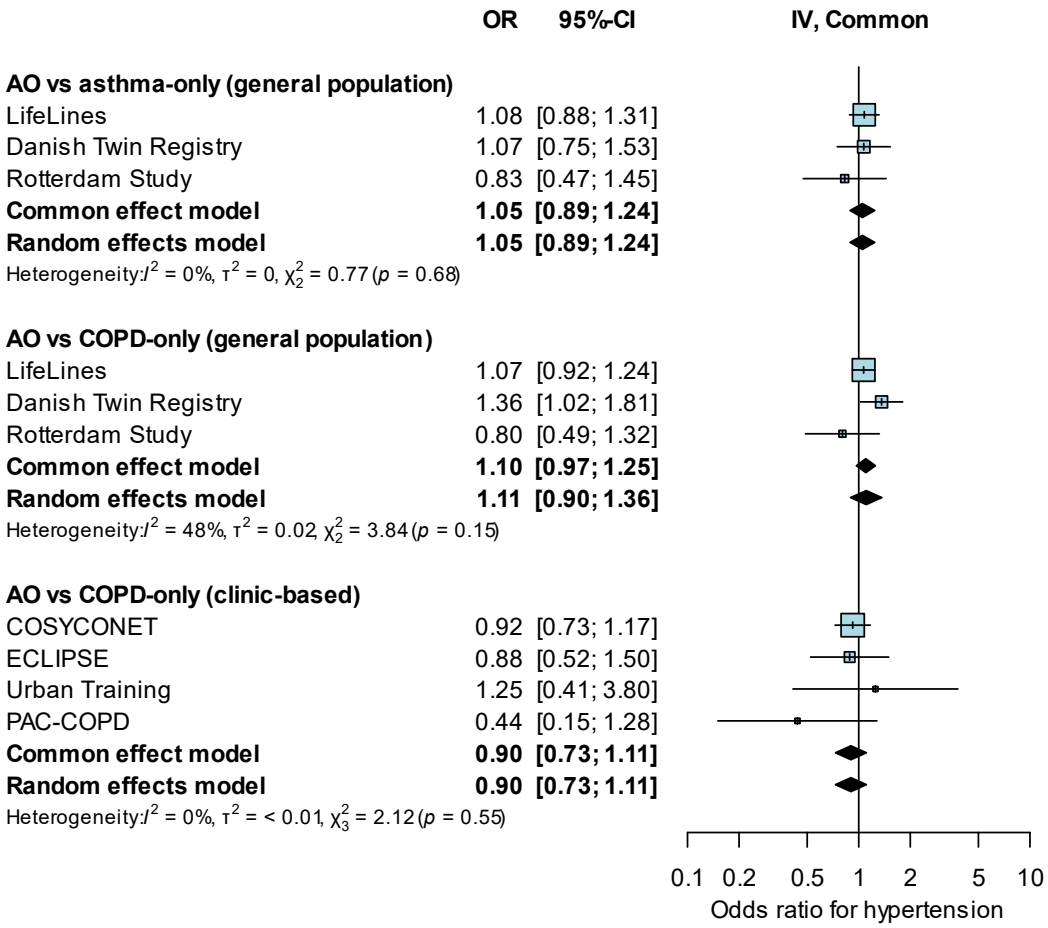

Figure S2.5. Meta-analyzed (adjusted odds) of hypertension.

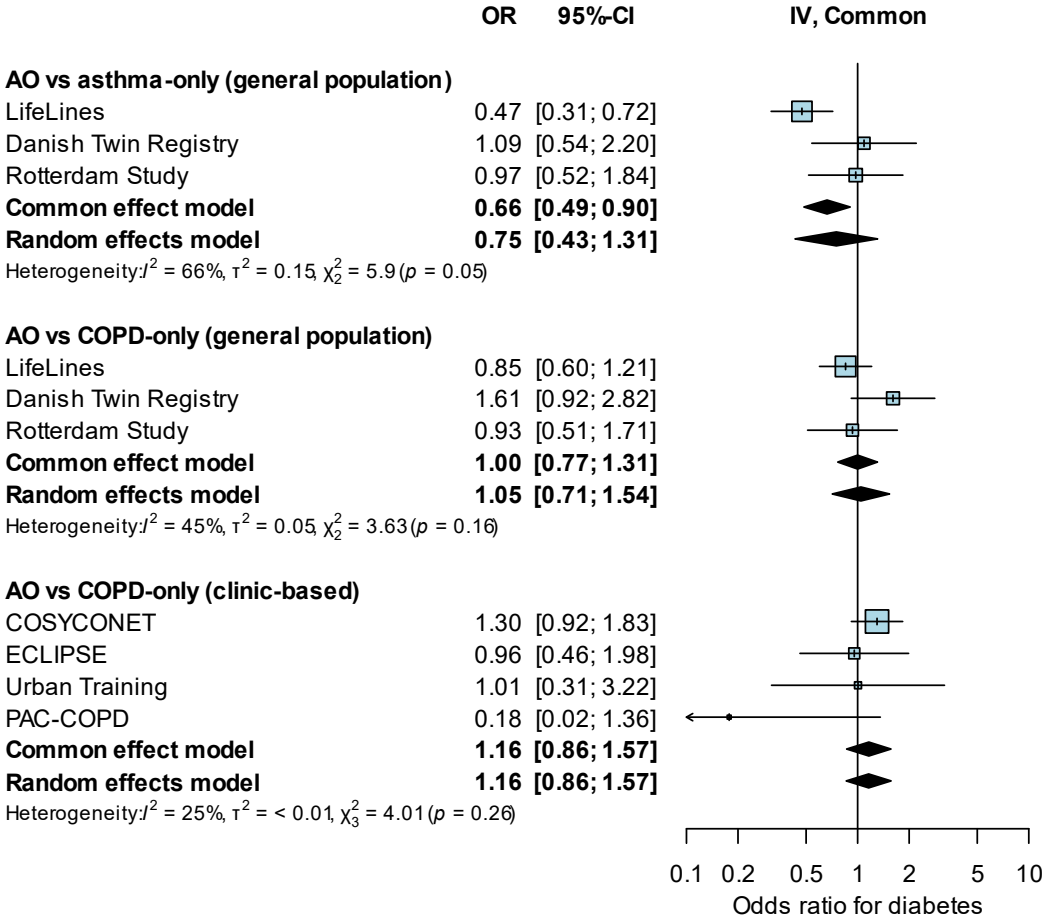

Figure S2.6. Meta-analyzed (adjusted odds) of diabetes mellitus type 2.

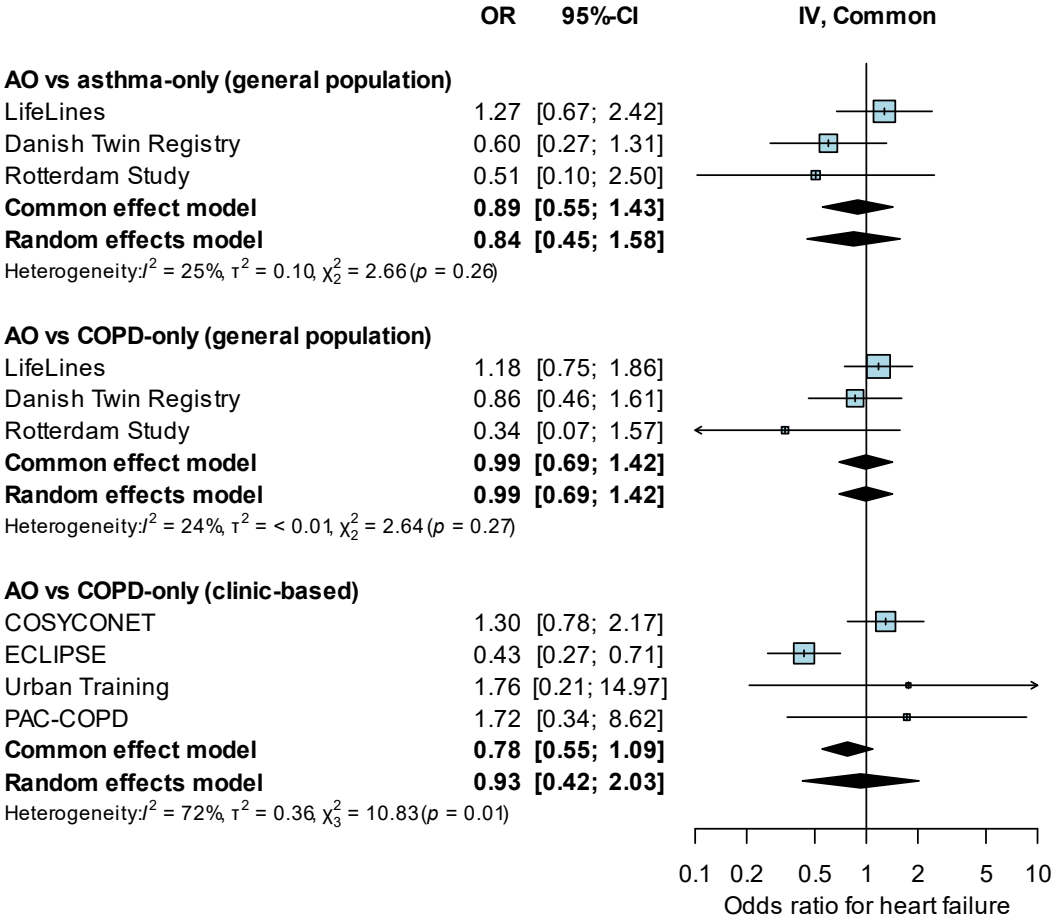

Figure S2.7. Meta-analyzed (adjusted odds) of heart failure.

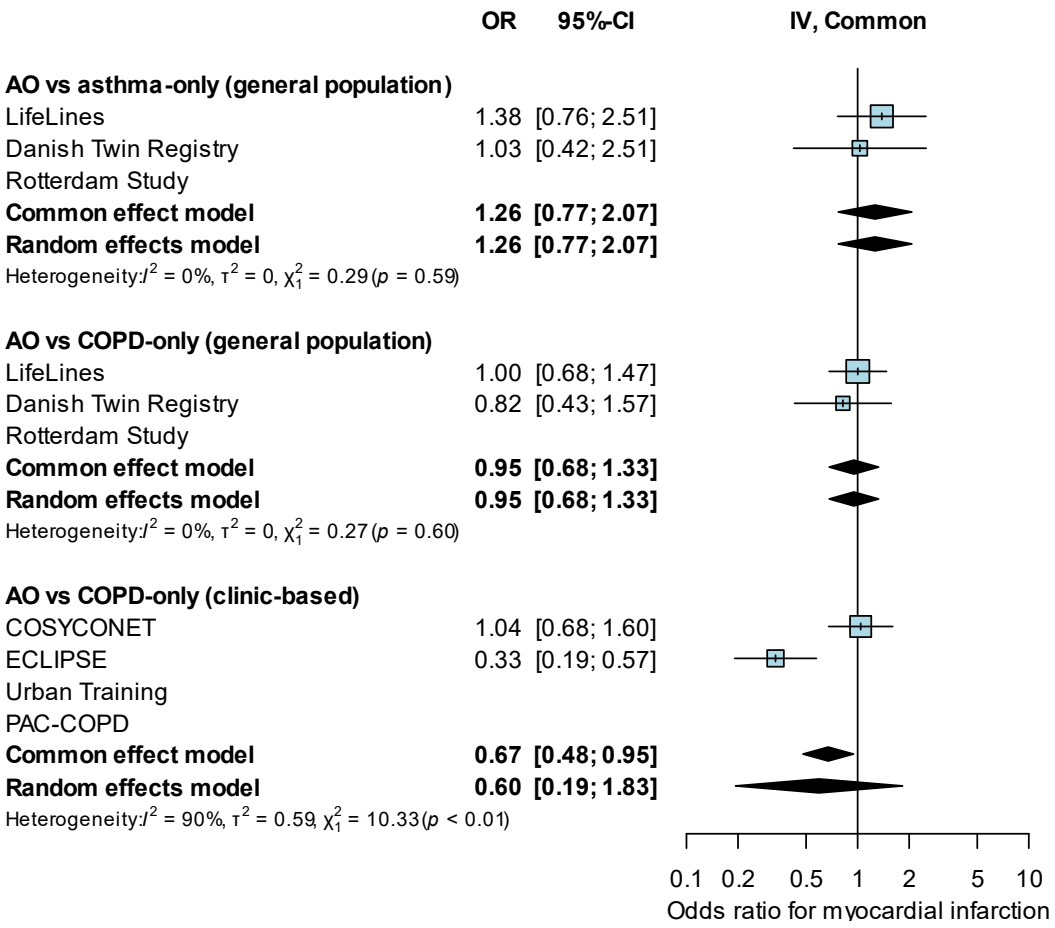

Figure S2.8. Meta-analyzed (adjusted odds) of myocardial infarction history.

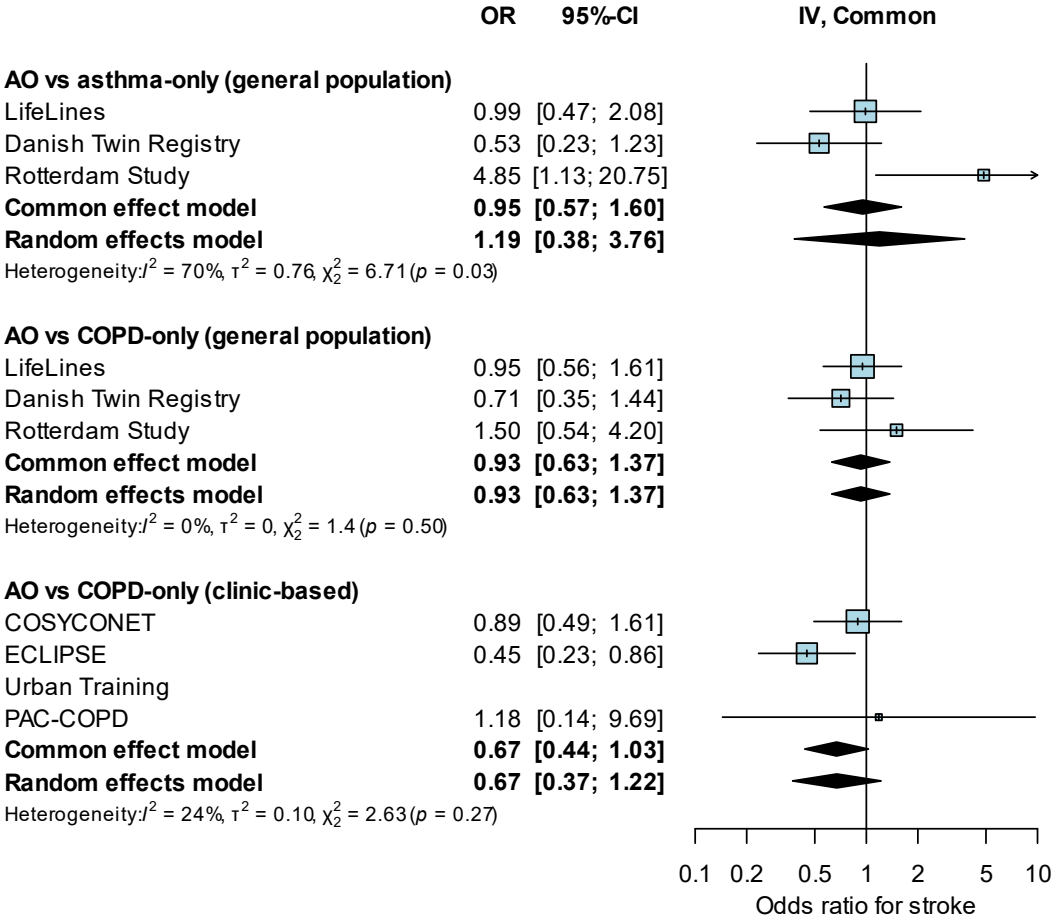

Figure S2.9. Meta-analyzed (adjusted odds) of stroke history.

Table S7. Adjusted odds ratio for comorbidities which could not be meta-analyzed.

	AO vs asthma-only		AO vs COPD-only	
	OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**
DTR (population-based cohort)				
Osteoporosis	1.22 (0.67-2.21)	0.52	**2.30 (1.43-3.72)**	**<0.01**
GERD	0.83 (0.48-1.44)	0.50	**1.68 (1.06-2.68)**	**0.03**
U-BIOPRED (clinic-based cohort)				
Osteoporosis	1.38 (0.74-2.60)	0.31	NA	NA
GERD	0.80 (0.45-1.43)	0.45	NA	NA
CAD	2.03 (0.61-6.71)	0.25	NA	NA
Depression	0.88 (0.28-2.81)	0.84	NA	NA
Hypertension	0.76 (0.41-1.41)	0.39	NA	NA
Diabetes	0.92 (0.37-2.26)	0.86	NA	NA

CAD = coronary artery disease; DTR = the Danish Twin Registry; GERD = gastro-esophageal reflux disease. Osteoporosis and GERD were not meta-analyzed as only data from DTR was available for population-based cohorts. Comorbidities in asthma-based cohorts were not meta-analyzed as only data from U-BIOPRED was available. Logistic regression models adjusted for age, sex, smoking status, and body mass index. Significant differences (P<0.05) are indicated in bold.

Table S8. Comorbidities verified by examinations or validated in medical files in the Rotterdam Study.

	AO vs Asthma-only OR (95% CI)	AO vs COPD-only OR (95% CI)
Hypertension	0.83 (0.47-1.45)	0.80 (0.49-1.32)
Coronary artery disease	**2.17 (1.10-4.27)**	**2.59 (1.40-4.78)**
Heart failure	0.51 (0.10-2.50)	0.34 (0.07-1.57)
Stroke history	**4.85 (1.13-20.75)**	1.50 (0.54-4.20)
Depression	0.99 (0.60-1.63)	1.31 (0.81-2.13)

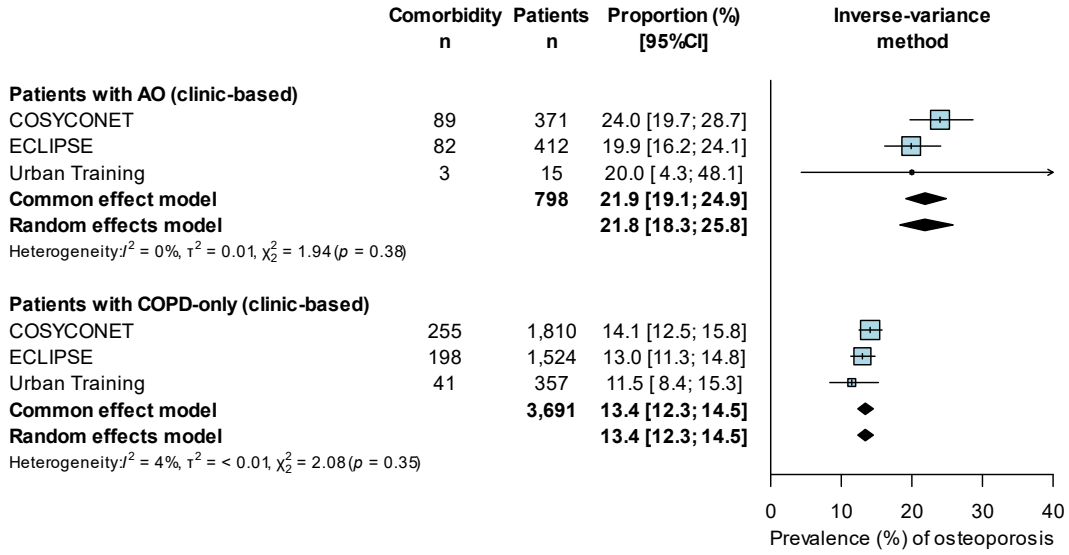

Figure S3.1. Meta-analyzed (prevalence) of osteoporosis.

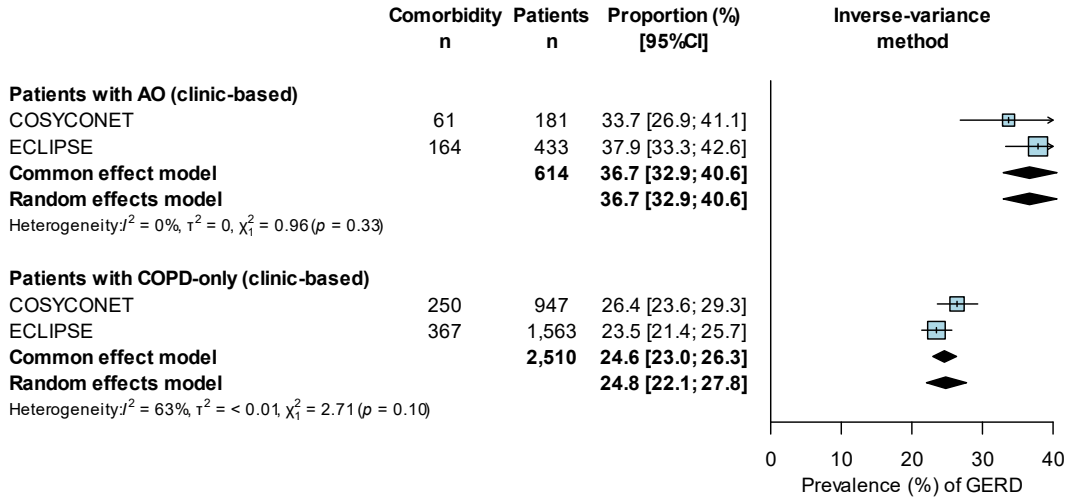

Figure S3.2. Meta-analyzed (prevalence) of gastro-esophageal reflux disease.

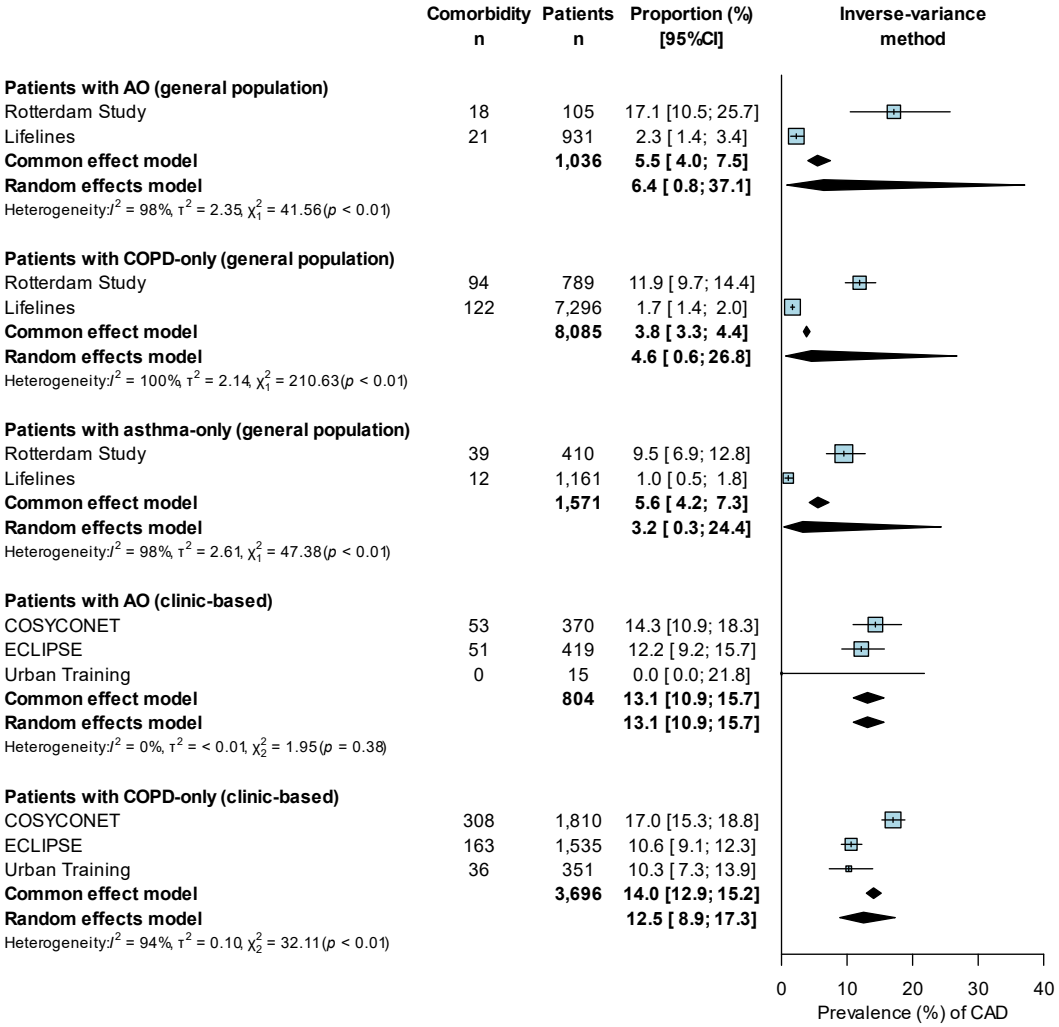

Figure S3.3. Meta-analyzed (prevalence) of coronary artery disease.

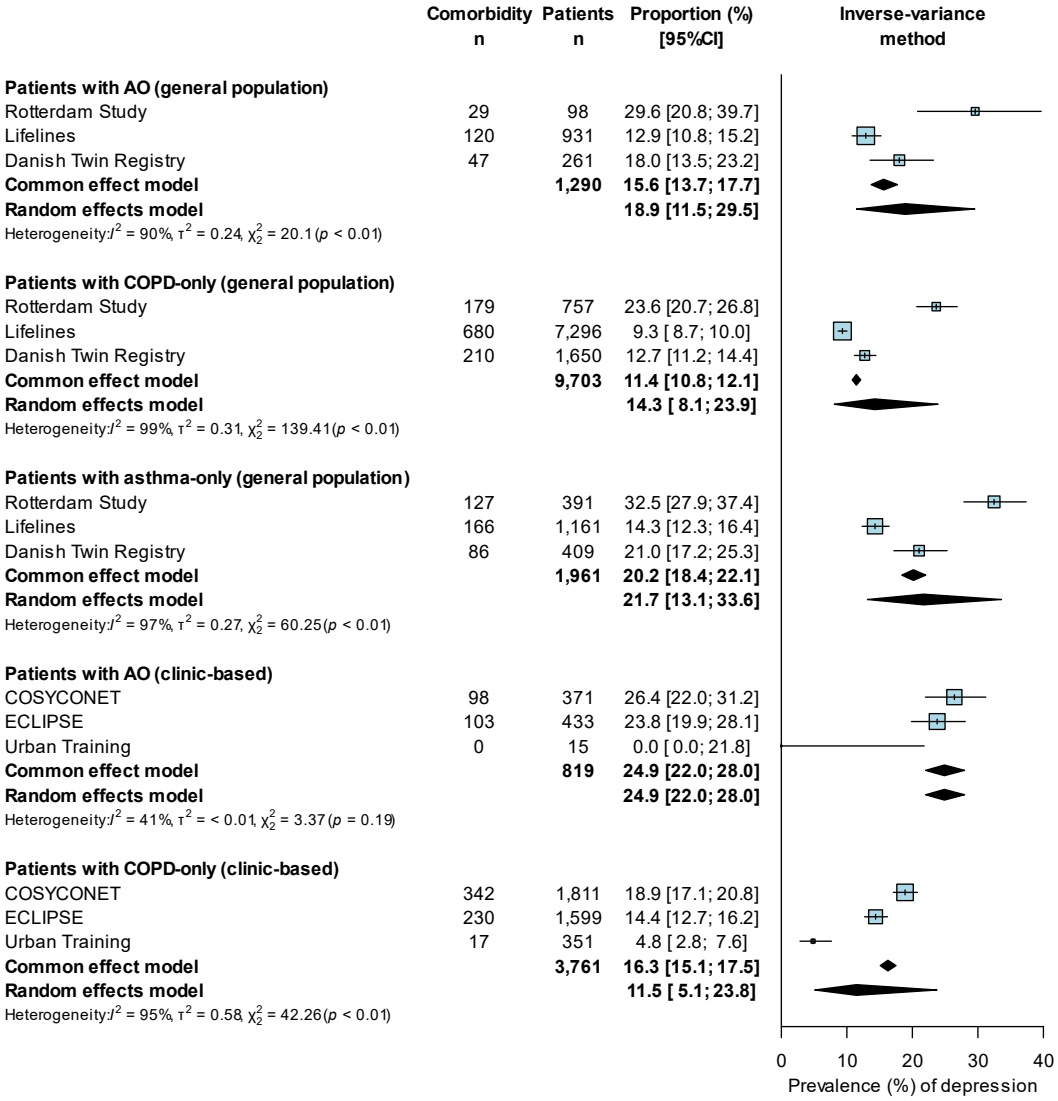

Figure S3.4. Meta-analyzed (prevalence) of depression.

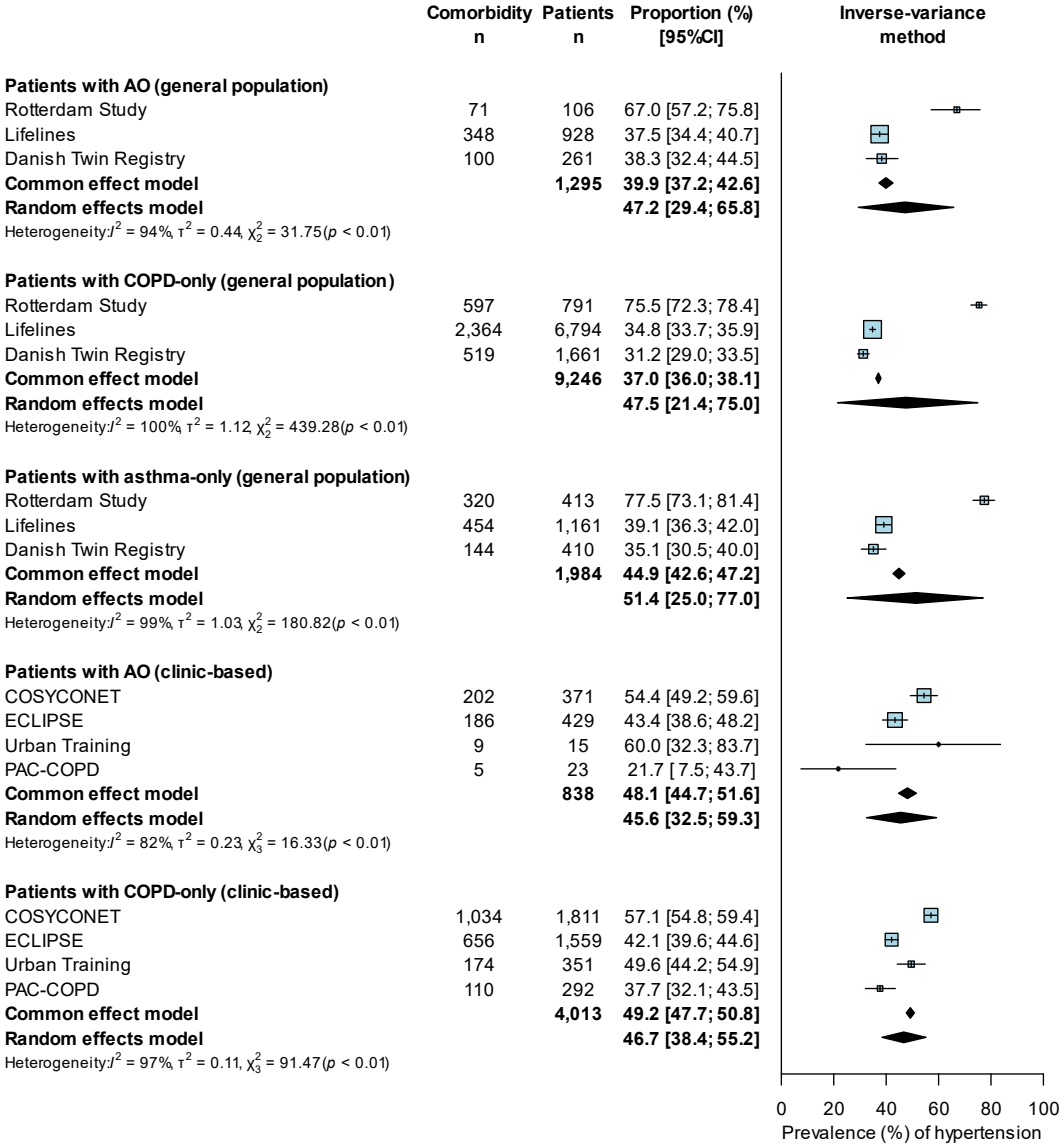

Figure S3.5. Meta-analyzed (prevalence) of hypertension.

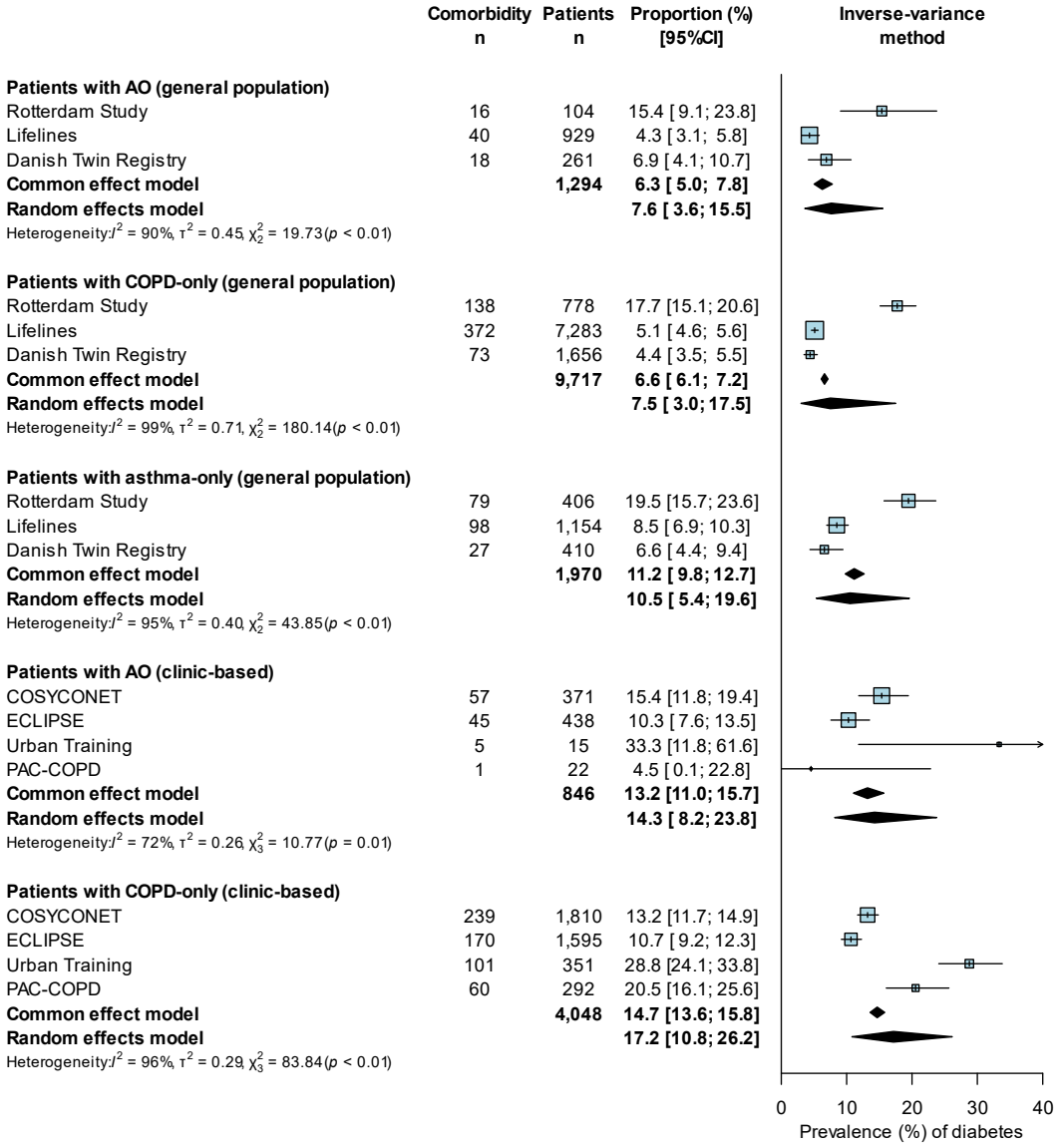

Figure S3.6. Meta-analyzed (prevalence) of diabetes mellitus type 2.

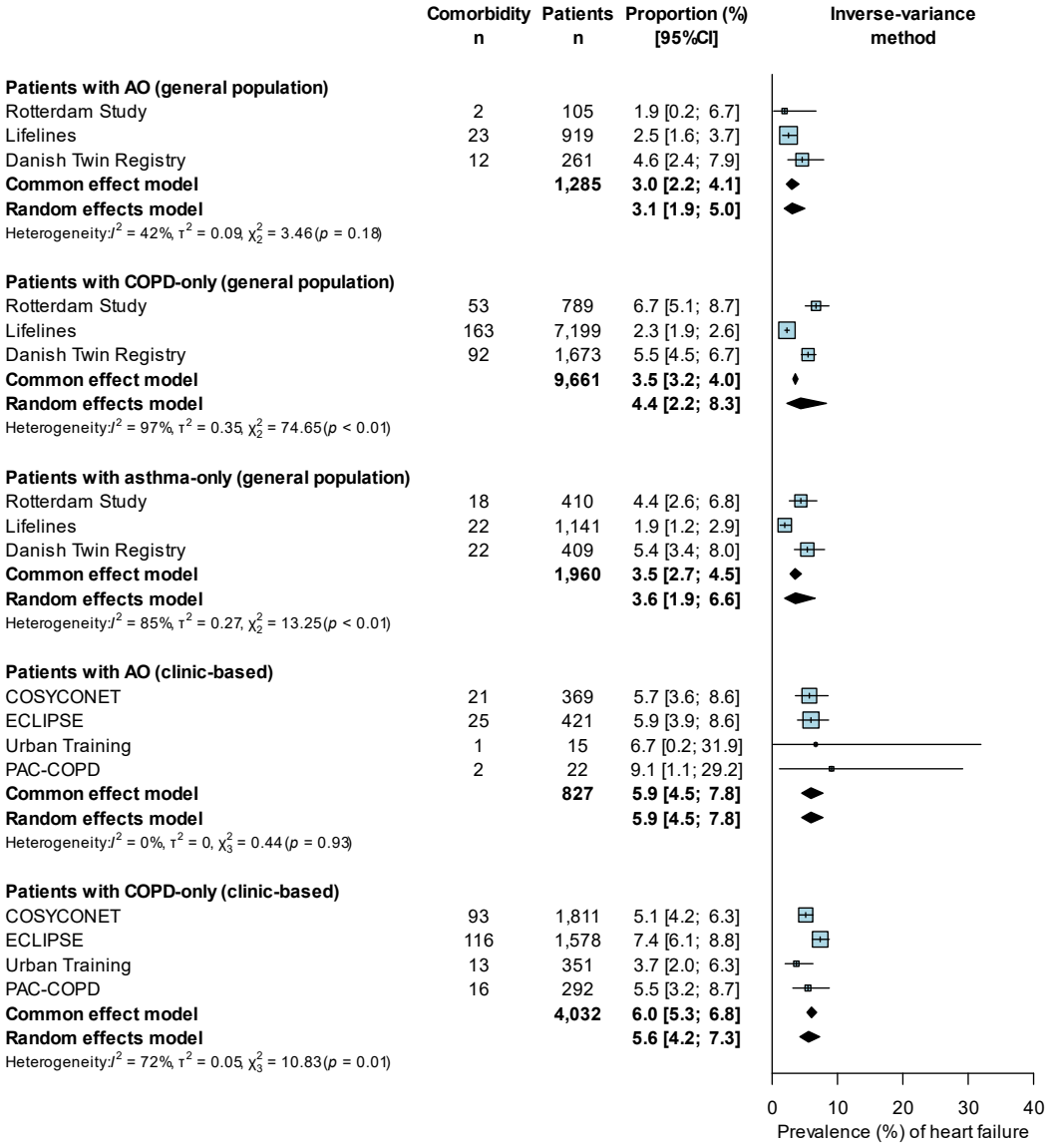

Figure S3.7. Meta-analyzed (prevalence) of heart failure.

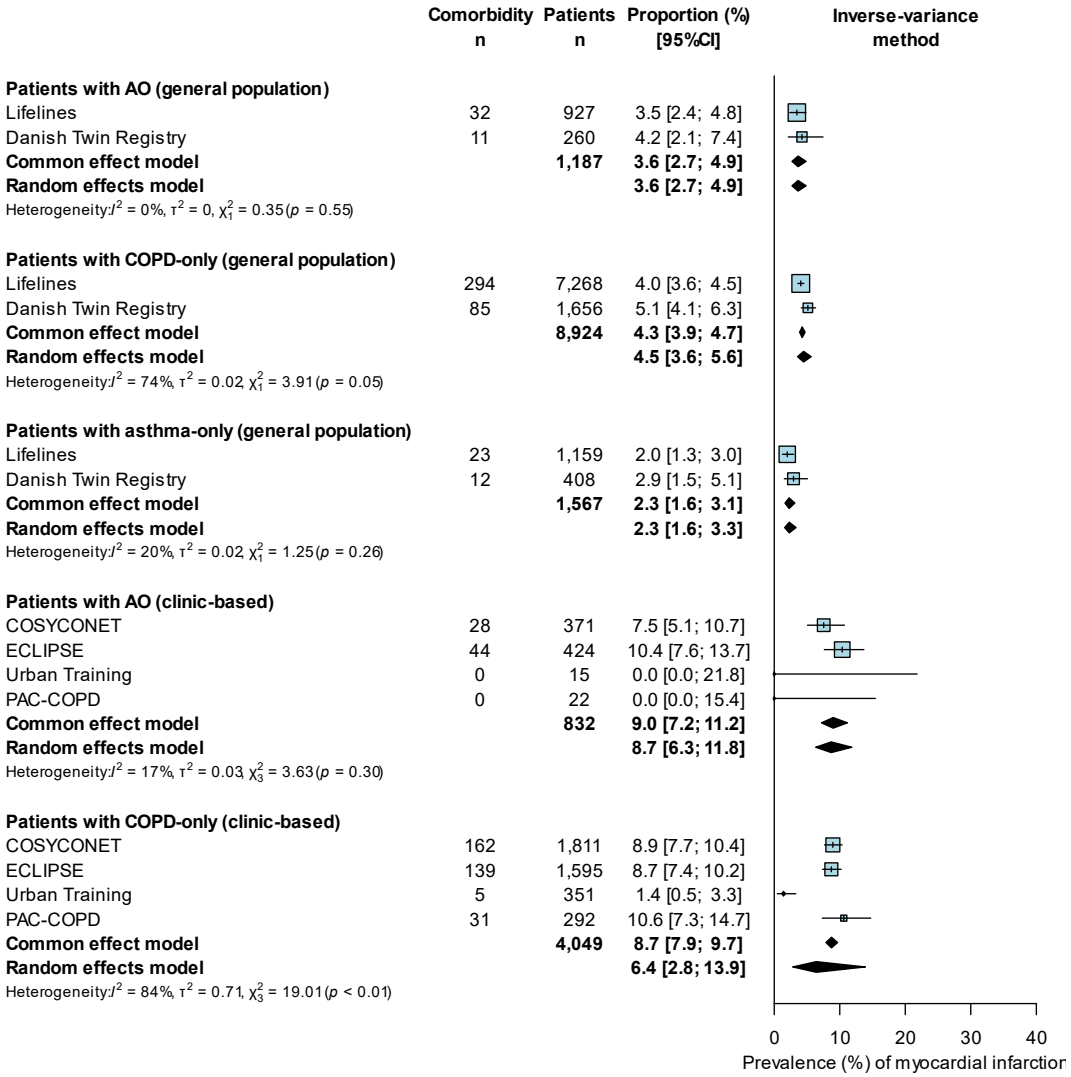

Figure S3.8. Meta-analyzed (prevalence) of myocardial infarction history.

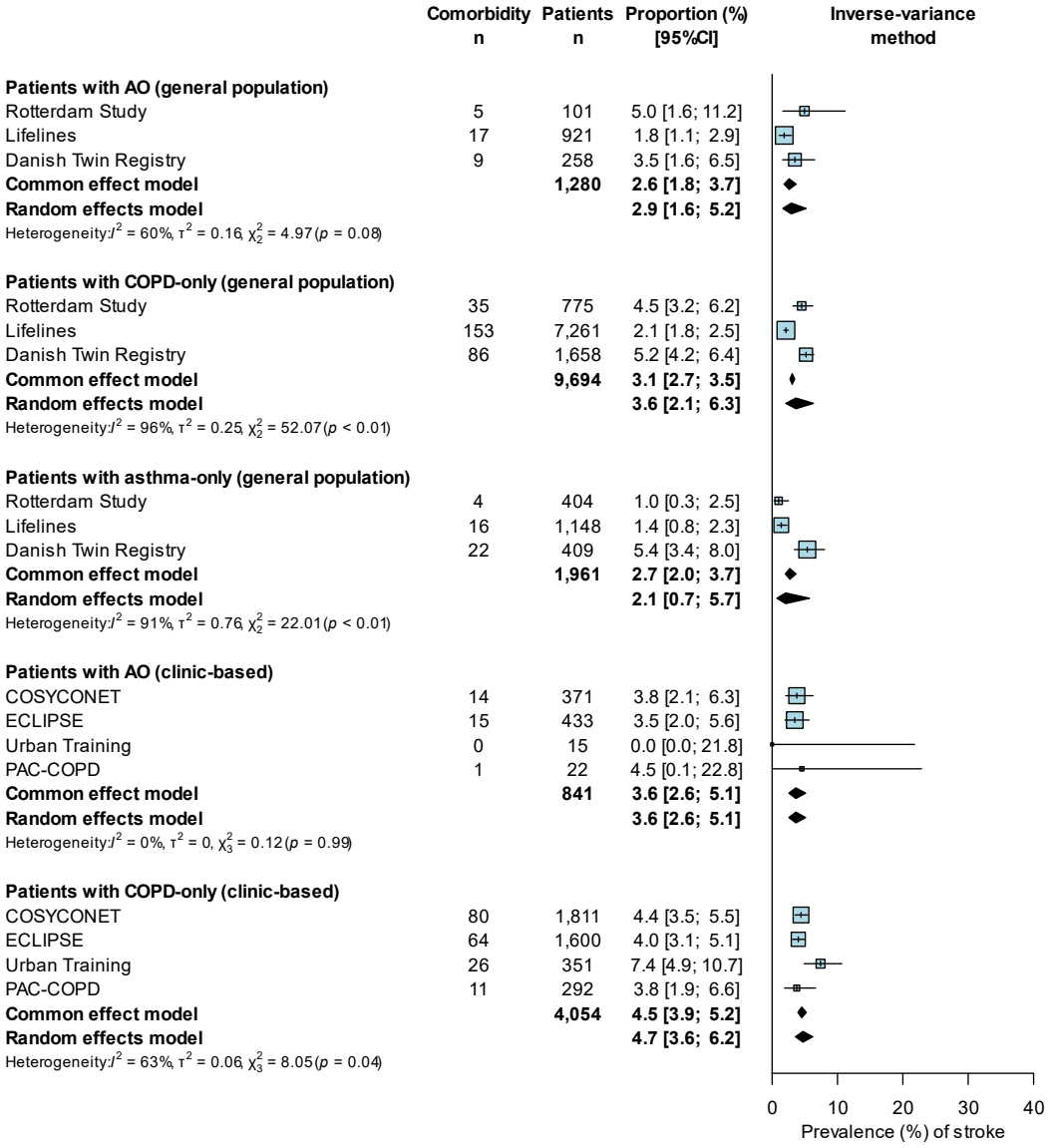

Figure S3.9. Meta-analyzed (prevalence) of stroke history.

Table S9. Prevalence of comorbidities which could not be meta-analyzed.

	AO	Asthma-only	COPD-only
	n (%)	n (%)	n (%)
DTR (population-based cohort)			
Osteoporosis	27 (10.3)	32 (7.8)	90 (5.4)
GERD	25 (9.7)	43 (10.5)	107 (6.5)
U-BIOPRED (clinic-based cohort)			
Osteoporosis	21 (31.3)	61 (28.4)	NA
GERD	27 (40.3)	104 (48.4)	NA
CAD	5 (7.5)	9 (4.2)	NA
Depression	4 (6.0)	19 (8.8)	NA
Hypertension	25 (37.3)	93 (43.3)	NA
Diabetes	7 (10.5)	27 (12.6)	NA

CAD = coronary artery disease; DTR = the Danish Twin Registry; GERD = gastro-esophageal reflux disease. Osteoporosis and GERD were not meta-analyzed as only data from DTR was available for population-based cohorts. Comorbidities in asthma-based cohorts were not meta-analyzed as only data from U-BIOPRED was available.

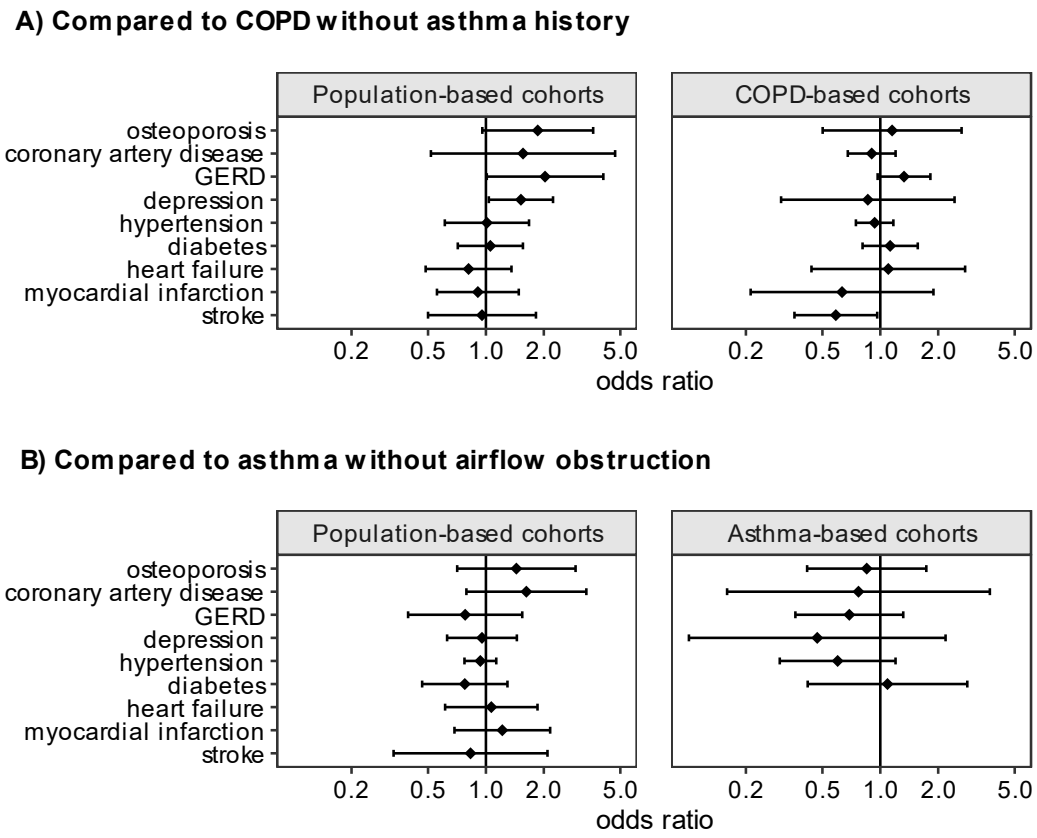

Figure S4. Meta-analysis of comorbidities of LLN-defined AO.

Comparison of asthma with LLN-defined airflow obstruction with COPD-only (A) and asthma-only (B). Odds ratios were adjusted for age, sex, smoking status, and body mass index.