



Asthma and its comorbidities in middle-aged and older adults; the Rotterdam Study

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ABSTRACT

Background: Little is known on the prevalence and characteristics of asthma in middle-aged and older adults, since previous studies mainly focused on children and young adults. Therefore, the aim was to investigate the prevalence of physician-diagnosed asthma and its comorbidities, in a population-based cohort of adults 45 years of age and over.

Methods: We identified participants with physician-diagnosed asthma in the Rotterdam Study; a prospective population-based cohort in the Netherlands. Pulmonary function measurements and comorbidities of the asthma cases were assessed at baseline and compared to those of the general population.

Results: Out of 14,621 participants (mean age 65.5 years; 59% women), 524 subjects (31.5% males) had physician-diagnosed asthma at study entry, implicating an asthma prevalence of 3.6% [95% Confidence Interval (CI) 3.3%–3.9%] (2.8% in males and 4.2% in females). Asthmatic subjects had a significantly higher prevalence of obesity and depressive symptoms (Odds Ratio [OR]: 2.02 [95% CI 1.66–2.47] and [OR]: 2.01 [95% CI 1.52–2.66] respectively). Longer duration of asthma and current smoking were associated with lower lung function in asthmatic subjects.

Conclusion: Four percent of middle-aged and older adults have physician-diagnosed asthma. These adult asthmatics suffer more frequently from obesity and depression than subjects without obstructive lung disease.

1. Introduction

Although asthma is a common airway disease in all age groups, middle-aged and older adults with asthma have been comparatively understudied [1]. Unjustly, because the burden of asthma is largest not only in children, but also in adults aged 55 years and over, as expressed in disability adjusted life years [2] or asthma related hospital admissions [3]. Recent studies on asthma-attacks underline the relevance of understanding asthma in middle-aged and older adults; attack rates, and associated costs, are reported to rise significantly in patients over 55 years of age [4–6].

Management and treatment of asthma follows a stepwise approach, usually guided by phenotyping. The Global Initiative for Asthma (GINA) [7] guidelines classically use physiologic and inflammatory

markers for phenotyping in all age groups, but recent studies in older asthma patients found concomitant morbidities and age at asthma onset also to be relevant for optimal treatment [1,8]. Onset of asthma in adulthood is not rare; an estimated one-third of all older patients with asthma develops the disease after the age of 40 [9,10], i.e. late-onset asthma, as opposed to early-onset asthma. Moreover, asthma in older adults differs from asthma in younger age groups with respect to genetic susceptibility, environmental exposures, pathogenic mechanisms, type of underlying airway inflammation, natural history of the disease, comorbidities, prognosis (i.e. low remission rates) and response to treatment [1,11–14].

However, most asthma research focuses on children and young adults, or selected asthma patients without comorbid conditions or more than 10 smoking pack-years. Population-based asthma research,

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on the other hand, is complicated by the fact that asthma is a dynamic disease without one uniform decisive test or (bio)marker [8]. Questionnaire data are often used, but these yield a risk of recall bias and misclassification of asthma when participants, for example, mistake anxiety-attacks for asthma [15].

In this study we describe the prevalence and the demographic and clinical characteristics of verified physician-diagnosed asthma in middle-aged and older adults on a population level. This information is needed [1,6] to better understand the late-onset asthma phenotype, and to study associations of asthma with other comorbidities in ageing populations [11,16].

2. Methods

2.1. Cohort and data collection

All subjects participated in the Rotterdam Study (RS), a prospective population-based cohort study that started in 1990 [17]. The objective of the Rotterdam Study is to investigate chronic diseases in an ageing population. From 1990 onwards, a total of 20744 inhabitants of Ommoord, a well-defined district of Rotterdam, the Netherlands were invited, in 3 subcohorts, based on age (initially over 55 years of age, and in the last cohort over 45 years) and postal code. 14,926 subjects (72%) accepted the invitation and were enrolled in the study. The first cohort (RS-I) comprised 7983 persons older than 55 years living in a suburb of the city of Rotterdam. In 2000, the original cohort (RS-I) was extended with a second cohort (RS-II; $n = 3,011$, aged ≥ 55 years), and in 2006 with a third cohort (RS-III; $n = 3,932$, aged ≥ 45 years). This resulted in a total study population of 14,926 men and women aged 45 years and over.

All participants underwent a standardized home interview on health status at baseline, including assessment of all drugs used in the week prior to the interview. This was followed by an extensive set of examinations performed at the research facility, including biometrics, laboratory analyses, spirometry, cerebral MRI, electrocardiogram, echocardiography, and other cardiovascular investigations [18]. Thereafter follow-up surveys and examinations have been conducted every 4–5 years.

The Rotterdam Study was approved by the Medical Ethics Committee and by the Netherlands Ministry of Health [18]. All participants in the current study provided written informed consent to participate in the study and to access their medical files.

2.2. Asthma case definition

Asthma cases were defined as participants with a physician's diagnosis of asthma reported in their medical file. Asthma cases were identified independently by two researchers (LL and EdR), and in case of discordance a senior respiratory physician finalized the validation (GB). Inter-agreement rate was 99%.

The identification of subjects with a diagnosis of asthma consisted of two steps; first, case finding, and second case validation. The case finding phase bundled all participants with either: ever asthma and/or respiratory complaints in the questionnaire, the use of respiratory medication, an obstructive pulmonary function test, asthma as reported in the patient's medical file, hospital admissions for asthma, or a death record that reported asthma.

Next, the medical files of all these possible asthma cases were systematically reviewed to search for asthma as diagnosed by a physician. Upon validation, asthma was classified as definite, probable and possible. Further information on the definition of asthma is provided in Table 1. Patients diagnosed with both asthma and Chronic obstructive pulmonary disease (COPD) were classified as an Asthma and COPD Overlap (ACO) case. Additional information in the files from the treating physician (e.g. specification of the allergic component of the asthma etc.) was reported.

Table 1

Validation and categorization of asthma subjects. Asthma symptoms according to GINA: “wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity” [8] * significant reversibility conform the GINA guidelines [8] #COPD was defined as an obstructive spirometry and/or physician diagnosed COPD; and no asthma diagnosis.

CRITERIA	
DEFINITE ASTHMA	diagnosis of asthma by pulmonary physician/allergist (as evidenced in the medical files) OR General Practitioner (GP) diagnosed asthma with ≥ 2 out of 3 criteria (as described in the file): - ≥ 2 episodes of asthma symptoms - use of respiratory medication for asthma - report of spirometry with significant reversibility* and/or significant peak flow variation all in the absence of COPD#
PROBABLE ASTHMA	GP diagnosed asthma with ≥ 2 asthma related GP consultations, but does not meet above criteria AND in the absence of COPD#
POSSIBLE ASTHMA	asthma diagnosis in the medical file, in the absence of COPD#
ASTHMA AND COPD OVERLAP	concomitant physician-diagnosis of both asthma (as classified as above into definite/probable/possible) and COPD#

The index date was defined as either: the date of asthma diagnosis as derived from the medical files, date of onset of symptoms preceding this diagnosis, the date of first prescription of asthma medication, or the questionnaire derived asthma-diagnosis date, whichever came first. Late-onset asthma was defined as asthma which started after 40 years of age.

2.3. Measurements

Within the RS, spirometry was performed since 2002 at each round in all participants, therefore baseline spirometries were only available in the third cohort. A Master Screen® PFT Pro was used by trained paramedical personnel according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [17]. As in many epidemiologic population-based studies reversibility was not tested. All spirometries were independently assessed by two trained researchers. Airway obstruction was defined as a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio < 0.7 , and further classified as mild airflow limitation when the $FEV_1\%$ predicted ≥ 80 , or moderate to severe airflow limitation if the $FEV_1\%$ predicted ≤ 80 . The predicted values were calculated according to the 2012 Global Lung Function Initiative/European Respiratory Society (ERS) equations [19].

Smoking status was classified as never, former or current smoker. The number of pack-years was computed as years times daily cigarettes divided by 20.

Blood eosinophil level was measured cross-sectionally within the Rotterdam Study since 2012. In the asthmatic subjects we also derived blood eosinophil levels from primary care laboratory. Cut-off values for analysis of blood eosinophilia were based on previous literature; absolute values ≥ 270 cells per μL and absolute values ≥ 400 cells per μL [20,21]. Measurements closest to the asthma index date since study start were used in the analysis.

2.4. Comorbidities

Comorbidities in all participants were assessed at study entrance. The most common diseases in ageing populations were derived directly from investigations at the study facility. In addition we studied the use of concomitant medication, derived from the home interview. The most commonly used medicines in the total cohort, as well as medication for asthma and related comorbid conditions (e.g. reflux or allergies) were

assessed. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or use of antihypertensive medication, according to the 2013 European Society of Cardiology (ESC) guidelines [22].

Heart failure was defined in accordance with the ESC criteria, as definite or probable, based on objective measures. Detailed diagnostic criteria for heart failure as used in the Rotterdam Study can be found elsewhere [23].

Type 2 Diabetes was defined according to the World Health Organization (WHO) guidelines as fasting blood glucose ≥ 7.0 mmol/l, a non-fasting blood glucose ≥ 11.1 mmol/l or the use of blood glucose lowering medication.

Obesity was defined as Body Mass Index (BMI) ≥ 30 Kg/M².

Depressive symptoms were assessed with the validated Center for Epidemiologic Studies Depression Scale (CES-D), with scores ranging from 0 (no symptoms) through 60 (many symptoms); a cut-off score of 16 is commonly used and has acceptable screening accuracy for detecting major depression [24]. A 2016 meta-analysis reports that a cut-off point of 20 yields higher specificity and lower sensitivity [24]. Both cut-offs were used in the analysis.

Validation of COPD has been described elsewhere [25]. In short, COPD was defined as either an obstructive spirometry without an asthma diagnosis, or a doctors diagnosis of COPD.

2.5. Statistical analysis

Baseline characteristics were described for both the asthma cases and the subjects without prevalent obstructive lung diseases (i.e. subjects with prevalent COPD without asthma were excluded). Prevalence was calculated as the number of participants diagnosed with asthma divided by the total number of subjects at baseline. Means with standard deviations (SD) and numbers with percentages were used to report continuous and categorical variables, respectively.

T-tests and χ^2 tests were used to study differences between subjects with and without asthma. Next a logistic regression analysis was conducted to study differences between participants with or without asthma, adjusting for age, gender, BMI, and smoking status. We considered a two-sided p value < 0.05 as statistically significant.

Missing data in covariates were reported as such, without use of imputation techniques as baseline missing data were not deemed missing at random. Except for missing data in the medication history (0.2%), these were imputed to zero as these subjects were regarded as a non-user.

All analyses were done with the software package SPSS (IBM SPSS statistics Version 21).

3. Results

3.1. Asthma cases and baseline characteristics

The total study population comprised 14621 participants (Fig. 1). The case-finding process identified 1649 participants as potential cases. Out of these participants, 524 had a validated physician-diagnosis of asthma at baseline, implicating an overall asthma prevalence of 3.6% [95% CI 3.3%–3.9%], and a sex-specific prevalence of 2.8% in males and 4.2% in females. The baseline asthma prevalence was correlated with the mean entry age of the individual cohorts: 1.4% (RS-I, mean age: 70.2years), 5.2% (RS-II, mean age: 65.2years) and 6.6% (RS-III, mean age: 57.1years). Fifteen of the subjects with asthma had a concomitant physician-diagnosis of prevalent COPD as well (prevalence ACO = 0.1%). We then classified the asthmatics according to the reported strength of the diagnosis into definite ($n = 242$ (46%)), probable ($n = 91$ (17%)), or possible asthma ($n = 191$ (37%)) as described in Table 1.

Table 2 shows the baseline characteristics of the study population stratified by subjects with asthma (ACO included) and the reference

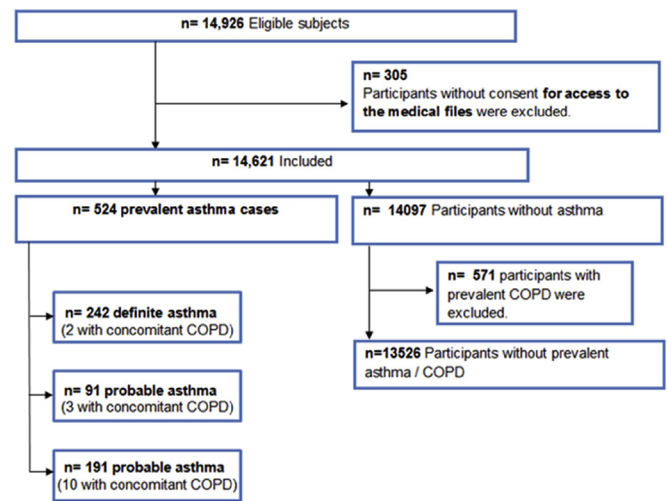


Fig. 1. Flowchart of the study population. Of the 14926 eligible participants, 305 participants were excluded because of absence of informed consent for access to the medical files. This resulted in a total study population of 14621 participants, which could be further divided into 524 participants with a valid asthma diagnosis at baseline and 14097 participants without prevalent asthma. 13526 subjects did not have asthma nor prevalent COPD and were regarded as the control population. The first, second, and third Rotterdam Study cohort contributed 111, 156 and 257 prevalent asthma cases respectively.

population (participants without asthma or COPD). The mean age overall was 65.5 years and 59.1% were female. Participants with prevalent asthma were more often female (68.5%), younger (mean age 60.3 years), and were less often current smokers. In ever smokers, 4.0% had asthma, in never smokers the prevalence of asthma was 3.6%.

Subjects with asthma had a higher body mass index (28.5 kg/m²) than control subjects without asthma (26.8 kg/m²) and were more often clinically obese (i.e. BMI ≥ 30) (33.2% versus 18.3%). The distribution of BMI in subjects with asthma as compared with control subjects is visualized in Fig. 2. Furthermore subjects with asthma more often had a history of diabetes mellitus (7.3% vs 4.1%), and had higher CES-D depression scores (8.3 vs 5.6) at baseline. 20.3% of the asthmatic participants had depressive symptoms, compared to 9.5% of the general population.

3.2. Asthma characteristics

Within the 524 asthma cases, 187 (35.7%) subjects were diagnosed with asthma by a respiratory physician, while 64.3% was diagnosed by their general practitioner. 37.9% of the cases with an asthma diagnosis by a respiratory physician had non-allergic, intrinsic asthma. The absolute blood eosinophil level was available in 61.6% of all asthma cases; the mean value was 234.8 cells/ μ L (median 190 cells/ μ L). In 72.3% of cases the blood eosinophil count yielded a value below 270 cells/ μ L, whereas 13.1% had a blood eosinophil count higher than 400 cells/ μ L.

The median age at onset of asthma in this adult population was 49 years. Within males, 18.1% had asthma since childhood, and in 34.0% of men, the asthma started before the age of 40 years. Within the female cases, 14.4% suffered from asthma since childhood and 27.7% had asthma before the age of 40.

3.3. Asthma and pulmonary function

Pulmonary function is reported for the third subcohort (RS-III). Overall, the ratio of the Forced Expiratory Volume in one second (FEV1) to the Forced Vital Capacity (FVC) (i.e. FEV1/FVC) differed significantly between subjects with asthma compared with the general population (COPD subjects excluded). Airflow limitation was evident at

Table 2

Baseline characteristics of the study population stratified by subjects with asthma (ACO included) and the reference population (participants without prevalent asthma or COPD). Entries represent original data without imputed values. For variables with missing data, valid percent is given. Categorical variables are presented as numbers (% of valid total). Values of continuous variables are presented as mean ($\pm$ sd). In the total population, baseline values were missing for ethnicity (18.7%) smoking (3.8%), smoking pack-years (3.7%), ethnicity (19%), body mass index (11.8%), blood pressure (10.7%), forced expiratory volume in 1 s (FEV₁) % predicted according to the 2012 Global Lung Function Initiative/European Respiratory Society (ERS) equations (80.6%: baseline data only at third cohort available), hs-CRP (15.3%), GFR (24.2%), Cholesterol (11.7%), diabetes mellitus (2.1%), hypertension (19.8%), and heart failure (4.1%). CES-D (53.9% baseline data second and third cohort). Abbreviations: FEV₁ = forced expiratory volume in 1 s, hs-CRP = high sensitivity C-reactive protein, GFR = glomerular filtration rate, CES-D = Center for Epidemiologic Studies Depression Scale.

	Prevalent Asthma (N = 524)		Reference Population (N = 13526)		P-value
AGE (YEARS)	60.3	(8.9)	66.1	(10.6)	< 0.01
FEMALES (%)	368	(68.5)	8190	(59.3)	< 0.01
ETHNICITY (%)					0.07
CAUCASIAN	413	(96.7)	10779	(98.0)	
EAST-ASIAN	7	(1.6)	133	(1.2)	
AFRICAN	4	(0.9)	65	(0.6)	
MIXED	3	(0.7)	17	(0.2)	
SMOKING STATUS					0.07
CURRENT SMOKER (%)	91	(17.7)	2772	(21.1)	
FORMER SMOKER (%)	253	(48.6)	5580	(42.5)	
NEVER SMOKER (%)	176	(33.7)	4741	(36.3)	
PACK-YEARS IN EVER SMOKERS	14.2	(20.1)	15.3	(21.7)	0.28
BODY MASS INDEX, KG/M2	28.5	(5.0)	26.8	(4.1)	< 0.01
SYSTOLIC BLOOD PRESSURE (MMHG)	137	(20.4)	138	(21.8)	0.08
DIASTOLIC BLOOD PRESSURE (MMHG)	80	(11.8)	77	(12.0)	< 0.01
FEV ₁ , % PREDICTED	94.4	(17.0)	102.7	(15.2)	< 0.01
HS-CRP (MG/L)	3.2	(4.5)	2.9	(6.0)	0.28
GFR (SEX SPECIFIC ML/MIN/1.73 M2)	84.5	(16.2)	79.3	(16.3)	< 0.01
CHOLESTEROL (MMOL/L)	5.9	(1.1)	6.2	(1.2)	< 0.01
OBESITY (%)	158	(29.8)	2230	(18.3)	< 0.01
HYPERTENSION (%)	225	(54.1)	6159	(55.4)	0.65
CES-D DEPRESSIONSCORE	8.3	(9.8)	5.6	(7.4)	< 0.01
CES-D DEPRESSIONSCORE $\geq$ 16 (%)	83	(20.3)	576	(9.5)	< 0.01
DIABETES MELLITUS (%)	38	(7.3)	560	(4.1)	0.44
REVASCULARIZATION OR MYOCARDIAL INFARCTION (%)	25	(4.7)	885	(6.9)	< 0.01
HEART FAILURE (%)	9	(1.8)	283	(2.1)	0.60

baseline in 16.2% of the asthma cases versus 4.7% of the general population. Furthermore, asthmatics had a significantly lower FEV₁% predicted value than the control population (94.4% vs 102.7%). The asthma cases treated by a respiratory physician had on average a 5% lower FEV₁%predicted value compared to GP treated patients. Subjects

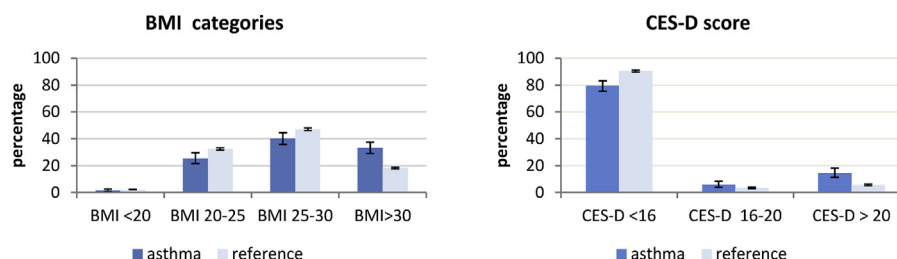


Fig. 2. BMI categories (underweight-normal weight-overweight-obese) and CESD scores (cutoff 16 and 20) in asthma cases versus the reference population. Abbreviations: BMI = body-mass index, CES-D = Center for Epidemiologic Studies Depression Scale.

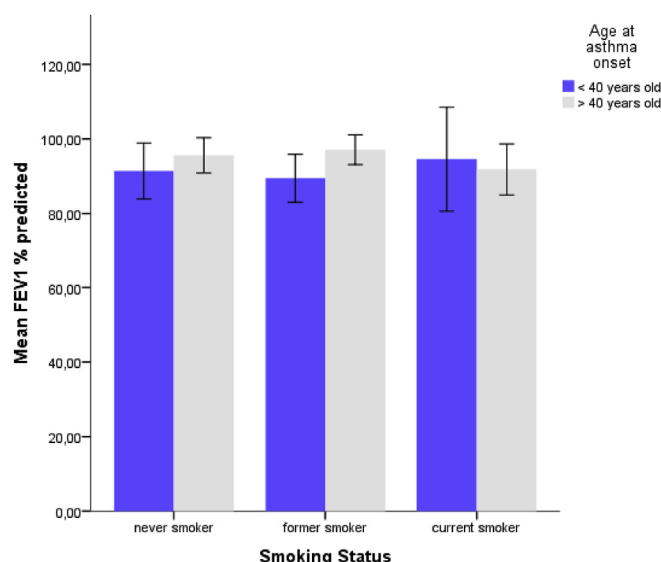


Fig. 3. FEV₁% predicted for the asthma cases by smoking status and age at onset. Data are given as mean FEV₁%predicted, error bars: 95% CI. Abbreviations: FEV₁ = forced expiratory volume in 1 s.

with early onset asthma had the lowest FEV₁ values, and current smoking was associated with an additional drop in pulmonary function, as shown in Fig. 3.

3.4. Asthma, comorbidities and medication use

Asthma cases had more often diabetes mellitus, depressive symptoms and obesity than the reference population. Table 3 shows the corresponding odds ratios (OR). When adjusted for age and sex the OR remained significant and clinically relevant: diabetes [OR 1.47(95%CI 1.11–1.95)], depression [OR 2.23(95%CI 1.72–2.89)], and obesity [OR 2.04(95%CI 1.67–2.49)]. Furthermore asthma was associated with arterial hypertension compared to subjects without asthma when adjusted for age and sex [OR 1.27 (95%CI 1.02–1.57)]. However, the association of asthma with both hypertension and diabetes mellitus, was no longer significant after additional adjustment for differences in BMI (Table 3, Model 2).

Asthma was strongly associated with higher CES-D scores, indicative of depressive symptomatology. The risk of having depressive symptoms was more than doubled in asthmatic patients compared to subjects without asthma adjusted for age, sex, smoking and BMI [OR 2.01 (95% CI 1.52–2.66)]. Out of the asthma patients with CES-D scores above 16, 25.3% (n = 21) used antidepressants versus 16.7% (n = 96) in the reference population. Anxiolytic drugs were used in 19.3% (n = 16) of the asthmatic subjects with depressive symptoms.

We performed a sex specific analysis to investigate the association between asthma and the comorbidities analyzed in Table 3, see online supplement. We did not find any significant differences between the

Table 3

Odds Ratio's of comorbid conditions in asthmatic subjects. Model 1: age, sex adjusted. Model 2: age, sex, BMI, pack-years adjusted. Obesity and Overweight were not adjusted for BMI in model 2. CES-D = Center for Epidemiologic Studies Depression Scale *CES-D cutoff at 20 points resulted in an OR (model 2) of 2.19 [95% CI 1.58–3.03] $p < 0.001$.

	CRUDE OR	(95% CI)	P	ADJUSTED OR MODEL 1	(95% CI)	P	ADJUSTED OR MODEL 2	(95% CI)	P
DIABETES MELLITUS	1.13	(0.85–1.49)	0.40	1.47	(1.11–1.95)	0.01	1.19	(0.87–1.61)	0.28
OBESITY (BMI > 30)	2.21	(1.82–2.69)	< 0.01	2.04	(1.67–2.49)	< 0.01	2.02	(1.66–2.47)	< 0.01
OVERWEIGHT (BMI 25–30)	0.76	(0.63–0.91)	< 0.01	0.79	(0.66–0.96)	0.02	0.78	(0.65–0.95)	0.01
HYPERTENSION	0.95	(0.78–1.16)	0.61	1.27	(1.04–1.56)	0.02	1.01	(0.81–1.25)	0.94
REVASCULARIZATION OR MYOCARDIAL INFARCTION	0.69	(0.46–1.03)	0.07	1.07	(0.71–1.63)	0.74	0.96	(0.60–1.53)	0.85
HEART FAILURE	0.84	(0.43–1.64)	0.61	1.68	(0.85–3.33)	0.14	1.69	(0.81–3.51)	0.16
CES-D DEPRESSIONSCORE $\geq 16^*$	2.41	(1.87–3.12)	< 0.01	2.23	(1.72–2.89)	< 0.01	2.01	(1.52–2.66)	< 0.01
OSTEOPOROSIS	0.42	(0.26–0.69)	< 0.01	0.62	(0.38–1.03)	0.06	0.80	(0.48–1.32)	0.38

Bold numbers indicate significant (i.e. $p \leq 0.05$) results.

Table 4

Medication used given as percentage users in asthma cases ($n = 524$) versus subjects without prevalent asthma or COPD ($n = 13526$). Medication use in the week of study start was assessed in the home-interview. In the total population, data were missing for 0.2%, and were analyzed as non-users. Bold numbers indicate significant (i.e. $p \leq 0.05$) difference based on χ^2 test (with Fisher corrections when $\% < 5$) (crude proportions).

ATC-CODE	Drug name	% users with asthma	% users without asthma
A02A	Antacids	20	9
A02BC	Proton pump inhibitors	15	4
C07	Beta Blocking agents	14	15
C09	Agents acting on the renin- angiotensin system	16	9
C10	Lipid modifying agents	15	9
H02	Corticosteroids, systemic use	4	1
N06	Psychoanaleptics	9	4
N06A	Antidepressants	8	4
N05B	Anxiolytics	7	7
R01AD	Nasal corticosteroids	9	1
R06	Antihistamines, systemic use	11	2
R03	Drugs for obstructive airway diseases	55	2
R03A	Adrenergic inhalants	42	1
R03BA	Glucocorticoid inhalants	29	1
R03DC	Leukotriene receptor antagonists	2	0

genders, but these data confirm the correlation between asthma and obesity and depressive disorders in both sexes.

The use of medication, as indicative for comorbid conditions, is presented in Table 4. The use of antacids, indicative of gastro-esophageal reflux disease, was significantly higher within the asthmatic subjects; 20% versus 9% in the general population ($p < 0.05$). 11% of the asthmatics used systemic antihistamines versus 2% in the general population. Nasal preparations (mainly steroid preparations, suggestive for allergic rhinitis and/or nasal polyposis) were also more frequently used within the asthma cases; 9.4% versus 1.1% ($p < 0.05$).

Respiratory medication (ATC R03) was taken by 54.6% of the participants with prevalent asthma in the week of study start versus 2.0% of the control population. In those patients where asthma was confirmed by a respiratory physician, the proportion of subjects using respiratory drugs was higher (68.4%). Of the asthmatic participants who used inhaled corticosteroids (29.1%), 69.0% also used another respiratory inhaler (e.g. beta-adrenergics). Within the asthma subjects using beta2-adrenergic inhalers (42.0%), 51.8% concomitantly used another inhaler as well. Current use of oral corticosteroids was 4.4% in asthma cases and 1.0% in the reference population ($p < 0.01$).

4. Discussion

This is the first report of validated physician-diagnosed asthma within a large population-based cohort in middle-aged and older adults. Our data demonstrate that 3.6% of adults over 45 years old suffers from asthma, with a higher prevalence in females (4.2%) compared with males (2.8%). Importantly, people afflicted with asthma are twice as likely to demonstrate depressive symptoms and obesity as compared to the general population. The considerable prevalence and associated comorbidities reflect the burden of asthma, implicating the need to investigate asthma in ageing populations.

The asthma prevalence of 3.6% as we report in this Dutch suburban population of middle-aged and older adults fits with the notion that asthma affects all age-groups, albeit it is lower than in other reports. Literature on epidemiology of asthma in middle-aged and elderly is limited, but previous studies estimate the prevalence to be between 5 and 13% [1,26,27].

The difference in asthma prevalence between the oldest (1.4%, mean age 70.2 years) and most recent RS cohort (RS-III 6.6%, mean age 57.1 years) is noteworthy, and may have several explanations. It can be a reflection of the time lapse between the starting points of the several cohorts (16 years between RS-I and RS-III) (see online supplement for a diagram of the RS). Asthma prevalence is reported to be increasing, although data are conflicting [28–30]. Participants in RS-III were also younger than RS-I participants, and the baseline asthma prevalence was correlated with the mean age of the individuals at entry into the three sub cohorts: 1.4% (RS-I, mean age: 70.2 years), 5.2% (RS-II, mean age: 65.2 years) and 6.6% (RS-III, mean age: 57.1 years). Furthermore, the reported prevalence in the oldest cohort (RS-I) can be an underestimation of the true prevalence because of several reasons: (1) elderly asthmatics are at risk for underdiagnoses of asthma, or misdiagnosis of COPD; (2) at the start of RS-I, the electronic health records were not standard procedure, implicating that we may have missed asthma diagnoses due to incomplete paper records; (3) misuse of the generic diagnosis of CARA (Chronische Aspecifieke Respiratoire Aandoening/Chronic Aspecific Respiratory Diseases), common in the Netherlands in the eighties and nineties.

Only a few studies describe the asthma prevalence in age groups comparable with RS-I, i.e. 70 years. The large GA²LEN survey in Europe found an asthma prevalence in the 65–74 years age group of 7.7%; asthma was defined as self-reported ever asthma and symptoms [31]. Another large survey in US adults aged 65 years and older (the National Health Interview Survey 2001–2010) found a self-reported asthma prevalence of 7.0% [27]. In Portugal was the self-reported physician-diagnosed asthma prevalence in subjects over 65 years 10.9% [32]. A Finnish report in subjects around seventy years of age [10] found an asthma prevalence around 7%. The asthma diagnosis was based on strict reimbursement criteria, and therefore more reliable than self-reported data. As asthma diagnosis depends on the combination of a

typical anamnesis and subsequent objective measures [8], epidemiologic asthma research is often hindered by this lack of a single discriminative measure.

We found an association between physician-diagnosed asthma and symptoms of depression. This finding is in line with prior evidence on depression in (severe) asthma cohorts [33]. In addition, several population-based studies also describe a correlation between self-reported asthma and symptoms of depression [15]. However, there is a risk of misclassification among self-reported asthma patients when they, for example, mistake anxiety-attacks for asthma. Therefore, although asthma is often thought of as a mild disease, our research findings demonstrate the mental distress in middle-aged and older asthma patients.

Obesity, and associated diabetes mellitus are also previously described to have an association with asthma, although the impact of asthma as a risk factor for these conditions is still unclear [16]. Furthermore, recent findings suggest asthma to be a risk factor for the development of cardiovascular comorbidity, mainly in woman, as reviewed by Kankaanranta *et al* [16]. In a sex specific analysis of our data, we did not find any significant differences between the genders. In their 2015 AJRCCM paper, Colak *et al.* did find the risks of cardiovascular comorbidities restricted to smokers with asthma [34]. Asthma patients who were never smokers did not have elevated risk levels, and this is concordant with our findings. However, more research is warranted, especially because an asthma population is generally younger and predominantly female compared to the reference population.

The major strength of our study is the strict validation of the asthma diagnosis based on data from the patient's medical files. This has two advantages: firstly, ascertainment of asthma diagnosis conform the GINA guidelines and thereby reducing possible misclassification, and secondly, an objective date of diagnosis which prevents recall bias as seen in self-reported asthma. Another strength is the general population-based setting, facilitating the investigation of associations in an unselected asthma population. Thanks to these multiple strengths, the Rotterdam Study has been able to participate in the recent meta-analysis of worldwide asthma genome-wide association studies, identifying five novel asthma loci and highlighting large overlaps in genetic variants with inflammatory and autoimmune diseases [35].

Our study has also limitations. First, a diagnosis of asthma had to be recorded in the medical file. It is conceivable that we missed asthmatic subjects who did not seek medical attention, who did not receive a (correct) diagnosis, or who did not have a complete medical file. Second, asthmatic subjects with persistent airflow limitation may have been misdiagnosed as COPD, and therefore not be included in our cases. However, subjects with both diagnoses of asthma and COPD were labeled as Asthma and COPD Overlap (ACO), in accordance with the 2017 GINA and Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines [7,36]. Furthermore we might have misclassified subjects with childhood asthma, which did not longer suffer from asthma and did not report a history of asthma. These limitations may have resulted in an under-estimation of the true asthma prevalence.

Findings from this study highlight the need for asthma research in middle-aged and elderly, where previous studies tend to focus on children and young adults [1]. With age, the cumulative burden of comorbid conditions increases, but it might be especially important to assess and treat associated comorbid conditions in patients with asthma to improve control and reduce the future risk of exacerbations; for example, depression has been shown to impair asthma control [11].

Asthma control often can be achieved with treatment, but correct diagnosis can be hindered by the changing physiology of the ageing lung [37,38], or falsely be regarded as COPD. Such misclassification should be avoided because asthma requires a different treatment than COPD. Asthma and COPD may also co-exist, and concomitant late-onset asthma and COPD has been associated with shorter life expectancy than either condition isolated [39]. Recognition of airway disease in older adults, and the distinction of asthma from COPD is therefore eminent for successful management and treatment.

In summary, asthma is not a rare disease in older age-groups, and affected individuals more often suffer from comorbid conditions such as depression and obesity than the general population. Thorough investigations into the burden and impact of asthma in older subjects, the different phenotypes and the underlying pathophysiologic mechanisms are urgently warranted. Future research should focus on differences between early-onset asthma and late-onset asthma, the bidirectional interaction between asthma and comorbidities in older asthmatics, and asthma disease trajectories throughout the lifespan [6].

Conflicts of interest

ER and **BS** state that they have no financial conflict of interest. **LL** has performed consultancy for Boehringer-Ingelheim GmbH and received an AstraZeneca and Chiesi Scientific Award and travel support from Novartis, the European Respiratory Society, and the Belgian Respiratory Society. **JV** has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, Novartis and Teva; he is a member of advisory boards for Boehringer-Ingelheim, Sanofi and Chiesi. **G-JB** has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, ALK-Abello, Mundipharma and Takeda; he is a member of advisory boards for Boehringer-Ingelheim, GlaxoSmithKline, ALK-Abello, Meda Pharma and Novartis. **GB** has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer and Teva; he is a member of advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Regeneron/Sanofi and Teva. **KV** works for a research group who received unconditional research grants from Boehringer Ingelheim, Yamanouchi, GSK, Novartis, none of which are related to the topic of this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2018.04.006>.

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ONLINE SUPPLEMENT

Asthma and its comorbidities in Middle-Aged and Older Adults; the Rotterdam Study

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Methods:

The diagram below can further clarify the Rotterdam study cohorts, and its examination cycles. The baseline examinations of the three subcohorts of the Rotterdam Study are marked with a blue circle; on the horizontal axes, further examination cycles of these closed cohorts are shown. In the current paper we focus only on the baseline measurements. The diagram below is adapted from *“The Rotterdam Study: 2018 update on objectives, design and main results. Eur J Epidemiol 2017;32:807-850. Ikram MA et al.”*



Diagram of examination cycles of the Rotterdam Study (RS). RS-I-1 refers to the baseline examination of the original cohort (pilot phase 07/1989–12/1989; cohort recruitment 01/1990–09/1993). RS-I-2, RS-I-3, RS-I-4, RS-I-5, and RS-I-6 refer to re-examinations of the original cohort members. RS-II-1 refers to the extension of the cohort with persons from the study district that had become 55 years since the start of the study or those of 55 years or over that migrated into the study district. RS-II-2, RS-II-3, and RS-II-4 refer to re-examinations of the extension cohort. RS-III-1 refers to the baseline examination of all persons aged 45 years and over living in the study district that had not been examined already (i.e., mainly comprising those aged 45–60 years). RS-III-2 refers to the first re-examination of this third cohort. Examination RS-I-4 and RS-II-2 were conducted as one project and feature an identical research program. Similarly, examinations RS-I-5, RS-II-3, and RS-III-2 share the same program items. Also, examinations RS-I-6 and RS-II-4 are conducted as one project.

Results:

SUPPLEMENTAL TABLE A. ODDS RATIO'S OF COMORBID CONDITIONS IN ASTHMATIC SUBJECTS COMPARED TO THE REFERENCE POPULATION, STRATIFIED BY GENDER.

	Model 1 OR	95% lower	95% upper	p	Model 2 OR	95% lower	95% upper	p
Diabetes Mellitus - all	1.47	1.11	1.95	0.01	1.18	0.87	1.61	0.28
male	1.62	1.05	2.52	0.03	1.41	0.87	2.30	0.17
female	1.38	0.95	2.01	0.09	1.08	0.72	1.62	0.70
Obesity (BMI>30)(%)[#] - all	2.04	1.67	2.49	0.00	2.02	1.66	2.47	0.00
male	1.92	1.32	2.80	0.00	1.90	1.30	2.79	0.00
female	2.14	1.69	2.71	0.00	2.13	1.68	2.69	0.00
BMI_overweight[#] - all	0.79	0.66	-0.96	0.02	0.78	0.65	-0.95	0.01
male	0.63	0.45	0.87	0.01	0.61	0.44	0.85	0.00
female	0.89	0.71	1.12	0.34	0.89	0.71	1.12	0.31
Hypertension - all	1.27	1.04	1.56	0.02	1.01	0.81	1.25	0.94
male	1.31	0.91	1.87	0.14	1.20	0.82	1.75	0.36
female	1.27	0.99	1.62	0.06	0.95	0.73	1.24	0.69
Revascularization or Myocardial infarction (%) - all	1.07	0.71	1.63	0.74	0.96	0.60	1.53	0.85
male	1.06	0.63	1.78	0.82	1.01	0.57	1.80	0.96
female	0.98	0.48	2.02	0.96	0.80	0.35	1.84	0.60
Heart failure (%) - all	1.68	0.85	3.33	0.14	1.69	0.81	3.51	0.16
male	1.72	0.62	4.80	0.30	2.20	0.78	6.21	0.14
female	1.64	0.65	4.11	0.29	1.39	0.50	3.89	0.53
CES-D depression score ≥16 - all	2.23	1.72	2.89	0.00	2.01	1.52	2.66	0.00
male	1.81	0.98	3.36	0.06	2.07	1.10	3.87	0.02
female	2.36	1.77	3.14	0.00	2.00	1.46	2.74	0.00

Osteoporosis (%) - all	0.62	0.38	1.03	0.06	0.80	0.48	1.32	0.38
male	0.77	0.31	1.92	0.58	0.99	0.39	2.49	0.98
female	0.59	0.33	1.08	0.09	0.77	0.42	1.41	0.39

Model 1, Age and sex adjusted for the analysis in all participants combined, and only age adjusted in the sex stratified analysis.

Model 2, Age, sex, pack-years and BMI adjusted for the analysis in all participants combined, and only age, pack-years and BMI adjusted in the sex stratified analysis.

not BMI adjusted

SUPPLEMENTAL TABLE B ODDS RATIO'S OF CORONARY ARTERY DISEASE OR HEART FAILURE IN ASTHMATIC SUBJECTS COMPARED TO THE REFERENCE POPULATION, STRATIFIED BY GENDER

	Crude OR	95% lower	95% upper	p	Model 1 OR	95% lower	95% upper	p	Model 2 OR	95% lower	95% upper	p
Revascularization or Myocardial infarction (%) - all	0.69	0.46	1.03	0.07	1.07	0.71	1.63	0.74	0.96	0.60	1.53	0.85
male	0.89	0.53	1.48	0.65	1.06	0.63	1.78	0.82	1.01	0.57	1.80	0.96
female	0.62	0.31	1.27	0.19	0.98	0.48	2.02	0.96	0.80	0.35	1.84	0.60
Heart failure (%) - all	0.84	0.43	1.64	0.61	1.68	0.85	3.33	0.14	1.69	0.81	3.51	0.16
male	1.20	0.44	3.29	0.73	1.72	0.62	4.80	0.30	2.20	0.78	6.21	0.14
female	0.68	0.28	1.66	0.39	1.64	0.65	4.11	0.29	1.39	0.50	3.89	0.53

Model 1, Age and sex adjusted for the analysis in all participants combined, and only age adjusted in the sex stratified analysis.

Model 2, Age, sex, pack-years and BMI adjusted for the analysis in all participants combined, and only age, pack-years and BMI adjusted in the sex stratified analysis.

not BMI adjusted