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Early View

Original article

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Incidence and predictors of asthma exacerbations in middle-aged and older adults: the Rotterdam Study

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Conflict of interest

ER, LL and **BS** state that they have no financial conflict of interest. **JV** has, within the last 5 years, received honoraria for lectures from AstraZeneca,, Chiesi, and Novartis; he is a member of advisory boards for Sanofiand GlaxoSmithKline . **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, Pfizer, Yamanouchi, GSK, Novartis, Chiesi none of wich are related to the content of this work.

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Take home message

Most middle-aged and older adults with asthma suffer from at least one severe exacerbation. Risk factors are previous exacerbations, use of SABA without concomitant controller medication, respiratory complaints, obesity, airway obstruction and depression.

ABSTRACT

Aim To investigate occurrence and determinants of asthma exacerbations in an ageing general population.

Methods Subjects aged 45 years or above with physician-diagnosed asthma in the Rotterdam Study, a population-based prospective cohort from January 1991 to May 2018 were assessed for asthma exacerbations. Exacerbations were defined as acute episodes of worsening asthma treated with oral corticosteroids. Cox proportional hazards analysis was used to investigate risk factors for a future exacerbation.

Results Out of 763 participants with asthma (mean age 61.3 years, 69.2% female), 427 (56.0%) experienced at least one exacerbation, in a mean follow-up time of 13.9 years. The mean annual exacerbation rate was 0.22. Most exacerbations occurred during winter months. Risk factors for exacerbations were a history of previous exacerbations (Hazard Ratio(HR) 4.25; CI 3.07-5.90, p<0.001)), respiratory complaints (HR 2.18; 1.48-3.21, p<0.001), airflow obstruction (HR 1.52; 1.07-2.15, p=0.019), obesity (HR 1.38; 1.01-1.87, p=0.040) and depressive symptoms (HR 1.55; 1.05-2.29, p=0.027). Compared to those not using respiratory medication, we observed higher HRs for those on short-acting beta2-agonists (SABA, i.e. rescue medication) only (HR 3.08, 95% CI 1.61-5.90, p=0.001) than those on controller medication (HR 2.50, 95% CI 1.59-3.92, p<0.001).

Conclusion Many older adults with asthma suffer from at least one severe exacerbation. Previous exacerbations, use of SABA without concomitant controller medication, respiratory complaints, obesity, airway obstruction and depression are independent risk factors for exacerbations.

Keywords asthma – older adults – exacerbation – general population – epidemiology – comorbidity

Introduction:

Asthma is a common chronic respiratory disease, with a global prevalence in adults of 4.3%[1]. Patients suffer from variable airflow obstruction resulting in respiratory symptoms, such as attacks of dyspnoea, limitation of activity [2] and impaired quality of life [3]. This burden of asthma is most substantial in those over 45 years of age (compared to the 18-45 year olds), although this age-group is comparatively understudied [1, 4]. As there is yet no cure for asthma, treatment relies on achieving control of symptoms, and the prevention of exacerbations[5].

A severe exacerbation is defined by the ATS/ERS as the need for systemic corticosteroids [6]. Exacerbations are responsible for a high human and financial burden (such as loss of working days and medical costs), and are the prelude to asthma related emergency care, morbidity and even death [5, 7-10]. Fortunately, not all afflicted individuals with asthma suffer from exacerbations, which is more frequent in patients with severe asthma [9, 11-13]. Nevertheless, since patients with mild asthma are most prevalent in the general population, patients with mild asthma still account for 30 to 40% of severe asthma exacerbations[14].

As most studies focus on specific patient cohorts, long term follow-up data on asthma exacerbations in the general population is scarce, especially in the aforementioned groups of middle-aged and older subjects with mild-to-moderate asthma. Therefore, we studied the incidence of, and risk factors for asthma exacerbations in middle-aged and older asthmatics, within a population-based sample with long term follow up.

Methods

Setting

All subjects participated in the Rotterdam Study, a prospective population-based cohort study that started in 1990[15]. The objective of the Rotterdam Study is to investigate chronic diseases in the elderly. In 2000, the original cohort (RS-I; n = 7,983) was extended with a second cohort (RS-II; n = 3,011), and in 2006 with a third cohort (RS-III; n = 3,932). This resulted in a total study population of 14,926 subjects (6,103 men and 8,823 women) aged 45 years and over **(supplemental figure 1)**. An extensive set of examinations is performed every 3–5 years at the research facility, including biometrics, laboratory analyses, spirometry, and cardiovascular investigations. Information on medication use is obtained from pharmacy-filled prescriptions from seven connected pharmacies in the region that serve >95 % of the study participants [15]. The Rotterdam Study was approved by the Medical Ethics Committee and by the Netherlands Ministry of Health [16]. All participants provided written informed consent to participate in the study.

Asthma and follow-up

Asthma cases were defined as participants with a physician's diagnosis of asthma reported in their medical file. The accuracy of diagnosis has been validated, as described in detail elsewhere[17]. Subjects without informed consent to access their medical files or without any medication data were excluded. Follow-up time for prevalent asthma cases started at study entrance, whereas in subjects with incident asthma follow-up started at the date of asthma diagnosis. In both prevalent and incident cases of asthma, the follow-up time was calculated until the first exacerbation, death, lost to follow-up, or end of the study period, whichever came first. (flowchart provided **in Supplemental figure 2**). Participants with COPD, defined as spirometry-confirmed airway obstruction in the absence of physician-diagnosed asthma, were excluded[18].

Assessment of Exacerbations

Exacerbations were defined as a worsening of asthma symptoms that required treatment with systemic corticosteroids, conform the ATS/ERS statement on severe exacerbations[6]. Courses of corticosteroids separated by 1 week or more were regarded as separate exacerbations, in line with an earlier consensus statement[8]. In participants with both asthma and any use of respiratory medication; oral use of prednisone, prednisolone, or hydrocortisone prescriptions in a dose of 20-50 mg for a duration of 3 to 21 days were extracted from pharmacy records and marked as an asthma exacerbation. These criteria were based on the manual validation of a subset of 12% from all (n=8,581) oral, intramuscular and intravenous

corticosteroid prescriptions from 1991 until 2016 in the medical files to determine the indication of the prescription. In this validation, 78.5% was prescribed for an asthma exacerbation, while most other indications were polymyalgia rheumatica, joint pain, skin disorders, gout and sinusitis. Further refinement entailed the selection of oral prednisone, prednisolone and hydrocortisone combined with dose and duration criteria. This raised the accuracy to 94% in our exacerbation validation set.

Exacerbation rate was calculated as the number of exacerbations/years of asthma follow-up time. Frequent exacerbators were defined as participants with an annual exacerbation rate of one or more.

Measurements and Covariates

Spirometry (without reversibility testing) was performed by trained paramedical personnel according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [15]. Predicted values were determined according to the Global Lung Initiative (GLI) values 2012 [19]. Airway obstruction was defined as a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio <0.7.

COPD within the physician-diagnosed asthma cohort was defined as a COPD diagnosis next to an asthma diagnosis in the medical file. Smoking status was classified as never, former or current smoker. Blood eosinophil level was measured cross-sectionally and on indication by the GP. The value closest to the study baseline was used in the current study. Blood eosinophil measurements during concomitant oral steroid use were excluded. Hypertension was defined as a systolic blood pressure(SBP) ≥ 140 mmHg or a diastolic blood pressure (DBP) ≥ 90 mmHg or use of antihypertensive medication[20]. Type 2 Diabetes Mellitus was defined as a fasting blood glucose ≥7.0 mmol/l, a non-fasting blood glucose ≥11.1 mmol/l or the use of blood glucose lowering medication[21]. Depressive symptoms were assessed with the validated Center for Epidemiologic Studies Depression Scale (CES-D), with scores ranging from 0 (no symptoms) to 60 (many symptoms); a cut-off score of 16 is commonly used and has acceptable screening accuracy for detecting major depression[22]. Osteoporosis was defined according to WHO criteria as a T-score ≤-2.5.

Respiratory medication (as derived from pharmacy-filled prescriptions) was categorized based on the Anatomic Therapeutic Chemical classification(ATC) codes. The prescribed daily dose of each ICS was expressed in standardized defined daily doses according to the ATC/DDD system of the World Health Organization (DDDs). ICS exposure was assessed based on pharmacy dispensing data on start of and during the follow-up period. Subjects were considered ICS users if their prescribed ICS covered 80% or more of their total follow-up time. For the calculation of the exacerbation hazards we classified the

medication use of the year past (as predictor) into controller (ICS, LABA+ICS, LTRA, nedocromil and anti-allergics), rescue (SAMA, SABA) or total medication (controller + rescue medication)[23]. Controller to total ratio (CTR) was calculated as the total number of controller devices / the total number of respiratory medication.

Statistical analysis

This study is composed of two parts. In the first part, we calculated the incidence rate of asthma exacerbations, and the exacerbation free survival time during the entire follow-up within the Rotterdam Study. Descriptive characteristics were reported as mean (standard deviation) for continuous variables and as count(%) for categorical variables. Survival curves for exacerbation free time during follow-up were computed with the *Survival* package in R [24, 25].

In the second part, we studied risk factors for exacerbations in a sub cohort; namely all participants with asthma in the fifth examination round and onwards (RS-I-5, RS-II-3, and RS-III-2, **supplemental figure 1**). This examination round offered more precise examinations including spirometry than the measurements taken at baseline from 1989 onwards and was therefore better suited to examine risk factors for future exacerbations. Baseline measures for these analyses were taken between 2009-2013 and follow-up was complete until June 2018.

The relationship between potential risk factors and the time to first exacerbation was analysed using a multi-variable Cox proportional hazard model. Variables of interest were derived from literature [9, 11, 12]. Variables were tabulated as crude hazard ratios (HR) and as age- and sex-adjusted HRs. Proportional hazards were inspected using plots and the proportional hazard assumption test from the *Survival* package in R[24, 25].

Possible interaction with sex, based on earlier reports, was investigated and when reported as significant, followed by a stratified analyses[26]. Missing values were reported as such, without use of imputation techniques as baseline missing data were not deemed missing at random. Statistical significance was set at 5%. Data were analysed using SPSS Statistics (IBM, version 24.0) and R (The R Foundation for Statistical Computing, version 3.5.1).

Results

Part A. Incidence rate of severe asthma exacerbations

Patient characteristics of asthma subjects stratified by exacerbation status

Within the Rotterdam Study, there were 778 subjects with doctor-diagnosed asthma and full informed consent to extract information from their medical files. Of these, 763 had medication data available and were included in the analyses. Mean age of the population at start of follow-up was 61.3 years (SD = 8.3; age range = 45.8 to 91.2 years), with 69.2% women. The majority (i.e. 618 subjects; 81%) had adult onset asthma. The total asthma follow-up time was 9,198.8 person years (mean duration of follow-up: 12.1 years, range 0.6 to 28.6 years). In that time period, 1,832 exacerbations were recorded, in 427 subjects (56.0%). Baseline characteristics of study participants, stratified by exacerbation status, are shown in **table 1**.

Exacerbation rate

The mean annual exacerbation rate was 0.22 (SD 0.42*).* The majority of asthma exacerbators (n=300 of 427) had more than one exacerbation, and 47 participants (6.2%) had 10 or more exacerbations. Thirty-one subjects had a mean annual exacerbation rate above 1.0 (i.e. 4.1% out of total population and 7.3% out of those with any exacerbations). These frequent exacerbators were younger (57.4 years old), were more often current smokers (36%), had more often depressive symptoms (37%) and developed asthma at younger age compared to those without exacerbations and those with infrequent exacerbations (***supplemental table I***). The evaluation of all exacerbations by month depicted a seasonal variation; with the majority of the exacerbations occurring during winter months, with a trough in the summer ***(figure A).***

Time to severe exacerbation

The median exacerbation-free survival time within the total follow-up time was 9.76 years (95% CI 8.45-11.34) ***(figure B)***. Sex did not significantly alter the median exacerbation-free survival time. When stratified by smoking status, current smokers had the shortest time to an exacerbation, followed by never smoking asthmatics and former smokers (median time to exacerbation 7.62, 9.88 and 11.20 years respectively).

A sub-analysis in those subjects who developed asthma during RS follow-up (n = 246) (i.e. incident asthma cases) depicted the same pattern as in the overall asthma cohort. Here the median severe exacerbation-free survival time was 8.67 years (95% CI 6.75-11.34) (***supplemental figure 3***). In this group 43 (17.5%) had a severe asthma exacerbation within the first year of diagnosis.

Part B. Risk factors for severe exacerbations

Patient characteristics at re-examination round

In the fifth examination round, 495 participants (=8.1% of total RS-5 n= 6,110) with asthma were included in the analysis of risk factors associated with a severe asthma exacerbation. Mean age then was 69.3 years (SD = 8.9; age range = 51.8 to 98.6 years), of whom 69.2% were women. Mean overall follow-up time was 4.2 years (range 0.5 to 9.1 years). During this follow-up, 177 participants had at least one severe exacerbation***(baseline characteristics are provided in supplemental table II).***

Risk factors for severe exacerbations

Table 2 shows the hazard ratios of a severe exacerbation per clinical determinant, adjusted for age and sex. A prior exacerbation in the past 12 months was associated with a significantly increased risk of subsequent exacerbations (HR 4.25, 95% CI 3.07-5.90, p<0.001), as was airway obstruction (HR 1.52, 95% CI 1.07-2.15, p=0.019), obesity (HR 1.38 , 95% CI 1.01-1.87, p=0.040) and a high score of depressive symptoms (HR 1.55, 95% CI 1.05-2.29, p=0.027). When participants reported complaints of either wheezing or dyspnoea at the study interview this was also associated with a doubled risk (HR 2.07, 95% CI 1.44-2.97, p<0.001 and HR 2.18, 95% CI 1.48-3.21, p<0.001, respectively). A concomitant diagnosis of COPD next to asthma did not yield significant higher exacerbation rates.

Smoking behaviour as risk factor for exacerbation was different in males and females (p value for the age adjusted interaction = 0.002). Therefore, we performed a sex-stratified analysis corrected for age and FEV1. Woman with asthma and persistent smoking had higher HRs (2.34, 95% CI 1.26-4.33 p= 0.007) compared to women who had stopped smoking (HR 2.06, 95% CI 1.33-3.18, p=0.001) or never smoked (reference), whereas in males this direction was not observed (***supplemental figure 4***).

Asthma medication and exacerbations

With regard to respiratory medication, with "no use" as reference category, we observed higher HRs for those on short-acting bronchodilator (i.e. SABA rescue) medication only than those on controller

medication only (HR 3.08, 95% CI 1.61-5.90, p=0.001 - HR 2.50, 95% CI 1.59-3.92, p<0.001, respectively). Subjects using both control and rescue medications had the highest risk.

When data were stratified according to the exacerbation status in the previous year, we observed - especially in asthma subjects with a previous exacerbation- a significant inverse relationship between the controller to total (controller + reliever) asthma medication ratio and the hazard of a subsequent exacerbation (HR age and sex adjusted: 0.26, 95% CI 0.09-0.76, p=0.014)(**Table 3).**

Discussion

Asthma is a heterogeneous disease as is reflected in the different levels of symptom control and the occurrence of exacerbations. In this study, encompassing a population-based asthma cohort of middle-aged and older patients, we demonstrated that although the majority of older adults with asthma have infrequent exacerbations, 17.5% of subjects with incident (thus late-onset) asthma, suffer from at least one severe exacerbation within the first year of diagnosis. Moreover, we showed that treatment of middle-aged and older asthmatics with short-acting bronchodilators alone (i.e. SABA use without concomitant ICS) is associated with a significantly increased risk of severe exacerbations, whereas a higher ratio of controller to total asthma medications is protective.

Our results show that 56% of asthma patients suffer at least one exacerbation during follow-up even though most subjects are regarded as having mild asthma. The annual rate of moderate to severe exacerbations in our study is 0.22. To compare: within the SYGMA trials, enrolling adolescent and adult patients with mild asthma, an annual exacerbation rate of 0.20 was reported in the as-needed SABA (terbutaline) group versus 0.07 in the as-needed budesonide–formoterol fixed dose combination (FDC) group [27]. Mean age in the SYGMA trial however was 41.0 years, which is significantly younger than in the Rotterdam Study (mean age at enrollment 61.7 years). Similarly, a retrospective study including >400,000 subjects from the UK and USA by Suruki *et al.,* found a mean annual rate of exacerbations of 0.16 in the USA cohort (mean age 38 years) and 0.11 in the UK set (mean age 45 years)[9]. In contrast with these findings is the high rate of 0.94 (9.4 per 10 PY in the original paper) that Bloom *et al.* report in their population of 55 years and older[11], stressing the fact that comparable data with our middle-aged and older cohort is scarce.

The seasonal distribution of asthma exacerbations in our data showed a peak in winter and a nadir from July to September. This resembles more the pattern as is seen in COPD than in children and young adults with asthma in whom often a peak is reported in February and September [28-30]. A recent study by Satia *et al.,* documents the respiratory viral pattern throughout the year and demonstrates a biphasic pattern for asthma exacerbations mainly discernable in children while this pattern becomes less pronounced in those above 70 years of age. COPD has the nadir in August, and has a fairly comparable pattern with the overall respiratory tract infections graph[31]. This may indicate that exacerbation risk factors attributed to COPD (such as viral respiratory tract infections and moist weather) are also important in older adult asthma, whereas aeroallergen exposure induced exacerbations become less

important. Comparing the seasonal pattern of asthma exacerbations in the middle-aged and older asthma patients in the RS with publicly available graphs on Dutch pollen counts[32], our data most closely resemble the data on viral respiratory tract infections, and lack a clear representation of aero-allergen induced exacerbations. This observation is in line with increased proportions of non-allergic mechanisms and neutrophilic and non-eosinophilic disease in late onset asthma[33]. **Risk factors for exacerbation**

Current asthma care would immensely benefit from a reliable prediction model for asthma exacerbations. Various attempts have been made, but so far previous healthcare use or a previous exacerbation remains the strongest predictor, and our data is no exception. A hurdle in the formation of a prediction model is often the lack of cross-validation, or discrepancy between the outcome measures. In a recent external validation of multiple prediction models, lung function, complaints and previous healthcare use were common themes[12], and this is in line with our results. However the prediction of exacerbations is also complicated by the high variation between the exacerbation intervals as reported by Bloom *and colleagues*[13]. By using a Cox-proportional hazard model instead of a logistic regression with Poisson modelling we aimed to account for this variability.

Others have reported female sex as an independent risk factor for exacerbations, and this effect is reported to be partially mediated by obesity[34, 35]. In our data this effect is driven by the interaction between smoking and sex, independent of obesity, where current smoking females are at the highest risk[11, 36, 37]. As the number of current smoking males is small, we put forward the hypothesis that smoking man, more often than smoking woman, unjustly, might get a GP diagnosis of COPD.

The use of medication is of course an indicator of disease severity and should therefore be cautiously interpreted. Several randomized controlled clinical trials have demonstrated the effectiveness of ICS/formoterol as needed therapy in mild asthma, preventing exacerbations as compared with SABA use only (e.g. novel START study and SYGMA trials [27, 38, 39]). Today, the Global Initiative for Asthma (GINA) does no longer recommend the use of short-acting bronchodilators alone in adolescents and adults with asthma[40]. In contrast, GINA now recommends ICS-containing treatments in mild asthma, either as daily controller treatment or as anti-inflammatory reliever. Our real world observations in a population-based sample of older patients with (mainly mild) asthma support this treatment strategy .

Finally, we replicated the finding that depressive symptoms in asthma subjects are independently predictive of future exacerbations. This finding is intriguing as it can be regarded as a treatable trait, apart from the fact that the causal direction is not certain[37, 41-44].

Strengths and limitations

The strength of the Rotterdam Study is its prospective, population-based design with long follow-up time that enabled us to study both those with prevalent asthma, as well as new incident asthma cases during follow-up. In a real life setting our data provide insight into the proportion of older adults suffering an exacerbation within a year after diagnosis.

Another strength is the assessment and validation of exacerbations to minimize misclassification. Several methods to assess OCS use as proxy for an exacerbation are reported in the literature; e.g. all OCS within two weeks of asthma code[9], all prescriptions <= 300 mg[11], any OCS equivalent to 20 mg prednisone for 3-28 days[9] or OCS courses during at least 3 days[45]. Most studies include (young) adults until an age of 50 years, whilst in an ageing population other reasons for corticosteroid prescriptions also become more eminent; e.g. polymyalgia rheumatica or gout.

This study also has limitations. Our data set lacks information on hospitalizations, and this could have led to an underestimation of the true occurrence of exacerbations. However, in the Netherlands the mean duration of asthma related hospital stay was 4.9 days in 2011, whereas the guidelines for the duration of OCS exceeded 7 days [46]. Therefore, subjects that had to continue OCS after discharge will be included in our data.

Also, as stated before, inferences based on medication use can lead to confounding by disease severity. As our real life observations are in line with previous large trials we consider these data of relevance to this study.

We acknowledge that the lack of specialist clinical parameters (FeNO , bronchial hyperresponsiveness) and patient reported outcomes (e.g. ACQ, ACT or AQLQ) due to the population based setting limits the current study, mainly with regard to the inference of exacerbation associated risk factors.

Finally, one can dispute our inclusion of participants with the combination of a valid asthma diagnosis with concomitant airway obstruction and a history of smoking. As this reflects the real-life population, we deemed this decision reasonable and provided insight in spirometry values as well as corrected for smoking and airway obstruction in our inferences.

Conclusions

In conclusion, most of the older adults with asthma will suffer from at least one severe exacerbation. Especially in patients with late-onset asthma, striving for good asthma control is warranted as 17.5% of these patients experience at least one severe exacerbation within the first year after diagnosis. Risk factors for exacerbations in this cohort of middle-aged and elderly are a history of previous exacerbations, lack of controller medication use, subjective respiratory complaints, obesity, airway obstruction and depression.

Tables and Figures

Table 1; Characteristics of study participants, stratified by exacerbation status

		Asthma subjects without exacerbations	Asthma subjects with exacerbations
		n= 336	**n= 427**
Females (%)		226 (67.3)	302 (70.7)
Age (mean (sd))		60.85 (8.43)	61.67 (8.21)
BMI (mean (sd))		28.20 (4.61)	28.25 (4.79)
Smoking status (%)	never	105 (31.5)	156 (36.6)
	former	188 (56.5)	213 (50.0)
	current	40 (12.0)	57 (13.4)
Total follow-up years (mean (sd))		11.98 (6.08)	14.69 (6.22)
Follow-up years with asthma (mean (sd))		10.74 (5.59)	13.09 (5.83)
Asthma onset age (median [IQR])		55.53 [45.25, 64.63]	58.17 [45.71, 67.20]
Asthma onset > 40 years (%)		274(81.5)	341(79.9)
Total N. exacerbations (mean (sd))		-	4.48 (5.59)
Exacerbation rate (mean (sd))		-	0.40 (0.53)
GINA class % (n)	*0*	4.17% (14)	0.01 % (4)
	1	18.2 % (61)	2.81 % (12)
	2	21.1% (71)	9.13% (39)
	3	35.7 % (120)	30.0 % (128)
	4+5	20.8% (70)	57.1 % (244)
Blood eosinophils 10^3/uL (mean (sd))		0.25 (0.13)	0.28 (0.19)
Hypertension (%)		142 (53.2)	171 (49.4)
Coronary Heart Disease (%)		13 (3.9)	20 (4.7)
Diabetes mellitus (%)		38 (11.3)	39 (9.1)
Depressive symptoms (%)		37 (15.5)	54 (20.9)
Osteoporosis (%)		9 (3.3)	18 (5.2)

Table 1, Baseline characteristics of study participants, stratified by exacerbation status. sd - standard deviation; IQR – inter quartile range; BMI - body mass index. Original data are provided. Data were missing in (n=): BMI (61), Smoking status(14), eosinophils(285), hypertension(12), Depressive symptoms(278), Osteoporosis (151).

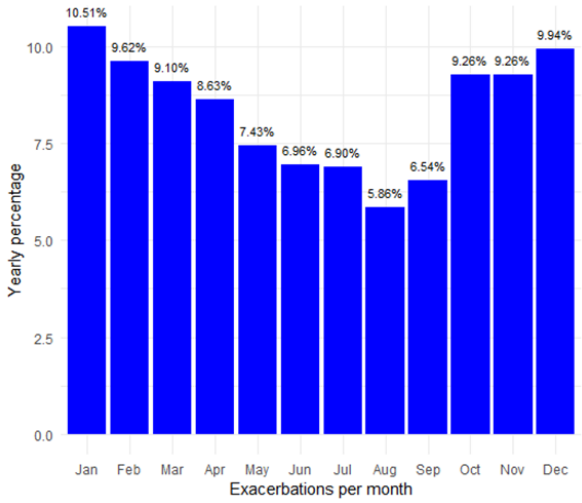

Figure A; Monthly exacerbation percentage

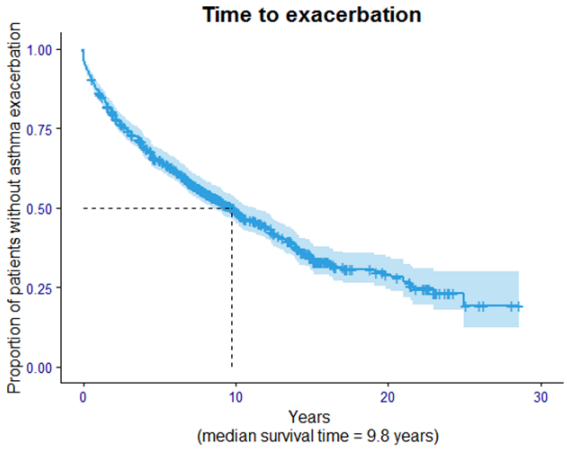

Figure B; Time to severe exacerbation

Figures part B

Table 2; Hazard ratios for the association between determinants and a subsequent asthma exacerbation

Determinant		N (%) / mean(SD)	HR Univariable (95% CI, p-value)	HR Model 1 (95% CI, p-value)
Age (sd)		69.3 (8.8)	**0.98 (0.96-1.00, p=0.048)**	
Sex (female) (%)		345 (69.7)	0.97 (0.70-1.33, p=0.842)	
Smoking (%)	never	164 (33.1)	*Reference*	*Reference*
	former	288 (58.2)	1.17 (0.84-1.63, p=0.348)	1.20 (0.84-1.70, p=0.312)
	current	43 (8.7)	1.62 (0.94-2.82, p=0.084)	1.59 (0.91-2.77, p=0.104)
Smoking * Sex				**(p = 0.0023)**
Obesity (%)	no	319 (64.4)	*Reference*	*Reference*
	yes	176(35.6)	**1.37 (1.01-1.84, p=0.041)**	**1.38 (1.01-1.87, p=0.040)**
Previous exacerbation (%)		74 (14.9)	**4.05 (2.94-5.56, p<0.001)**	**4.25 (3.07-5.90, p<0.001)**
R03 medication (%)	None	165 (33.3)	*Reference*	
	Rescue	35 (7.1)	**2.82 (1.49-5.37, p=0.002)**	**3.08 (1.61-5.90, p=0.001)**
	Controller	167 (33.7)	**2.45 (1.57-3.82, p<0.001)**	**2.50 (1.59-3.92, p<0.001)**
	Rescue +Controller	128 (25.9)	**4.50 (2.90-7.00, p<0.001)**	**4.42 (2.82-6.94, p<0.001)**
R03 Controller to Total Ratio		0.8 (0.3)	0.79 (0.50-1.26, p=0.324)	0.77 (0.48-1.23, p=0.276)
Respiratory complaints (%)	Wheezing	323 (65.8)	**2.08 (1.45-2.96, p<0.001)**	**2.07 (1.44-2.97, p<0.001)**
	Dyspnea	301 (65.4)	**2.02 (1.39-2.91, p<0.001)**	**2.18 (1.48-3.21, p<0.001)**
	Chronic cough	105 (21.2)	1.32 (0.95-1.83, p=0.105)	1.34 (0.96,1.87, p=0.085)
Lung function (%)	normal	359 (76.2)	*Reference*	*Reference*
	restriction	11 (2.3)	1.27 (0.47-3.44, p=0.643)	1.20 (0.44-3.27, p=0.722)
	obstruction	101 (21.4)	**1.57 (1.11-2.20, p=0.010))**	**1.52 (1.07-2.15, p=0.019)**
FEV1% predicted (sd)		91.2 (17.4)	**0.98 (0.97-0.99, p<0.001)**	**0.97 (0.97-0.99, p<0.001)**
COPD co-diagnosis (%)		48 (9.7)	1.45 (0.96-2.21, p=0.080)	1.48 (0.97-2.28, p=0.071)
Depressive symptoms (%)		72 (14.7)	**1.50 (1.02-2.19, p=0.038)**	**1.55 (1.05-2.29, p=0.027)**
Diabetes Mellitus (%)		44 (9.0)	1.18 (0.70-1.97, p=0.530)	1.12 (0.66-1.91, p=0.678)
Coronary Heart Disease (%)		16 (3.3)	0.98 (0.44-2.23, p=0.971)	1.05 (0.46-2.41, p=0.899)

Table 2. Hazard ratios for the association between determinants and a subsequent asthma exacerbation in 495 participants, Univariate and Model 1 = age and sex adjusted.

Previous exacerbation = Prior exacerbation last 12 months; Respiratory Medication – any valid R03 prescription; Obesity – body mass index > 30; Respiratory complaints ; confirmative answer to: did you suffer from wheezing / did you suffer from dyspnea/ did you cough daily for >3 months in the past 2 years?; FEV1 -forced expiratory volume in one second ; Depressive symptoms = CES-D score (Center for Epidemiologic Studies Depression scale) > 16

Table 3 : ***Hazard ratios for the association between respiratory medication and a subsequent asthma exacerbation, stratified by exacerbation status in the previous year.***

			Severe exacerbation last year (n= 74)		No severe exacerbation last year (n= 421)
		N(%)	HR age +sex adjusted	N(%)	HR age +sex adjusted
R03 medication (%)	None	5 (6.8)	-	160 (38.0)	-
	Rescue	5 (6.8)	**4.78 (1.10-20.82, p=0.037)**	30 (7.1)	2.06 (0.96-4.44, p=0.065)
	Controller	20 (27.0)	1.04 (0.30-3.65, p=0.953)	147 (34.9)	**2.27 (1.41-3.67, p=0.001)**
	Controller and rescue	44 (59.5)	1.09 (0.33-3.56, p=0.889)	84 (20.0)	**3.64 (2.16-6.16, p<0.001)**
Controller to total ratio	Controller/controller+ rescue	74 (100)	**0.26 (0.09-0.76, p=0.014)**	421 (100)	1.13 (0.61-2.10, p=0.691

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SUPPLEMENTAL DATA

Incidence and predictors of asthma exacerbations in middle-aged and older adults: the Rotterdam Study

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Supplemental figure 1; The Rotterdam Study

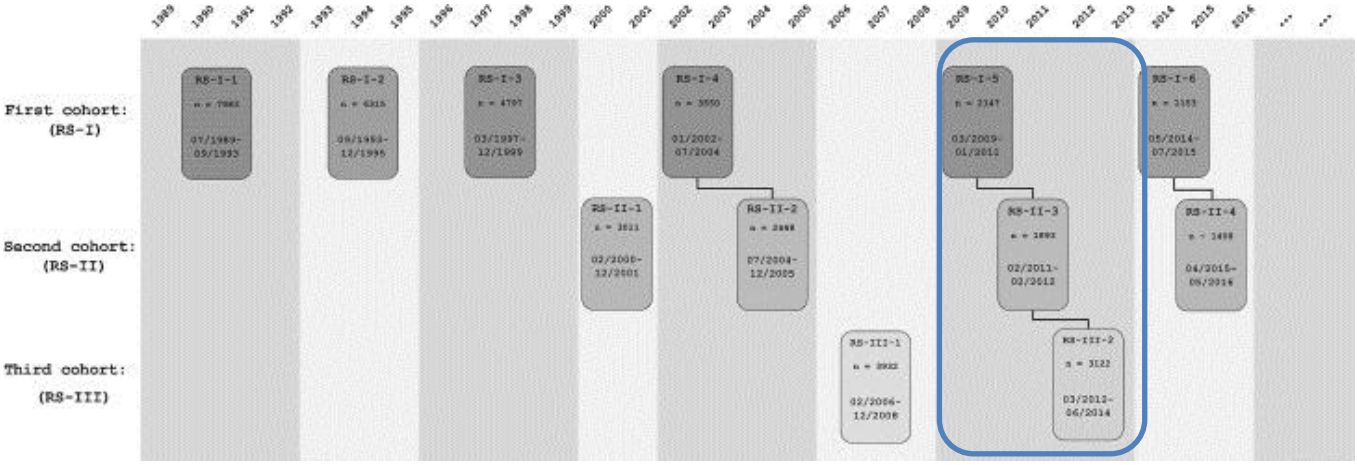


Diagram of examination cycles of the Rotterdam Study (RS). The three cohorts and their re-examinations are horizontally depicted; RS-I, RS-II and RS-III.

Outlined in blue are examinations RS-I-5, RS-II-3, and RS-III-2, these share the same program items and were used to determine determinants of asthma exacerbations.

Figure derived from [16],
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5662692/figure/Fig1/?report=objectonly

Supplemental figure 2; FLOWCHART

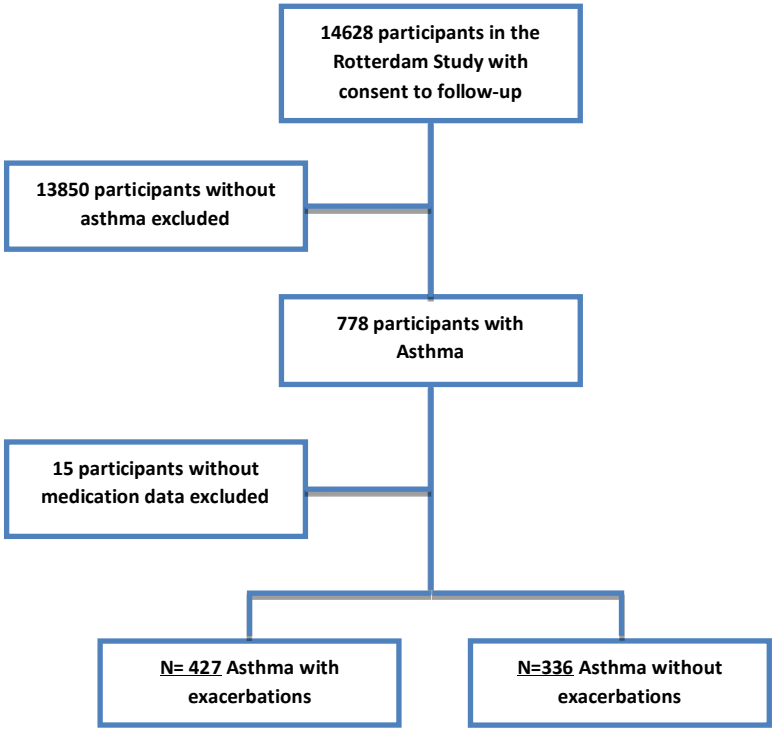


Figure 2. Study profile of participants with the exacerbation status determined at end of follow-up.

Supplemental table I with frequent exacerbators

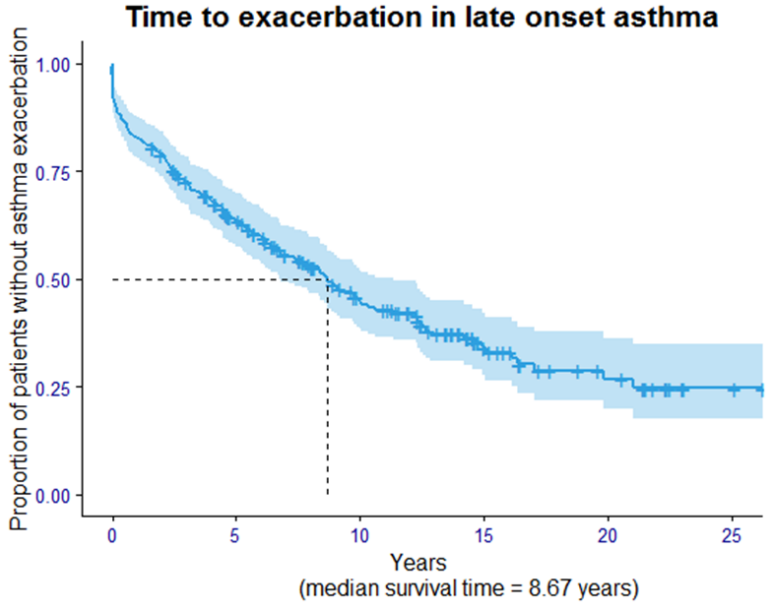
		Asthma subjects without exacerbations	Asthma subjects with exacerbations (not frequent)	Asthma subjects with frequent exacerbations
n		336	396	31
Females (%)		226 (67.3)	282 (71.2)	20 (64.5)
Age (mean (sd))		60.85 (8.43)	62.00 (8.17)	57.40 (7.59)
BMI (mean (sd))		28.20 (4.61)	28.16 (4.70)	29.42 (5.77)
Smoking status (%)	never	103 (31.2)	142 (36.4)	8 (25.8)
	former	171 (51.8)	174 (44.6)	12 (38.7)
	current	56 (17.0)	74 (19.0)	11 (35.5)
Packyears(mean(sd))		14.17 (19.66)	15.01 (20.54)	17.92 (23.53)
Total follow-up years (mean (sd))		11.98 (6.08)	14.97 (6.20)	11.22 (5.37)
Follow-up years with asthma (mean (sd))		10.74 (5.59)	13.36 (5.82)	9.74 (4.86)
Asthma onset after 40 yo (%)		274 (81.5)	321 (81.1)	20 (64.5)
Asthma onset age (mean (sd))		54.81 (17.43)	53.48 (21.98)	46.34 (20.86)
Total N. exacerbations (mean (sd))		0.00 (0.00)	3.49 (3.32)	17.03 (11.06)
Exacerbation rate (mean (sd))		0.00 (0.00)	0.29 (0.23)	1.81 (1.06)
Diabetes mellitus (%)		38 (11.3)	35 (8.8)	4 (12.9)
Hypertension (%)		170 (53.5)	197 (51.8)	19 (61.3)
Depressive symptoms (%)		37 (15.5)	44 (19.0)	10 (37.0)
Osteoporosis (%)	normal	132 (48.4)	138 (42.9)	12 (48.0)
	osteopenia	132 (48.4)	167 (51.9)	12 (48.0)
	osteoporosis	9 (3.3)	17 (5.3)	1 (4.0)

Supplemental table II; Baseline characteristics of fifth examination round participants, stratified by sex

		Males (n=150)	Females (n=345)	p
Age		69.5 (8.3)	69.1 (9.1)	0.401
BMI	<30	104 (69.3)	215 (62.3)	0.134
	>30	46 (30.7)	130 (37.7)	
Smoking	never	33 (22.0)	131 (38.0)	<0.001
	former	107 (71.3)	181 (52.5)	
	current	10 (6.7)	33 (9.6)	
Education	low	42 (28.4)	224 (64.9)	<0.001
	intermediate	69 (46.6)	71 (20.6)	
	high	37 (25.0)	50 (14.5)	
Follow-up time		4.2 (1.8)	4.2 (1.7)	0.800
Time to exacerbation*		3.2 (1.9)	2.9 (1.9)	0.347
Spirometry	normal	102 (69.4)	257 (79.3)	0.042
	restriction	4 (2.7)	7 (2.2)	
	obstruction	41 (27.9)	60 (18.5)	
FEV1%predicted		91.1 (17.3)	91.3 (17.4)	0.900
FEV1/FVC		72.6 (8.4)	75.3 (7.4)	<0.001
Prior exacerbation[#]		0.2 (0.6)	0.2 (0.7)	0.355
Respiratory medication		63 (42.0)	131 (38.0)	0.399
Complaints (≥3)		71 (47.3)	225 (65.4)	<0.001
Wheezing		87 (58.0)	236 (69.2)	0.016
Dyspnea		67 (48.2)	234 (72.9)	0.011
Chronic cough		27 (18.1)	78 (22.8)	0.296
COPD co-diagnosis		23(15.3)	25(7.2)	0.009
Diabetes		21 (14.0)	23 (6.8)	0.011
Heart Failure		9 (6.0)	12 (3.5)	0.203
CHD		34 (22.8)	20 (5.9)	
Depressive symptoms		11 (7.4)	61 (17.8)	

Original data are given and presented as mean(sd) or %. Follow-up time given in years.
* N=177, 318 participants did not exacerbate during follow-up
[#]exacerbation rate of previous year.
Data were missing in (n=): Education(2), Physical Activity (128), NLR and PLR and SII (8), Spirometry and FEV1 and FEF1/FVC (24), Complaints (1), Diabetes(8), Heart failure (1), CHD(6), Depressive symptoms(4)

Supplemental figure 3; Asthma exacerbation free survival probabilities in subjects with incident (i.e. late onset) asthma



Supplemental Figure C2. Asthma exacerbation free survival probabilities from 2009 onwards

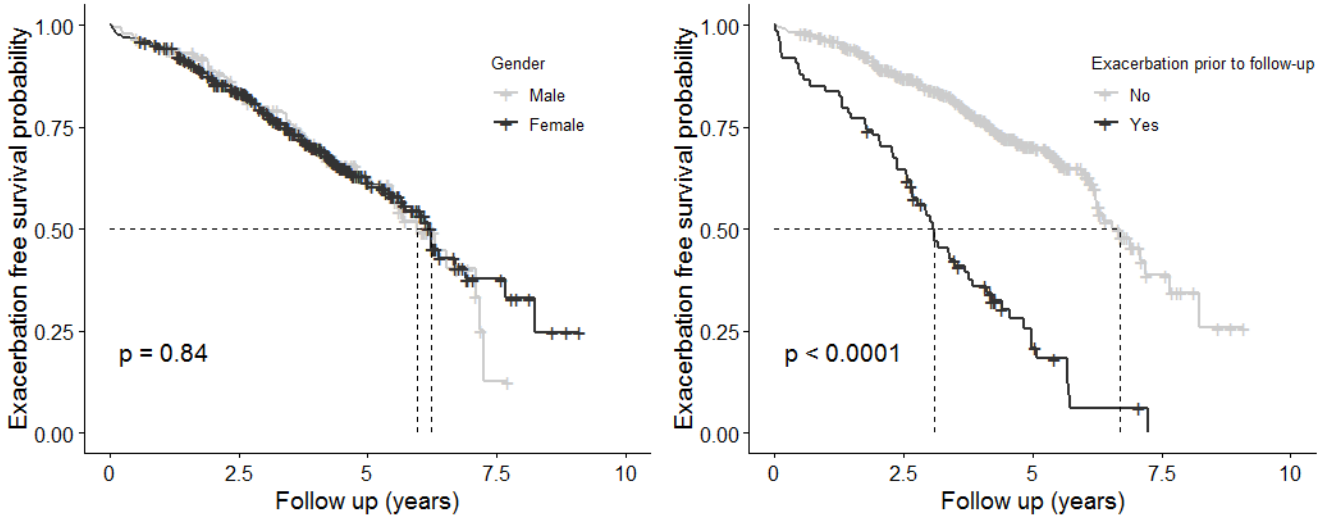


Figure C2. Asthma exacerbation free survival probabilities by sex and by previous asthma exacerbation in the last year. Median survival times (lower-upper): males 5.96 (5.48 – NA), females 6.23(5.67-7.67), no exacerbation in the past year 6.70(6.23-NA), exacerbation in the past year 3.09(2.68- 3.83).

Supplemental Figure 4; Forest plot of the interaction between smoking and sex