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Age- and sex-dependent differences in patients with severe asthma included in the German Asthma Net cohort

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ABSTRACT

Background: Severe asthma affects less than 5% of asthmatics, but is associated with high costs and increased mortality. The aim of this study was to assess age- and sex-dependent differences in this patient group.
Methods: Retrospective analysis of 1317 children and adults with severe asthma who are included in the German Asthma Net registry.
Results: There were more adults than children in the registry and patients' mean age was 52. Apart from children <18 years, there were more women (57%) than men. The age of first diagnosis ranged from 0 to 76 years. 38% of patients had a positive bronchial reversibility after short acting bronchodilators. Quality of life, FEV1 and MEF 25 decreased with older age whereas treatment with oral steroids and monoclonal antibodies increased. An anti-eosinophil treatment was most frequently used in patients aged around 57 years, while an anti-IgE treatment was used in all age-groups including children. There were sex-dependent differences with lower values in men for FEV1, FVC, MEF 25 and DLCO. Yet, women were more frequently unable to work than men due to the disease.
Conclusion: In patients with severe asthma, clinical characteristics, but also treatments differed between age groups and between the sexes, reflecting different phenotypes of the disease.

1. Introduction

Asthma is a heterogenous, multifactorial and chronic inflammatory airway disease, accompanied with a variable airway obstruction or bronchial hyperresponsiveness [1].

While asthma is a frequent disease with a prevalence of 6% in adults and 4% in minors, severe asthma is relatively rare [2–4]. In Western countries less than 5% of asthmatics fit into this definition [5]. However, severe asthma is associated with increased mortality and high cost [6]. In the last years different antibodies have been approved for severe asthma. These are directed against different components of the type-2 inflammation: anti-IgE (Omalizumab) for allergic asthma, anti-Interleukin-5 (anti-IL5, Reslizumab, Mepolizumab), anti-Interleukin-5 receptor α (anti-IL5R, (Benralizumab) for eosinophilic asthma and recently anti-Interleukin-4 receptor α (anti-IL4R, Dupilumab) for asthmatics with increased eosinophils or FeNO.

If symptoms remain uncontrolled despite maximal inhaled therapy and specific biomarkers of type-2 inflammation are increased, these antibodies can be used in order to improve symptoms, lung function and reduce exacerbations. These biological therapies shall be preferred over systemic steroids as the latter cause more side-effects, however use of biologicals causes high costs [2].

Launched in 2009, the German Asthma Net is a central, prospective registry for severe asthma. Its aim is to promote research and public health in the area of severe asthma. Currently, more than 1200 patients have been included from more than 50 centers in Germany. Previous analyses from the registry have shown that the majority (96%) of patients had signs of type-2 inflammation. The mean age was 47 years and 57% of patients were female. The lung function was clearly impaired

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Abbreviations

ACT	Asthma Control Test
AQLQ	Asthma Quality of Life Questionnaire
ACQ	Asthma Control Questionnaire
BMI	Body Mass Index
DLCO	Diffusing capacity for carbon monoxide
EGPA	Eosinophilic Granulomatosis with Polyangiitis
FeNO	Fractional exhaled Nitric Oxide
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
HES	Hypereosinophilic Syndrome
ICS	Inhaled corticosteroid
ICU	Intensive Care Unit
LABA	Long-acting beta2-agonist
MEF 25	Maximal Expiratory Flow at 25% of the FVC
OCS	Oral corticosteroid
PEF	Peak expiratory flow
ppb	parts per billion
VCD	Vocal Cord Dysfunction

with a FEV1 of 66.8% predicted. Patients had a mean annual exacerbation rate of 4 [7].

Recent phase-III trials in severe asthma as well as everyday experience in the clinic, have suggested that phenotypes of severe asthma differ according to age and sex. In the antibody licensing trials, the mean age of patients was 50 years [8–10]. When looking at patients with asthma of all severities, the age distribution shows two peaks, one in childhood between 5 and 18 years and another one in later adulthood of over 60 years [11].

We aimed to describe age- and sex-dependent differences in patients with severe asthma by analyzing all patients included in the German Asthma Network.

2. Material and methods

Data for this study were retrieved from the German Asthma Net Mainz, a registry for severe asthma with 83 participating centers. The criteria for severe asthma are shown in Table 1 [12].

Table 1
Definition of severe bronchial asthma according to ERS/ATS Guidelines 2014.

Definition of severe bronchial asthma:
1. Adults:
Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose inhaled corticosteroids (ICS) and long acting beta agonists (LABA) or leukotriene modifier/theophylline) for the previous year *or* systemic corticosteroids for ≥50% of the previous year to prevent it from becoming "uncontrolled'' or which remains "uncontrolled" despite this therapy. Uncontrolled asthma defined as at least one of the following:
• Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled'' by NAEPP/GINA guidelines)
• Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year
• Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year
• Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
• Controlled asthma that worsens on tapering of these high doses of ICS or systemic corticosteroids (or additional biologics)
2. Children:
- Long-term (>6 months) use of high-dose ICS with or without add-on treatment; or medium dose ICS with at least 2 add-on treatment options e.g LABA; with or without montelukast add-on therapy; with or without tiotropium (LAMA); with or without biologicals to achieve and maintain asthma control.

Participation in the registry was approved by local ethic committees of all centers. All patients in the registry gave written informed consent for participation in the registry and use of their anonymized data. Clinical data of the patients and functional parameters from lung function were included in the database. Furthermore, information concerning patients' quality of life and asthma control were documented (mini AQLQ, ACQ5 and ACT). Here, baseline data was analyzed, when patients were included in the registry.

2.1. Parameter

We analyzed the parameters age, sex, allergies, comorbidities, drug therapy, smoking history, family history, fitness for work and retirement, lung function (FEV1, FVC, MEF, PEF, DLCO), FeNO, blood eosinophils, IgE paO2 and paCO2. Moreover, data from the questionnaires ACT, mini AQLQ and ACQ5 were included. The ACT is a 5 item questionnaire assessing asthma control [13,14]. The score ranges on a scale from 1 (poorly controlled) to 5 (well controlled), with a maximum score of 25. The cut-off for GINA-defined uncontrolled asthma is ≤ 19; the recommendation for patients with severe asthma is ≤ 16 (Korn et al., 2011). Another test for asthma control is the ACQ5 score, containing 5 questions (7-point scale with 0 = no impairment, 6 = maximum impairment) about symptoms, lung function and use of a rescue bronchodilator [15]. Clinic staff scores the FEV1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean value of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled). The mini AQLQ includes 15 questions for physical, emotional, social and occupational issues. Similar to the ACQ5, there is a 7-point scale and mean value is calculated [16].

2.2. Statistical analysis

Continuous parameters are shown as median and interquartile range (IQR). Patients were stratified according to age and explorative analysis was performed. Noticeably descriptive differences were further analyzed using Mann-Whitney *U* Test hence we found the parametric data not to be normally distributed. The age classification was made by using 5 groups (see Table 2; age <18, 18–30, 31–50, 51–65, ≥66 years). Categorical variables were compared using Chi-Square-Test. All tests were two tailed. P-values < 0.05 were considered significant.

3. Results

Up to June 2019, 1329 patients aged 0–90 years were included in the German Asthma Net Registry for severe asthma. For 12 patients the age was not documented and these were excluded from further analysis. Distribution of age, sex and age at the time of first diagnosis is shown in Fig. 1. In childhood (<18 years) there were more male than female patients with severe asthma, whereas in all other age categories there were more female than male patients ($p < 0.01$) (Fig. 1a). The frequency distribution for both sexes has two peaks, one in childhood (<18years) and one in later adulthood (50–60years). Both peaks occur slightly later in female than in male patients.

Table 2 shows clinical and functional characteristics of the patients. The BMI was significantly lower in children than in all other age groups ($p < 0.001$).

The age at diagnosis was available for 850 patients. A first diagnosis of asthma occurred in all ages from 0 to 76 years (Fig. 1b). The proportion of patients who were diagnosed early in childhood (<12 years) was significantly lower in patients over 51 years than in the younger patients ($p < 0.001$). Median age at diagnosis was 17 years for patients under 51 years (IQR 8; 29) and 37 years for patients >51 years (24; 48) ($p < 0.01$).

The symptoms of asthma measured by ACT, ACQ and mini AQLQ were significantly less in patients under 18 years than in older patients

Table 2
Patients characteristics by age. Abbreviations: EGPA, Eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; FVC, forced vital capacity; MEF, mean expiratory flow; PEF, peak expiratory flow; VCD, vocal cord dysfunction.

	all patients	<18 years	18–30 years	31–50 years	51–65 years	≥66 years
n	1317	135	91	397	515	179
BMI[a]	26 (22; 30)	20 (17; 23)	25 (21; 29)	27 (23; 32)	26 (23; 30)	26 (23; 30)
First diagnosis childhood (before 12th year of life), n (% group)	397 (30)	122 (90	58 (63)	120 (30)	82 (15)	15 (8)
Asthma in the family, n (% group)	638 (48)	85 (63)	42 (46)	190 (47)	233 (45)	88 (49)
Nicotine consumption, n (% group)	527 (40)	3 (2)	26 (28)	178 (44)	248 (48)	72 (40)
Unable to work, n [b]						
Unable	322 (24)		40 (43)	130 (32)	146 (28)	6 (3)
Not incompetent	686 (52)		45 (49)	241 (60)	296 (57)	104 (58)
unknown	168 (12)		6 (8)	25 (8)	69 (25)	68 (39)
Retired, n	167	1	2	43	86	35
ACT[a]	15 (10; 20)	19 (16; 93)	14 (10; 19)	14 (10; 19)	14 (10; 20)	14 (10; 19)
Mini AQLQ[a]	60 (46; 77)	77 (61; 93)	56 (47; 76)	55 (44; 72)	60 (45; 76)	58 (44; 73)
ACQ 5[a]	2,6 (1.4; 3.8)	1.4 (0.8; 2.4)	3 (1.6; 3.8)	3 (1.8; 4)	2.6 (1.4; 3.8)	2.6 (1.4; 3.4)
FEV1/FVC (% predicted)[a]	66 (56; 76)	82 (69; 91)	73 (64; 81)	67 (56; 76)	63 (55; 74)	64 (53; 72)
FEV1 (%predicted)[a]	66 (50; 83)	92 (80; 103)	72 (57; 88)	65 (50; 81)	62 (47; 77)	61 (49; 78)
FVC (%predicted)[a]	84 (70; 96)	98 (87; 106)	88 (73; 100)	82 (69; 96)	80 (67; 92)	81 (70; 90)
PEF (%predicted)[a]	70 (51; 89)	91 (78; 104)	71 (55; 86)	72 (53; 89)	66 (47; 87)	59 (46; 81)
MEF 25 (% predicted)[a]	28 (17; 47)	66 (47; 94)	35 (20; 63)	26 (16; 41)	24 (15; 39)	25 (17; 45)
Reversibility (%)[a]/[c]	8.4 (1.6; 17.3)	6.8 (1.4; 13.8)	6.4 (0.6; 18.4)	8.8 (1.8; 20.1)	8.6 (2.2; 16.8)	7.4 (0; 15)
DLCO (% predicted)[a]	77/66; 88)	98 (70; 102)	79 (69; 90)	78 (68; 89)	76 (64; 87)	71 (56; 85)
FeNO (ppb)[a]	34 (17; 59)	23 (11; 38)	20 (12; 44)	30 (15; 57)	38 (22; 70)	42 (25; 66)
pO2 (mmHg)[a]	72 (67; 78)	72 (69; 85)	79 (69; 89)	74 (69; 83)	71 (66; 76)	69 (64; 74)
Eosinophil granulocytes (per µl) [a]						
all	248 (98; 529)	400 (160; 751)	166 (69; 462)	234 (104; 551)	267 (107; 546)	230 (66; 581)
with OCS (n = 353)	200 (72; 533)	–	150 (88; 394)	175 (86; 515)	245 (83; 562)	162 (53; 587)
without OCS (n = 473)	276 (115; 529)	400 (160; 751)	227 (50; 478)	266 (127; 552)	287 (125; 544)	297 (90; 569)
Neutrophil granulocytes (Thous. per µl)[a]	5.1 (3.7; 7.1))	3.7 (2.5; 4.9)	4.8 (3.7; 6.5)	5.2 (4; 7.4)	5.1 (3.7; 7.2)	5.8 (4.2; 7.2)
Total IgE kU/l	187 (66; 490)	416 (151; 2055)	228 (103; 588)	169 (61; 399)	192 (59; 525)	139 (62; 412)
Therapy, n (% group)						
OCS	484 (36)	6 (4)	31 (34)	153 (38)	217 (42)	77 (43)
Anti IgE	314 (23)	46 (34)	34 (37)	107 (26)	101 (19)	26 (14)
Anti IL5***	236 (17)	0 (0)	8 (8)	63 (15)	116 (22)	49 (23)
Comorbidities						
COPD	77 (6)	0 (0)	2 (2)	20 (5)	41 (7)	14 (7)
HES	35 (3)	1 (1)	1 (1)	14 (4)	14 (3)	5 (3)
EGPA	28 (2)	0 (0)	4 (4)	7 (2)	13 (3)	4 (2)
VCD	12 (1)	4 (3)	0 (0)	3 (1)	5 (1)	0 (0)
Bronchiectasis	37 (3)	1 (1)	0 (0)	13 (3)	16 (3)	7 (4)

[a] Median (IQR).
[b] Except patients < 18 years, **>12% from baseline.
[c] Including IL5-receptor antibodies.

(for all $p < 0.001$). With increasing age, there was a decrease in FEV1 ($p = 0.02$) compared to patients under 18 years. No changes were found for FVC ($p = 0.08$) and MEF25 ($p = 0.54$). DLCO was lower in patients over 66 years ($p = 0.003$). For 605 patients, data for reversibility of obstruction after inhalation of a short acting beta-agonist (SABA) were available. 230 patients (38%) had a positive bronchial reversibility defined by an increase of FEV1 of more than 12%. Regarding reversibility no differences between the age groups were observed.

The mean IgE in serum was significantly higher in children than in all other age groups combined ($p < 0.024$). Likewise, eosinophils were higher in children with a median of 400 (163; 580) vs. 240 (96; 527) cells per microliter ($p = 0.027$). Yet, median FeNO values increased with age.

Most patients were treated with inhaled corticosteroids (ICS 93%), with no differences between the age groups. 77% of patients were treated with an ICS/LABA dual combination inhaler, only 13% received a LABA in a mono-inhaler. A LAMA was additionally used in 46% of the patients, but less frequently in children <18 years (25%) than in adults (40–54%) ($p < 0.001$). 35% of patients were taking the leukotriene receptor antagonist montelukast, with decreasing frequency in increasing age, 46% in children, 45% in adults of 18–30 years, 38% in adults of 31–50 years, 33% in adults of 51–65 years and 26% in patients >65 years ($p = 0.01$). Theophylline was used in 14% of patients, mostly in patients over 30 years ($p = 0.01$) (data not presented in table). Additionally, 36% of patients were taking oral steroids, and usage was increasing with age (children versus adults: $p < 0.01$). An antibody treatment was applied in 40% of patients. While anti-IgE therapy was used in all age groups, with one peak in adolescence and one in middle age, anti-IL5 therapy was only used in adulthood. The percentage of patients treated with anti-IL5 or anti-IL5-receptor-antibodies is increasing with age till the age of 51 years (peak) and then decreasing (Fig. 2).

3.1. Sex differences

Looking at the continuous variables FEV1/FVC, FEV1, FVC, DLCO and MEF 25 for adult patients (≥18), women showed significantly higher values for all parameters (FEV1/FVC $p < 0.001$; FEV1 $p = 0.048$; FVC $p = 0.004$; DLCO $p = 0.003$; MEF 25 $p < 0.001$). Regarding reversibility, blood eosinophils and IgE, there was no significant difference between the sexes. There was no difference for these parameters

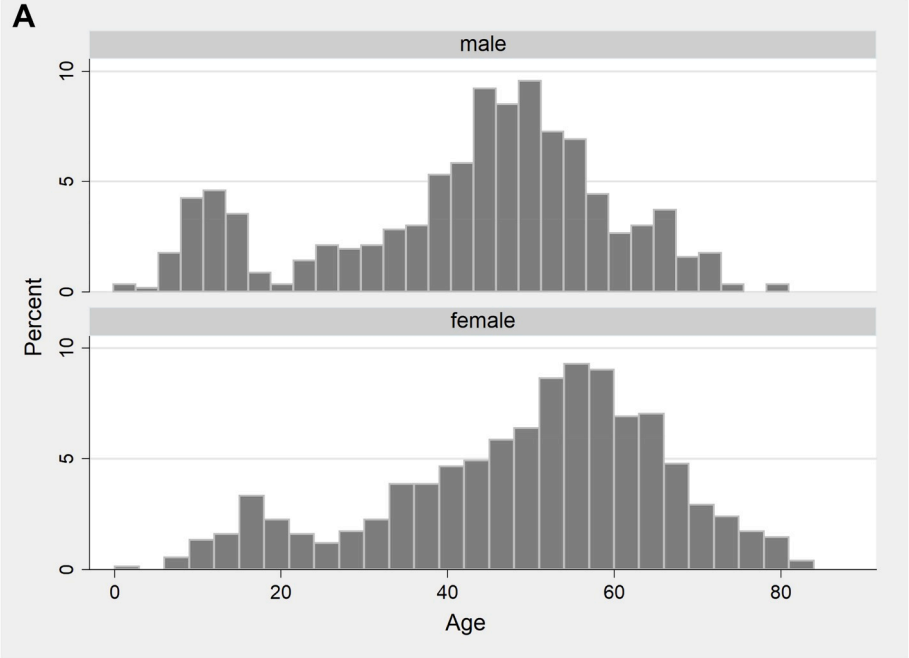

Fig. 1a. Age of patients.

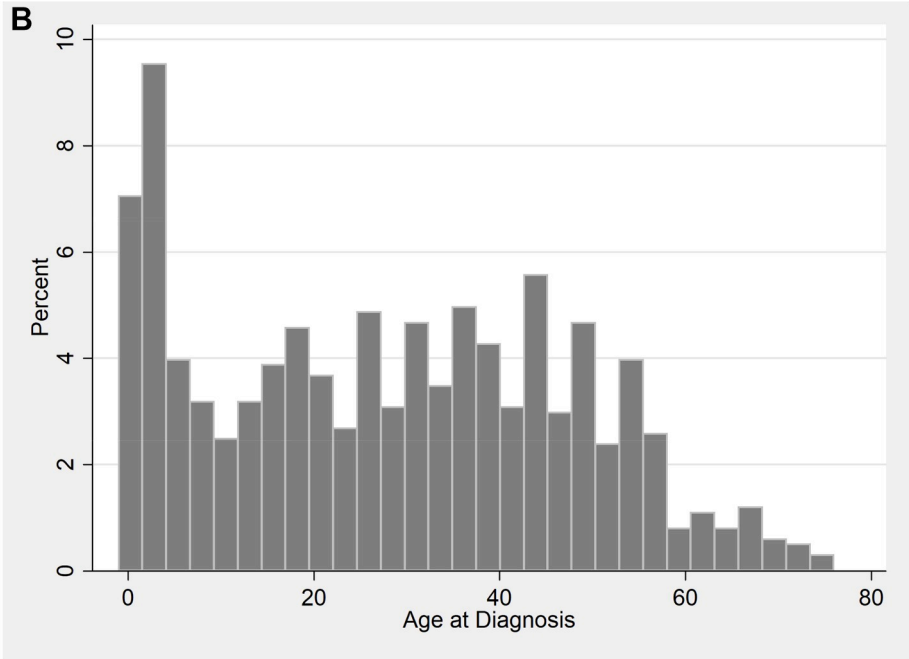

Fig. 1b. Time of first diagnosis.

in children.

The age at first diagnosis was <12 years for 32.4% of men and only 28.4% of women ($p = 0.04$). Inability to work was more frequent in women than men (31 versus 26%, $p = 0.05$), likewise retirement (15% of women and 9% of men, $p < 0.001$). The use of oral steroids was not different between the sexes ($p = 0.9$).

Anti-IgE antibodies were more frequently used in female than in male patients (men 21% and women 26%; $p = 0.05$), whereas there was no significant difference for anti-IL5 antibodies (men 17%, women 18.6%; $p = 0.06$).

4. Discussion

The present analysis offers an overview of age- and sex-specific differences in patients with severe asthma in Germany.

It should be considered that this is a selected cohort of patients with severe asthma, with no conclusions to be drawn for patients with mild to moderate asthma. A selection bias within the cohort of severe asthmatics cannot be excluded. For example, it could be possible that patients who receive biological therapies are preferentially included in the registry.

Strikingly, only 38% of the patients had a positive bronchial reversibility after SABA inhalation. This percentage was stable even in

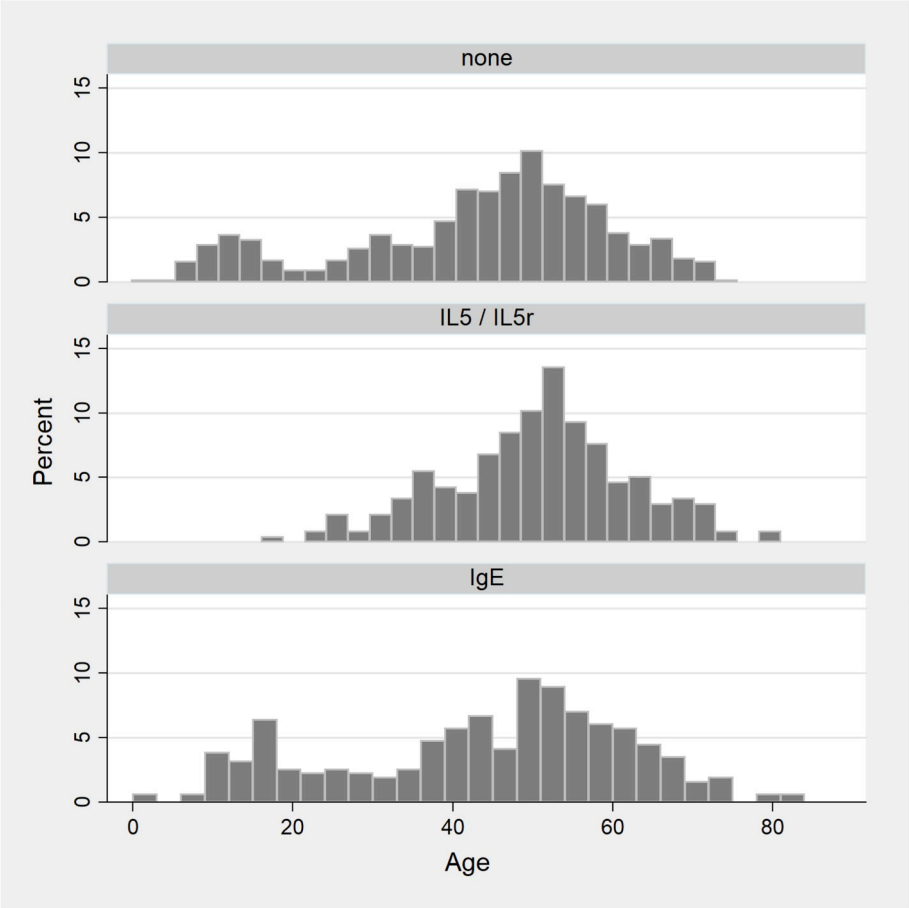

Fig. 2. Antibody-therapy.

young patients. Thus, the criterion of bronchial reversibility is not useful for patients with severe asthma in clinical routine and it raises the question why reversibility is still an inclusion criterion for most drug trials. For example, the mean reversibility in a recent trial of mepolizumab was above 20% [17]. One might think of comorbid COPD as an explanation for the low reversibility in our cohort, but only 5% of patients had also COPD. Therefore there must be other causes of the low reversibility, e.g. remodeling or receptor downregulation. The severity of the disease in the present patient cohort could be an explanation, as the ACQ5-Score of the patients was considerably higher than in studies (2.6 versus 2,1) [17]. Future studies should elucidate if real-world patients without significant acute bronchial reversibility display the same beneficial effects on lung function and quality of life under antibody therapies observed in the clinical trials.

The age distribution shows that in younger patients the male sex is more frequently affected by severe asthma, while with increasing age female sex prevails. This corresponds to observations of the overall cohort of asthmatics of all severities: before puberty boys are more frequently affected, from puberty onwards girls predominate. A relationship with male and female hormones has been suggested, testosterone seems to suppress type 2 inflammation [18]. The reason why women in our cohort are more frequently affected at age over 55 years is not clear. Possibly, a recently described post-menopause phenotype of asthma plays a role [19,20].

The age of first diagnosis underlines that asthma can occur at any age. Hence, also older patients with obstructive lung disease should undergo complete diagnosis, and not be designated as COPD prematurely.

Late-onset asthma is mostly non-allergic and characterized by eosinophilia. Several studies described this distinct phenotype of late-onset eosinophilic asthma [21].

However, in our current analysis eosinophils were not strongly increased at median in the adults. In this regard it has to be taken into account, that eosinophils are decreased by treatments, especially systemic steroids and anti-eosinophil antibodies, but to a lesser degree also by ICS. Contrary, FeNO, which is also a marker of eosinophilic airway inflammation, is decreased by steroids, but not by anti-eosinophil antibodies. Thus, the increased FeNO as well as the use of anti-eosinophil antibodies point towards an eosinophilic phenotype in the older patients.

Here, adult men had a significantly worse lung function than women, while other parameters, notably the symptoms did not differ. One influencing factor could be the higher percentage of patients with smoking history in male compared to female patients. Contrary women were more often unable to work or retired. Additionally, women were more frequently treated with biological therapies than men. This should be carefully observed in future studies in order to understand the reasons for this differential treatment.

The use of oral steroids in the registry was 38%, which is clearly higher than in current analyses of the overall cohort of asthmatics in Germany (8%) [22]. This may be explained by the severity of the disease and reflects the current reality of care of severe asthmatics. The increase of steroid use with age goes in parallel with increasing disease severity as measured by symptoms and lung function. Yet, even in the present cohort, the use of systemic steroids must be questioned, as their use was as frequent as antibody therapies. The latter should be preferred because of reduced side-effects. It remains to be seen if the recent approvals of antibodies for severe asthma will decrease the use of oral steroids.

While anti-IL5-therapies were frequently used in adult patients with severe asthma, so far there was no child registered who obtained such

therapy. This is understandable, since mepolizumab was only recently licensed for use in children (June 2018), a short period compared to the existence of the registry. It will be important to collect more data on the use in children by collection and publication of cases in registries. As allergic asthma prevails in childhood, most children with severe asthma are eligible for treatment with anti-IgE antibody (omalizumab). For omalizumab there is much greater experience in children than for anti-eosinophilic antibodies.

In summary, we have shown significant age- and sex-related differences in patients with severe asthma. Our data show that the most frequent phenotype in young patients is allergic asthma, while eosinophilic asthma increases with age. Phenotypes are reflected by the use of antibody treatments and also differ with regard to the age of disease onset, as the late-onset asthma mostly corresponds to the eosinophilic phenotype. Further studies are needed to characterize possible subtypes of late-onset asthma, such as menopausal manifestation in women.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Katrin Milger: Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing. **Stephanie Korn:** Resources, Writing - original draft, Writing - review & editing. **Roland Buhl:** Resources, Writing - original draft, Writing - review & editing. **Eckard Hamelmann:** Resources, Writing - original draft, Writing - review & editing. **Felix JF. Herth:** Resources, Writing - original draft, Writing - review & editing. **Monika Gappa:** Resources, Writing - original draft, Writing - review & editing. **Nora Drick:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Jan Fuge:** Formal analysis, Writing - original draft, Writing - review & editing. **Hendrik Suhling:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

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