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Early View

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IgA$^+$ memory B cells are significantly increased in patients with asthma and small airways dysfunction

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Take home message

Circulating B cells are altered in asthma patients. Especially, IgA^+ memory B cells are significantly increased in patients with impaired lung function particularly of the small airways thus suggesting a contribution to inflammation in the peripheral lung.

Total word count: 3533

Abstract

Background: Comprehensive studies investigated the role of T cells in asthma leading to personalized treatment options targeting severe eosinophilic asthma. However, little is known about the contribution of B cells to this chronic inflammatory disease. In this study, we investigated the contribution of various B cell populations to specific clinical features in asthma.

Methods: In the All Age Asthma Cohort (ALLIANCE) a subgroup of 154 adult asthma patients and 28 healthy controls were included for B cell characterization by flow cytometry. Questionnaires, lung function measurements, blood differential counts and allergy testing of participants were analysed together with comprehensive data on B cells via association studies and multivariate linear models.

Results: Patients with severe asthma showed decreased immature B cell populations while memory B cells were significantly increased compared to both mild-moderate asthma patients and healthy controls. Furthermore, increased frequencies of immunoglobulin A positive (IgA^+) memory B cells were associated with impaired lung function and specifically with parameters indicative for augmented resistance in the peripheral airways. Accordingly, asthma patients with small airway dysfunction (SAD) defined by impulse oscillometry showed increased frequencies of IgA^+ memory B cells, particularly in patients with mild to moderate asthma. Additionally, IgA^+ memory B cells significantly correlated with clinical features of SAD such as exacerbations.

Conclusions: With this study we demonstrate for the first time a significant association of increased IgA^+ memory B cells with asthma and SAD, pointing towards future options for B cell-directed strategies in preventing and treating asthma.

Abstract word count: 244

Keywords: Lung function, R5-R20, asthma severity, exacerbations

Introduction

Asthma is one of the most prevalent chronic respiratory diseases characterized by airway inflammation, airway hyperreactivity and impaired lung function with obstruction of the central and peripheral airways [1, 2]. In the past decades, a better understanding of distinct phenotypes and endotypes of this heterogeneous disease supported the development of personalized therapeutic approaches, mainly directed against type 2 cytokines in severe eosinophilic asthma [3]. In contrast, knowledge of the impact of B cells on asthma is still very limited and mostly acknowledges their role in allergic asthma as IgE producers [4]. More recently, research revealed immunomodulatory functions of regulatory B cells on allergic airway inflammation [5] and allergen tolerance [6]. Additionally, we could show that B cells control airway hyperreactivity and airway remodeling in a murine asthma model [7], pointing towards a possible role of B cells for future diagnostic and preventive strategies in asthma.

The peripheral B cell compartment consists of various populations ranging from immature so called transitional B cells to mature naïve B cells. Activation of naïve B cells leads to highly specialized antigen-experienced $CD27^+$ memory B cells or plasma cells producing immunoglobulin (Ig) M, A G, or E [8, 9]. Additionally, less antigen-specific and therefore polyreactive IgA is produced by $CD27^-$ memory B cells which play a role in mucosal host-microbiome homeostasis [10]. Memory B cells recirculate in blood, secondary lymphoid tissues [11] and mucosal organs such as the lung [12] and their reactivation results in a strengthened immunoglobulin response [11, 13].

In particular, IgA and IgA^+ B cells are crucial for pulmonary mucosal immune defense [14] and also show immunomodulatory properties [15]. Histology studies in chronic obstructive pulmonary disease (COPD) connected IgA^+ B cells and locally impaired secretion of IgA to inflammation of the small airways [16, 17]. This is of particular interest as inflammation and obstruction of the peripheral airways (bronchioles < 2 mm) is also an important clinical feature of asthma called small airway dysfunction (SAD) [18, 19]. SAD occurs in patients

with mild-moderate and severe asthma and significantly affects exacerbation rates, quality of life, and daily physical activity [20, 21]. While lung function and imaging correlates of SAD have been frequently investigated in recent years [18, 21], little is known about the inflammatory processes contributing to SAD due to the relative inaccessibility of the small airways for cellular specimen collection.

Based on our previous findings in experimental asthma mouse models [5, 7], we hypothesized that B cells influence asthma pathogenesis in humans and are linked to specific clinical characteristics in asthma patients. We therefore analysed immature, mature and memory B cells in peripheral blood of asthma patients and healthy controls of the All Age Asthma Cohort (ALLIANCE). We used supervised and unsupervised statistical methods to search for associations between specific B cell populations and essential clinical asthma features such as disease severity, markers of airway inflammation and lung function. Overall, we aimed to delineate the influence of B cells on inflammatory processes driving asthma pathogenesis or specific traits to address the existing knowledge gap about B cells and asthma and explore the potential of B cells for disease phenotyping and diagnostics to improve personalized asthma care.

Materials and methods

Subjects and sample collection

B cell analysis was done in a subgroup with available blood specimen comprising 154 adult patients and 28 healthy controls of the ALLIANCE Cohort, a longitudinal multicentre clinical cohort of the German Center for Lung Research (DZL) recruiting children with preschool wheeze and asthma as well as adult asthma patients [22]. All local Medical Ethics Committees of the participating centres approved the study protocol and all participants gave their written informed consent. Adults were recruited at the DZL sites of the Airway Research Center North (ARCN). The study was registered at *clinicaltrials.gov* (adult arm:

NCT02419274). Study design, inclusion and exclusion criteria, detailed data and biomaterial collected at yearly study visits have been reported elsewhere [22]. Adult patients with asthma diagnosed according to international [23] and national guidelines [24] were eligible for inclusion as well as healthy controls without a previous asthma diagnosis and respective clinical symptoms. Further information concerning study design, methods, and definition of clinical variables are specified in the online data supplement.

B cell characterization

Isolated peripheral blood mononuclear cells (PBMCs) were used for phenotypic characterization of B cell subpopulations. Cells were blocked, stained and analyzed via flow cytometry. Further details are specified in the online data supplement.

Statistical Analysis

The analysis was done using R (version 4.0.4) with the R packages stats (version 4.0.4), qvalue (version 2.20.0) and ggpubr (version 0.4.0).

For patient characterization, the median (with 25% and 75% inter quartile range) or percentage were calculated, for continuous or categorical variables, respectively. Wilcoxon-Test or Chi-Square Test of Independence were used to calculate the p-values.

The association between pairs of B cell populations and clinical variables was analysed using Kruskal-Wallis Test for categorical and Spearman's correlation for continuous clinical variables. To adjust for multiple testing the Benjamini-Hochberg procedure was used. For continuous variables linear regression lines were generated and for categorical variables the p-values (using Wilcoxon Test) between the categories were calculated. The same method was also used to examine association between pairs of clinical variables.

Multivariate linear regression was used to assess the relationship between B cell populations (percentage of $CD19^+$ B cells) and all clinical variables as used in the association analysis

while accounting for additional confounders such as age and oral corticosteroid (OCS) intake. To determine the significance of the clinical variable term, a model comparison approach was taken. A null model consisting of age and OCS (but without the clinical variable of interest) was compared to the full model consisting of the clinical variable, age and OCS using ANOVA. The resulting ANOVA derived p-values were subsequently corrected for multiple testing using Storey q-values [25].

To define SAD the upper limit of normal and percent predicted values of impulse oscillometry (IOS) parameters were determined according to the 95th centile of a German cohort of healthy adults [26].

To analyse the relationship between SAD and IgA^{+} B cells and clinical variables, a multivariate linear model was built. Features for the model were chosen from age, gender, FeNO, sputum and blood eosinophils, sum of allergen-specific IgE, smoking (pack-years), body mass index (BMI) and OCS intake using a stepwise model selection by Akaike information criteria (AIC). Further information regarding the clinical variables are specified in the online data supplement.

Results

Study population

The study population included n=154 patients with asthma and n=28 healthy subjects from the ALLIANCE cohort. Mean age was comparable between patients and controls. 40% of patients suffered from severe asthma according to ERS/ATS guidelines [27]. More details are presented in table 1 and 2.

TABLE 1. Clinical characteristics of patients with asthma and healthy controls.

Clinical characteristics	Asthma patients (n=154)	Healthy controls (n=28)	p-value
Subjects			
Age [yrs]	53.1 (45.0, 64.9)	56.2 (36.1, 68.7)	0.97
BMI [Kg/m^2]	27.2 (24.4, 30.7)	24.9 (22.4, 27.1)	0.012
Female, n	86 (56%)	12 (43%)	0.288
Current or former smokers ≥10PY, n	40 (26%)	4 (14%)	0.276
Atopy, blood and sputum differential counts			
Atopy, n	88 (59%)	9 (33%)	0.024
Blood eosinophil granulocytes [1000/µl]	0.29 (0.14, 0.49)	0.12 (0.07, 0.17)	<0.001
Blood neutrophil granulocytes [1000/µl]	4.32 (3.37, 5.88)	3.20 (2.53, 3.59)	<0.001
Sputum eosinophil granulocytes [%]	1.8 (0.5, 6.7)	0.1 (0.0, 0.5)	<0.001
Sputum neutrophil granulocytes [%]	56.0 (32.0, 73.1)	53.4 (21.4, 72.8)	0.490
Blood eosinophils ≥ 300/µl, n	75 (49%)	2 (7%)	<0.001
Sputum eosinophils ≥ 2%, n	65 (49%)	0 (0%)	<0.001
Lung function			
FEV_1 [z-score]	-1.53 (-2.40, -0.49)	-0.03 (-0.49, 0.46)	<0.001
FEV_1 [% predicted]	78.55 (65.18, 92.8)	99.62 (92.26, 107.68)	<0.001
FEV_1/FVC [z-score]	-1.73 (-2.69, -0.81)	-0.65 (-0.95, -0.12)	<0.001
FEV_1/FVC [% predicted]	84.95 (74.09, 92.99)	94.52 (90.95, 98.94)	<0.001
FEF_{25-75} [z-score]	-1.69 (-2.78, -0.80)	-0.43 (-0.77, 0.06)	<0.001
FEF_{25-75} [% predicted]	51.55 (30.23, 75.27)	86.05 (73.52, 101.97)	<0.001
FeNO [ppb]	26.0 (16.0, 44.0)	17.0 (13.0, 19.8)	<0.001
R5-R20 [kPa/l/s]	0.11 (0.06, 0.19)	0.03 (0.01, 0.06)	<0.001
R5-R20 [% predicted]	186 (107, 331)	93 (30, 125)	<0.001
AX [kPa/l/s]	0.67 (0.31, 1.61)	0.17 (0.10, 0.27)	<0.001
AX [% predicted]	244 (116, 498)	60 (25, 107)	<0.001
FRES [1/s]	17.07 (12.68, 21.29)	9.44 (8.45, 13.08)	<0.001
FRES [% predicted]	134 (109, 166)	98 (80, 124)	<0.001

Table 1: Data is presented as median (25%, 75% IQR), and number (%). BMI, body mass index; n, number of subjects; PY, pack-years; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow

at 25% - 75% of FVC; FeNO, fractional exhaled nitric oxide; ppb, parts per billon; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; AX, reactance area [kPa/l/s]; FRES, resonance frequency [1/s].

TABLE 2. Clinical characteristics of asthma patients.

Clinical characteristics	**Asthma patients (n=154)**
Disease duration [yrs]	19 (8, 32)
Adult onset, n	102 (67%)
Patients with ≥ 1 severe exacerbation, n	82 (53%)
Severity	
Mild-moderate asthma, n	92 (60%)
Severe asthma, n	62 (40%)
Asthma Control Test [score]	20 (14, 23)
GINA control status	
Controlled, n	48 (31%)
Partly controlled, n	46 (30%)
Uncontrolled, n	60 (39%)
Medication	
Mean ICS dose [Fluticasone equivalent as µg/d]	450 (480)
LTRA, n	25 (16%)
LABA, n	129 (84%)
LAMA, n	37 (24%)
Oral corticosteroids, n	36 (23%)
Omalizumab, n	5 (3%)
Mepolizumab, n	2 (1%)

Table 2: Data is presented as median (25%, 75% IQR), number (%), mean (SD). GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LTRA, leukotriene antagonist; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist, n, number of patients; yrs, years.

Patients with severe asthma have altered frequencies of B cell populations

We investigated peripheral B cells of patients and healthy volunteers by flow cytometry (supplementary figure S1).

Percentages of different B cell subpopulations were significantly associated with important clinical characteristics such as asthma severity, exacerbation frequency, blood neutrophils, sputum eosinophilia and lung function parameters (figure 1, table S3).

Patients with severe asthma showed a significant reduction of the immature B cell populations early transitional 1 (T1) and late transitional 2 (T2) B cells compared to patients with mild-moderate asthma and healthy subjects. Similarly, percentages of mature naïve B cells were diminished in patients with severe versus mild-moderate asthma, but comparable to the percentage of healthy volunteers (figure 2A, figure S2A, table S3). Conversely, proportions of unswitched $CD27^+IgM^+$, as well as class-switched $CD27^+IgG^+$ and $CD27^+IgA^+$ memory B cells were strongly increased in severe compared to mild-moderate asthma. In addition, $CD27^+IgM^+$ and $CD27^+IgA^+$ but not $CD27^+IgG^+$ memory B cells were increased in severe asthma patients compared to healthy controls (figure 2A, figure S2A).

Patients with regular OCS intake showed similar findings as patients with severe asthma (figure 2B and S2B). An increased frequency of $CD27^+IgA^+$ memory B cells occurred in uncontrolled disease according to GINA and was also associated with sputum eosinophilia, but not with blood eosinophilia or atopy (figure 2C, table S3).

Impaired lung function is associated with increased $CD27^+IgA^+$ memory B cell frequency

Several lung function parameters indicative for airway obstruction were moderately associated with distinct B cell patterns. Increased frequencies of IgA^+ memory B cells were associated with central airway obstruction measured by FEV_1 and FEV_1/FVC and small

airway obstruction measured by FEF_{25-75} as well as IOS parameters reactance (AX) and R5-R20 (figure 2D, figure S2C, table S3).

Association of IgA^+ memory B cells and airway obstruction is independent from OCS treatment

As presented above, regular treatment with OCS showed a significant association with all investigated B cell populations (figure 1, table S3). We chose a linear model to investigate if any of the associations seen in figure 1 remained significant independently of OCS intake and age (table 3).

TABLE 3. Linear Model.

B cell variable	Clinical variable	Independent variables per model				q-value of clinical variable
		Term	estimate	standard error	p-value	
$CD27^{+}IgA^{+}$ memory B cell	AX	AX	0.886	0.167	< 0.001	< 0.001
		Age	0.034	0.016	0.039	
		Regular OCS	2.001	0.624	0.002	
		(Intercept)	1.358	0.869		
$CD27^{+}IgA^{+}$ memory B cell	R5-R20	R5-R20	9.117	2.240	< 0.001	0.002
		Age	0.031	0.017	0.066	
		Regular OCS	2.156	0.627	0.001	
		(Intercept)	1.307	0.896		
$CD27^{+}IgA^{+}$ memory B cell	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	-0.683	0.225	0.003	0.026
		Age	0.046	0.019	0.020	
		Regular OCS	2.154	0.713	0.003	
		(Intercept)	0.764	1.097		
$CD27^{+}IgA^{+}$ memory B cell	FEV_1 [z-score]	FEV_1 [z-score]	-0.541	0.177	0.003	0.026
		Age	0.049	0.017	0.005	
		Regular OCS	2.137	0.663	0.002	
		(Intercept)	0.902	0.940		
$CD27^{+}IgA^{+}$ memory B cell	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.597	0.192	0.002	0.026
		Age	0.044	0.017	0.010	
		Regular OCS	2.279	0.649	0.001	
		(Intercept)	0.815	0.944		
$CD27^{-}IgA^{+}$ memory B cell	Number of severe exacerbations	Number of severe exacerbations	0.223	0.068	0.001	0.026
		Age	0.0003	0.011	0.975	
		Regular OCS	0.613	0.475	0.199	
		(Intercept)	2.097	0.591		
$CD27^{-}IgA^{+}$ memory B cell	AX	AX	0.339	0.111	0.003	0.026
		Age	-0.003	0.011	0.803	
		Regular OCS	0.997	0.415	0.017	
		(Intercept)	2.173	0.578		
$CD27^{-}IgA^{+}$ memory B cell	R5-R20	R5-R20	4.224	1.448	0.004	0.032
		Age	-0.004	0.011	0.718	
		Regular OCS	1.152	0.406	0.005	
		(Intercept)	2.084	0.579		

Table 3: Linear model describing B cell subpopulations as a function of clinical characteristics with oral corticosteroids and age as confounders. Coefficient estimates, standard error, and p-value are given for each term in the model. P-values for the clinical variables were corrected for multiple tests (q-value) and all significant results are shown (q-value < 0.05). AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz–resistance at 20 Hz; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

The linear model confirmed the association of increased percentages of $CD27^+IgA^+$ memory B cells with small airway dysfunction which was independent from OCS intake and age. The OCS-independent association was strongest between $CD27^+IgA^+$ B cells and the IOS parameters AX (p-value 3.3×10^{-7}) and R5-R20 (R5-R20 p-value 7.2×10^{-5}) both indicating small airway obstruction (table 3). Comparing the association between R5-R20 and $CD27^+IgA^+$ B cells in the linear model between patients with and without regular OCS intake showed no significant difference in the slope describing the association (p = 0. 148) however percentages of IgA^+ memory B cells were overall higher in patients with OCS (supplementary figure S3).

Additional associations were found for FEF_{25-75}, FEV_1 and FEV_1/FVC (table 3). Furthermore, percentages of $CD27^-IgA^+$ B cell frequencies were also associated with AX and R5-R20 and additionally with frequency of severe exacerbations. All other associations seen between B cell populations were not independent from effects of oral steroid intake (table S4).

IgA^+ memory B cells are increased in asthma patients with SAD

As shown by the linear model, lung function parameters indicative of peripheral airway obstruction showed a significant association with $CD27^+$ and $CD27^-IgA^+$ memory B cells.

The strongest association was seen for both IOS parameters AX and R5-R20, which measure airway distensibility and small airway obstruction respectively. We were therefore interested to further investigate if these cells were also increased in patients with SAD. The IOS parameter R5-R20 has been shown to appropriately reflect resistance of the small airways [18], detect SAD in asthma patients [21] and corresponds well to important clinical outcomes of SAD in asthma patients [18, 21]. We consecutively used R5-R20 values above the upper limit of normal (95th centile) according to published reference equations [26] to define SAD in our cohort and to analyse its association with proportions of IgA^+ B cells in more detail.

SAD was present in 42% (63/152) of all asthma patients in our cohort. Of these, 43% (27/63) had mild-moderate asthma and 57% (36/63) had severe asthma. Further clinical characteristics of all asthma patients with and without SAD are specified in supplementary table 5.

Percentages of $CD27^+IgA^+$ memory B cells were increased in patients with SAD (figure 3A), while $CD27^-IgA^+$ memory B did not show any differences (figure S4A). Furthermore, we observed differences in $CD27^+IgA^+$ memory B cells depending on disease severity (figure 3B). IgA^+ memory B cells were lowest in patients with mild-moderate asthma who did not have SAD and were significantly higher in mild-moderate asthma patients with SAD. Patients with severe asthma had overall increased percentages of IgA^+ B cells without a difference between patients with and without SAD.

SAD and peripheral airway obstruction can occur independently from central airway obstruction. IgA^+ memory B cells were only increased in patients with both central airway obstruction measured by FEV_1/FVC and small airway obstruction measured by IOS (figure 3C). In patients with normal FEV_1/FVC and SAD, increase in percentage of IgA^+ memory B cells did not reach statistical significance compared to patients without central or peripheral airway obstruction ($p = 0.0662$).

To investigate if IgA^+ memory B cells were associated with SAD in the context of other known risk factors such as age, gender, BMI, smoking and markers of T2 inflammation such as blood and sputum eosinophils, specific IgE and FeNO [20] we used a multivariate regression model. In patients with mild-moderate asthma, IgA^+ memory B cells were associated with SAD in addition to other known risk factors such as sputum eosinophils and gender (table 4). Adding severe asthma patients to the model did not show an association between SAD and IgA^+ memory B cells (table S6).

TABLE 4. Regression model for SAD defined by R5-R20 in mild-moderate asthma patients.

	Estimate	**Standard Error**	**p-value**	**95% CI Lower Bound**	**95% CI Upper Bound**
$CD27^+IgA^+$ memory B cell	0.29	0.109	0.008	1.087	1.683
Sputum eosinophils	0.095	0.04	0.017	1.022	1.197
Blood eosinophils	-4.805	2.015	0.017	0.0001	0.294
Gender (female)	-1.392	0.599	0.02	0.071	0.769
Sum of sIgE	0.004	0.002	0.13	0.998	1.008

Table 4: Result of stepwise multivariate regression model (n=80). The dependent variable is SAD defined by the 95th centile of R5-R20. A stepwise-forward regression was used to find the best model using AIC. The table shows the variables with best model fit ($CD27^+IgA^+$ memory B cells [%], sputum eosinophils [%], blood eosinophils [1000/µl], gender, sum of sIgE, sum of 36 allergen-specific Immunoglobulin E [kU/l]. Variables not selected by best model fit are not shown (regular OCS intake (yes/ no), FeNO [ppb], BMI [Kg/m^2], age, and smoking [pack-years]).

IgA^+ memory B cells and clinical features of SAD

Patients with SAD present more often with uncontrolled asthma [28], frequent exacerbations [21] and impaired quality of life [18]. Percentages of $CD27^+IgA^+$ and $CD27^-IgA^+$ B cells correlated with the number of exacerbations similarly as sputum eosinophils (figure 4, table S7). Equally, $CD27^+IgA^+$ were correlated with impaired asthma control and reduced quality of life as assessed by the Asthma Control Questionnaire (ACQ-7) and Asthma Quality of Life Questionnaire respectively (figure S5, table S8-9).

Since IgA^+ B cells play an important role in mucosal immune defence, we analysed IgA^+ memory B cells in SAD patients with frequent (≥ 2x per year) respiratory tract infections (RTIs). In the ALLIANCE cohort, patients with and without SAD did not differ regarding the occurrence of frequent RTIs (17/63 patients with SAD reported frequent RTIs, 17/89 without SAD and with frequent RTIs, p=0.341). Equally, in patients with SAD, frequencies of IgA^+ memory B cells did not differ depending on presence or absence of frequent RTIs (figure S6).

Discussion

In this study we demonstrated significant alterations of immature and mature B cell populations in asthma. Importantly, we described for the first time an unappreciated connection of IgA^+ memory B cells with SAD. IgA^+ memory B cells were associated with peripheral airway obstruction measured by R5-R20 irrespective of disease severity and correlated with an increased number of severe exacerbations and worse asthma control.

OCS intake is known to be a major confounder of systemic immune responses, an effect that was evident for most B cell populations examined in our study. Importantly, the link between increased systemic IgA^+ memory B cell frequencies and lung function parameters indicative for peripheral airway obstruction such as R5-R20, AX and FEF_{25-75} [18, 21] was independent of the influence of OCS intake and age. R5-R20 has been shown to reflect increased narrowing of the small airways [18, 21] and important clinical outcomes [18, 29]. We

therefore used published reference equations for R5-R20 to define SAD and demonstrated an increase of IgA^+ B cells in patients with SAD. This link was particularly evident in patients with mild-moderate asthma indicating a role for IgA^+ B cells in SAD irrespective of disease severity. This is important as SAD is not only found in severe asthma patients but also in mild-moderate disease [20, 21].

Little is known so far about inflammation or remodelling processes in the peripheral airways in asthma mostly due to their difficult accessibility. Histology data originates mostly from patients with fatal asthma attacks [30], limiting its translation to asthma patients in general. There is some evidence for a role of T2 inflammation in SAD from *in vitro* experiments [31] and histology of transbronchial biopsies revealed eosinophilic inflammation, particularly in the parenchyma of patients with nocturnal asthma symptoms [32] – symptoms that are connected to SAD [28]. Clinical markers of T2 inflammation for example blood and sputum eosinophils have also been linked to the presence of SAD [20] and T2 targeting biologicals have been shown to ameliorated peripheral airway resistance measured by R5-R20 [33]. However, overall knowledge about inflammation connected to SAD is still very limited particularly also regarding the impact of B cells on SAD in asthma patients.

While our study is the first to link IgA^+ memory B cells with SAD in asthma, our finding is supported by several studies linking IgA^+ B cells to small airway inflammation in chronic obstructive pulmonary disease (COPD). Histology studies of lungs from patients with COPD show increased IgA^+ B cell frequencies in lymphoid follicles, particularly in the distal lung parenchyma and close to small airways, which correlate with disease severity [16]. Furthermore, in COPD there is a strong link between localized mucosal deficiency of secretory IgA (sIgA) and increased inflammation and airway remodelling most likely driven by impaired local pathogen defense [17, 34]. Additionally, reduced capacity for transcytosis of IgA over the epithelial barrier has been shown in both small airways of COPD patients [34]

and airway epithelial cells in asthma [35] and sIgA in bronchoalveolar lavage fluid inversely correlates with asthma symptoms [36].

It remains however unsolved if increased presence of IgA^+ B cells in the lung periphery of COPD patients with small airway disease reflect an exacerbated response against pathogens, potentially due to intraluminal sIgA deficiency or if they could drive inflammation and remodelling for example by producing antibodies against self-antigens [16].

Here, we showed for the first time that SAD in asthma patients is associated with increased frequencies of circulatory IgA^+ memory B cells. This is in concordance with previous observations showing that systemic and pulmonary memory B cells pools are connected, as memory B cells in the lung depend on both local induction [37] as well as replenishment from extra-pulmonary organs [38, 39]. Furthermore, we carefully investigated and excluded other reasons for increased blood IgA^+ memory B cells in the context of asthma as frequent respiratory tract infections, smoking [40] and atopy [41].

Based on our analysis and previously published histological evidence [30], IgA^+ memory B cells could serve as a biomarker for inflammation of the small airways – a compartment of the lung which is difficult to reach for diagnostic evaluation especially in asthma patients in whom lung histology is usually not available. However, due to the observational character of the ALLIANCE cohort, we cannot answer the question whether increased IgA^+ memory B cells are a cause or co-phenomenon of SAD. Future studies need to confirm this link and assess its use as a biomarker for SAD development and progression.

In addition to our results regarding IgA^+ memory B cells, we demonstrate substantial changes of other B cell populations in asthma. Naïve mature B cells, as well as T1 and T2 B cells were reduced in patients with severe asthma compared to mild-moderate asthmatics, while IgG^+ and IgM^+ memory B cells were increased in severe asthma. However, these findings did not remain significant after correction for regular OCS intake, a treatment which affected 58% of the severe asthma patients in our cohort demonstrating the importance of considering steroid

effects in the analysis. Further differentiation between asthma-specific or steroid-effects or a combination of both was therefore not possible for these B cell populations – a problem which has been described by other authors as well, particularly in regards to early B cell differentiation [42] [43]. Equally, the association seen between several B cell populations and blood neutrophils in our data set did not remain significant after correction for OCS, most likely also due to effects of OCS on neutrophil frequencies [44]. Noteworthy, we were able to uncover a significant and OCS independent association between IgA^+ memory B cells and SAD. Still, we cannot completely exclude an additional effect of OCS on IgA^+ memory B cell frequencies in patients with severe asthma. This could also explain why the multivariate model which compared IgA^+ memory B cells to other known risk factors for SAD, only revealed a significant association when focusing on patients with mild-moderate asthma who are not exposed to OCS or high inhaled doses of corticosteroids.

A particular strength of our study is the stringent statistical design. Treatment effects are an inevitable problem in asthma research since most patients are already under treatment at the time of inclusion into an observational study. Therefore, appropriate statistical measures need to be applied to control for OCS effects which confirmed in our study a new and until now undescribed role of IgA^+ memory B cells in asthma patients with SAD.

A weakness of our study is that we did not investigate B cells in lung tissue or in the airways. Lung histology as used in COPD studies is rarely available for patients with asthma. Future studies should explore and correlate lung and blood IgA^+ memory B cells, using bronchoalveolar fluid or sputum and ideally lung tissue in combination with additional support from experimental murine models [7]. Additionally, more data is needed regarding the predictive use of IgA^+ memory B cells for SAD development.

In conclusion, we showed that B cell populations are altered in asthma compared to controls, differ between mild-moderate and severe asthma and described disease-specific changes in the B cell repertoire which are independent from systemic corticosteroid effects.

Our results reveal a new and until now undescribed association of IgA^+ memory B cells in asthma patients with SAD, an important clinical feature of asthma with significant impact on symptom burden and quality of life. Most importantly, our data highlights for the first time a role for IgA^+ B cells in asthma and particularly in SAD even in milder disease stages. Future studies are needed to elucidate the specific effects of IgA^+ B cells on the development of SAD and to investigate the use of IgA^+ memory B cells as a biomarker for early diagnosis of SAD in asthma and prevention of lung function decline.

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Figure Legends

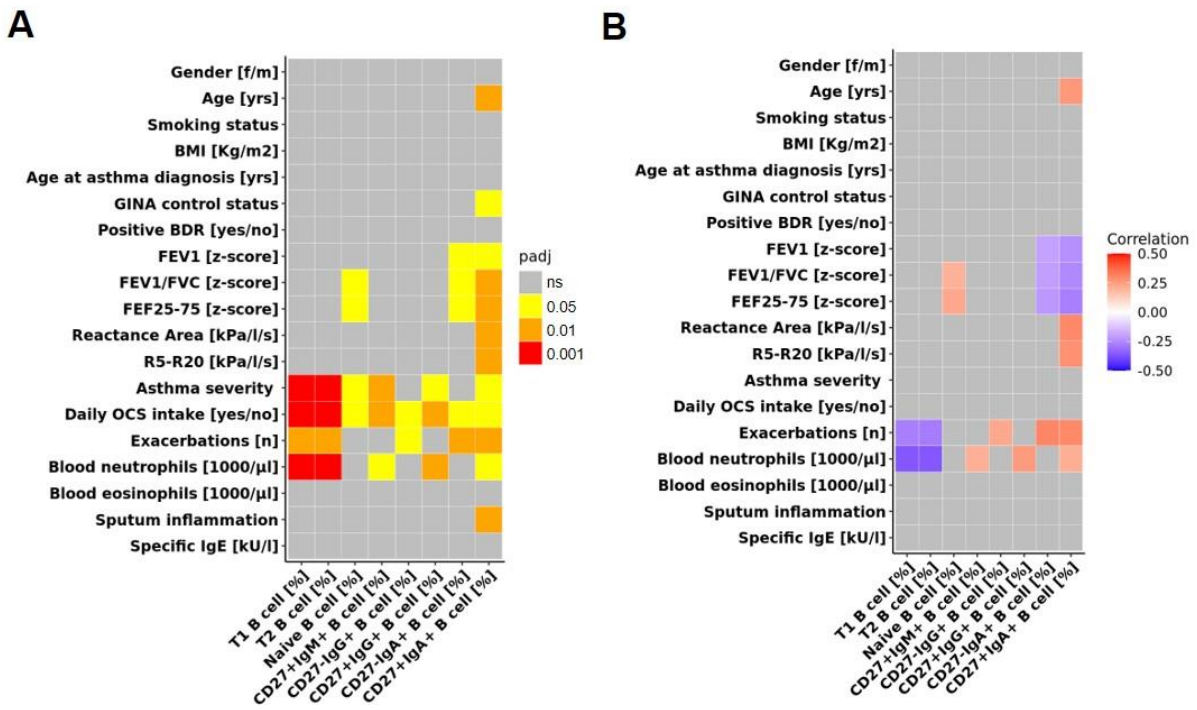

FIGURE 1. Pairwise comparisons (A) and correlations (B) between B cell populations and clinical parameters of asthma patients and healthy controls. Colour code shows significant p-values (A) and estimate for significant correlations (B) analysed by Kruskal-Wallis or Spearman`s correlation respectively with adjustment for multiple testing (padj). B cell subsets are presented as percentage of total $CD19^+$ B cells. BMI, body mass index; GINA, Global Initiative for Asthma; BDR, bronchodilator response; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; OCS, oral corticosteroids; IgE, Immunoglobulin E; T1 B cell, Transitional 1 B cells; T2 B cell, Transitional 2 B cells; ns, not significant.

FIGURE 2.

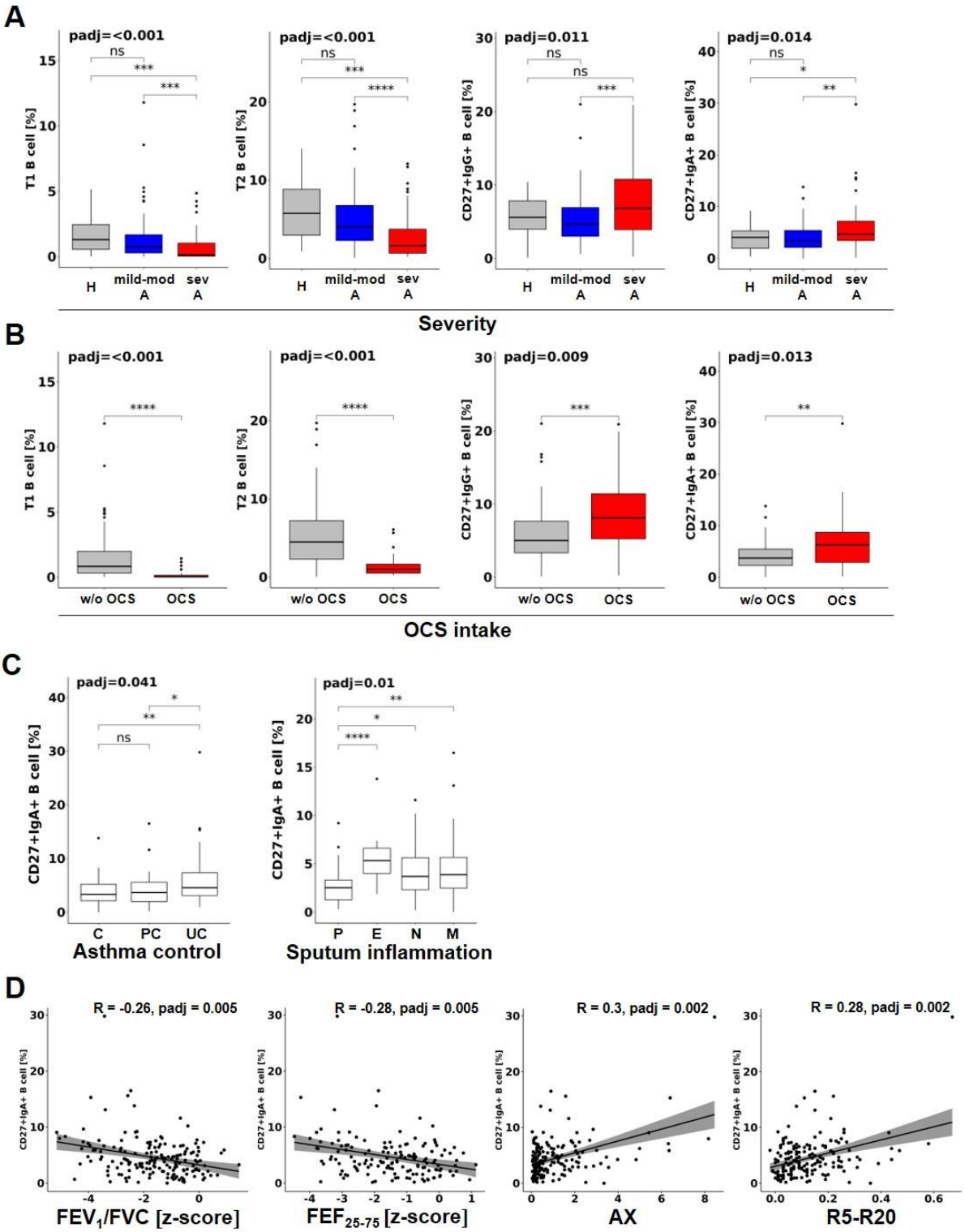

FIGURE 2. Associations between B cell subsets and clinical parameters of asthma patients and healthy controls. Association with asthma severity (A) and OCS intake (B),

asthma control, sputum inflammation (C), and FEV_1/FVC, FEF_{25-75}, AX, R5-R20 (D) are shown for asthma patients and healthy controls. Overall adjusted p-values after multiple test corrections and p-values from categorical group comparisons are shown as well as R and adjusted p-values from Spearman correlations. Other significant associations are shown in Figure S2. T1, Transitional 1 B cells; T2, Transitional 2 B cells; H, healthy; mild-mod A, mild-moderate asthma; sev A, severe asthma; OCS, oral corticosteroids; w/o OCS, without OCS; P, paucigranulocytic; E, eosinophilic; N, neutrophilic; M, mixed granulocytic; C, controlled; PC, partly controlled; UC, uncontrolled; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz–resistance at 20 Hz; ns, not significant; * $p < .05$, ** $p < .01$; *** $p < .001$; **** $p < .0001$.

FIGURE 3

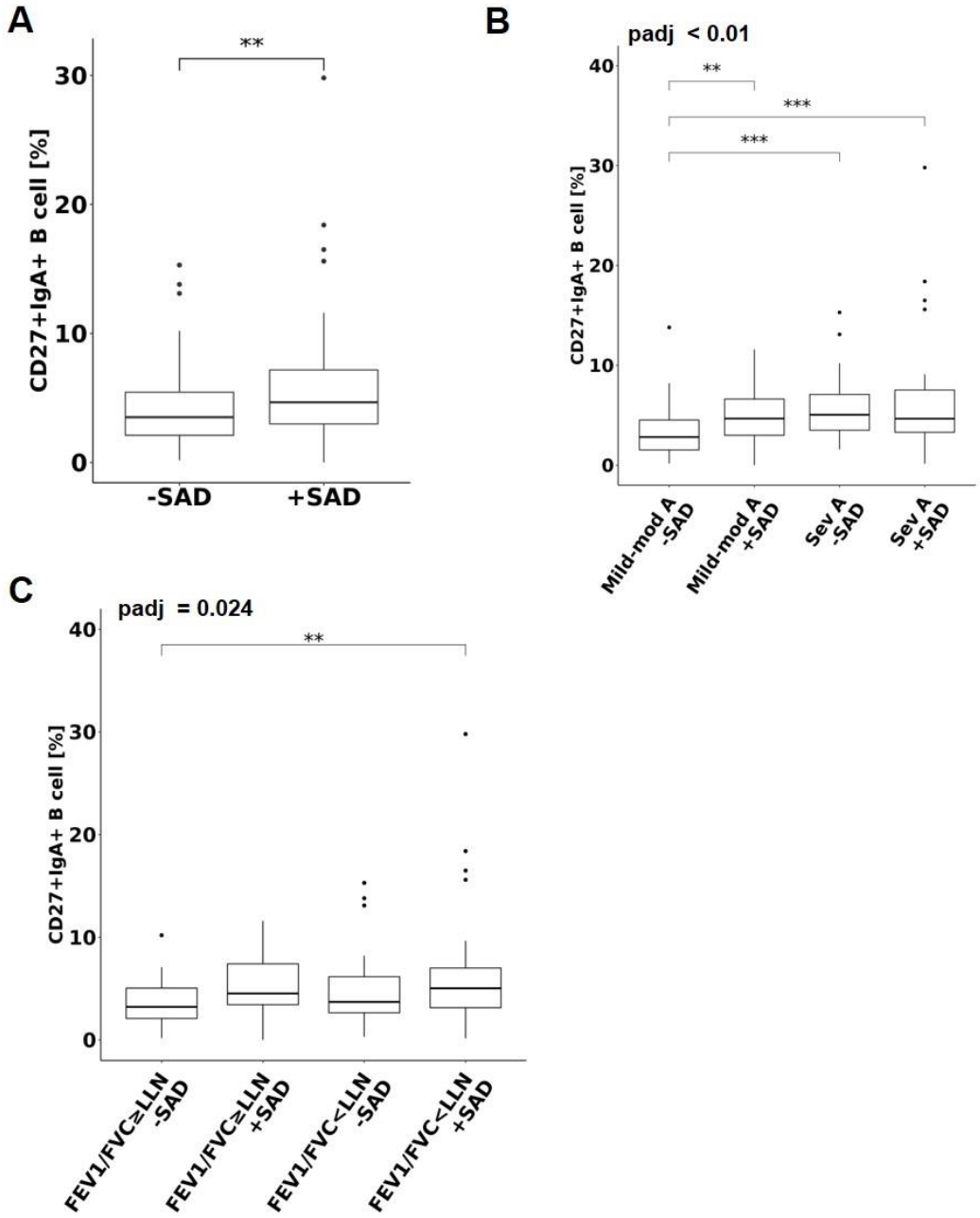

FIGURE 3. IgA$^+$ memory B cells and small airway dysfunction (SAD). CD27$^+$IgA$^+$ memory B cells in patients with and without SAD (A). CD27$^+$IgA$^+$ B cells in patients with / without SAD in mild-moderate and severe asthma (B). CD27$^+$IgA$^+$ B cells in patients with and without central airway obstruction (FEV_1/FVC < LLN) and with / without SAD (C).

SAD, small airway dysfunction; $FEV_1/FVC \geq LLN$ = $FEV_1/FVC \geq$ z-score of -1,64; $FEV_1/FVC < LLN$ = $FEV_1/FVC <$ z-score of -1,64; sev A, severe asthma; mild-mod A, mild-moderate asthma; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal. * $p < .05$, ** $p < .01$; *** $p < .001$.

FIGURE 4

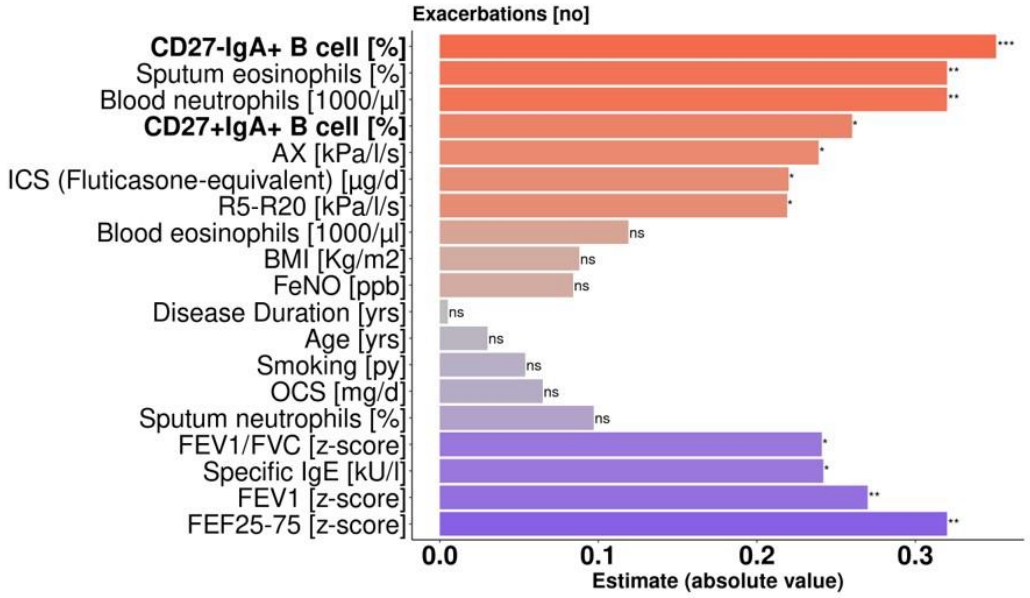

FIGURE 4. Correlations of number of exacerbations with clinical and B cell parameters. Dark red defines the highest positive correlation between the parameters and dark blue shows the lowest negative correlation between the variables. Adjusted p-values after multiple test corrections are shown next to the bars. no, number; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide; ppb, parts per billon; BMI, body mass index; yrs, years; PY, pack-years; ICS, inhaled corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; ns, not significant; * $p < .05$, ** $p < .01$; *** $p < .001$.

IgA^{+} memory B cells are significantly increased in patients with asthma and small airways dysfunction

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Online Data Supplement

Materials and methods

Study design, methods, and definition of clinical variables

Study visits were only scheduled if a patient was without respiratory tract infections and asthma exacerbations for at least 4 weeks prior to the study visit. During each visit comprehensive questionnaire data was collected regarding asthma and rhinitis symptoms, medication, asthma control, exacerbation and quality of life. Lung function tests including spirometry with reversibility testing, body plethysmography and impulse oscillometry (IOS) were performed using a Masterscreen Body and IOS (Vyaire Medical, Germany) according to established guidelines [1-4]. Lung function parameters were expressed as z-scores [3]. Specific IgE against 36 aero- and food allergens were analysed centrally by Immunoblot (EuroImmun AG, Lübeck, Germany), differential blood counts were assessed in local laboratories. Induced sputum was obtained using an established protocol [5].

Definitions of clinical variables used in the analysis are specified in supplementary Table S1.

TABLE S1. Definition of clinical variables

Variable	Definition
Asthma severity	Defined as mild-moderate or severe asthma according to ERS / ATS guideline 2014 [6]
Asthma control	Assessed by Asthma Control Test (ACT) [7], Asthma Control Questionnaire (ACQ-7) [8] or defined as controlled, partly controlled or uncontrolled according to GINA guideline [9]
Asthma related quality of life	Assessed by the Asthma Quality of Life Questionnaire (AQLQ) [10]
Severe exacerbation	Three days of oral corticosteroids (OCS) treatment or increase of regular OCS dose over a period of at least three days
Atopy	Sensitization against at least one allergen with a specific IgE $\geq$ 0,7 kU/l from a panel of 36 aero- and food allergens

Sum of specific IgE [kU/l]	Sum of 36 allergen-specific IgE measurements /36
Sputum inflammation [11]	Paucigranulocytic (eosinophils < 2%, neutrophils < 40%)
	Eosinophilic (eosinophils ≥ 2%, neutrophils < 40%)
	Neutrophilic (eosinophils < 2%, neutrophils ≥ 40%)
	Mixed (eosinophils ≥ 2%, neutrophils ≥ 40%)
Inhaled corticosteroids (ICS)	Expressed as fluticasone proprionate equivalent
Smoking status	Never or former smokers <10PY
	Current or former smokers ≥10PY
Positive bronchodilator response (BDR)	Increase of FEV_1 ≥ 12% or 200ml after inhalation of 400µg salbutmatol
Adult onset	Asthma onset at adult age (≥ 18 years)
Body mass index (BMI)	weight (Kg) / [height (m)]^2
Small airway dysfunction (SAD)	Defined as R5-R20 (IOS) above the upper limit of normal (95th centile) using age, sex, weight and height adapted reference equations of a German cohort of healthy adults [12]

GINA, Global Initiative for Asthma; PY, pack-years; FEV_1, forced expiratory volume in 1 second; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; OCS, oral corticosteroids; IgE, Immunoglobulin E.

B cell characterization

PBMCs were isolated from heparinized blood by Biocoll (Biochrom, Berlin, Germany) density-gradient centrifugation. Until further use cells were stored in freezing medium (90% FBS, 10% DMSO; Biochrom; Sigma-Aldrich, Steinheim, Germany, respectively) in liquid nitrogen. For phenotypic analyses of B cell subpopulations, isolated PBMCs were blocked with normal rat and mouse serum, followed by incubation with suitable antibodies. Dead cells were excluded by Live/Dead staining according to the manufacturer`s instructions (supplementary table S2). B cell subsets were measured on a FACSCanto II flow cytometer (BD, Heidelberg, Germany) and analyzed by FlowJo software (TreeStar, Ashland, OR, USA). Gating strategies are shown in supplementary figure S1. B cell populations were always presented as percentage of total live $CD19^+$ B cells.

TABLE S2. Anti-human antibodies used for flow cytometric analyses of B cell subsets in peripheral blood

Marker / Dye	Fluorophore	Clone	Company
LIVE/DEAD Fixable Dead Cell Stain	amcyan		Invitrogen, Carlsbad, CA, USA
CD19	PE Cy7	HIB19	BioLegend, San Diego, CA, USA
CD19	PerCP Cy5.5	HIB19	BioLegend, San Diego, CA, USA
CD24	FITC	ML5	BD, Franklin Lakes, NJ, USA
CD27	Pacific Blue	M-T271	BioLegend, San Diego, CA, USA
CD27	APC	O323	eBioscience, San Diego, CA, USA
CD38	PerCP Cy5.5	HIT2	BioLegend, San Diego, CA, USA
IgM	Pacific Blue	MHM-88	BioLegend, San Diego, CA, USA
IgG	PE Cy7	G18-145	BD, Franklin Lakes, NJ, USA
IgA	PE	IS11-8E10	MACS Miltenyi Biotec, Bergisch Gladbach, Germany

Statistical analysis

Clinical variables and B cell populations included in the association analysis are specified in figure 1 and supplementary table S1. Categorical variables comprised gender, smoking status (never or former smoker <10 pack-years/ current or former smoker ≥10 pack-years), GINA control status (controlled/ partly controlled/ uncontrolled), positive bronchodilator response defined as increase of $FEV_1 \geq 12\%$ or 200ml after inhalation of salbutmatol (yes/no), asthma severity according to ERS/ATS Guideline 2014 (mild-moderate/ severe), regular oral corticosteroid intake (yes/no), sputum inflammation type (neutrophilic/ eosinophilic/ mixed/ paucigranulocytic). Continuous variables comprised age, BMI [Kg/m^2], age at first asthma diagnosis, FEV_1 [z-score], FEV_1/FVC [z-score], FEF_{25-75} [z-score], reactance area [kPa/l/s], R5-R20 [kPa/l/s]; blood neutrophils [1000/µl], blood eosinophils [1000/µl], specific IgE (sum of 36 specific IgE against allergens/36), and severe exacerbations. The dataset version used for the analysis was 20180731_V2-1.

B cell subsets were always displayed as percentage of total B cells ($CD19^+$ B cells) and included naïve B cells ($CD19^+CD27^-CD24^{low}CD38^{low}$), early transitional 1 B cells (T1 B cells, $CD19^+CD27^-CD24^{high}CD38^{high}$) and late transitional 2 B cells (T2 B cells, $CD19^+CD27^-CD24^{high}CD38^{med}$), unswitched $CD27^+IgM^+$ memory B cells, class-switched $CD27^-IgG^+$ and $CD27^+IgG^+$ as well as $CD27^-IgA^+$ and $CD27^+IgA^+$ memory B cells.

The same variables were included into the linear regression model with age and regular systemic corticosteroid intake as co-variables.

Some variables have missing data: Sputum cell counts are missing in n=5 healthy controls and n=21 asthma patients; FEF_{25-75} is missing in n=30 asthma patients, number of severe exacerbations in n=9, asthma quality of life questionnaire in n=8 asthma patients.

The multivariate regression model included SAD defined by the 95th centile of R5-R20 and percentage of $CD27^+IgA^+$ memory B cells, regular OCS intake (yes/ no), blood eosinophils [1000/µl], sputum eosinophils [%], FeNO [ppb], BMI [Kg/m^2], gender, age, sum of 36 allergen-specific IgE and smoking [pack-years].

Supplement References

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Supplementary Figure Legends

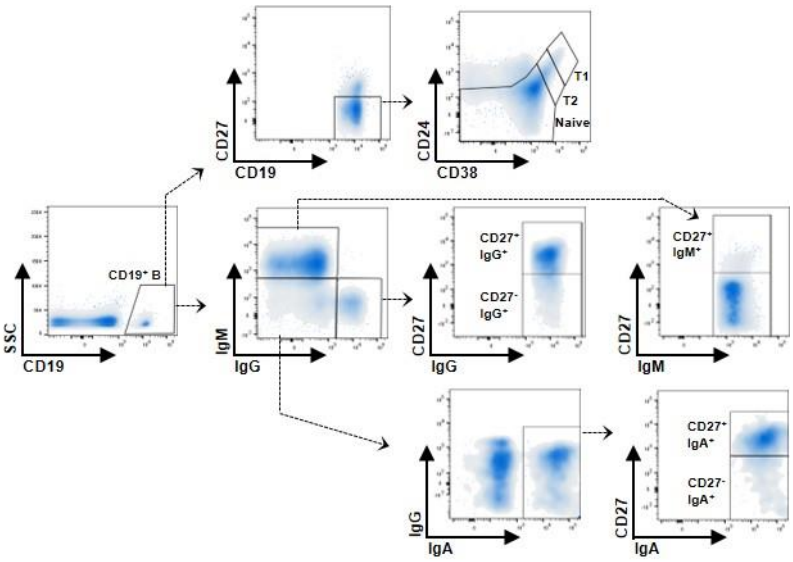

FIGURE S1. Flow cytometry gating strategy of peripheral blood B cell subpopulations. After dead cell exclusion, total B cells were gated as $CD19^{+}$. $CD27^{-}$ B cells were further subdivided into Transitional 1 (T1) B cells, Transitional 2 (T2) B cells and Naïve B cells via CD24 and CD38. $CD19^{+}$ memory B cell subpopulations were gated as IgM^{+}, IgG^{+}, and IgA^{+} cells and subdivided into $CD27^{+}IgM^{+}$ cells as well as $CD27^{+}$ and $CD27^{-}$ IgG^{+} and IgA^{+} cells, respectively.

FIGURE S2

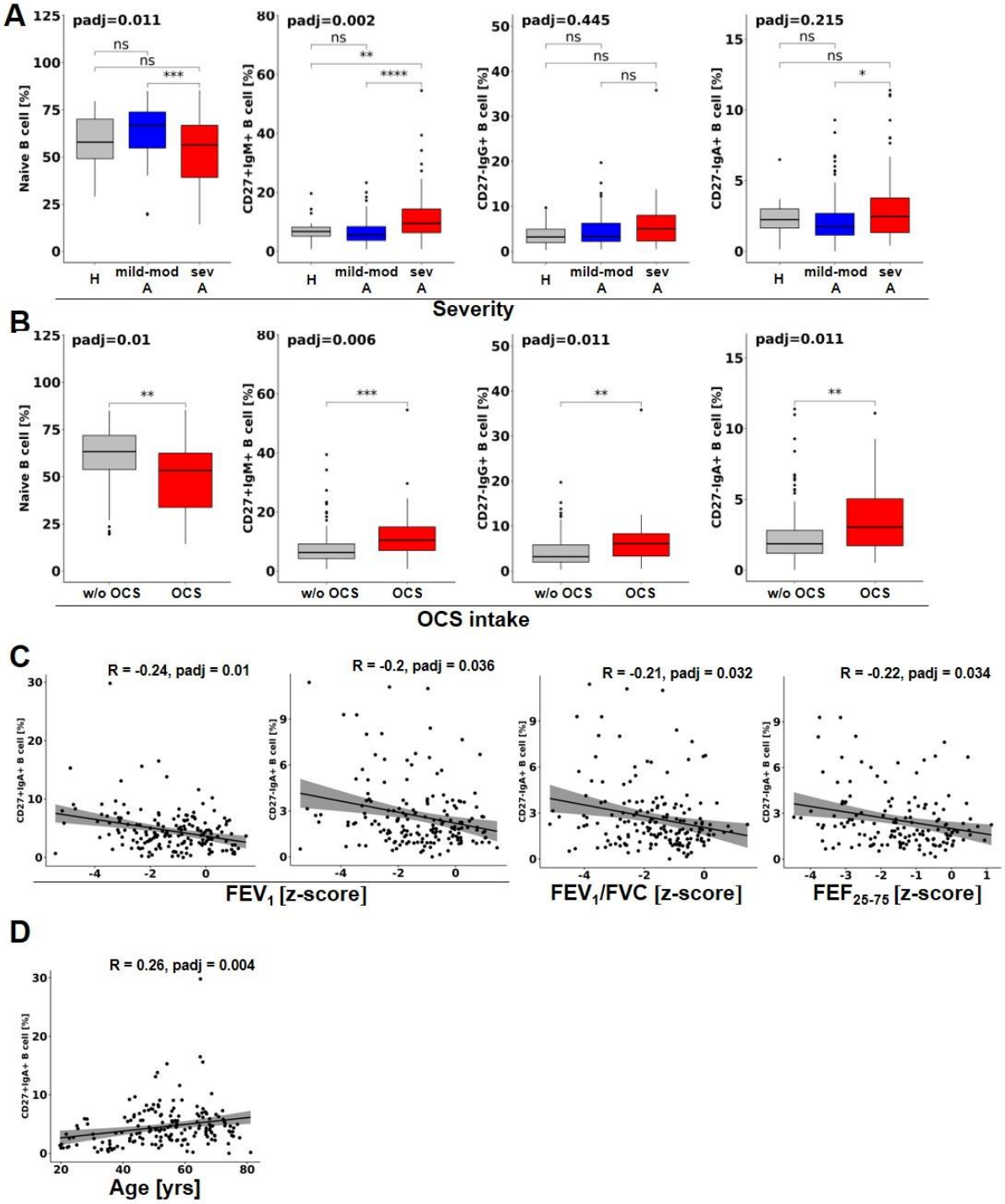

FIGURE S2. Associations between B cell subsets and clinical parameters. Association with asthma severity (A), and OCS intake (B), FEV_1 and FEV_1/FVC, FEF_{25-75} (C) and age (D)

are shown. Overall adjusted p-values after multiple test corrections and p-values from categorical group comparisons are shown as well as R and adjusted p-values from Spearman correlations. H, healthy; mild-mod A, mild-moderate asthma; sev A, severe asthma; OCS, oral corticosteroids; w/o OCS, without OCS; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz–resistance at 20 Hz; ns, not significant; * $p < .05$, ** $p < .01$; *** $p < .001$; **** $p < .0001$.

FIGURE S3.

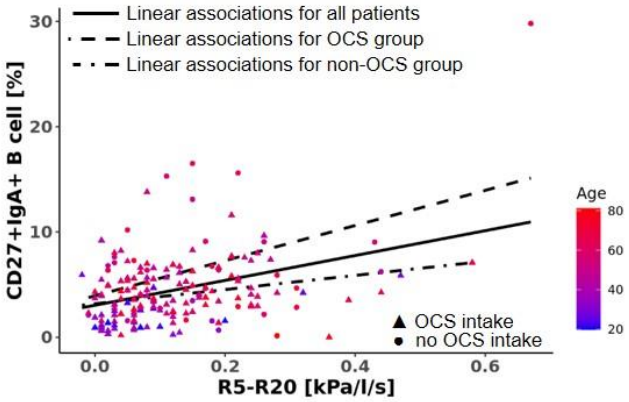

FIGURE S3. OCS independent association between R5-R20 and CD27$^+$IgA$^+$ B cells. CD27$^+$IgA$^+$ B cell frequencies were associated with R5-R20 regardless of OCS treatment (adjusted p-value < 0.002). The linear associations for all patients is given as a solid line and the dotted lines represent the linear associations for OCS (---) and non-OCS (-·-) groups. The difference in slope between the two groups is not significant (p = 0.148). Age is illustrated by color; ▲OCS intake, ● no OCS intake; OCS, oral corticosteroids.

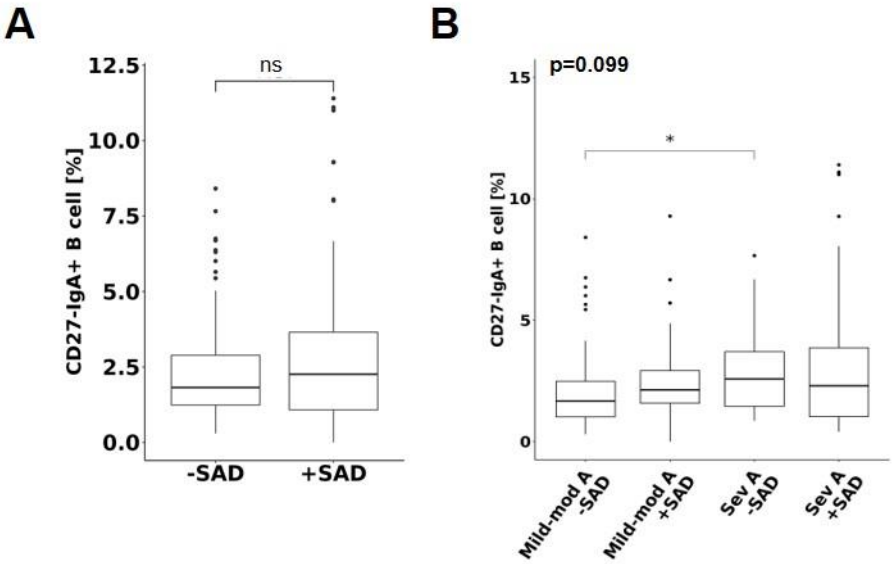

FIGURE S4. CD27$^-$IgA$^+$ memory B cells and small airway dysfunction. CD27$^-$IgA$^+$ B cells in patients with and without SAD (A), in patients with mild-moderate or severe asthma (B). SAD, small airway dysfunction; sev A, severe asthma; mild-mod A, mild-moderate asthma. ns, not significant; * $p < .05$.

FIGURE S5

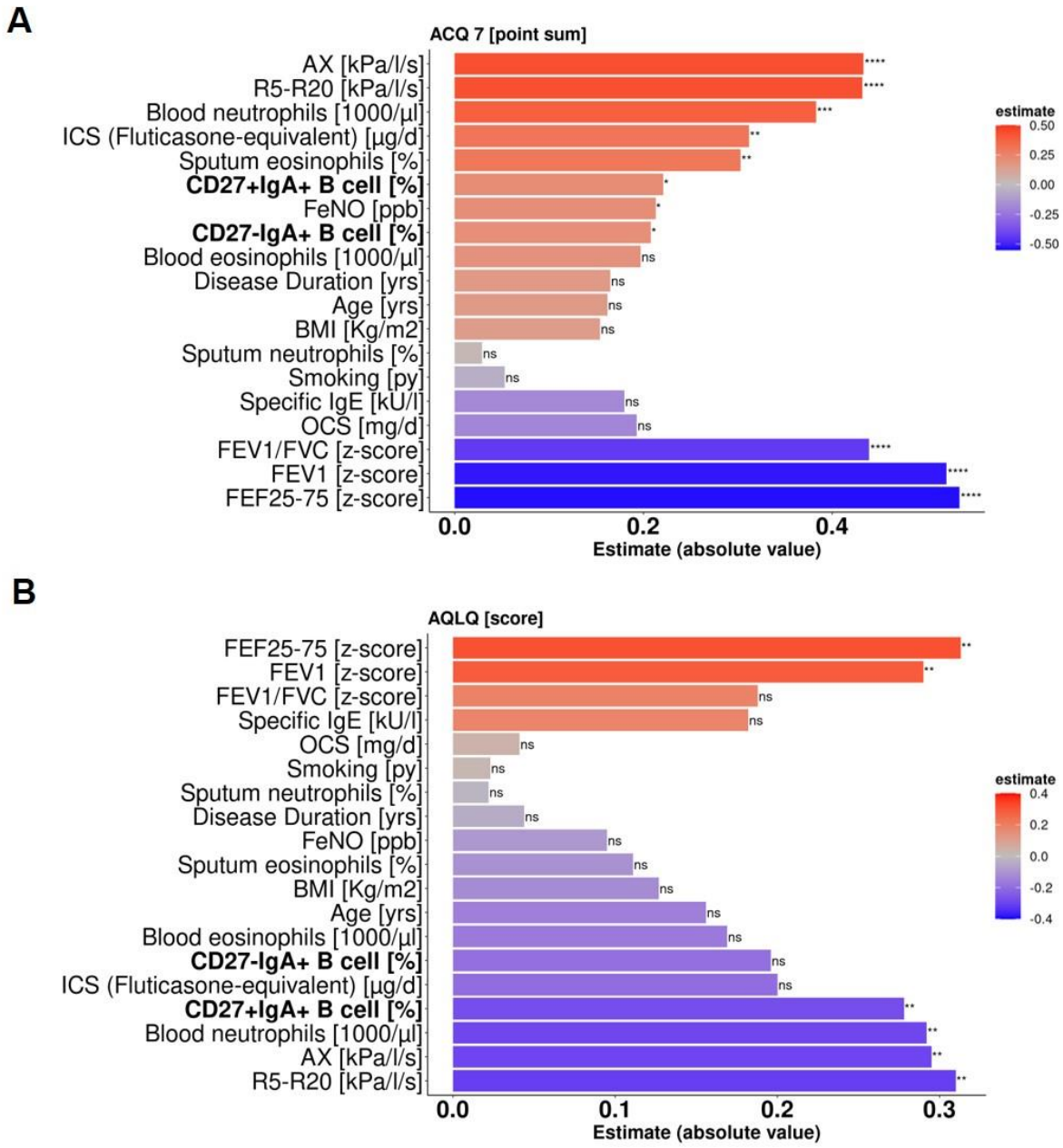

FIGURE S5. Correlations of Asthma Control Questionnaire 7 and Asthma Quality of Life Questionnaire with clinical and B cell parameters. Dark red defines the highest positive correlation between the parameters and dark blue shows the lowest negative correlation between the variables. Adjusted p-values are depicted at the right bar side. no, number; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC,

FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled Nitric oxide; ppb, parts per billion; BMI, Body Mass Index; yrs, years; ICS, inhaled corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; ns, not significant; * $p < .05$, ** $p < .01$; *** $p < .001$; **** $p < .0001$.

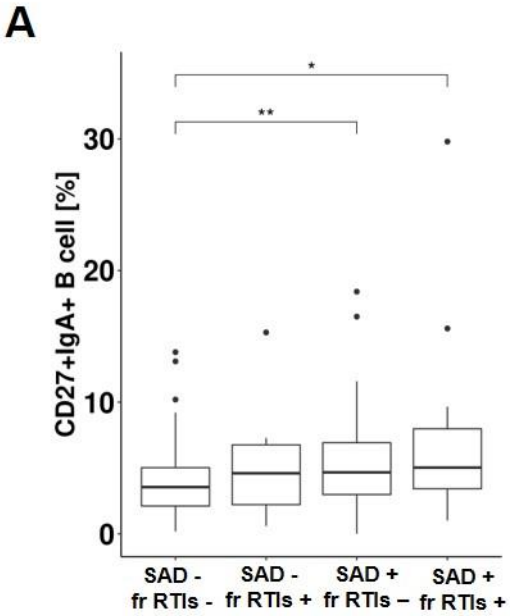

Figure S6: IgA+ memory B cells of asthmatic patients with or without SAD in combination with frequent respiratory infections.

SAD, small airways dysfunction; fr, frequent; RTIs, respiratory tract infections; * $p < .05$, ** $p < .01$;

Supplementary Table Legends

TABLE S3. Pairwise comparisons between B cell populations and clinical variables in asthma patients and healthy controls. Overall comparisons between categorical clinical parameters and B cell variables (A). Comparisons between all categorical groups of the clinical parameters and B cell variables (B). Comparisons between B cell populations and continuous clinical variables in asthma patients and healthy controls (C). B cell subsets are presented as percentage of $CD19^+$ B cells. Coefficient estimates, p-values and adjusted p-values after multiple test corrections are shown. GINA, Global Initiative for Asthma; BDR, bronchodilator response; OCS, oral corticosteroids; BMI, Body Mass Index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; IgE, Immunoglobulin E; T1 B cell, Transitional 1 B cells; T2 B cell, Transitional 2 B cells.

TABLE S4. Linear Model. Linear models describing B cell subpopulations as a function of clinical characteristics with oral corticosteroids and age as confounders. Coefficient estimates, standard error, and p-value are given for each term in the model. P-values for the clinical variables were corrected for multiple tests (q-value). BMI, Body Mass Index; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz–resistance at 20 Hz; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BDR, bronchodilator response; PY, pack-years.

TABLE S5. Clinical characteristics of patients with versus without SAD. Data is presented as median (25%, 75% IQR), and number (%). Yrs, years, BMI, Body Mass Index; PY, pack-years; GINA, Global Initiative for Asthma; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality Of Life Questionnaire; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; AX, reactance area [kPa/l/s]; ULN, upper limit of normal; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; LTRA, leukotriene antagonist; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist.

TABLE S6. Regression model for SAD defined by R5-R20. Result of stepwise multivariate regression model including asthma patients with severe and mild-moderate asthma (n=121). The dependent variable is SAD defined by the 95th centile of R5-R20. A stepwise-forward regression was calculated to find the best model using AIC. The table shows the variables with best model fit (sputum eosinophils [%], gender, and age). Variables not selected by best model fit are not shown (regular OCS intake (yes/ no), blood eosinophils [1000/µl], sum of sIgE, sum of 36 allergen-specific Immunoglobulin E [kU/l], FeNO [ppb], BMI [Kg/m^2], smoking [pack-years], and $CD27^+IgA^+$ memory B cells [%]).

TABLE S7. Correlations between exacerbation frequency and clinical parameters and IgA^+ memory B cells. Estimates and adjusted p-values after multiple test corrections are shown. No, number; BMI, Body Mass Index; yrs, years; PY, pack-years; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; ICS, inhaled

corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s].

TABLE S8. Correlations between Asthma Control Questionnaire (ACQ-7) and clinical parameters and IgA$^+$ memory B cells. Estimates and adjusted p-values after multiple test corrections are shown. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; BMI, Body Mass Index; yrs, years; PY, pack-years; ICS, inhaled corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s].

TABLE S9. Correlations between Asthma Quality Of Life Questionnaire (AQLQ) and clinical parameters and IgA$^+$ memory B cells. Estimates and adjusted p-values after multiple test corrections are shown. FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; BMI, Body Mass Index; yrs, years; PY, pack-years; ICS, inhaled corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s].

TABLE S3. Pairwise comparisons between B cell populations and clinical variables of asthma patients and healthy controls

Table S3A. Comparisons between categorical clinical parameters and B cell variables

Categorical clinical variable	B cell subset	H	p-value	adjusted p-value
Daily OCS intake [yes/no]	T1 B cell [%]	44,3087	< 0,001	< 0,001
Asthma severity	T1 B cell [%]	20,5009	< 0,001	< 0,001
GINA control status	T1 B cell [%]	3,0867	0,2137	0,4452
Age at asthma diagnosis [yrs]	T1 B cell [%]	3,2196	0,3590	0,6210
Smoking status	T1 B cell [%]	0,3863	0,5342	0,7192
Positive BDR [yes/no]	T1 B cell [%]	0,3011	0,5832	0,7393
Sputum inflammation	T1 B cell [%]	1,0991	0,7773	0,8577
Gender [f/m]	T1 B cell [%]	0,0016	0,9680	0,9834
Daily OCS intake [yes/no]	T2 B cell [%]	42,3446	< 0,001	< 0,001
Asthma severity	T2 B cell [%]	23,6881	< 0,001	< 0,001
Age at asthma diagnosis [yrs]	T2 B cell [%]	6,3263	0,0968	0,2693
Positive BDR [yes/no]	T2 B cell [%]	1,6875	0,1939	0,4433
GINA control status	T2 B cell [%]	3,0684	0,2156	0,4452
Smoking status	T2 B cell [%]	0,5338	0,4650	0,6764
Gender [f/m]	T2 B cell [%]	0,2740	0,6007	0,7393
Sputum inflammation	T2 B cell [%]	1,5197	0,6777	0,7745
Daily OCS intake [yes/no]	Naive B cell [%]	10,1220	0,0015	0,0104
Asthma severity	Naive B cell [%]	12,3739	0,0021	0,0108
GINA control status	Naive B cell [%]	4,3592	0,1131	0,3016
Smoking status	Naive B cell [%]	0,8782	0,3487	0,6199
Gender [f/m]	Naive B cell [%]	0,4755	0,4905	0,6976
Positive BDR [yes/no]	Naive B cell [%]	0,1779	0,6732	0,7745
Sputum inflammation	Naive B cell [%]	1,4431	0,6955	0,7809
Age at asthma diagnosis [yrs]	Naive B cell [%]	0,0645	0,9957	0,9957
Asthma severity	$CD27^{+}IgM^{+}$ B cell [%]	17,1772	< 0,001	< 0,001
Daily OCS intake [yes/no]	$CD27^{+}IgM^{+}$ B cell [%]	11,7697	0,0006	0,0064
GINA control status	$CD27^{+}IgM^{+}$ B cell [%]	5,2992	0,0707	0,2154
Age at asthma diagnosis [yrs]	$CD27^{+}IgM^{+}$ B cell [%]	5,5025	0,1385	0,3474
Smoking status	$CD27^{+}IgM^{+}$ B cell [%]	2,1657	0,1411	0,3474
Gender [f/m]	$CD27^{+}IgM^{+}$ B cell [%]	0,6412	0,4233	0,6630
Positive BDR [yes/no]	$CD27^{+}IgM^{+}$ B cell [%]	0,5812	0,4458	0,6764
Sputum inflammation	$CD27^{+}IgM^{+}$ B cell [%]	1,0312	0,7937	0,8610
Daily OCS intake [yes/no]	$CD27^{-}IgG^{+}$ B cell [%]	9,3733	0,0022	0,0108
Gender [f/m]	$CD27^{-}IgG^{+}$ B cell [%]	4,2853	0,0384	0,1447
Asthma severity	$CD27^{-}IgG^{+}$ B cell [%]	3,1218	0,2099	0,4452

Age at asthma diagnosis [yrs]	$CD27^{-}IgG^{+}$ B cell [%]	4,3730	0,2239	0,4478
Smoking status	$CD27^{-}IgG^{+}$ B cell [%]	1,4090	0,2352	0,4562
GINA control status	$CD27^{-}IgG^{+}$ B cell [%]	1,8035	0,4059	0,6630
Sputum inflammation	$CD27^{-}IgG^{+}$ B cell [%]	2,5958	0,4582	0,6764
Positive BDR [yes/no]	$CD27^{-}IgG^{+}$ B cell [%]	0,1950	0,6588	0,7745
Daily OCS intake [yes/no]	$CD27^{+}IgG^{+}$ B cell [%]	10,9116	0,0010	0,0087
Asthma severity	$CD27^{+}IgG^{+}$ B cell [%]	12,4455	0,0020	0,0108
GINA control status	$CD27^{+}IgG^{+}$ B cell [%]	4,6943	0,0956	0,2693
Positive BDR [yes/no]	$CD27^{+}IgG^{+}$ B cell [%]	0,7217	0,3956	0,6630
Smoking status	$CD27^{+}IgG^{+}$ B cell [%]	0,6373	0,4247	0,6630
Sputum inflammation	$CD27^{+}IgG^{+}$ B cell [%]	1,9819	0,5762	0,7393
Age at asthma diagnosis [yrs]	$CD27^{+}IgG^{+}$ B cell [%]	1,9066	0,5920	0,7393
Gender [f/m]	$CD27^{+}IgG^{+}$ B cell [%]	0,0344	0,8529	0,8805
Daily OCS intake [yes/no]	$CD27^{-}IgA^{+}$ B cell [%]	9,6624	0,0019	0,0108
Smoking status	$CD27^{-}IgA^{+}$ B cell [%]	3,3203	0,0684	0,2154
Asthma severity	$CD27^{-}IgA^{+}$ B cell [%]	5,3308	0,0696	0,2154
GINA control status	$CD27^{-}IgA^{+}$ B cell [%]	3,6240	0,1633	0,3871
Positive BDR [yes/no]	$CD27^{-}IgA^{+}$ B cell [%]	1,0401	0,3078	0,5794
Age at asthma diagnosis [yrs]	$CD27^{-}IgA^{+}$ B cell [%]	3,3916	0,3351	0,6127
Gender [f/m]	$CD27^{-}IgA^{+}$ B cell [%]	0,4277	0,5131	0,7139
Sputum inflammation	$CD27^{-}IgA^{+}$ B cell [%]	2,1625	0,5394	0,7192
Sputum inflammation	$CD27^{+}IgA^{+}$ B cell [%]	15,8852	0,0012	0,0096
Daily OCS intake [yes/no]	$CD27^{+}IgA^{+}$ B cell [%]	8,9200	0,0028	0,0129
Asthma severity	$CD27^{+}IgA^{+}$ B cell [%]	11,4026	0,0033	0,0143
GINA control status	$CD27^{+}IgA^{+}$ B cell [%]	9,1722	0,0102	0,0408
Smoking status	$CD27^{+}IgA^{+}$ B cell [%]	3,7307	0,0534	0,1899
Age at asthma diagnosis [yrs]	$CD27^{+}IgA^{+}$ B cell [%]	1,7078	0,6352	0,7670
Gender [f/m]	$CD27^{+}IgA^{+}$ B cell [%]	0,0528	0,8182	0,8666
Positive BDR [yes/no]	$CD27^{+}IgA^{+}$ B cell [%]	0,0483	0,8260	0,8666

Table S3B. Comparisons between all categorical groups of the clinical parameters and B cell variables

Categorical clinical variable	**category 1**	**category 2**	**B cell subset**	**p-value**
Daily OCS intake [yes/no]	No	Yes	T1 B cell [%]	< 0,001
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	T1 B cell [%]	0,7230
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	T1 B cell [%]	0,0963
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	T1 B cell [%]	0,9574

Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	T1 B cell [%]	0,9004
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	T1 B cell [%]	0,5751
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	T1 B cell [%]	0,5354
Gender [f/m]	Male	Female	T1 B cell [%]	0,9692
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	T1 B cell [%]	0,6390
GINA control status	Controlled	Uncontrolled	T1 B cell [%]	0,2343
Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	T1 B cell [%]	0,5079
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	T1 B cell [%]	0,3485
Asthma severity	Healthy	Mild-moderate asthma	T1 B cell [%]	0,0759
Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	T1 B cell [%]	0,6209
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	T1 B cell [%]	0,2321
Asthma severity	Mild-moderate asthma	Severe asthma	T1 B cell [%]	< 0,001
GINA control status	Partly controlled	Uncontrolled	T1 B cell [%]	0,0891
Asthma severity	Healthy	Severe asthma	T1 B cell [%]	< 0,001
GINA control status	Controlled	Partly controlled	T1 B cell [%]	0,7149
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	T1 B cell [%]	0,2984
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	T1 B cell [%]	0,8046
Positive BDR [yes/no]	Yes	No	T1 B cell [%]	0,5845
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	T2 B cell [%]	0,6533
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	T2 B cell [%]	0,5960
Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	T2 B cell [%]	0,4987
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	T2 B cell [%]	0,4072
GINA control status	Controlled	Uncontrolled	T2 B cell [%]	0,1653
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	T2 B cell [%]	0,8936
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	T2 B cell [%]	0,3154
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	T2 B cell [%]	0,1802
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	T2 B cell [%]	0,7441
Positive BDR [yes/no]	Yes	No	T2 B cell [%]	0,1946
GINA control status	Controlled	Partly controlled	T2 B cell [%]	0,9115
Asthma severity	Healthy	Mild-moderate asthma	T2 B cell [%]	0,2104
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	T2 B cell [%]	0,4661

Daily OCS intake [yes/no]	No	Yes	T2 B cell [%]	< 0,001
GINA control status	Partly controlled	Uncontrolled	T2 B cell [%]	0,1174
Gender [f/m]	Male	Female	T2 B cell [%]	0,6017
Asthma severity	Mild-moderate asthma	Severe asthma	T2 B cell [%]	0,0000
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	T2 B cell [%]	0,1198
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	T2 B cell [%]	0,0189
Asthma severity	Healthy	Severe asthma	T2 B cell [%]	0,0002
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	T2 B cell [%]	0,6643
Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	T2 B cell [%]	0,2800
GINA control status	Partly controlled	Uncontrolled	Naive B cell [%]	0,0383
GINA control status	Controlled	Partly controlled	Naive B cell [%]	0,3551
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	Naive B cell [%]	0,7211
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	Naive B cell [%]	0,5866
Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	Naive B cell [%]	0,7902
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	Naive B cell [%]	0,9373
Asthma severity	Mild-moderate asthma	Severe asthma	Naive B cell [%]	0,0008
GINA control status	Controlled	Uncontrolled	Naive B cell [%]	0,2730
Asthma severity	Healthy	Mild-moderate asthma	Naive B cell [%]	0,0669
Positive BDR [yes/no]	Yes	No	Naive B cell [%]	0,6746
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	Naive B cell [%]	0,8786
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	Naive B cell [%]	0,4918
Daily OCS intake [yes/no]	No	Yes	Naive B cell [%]	0,0015
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	Naive B cell [%]	0,9211
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	Naive B cell [%]	0,3496
Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	Naive B cell [%]	0,6544
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	Naive B cell [%]	0,2561
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	Naive B cell [%]	0,9337
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	Naive B cell [%]	0,9272

Asthma severity	Healthy	Severe asthma	Naive B cell [%]	0,2756
Gender [f/m]	Male	Female	Naive B cell [%]	0,4914
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	Naive B cell [%]	0,7990
Asthma severity	Mild-moderate asthma	Severe asthma	$CD27^{+}IgM^{+}$ B cell [%]	< 0,001
GINA control status	Controlled	Partly controlled	$CD27^{+}IgM^{+}$ B cell [%]	0,6885
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	$CD27^{+}IgM^{+}$ B cell [%]	0,6696
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	$CD27^{+}IgM^{+}$ B cell [%]	0,4725
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	$CD27^{+}IgM^{+}$ B cell [%]	0,7781
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	$CD27^{+}IgM^{+}$ B cell [%]	0,0340
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	$CD27^{+}IgM^{+}$ B cell [%]	0,1416
Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	$CD27^{+}IgM^{+}$ B cell [%]	0,6571
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	$CD27^{+}IgM^{+}$ B cell [%]	0,5042
Daily OCS intake [yes/no]	No	Yes	$CD27^{+}IgM^{+}$ B cell [%]	0,0006
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	$CD27^{+}IgM^{+}$ B cell [%]	0,1378
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	$CD27^{+}IgM^{+}$ B cell [%]	0,7319
GINA control status	Partly controlled	Uncontrolled	$CD27^{+}IgM^{+}$ B cell [%]	0,0518
Gender [f/m]	Male	Female	$CD27^{+}IgM^{+}$ B cell [%]	0,4241
Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	$CD27^{+}IgM^{+}$ B cell [%]	0,6320
Positive BDR [yes/no]	Yes	No	$CD27^{+}IgM^{+}$ B cell [%]	0,4470
Asthma severity	Healthy	Severe asthma	$CD27^{+}IgM^{+}$ B cell [%]	0,0074
Asthma severity	Healthy	Mild-moderate asthma	$CD27^{+}IgM^{+}$ B cell [%]	0,2876
GINA control status	Controlled	Uncontrolled	$CD27^{+}IgM^{+}$ B cell [%]	0,0543
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	$CD27^{+}IgM^{+}$ B cell [%]	0,3553
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	$CD27^{+}IgM^{+}$ B cell [%]	0,0459
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	$CD27^{+}IgM^{+}$ B cell [%]	0,7516
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	$CD27^{-}IgG^{+}$ B cell [%]	0,1140
Gender [f/m]	Male	Female	$CD27^{-}IgG^{+}$ B cell [%]	0,0386

GINA control status	Partly controlled	Uncontrolled	$CD27^{-}IgG^{+}$ B cell [%]	0,3170
Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	$CD27^{-}IgG^{+}$ B cell [%]	0,3381
Positive BDR [yes/no]	Yes	No	$CD27^{-}IgG^{+}$ B cell [%]	0,6602
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	$CD27^{-}IgG^{+}$ B cell [%]	0,0801
GINA control status	Controlled	Partly controlled	$CD27^{-}IgG^{+}$ B cell [%]	0,2069
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	$CD27^{-}IgG^{+}$ B cell [%]	0,7045
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	$CD27^{-}IgG^{+}$ B cell [%]	0,8047
Asthma severity	Healthy	Severe asthma	$CD27^{-}IgG^{+}$ B cell [%]	0,1286
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	$CD27^{-}IgG^{+}$ B cell [%]	0,0985
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	$CD27^{-}IgG^{+}$ B cell [%]	0,3040
Daily OCS intake [yes/no]	No	Yes	$CD27^{-}IgG^{+}$ B cell [%]	0,0022
Asthma severity	Mild-moderate asthma	Severe asthma	$CD27^{-}IgG^{+}$ B cell [%]	0,1390
Asthma severity	Healthy	Mild-moderate asthma	$CD27^{-}IgG^{+}$ B cell [%]	0,6585
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	$CD27^{-}IgG^{+}$ B cell [%]	0,2359
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	$CD27^{-}IgG^{+}$ B cell [%]	0,3310
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	$CD27^{-}IgG^{+}$ B cell [%]	0,9254
Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	$CD27^{-}IgG^{+}$ B cell [%]	0,9070
GINA control status	Controlled	Uncontrolled	$CD27^{-}IgG^{+}$ B cell [%]	0,6777
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	$CD27^{-}IgG^{+}$ B cell [%]	0,3687
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	$CD27^{-}IgG^{+}$ B cell [%]	0,3968
Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	$CD27^{+}IgG^{+}$ B cell [%]	0,2871
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	$CD27^{+}IgG^{+}$ B cell [%]	0,6416
GINA control status	Controlled	Partly controlled	$CD27^{+}IgG^{+}$ B cell [%]	0,2875
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	$CD27^{+}IgG^{+}$ B cell [%]	0,4151
Gender [f/m]	Male	Female	$CD27^{+}IgG^{+}$ B cell [%]	0,8541
Daily OCS intake [yes/no]	No	Yes	$CD27^{+}IgG^{+}$ B cell [%]	0,0010
GINA control status	Controlled	Uncontrolled	$CD27^{+}IgG^{+}$ B cell [%]	0,2323

Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	$CD27^{+}IgG^{+}$ B cell [%]	0,9213
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	$CD27^{+}IgG^{+}$ B cell [%]	0,4830
Asthma severity	Healthy	Severe asthma	$CD27^{+}IgG^{+}$ B cell [%]	0,0553
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	$CD27^{+}IgG^{+}$ B cell [%]	0,4561
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	$CD27^{+}IgG^{+}$ B cell [%]	0,2135
GINA control status	Partly controlled	Uncontrolled	$CD27^{+}IgG^{+}$ B cell [%]	0,0377
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	$CD27^{+}IgG^{+}$ B cell [%]	0,1981
Asthma severity	Mild-moderate asthma	Severe asthma	$CD27^{+}IgG^{+}$ B cell [%]	0,0007
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	$CD27^{+}IgG^{+}$ B cell [%]	0,3297
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	$CD27^{+}IgG^{+}$ B cell [%]	0,7111
Asthma severity	Healthy	Mild-moderate asthma	$CD27^{+}IgG^{+}$ B cell [%]	0,2462
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	$CD27^{+}IgG^{+}$ B cell [%]	0,4257
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	$CD27^{+}IgG^{+}$ B cell [%]	0,5434
Positive BDR [yes/no]	Yes	No	$CD27^{+}IgG^{+}$ B cell [%]	0,3967
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	$CD27^{+}IgG^{+}$ B cell [%]	0,5234
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	$CD27^{-}IgA^{+}$ B cell [%]	0,6814
Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	$CD27^{-}IgA^{+}$ B cell [%]	0,8019
Asthma severity	Mild-moderate asthma	Severe asthma	$CD27^{-}IgA^{+}$ B cell [%]	0,0329
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	$CD27^{-}IgA^{+}$ B cell [%]	0,8713
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	$CD27^{-}IgA^{+}$ B cell [%]	0,3297
GINA control status	Controlled	Uncontrolled	$CD27^{-}IgA^{+}$ B cell [%]	0,3493
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	$CD27^{-}IgA^{+}$ B cell [%]	0,2976
GINA control status	Partly controlled	Uncontrolled	$CD27^{-}IgA^{+}$ B cell [%]	0,0608
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	$CD27^{-}IgA^{+}$ B cell [%]	0,1734
Asthma severity	Healthy	Severe asthma	$CD27^{-}IgA^{+}$ B cell [%]	0,3216
Asthma severity	Healthy	Mild-moderate asthma	$CD27^{-}IgA^{+}$ B cell [%]	0,2035
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	$CD27^{-}IgA^{+}$ B cell [%]	0,9939

Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	$CD27^{-}IgA^{+}$ B cell [%]	0,3951
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	$CD27^{-}IgA^{+}$ B cell [%]	0,4114
Gender [f/m]	Male	Female	$CD27^{-}IgA^{+}$ B cell [%]	0,5141
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	$CD27^{-}IgA^{+}$ B cell [%]	0,0687
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	$CD27^{-}IgA^{+}$ B cell [%]	0,1123
Positive BDR [yes/no]	Yes	No	$CD27^{-}IgA^{+}$ B cell [%]	0,3087
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	$CD27^{-}IgA^{+}$ B cell [%]	0,1965
GINA control status	Controlled	Partly controlled	$CD27^{-}IgA^{+}$ B cell [%]	0,3408
Daily OCS intake [yes/no]	No	Yes	$CD27^{-}IgA^{+}$ B cell [%]	0,0019
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	$CD27^{-}IgA^{+}$ B cell [%]	0,4551
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 6-18yrs	$CD27^{+}IgA^{+}$ B cell [%]	0,4991
Sputum inflammation	Paucigranulocytic inflammation	Eosinophilic inflammation	$CD27^{+}IgA^{+}$ B cell [%]	< 0,001
GINA control status	Controlled	Uncontrolled	$CD27^{+}IgA^{+}$ B cell [%]	0,0073
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis 18-40yrs	$CD27^{+}IgA^{+}$ B cell [%]	0,8550
Asthma severity	Healthy	Mild-moderate asthma	$CD27^{+}IgA^{+}$ B cell [%]	0,8904
Asthma severity	Mild-moderate asthma	Severe asthma	$CD27^{+}IgA^{+}$ B cell [%]	0,0010
GINA control status	Partly controlled	Uncontrolled	$CD27^{+}IgA^{+}$ B cell [%]	0,0155
Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	Age at diagnosis >40yrs	$CD27^{+}IgA^{+}$ B cell [%]	0,2586
Sputum inflammation	Neutrophilic inflammation	Mixted inflammation	$CD27^{+}IgA^{+}$ B cell [%]	0,6855
Gender [f/m]	Male	Female	$CD27^{+}IgA^{+}$ B cell [%]	0,8194
GINA control status	Controlled	Partly controlled	$CD27^{+}IgA^{+}$ B cell [%]	0,7842
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis 18-40yrs	$CD27^{+}IgA^{+}$ B cell [%]	0,5912
Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	Age at diagnosis >40yrs	$CD27^{+}IgA^{+}$ B cell [%]	0,7776
Asthma severity	Healthy	Severe asthma	$CD27^{+}IgA^{+}$ B cell [%]	0,0321
Age at asthma diagnosis [yrs]	Age at diagnosis <6yrs	Age at diagnosis >40yrs	$CD27^{+}IgA^{+}$ B cell [%]	0,3040
Sputum inflammation	Paucigranulocytic inflammation	Mixted inflammation	$CD27^{+}IgA^{+}$ B cell [%]	0,0071
Smoking status	Never or former smokers <10PY	Current or former smokers ≥10PY	$CD27^{+}IgA^{+}$ B cell [%]	0,0536

Positive BDR [yes/no]	Yes	No	$CD27^+IgA^+$ B cell [%]	0,8276
Sputum inflammation	Paucigranulocytic inflammation	Neutrophilic inflammation	$CD27^+IgA^+$ B cell [%]	0,0164
Sputum inflammation	Eosinophilic inflammation	Mixted inflammation	$CD27^+IgA^+$ B cell [%]	0,0900
Sputum inflammation	Eosinophilic inflammation	Neutrophilic inflammation	$CD27^+IgA^+$ B cell [%]	0,0338
Daily OCS intake [yes/no]	No	Yes	$CD27^+IgA^+$ B cell [%]	0,0028

Table S3C. Comparisons between B cell populations and continuous clinical variables

Continuous clinical variable	**B cell subset**	**estimate**	**p-value**	**adjusted p-value**
Blood neutrophils [1000/µl]	T1 B cell [%]	-0.3619	< 0,001	< 0,001
Exacerbations [n]	T1 B cell [%]	-0.2760	< 0,001	0.0034
Specific IgE [kU/l]	T1 B cell [%]	0.1843	0.0143	0.0573
FEV_1 [z-score]	T1 B cell [%]	0.1815	0.0168	0.0644
FEF_{25-75} [z-score]	T1 B cell [%]	0.1767	0.0329	0.1006
Blood eosinophils [1000/µl]	T1 B cell [%]	-0.0916	0.2279	0.3800
FEV_1/FVC [z-score]	T1 B cell [%]	0.0817	0.2851	0.4252
BMI [Kg/m^2]	T1 B cell [%]	-0.0444	0.5583	0.7018
Reactance Area [kPa/l/s]	T1 B cell [%]	-0.0255	0.7403	0.8461
R5-R20 [kPa/l/s]	T1 B cell [%]	-0.0214	0.7795	0.8546
Age [yrs]	T1 B cell [%]	0.0049	0.9481	0.9481
Blood neutrophils [1000/µl]	T2 B cell [%]	-0.3615	< 0,001	< 0,001
Exacerbations [n]	T2 B cell [%]	-0.2823	< 0,001	0.0027
Specific IgE [kU/l]	T2 B cell [%]	0.1736	0.0212	0.0748
FEV_1 [z-score]	T2 B cell [%]	0.1724	0.0233	0.0789
FEF_{25-75} [z-score]	T2 B cell [%]	0.1748	0.0349	0.1019
Blood eosinophils [1000/µl]	T2 B cell [%]	-0.1066	0.1604	0.2940
FEV_1/FVC [z-score]	T2 B cell [%]	0.0881	0.2491	0.3914
R5-R20 [kPa/l/s]	T2 B cell [%]	-0.0604	0.4284	0.5800
Age [yrs]	T2 B cell [%]	-0.0574	0.4489	0.5986
Reactance Area [kPa/l/s]	T2 B cell [%]	-0.0439	0.5682	0.7043
BMI [Kg/m^2]	T2 B cell [%]	-0.0227	0.7647	0.8546
FEF_{25-75} [z-score]	Naive B cell [%]	0.2241	0.0066	0.0323
FEV_1/FVC [z-score]	Naive B cell [%]	0.1990	0.0087	0.0363
Exacerbations [n]	Naive B cell [%]	-0.1658	0.0323	0.1006
FEV_1 [z-score]	Naive B cell [%]	0.1596	0.0359	0.1019
Specific IgE [kU/l]	Naive B cell [%]	0.1114	0.1409	0.2637
R5-R20 [kPa/l/s]	Naive B cell [%]	-0.0917	0.2289	0.3800

Blood neutrophils [1000/µl]	Naive B cell [%]	-0.0823	0.2789	0.4232
Blood eosinophils [1000/µl]	Naive B cell [%]	0.0718	0.3451	0.4978
Reactance Area [kPa/l/s]	Naive B cell [%]	-0.0409	0.5951	0.7273
Age [yrs]	Naive B cell [%]	-0.0392	0.6053	0.7297
BMI [Kg/m^2]	Naive B cell [%]	0.0205	0.7867	0.8546
Blood neutrophils [1000/µl]	CD27$^+$IgM$^+$ B cell [%]	0.2046	0.0066	0.0323
R5-R20 [kPa/l/s]	CD27$^+$IgM$^+$ B cell [%]	0.1507	0.0471	0.1123
FEV$_1$/FVC [z-score]	CD27$^+$IgM$^+$ B cell [%]	-0.1446	0.0577	0.1302
Age [yrs]	CD27$^+$IgM$^+$ B cell [%]	0.1273	0.0921	0.1952
Specific IgE [kU/l]	CD27$^+$IgM$^+$ B cell [%]	-0.1269	0.0932	0.1952
FEF$_{25-75}$ [z-score]	CD27$^+$IgM$^+$ B cell [%]	-0.1047	0.2087	0.3673
Exacerbations [n]	CD27$^+$IgM$^+$ B cell [%]	0.0953	0.2203	0.3800
Reactance Area [kPa/l/s]	CD27$^+$IgM$^+$ B cell [%]	0.0878	0.2535	0.3914
FEV$_1$ [z-score]	CD27$^+$IgM$^+$ B cell [%]	-0.0667	0.3832	0.5353
Blood eosinophils [1000/µl]	CD27$^+$IgM$^+$ B cell [%]	-0.0476	0.5313	0.6876
BMI [Kg/m^2]	CD27$^+$IgM$^+$ B cell [%]	0.0192	0.8001	0.8586
Exacerbations [n]	CD27$^-$IgG$^+$ B cell [%]	0.2259	0.0033	0.0209
Blood neutrophils [1000/µl]	CD27$^-$IgG$^+$ B cell [%]	0.1611	0.0332	0.1006
Age [yrs]	CD27$^-$IgG$^+$ B cell [%]	-0.1539	0.0414	0.1105
FEF$_{25-75}$ [z-score]	CD27$^-$IgG$^+$ B cell [%]	-0.1663	0.0448	0.1123
FEV$_1$ [z-score]	CD27$^-$IgG$^+$ B cell [%]	-0.1246	0.1025	0.2097
FEV$_1$/FVC [z-score]	CD27$^-$IgG$^+$ B cell [%]	-0.1156	0.1300	0.2486
Blood eosinophils [1000/µl]	CD27$^-$IgG$^+$ B cell [%]	0.0505	0.5067	0.6655
R5-R20 [kPa/l/s]	CD27$^-$IgG$^+$ B cell [%]	0.0378	0.6201	0.7367
Reactance Area [kPa/l/s]	CD27$^-$IgG$^+$ B cell [%]	0.0373	0.6279	0.7367
BMI [Kg/m^2]	CD27$^-$IgG$^+$ B cell [%]	0.0169	0.8235	0.8648
Specific IgE [kU/l]	CD27$^-$IgG$^+$ B cell [%]	-0.0077	0.9192	0.9298
Blood neutrophils [1000/µl]	CD27$^+$IgG$^+$ B cell [%]	0.2573	0.0006	0.0052
FEF$_{25-75}$ [z-score]	CD27$^+$IgG$^+$ B cell [%]	-0.1957	0.0179	0.0657
FEV$_1$/FVC [z-score]	CD27$^+$IgG$^+$ B cell [%]	-0.1517	0.0463	0.1123
Exacerbations [n]	CD27$^+$IgG$^+$ B cell [%]	0.1306	0.0926	0.1952
FEV1 [z-score]	CD27$^+$IgG$^+$ B cell [%]	-0.1191	0.1185	0.2317
Age [yrs]	CD27$^+$IgG$^+$ B cell [%]	-0.0995	0.1889	0.3392
R5-R20 [kPa/l/s]	CD27$^+$IgG$^+$ B cell [%]	0.0890	0.2429	0.3914
Reactance Area [kPa/l/s]	CD27$^+$IgG$^+$ B cell [%]	0.0676	0.3799	0.5353
Blood eosinophils [1000/µl]	CD27$^+$IgG$^+$ B cell [%]	0.0603	0.4276	0.5800
BMI [Kg/m^2]	CD27$^+$IgG$^+$ B cell [%]	-0.0161	0.8322	0.8648
Specific IgE [kU/l]	CD27$^+$IgG$^+$ B cell [%]	-0.0136	0.8579	0.8779
Exacerbations [n]	CD27$^-$IgA$^+$ B cell [%]	0.3067	< 0,001	0.0015
FEV$_1$/FVC [z-score]	CD27$^-$IgA$^+$ B cell [%]	-0.2079	0.0060	0.0323
FEF$_{25-75}$ [z-score]	CD27$^-$IgA$^+$ B cell [%]	-0.2213	0.0073	0.0336
FEV$_1$ [z-score]	CD27$^-$IgA$^+$ B cell [%]	-0.2002	0.0083	0.0363

Blood neutrophils [1000/µl]	$CD27^-IgA^+$ B cell [%]	0.1549	0.0407	0.1105
R5-R20 [kPa/l/s]	$CD27^-IgA^+$ B cell [%]	0.1507	0.0472	0.1123
Reactance Area [kPa/l/s]	$CD27^-IgA^+$ B cell [%]	0.1480	0.0534	0.1237
Age [yrs]	$CD27^-IgA^+$ B cell [%]	0.1201	0.1124	0.2248
Specific IgE [kU/l]	$CD27^-IgA^+$ B cell [%]	-0.0792	0.2959	0.4339
Blood eosinophils [1000/µl]	$CD27^-IgA^+$ B cell [%]	-0.0294	0.6991	0.8095
BMI [Kg/m^2]	$CD27^-IgA^+$ B cell [%]	0.0158	0.8353	0.8648
Reactance Area [kPa/l/s]	$CD27^+IgA^+$ B cell [%]	0.2997	< 0,001	0.0015
Exacerbations [n]	$CD27^+IgA^+$ B cell [%]	0.2993	< 0,001	0.0015
R5-R20 [kPa/l/s]	$CD27^+IgA^+$ B cell [%]	0.2826	< 0,001	0.0023
Age [yrs]	$CD27^+IgA^+$ B cell [%]	0.2619	< 0,001	0.0044
FEV_1/FVC [z-score]	$CD27^+IgA^+$ B cell [%]	-0.2565	< 0,001	0.0053
FEF_{25-75} [z-score]	$CD27^+IgA^+$ B cell [%]	-0.2768	< 0,001	0.0053
FEV_1 [z-score]	$CD27^+IgA^+$ B cell [%]	-0.2397	0.0015	0.0101
Blood neutrophils [1000/µl]	$CD27^+IgA^+$ B cell [%]	0.2077	0.0058	0.0323
BMI [Kg/m^2]	$CD27^+IgA^+$ B cell [%]	0.0874	0.2487	0.3914
Specific IgE [kU/l]	$CD27^+IgA^+$ B cell [%]	-0.0456	0.5475	0.6983
Blood eosinophils [1000/µl]	$CD27^+IgA^+$ B cell [%]	-0.0209	0.7836	0.8546

TABLE S3. Pairwise comparisons between B cell populations and clinical variables in asthma patients and healthy controls. Overall comparisons between categorical clinical parameters and B cell variables (A). Comparisons between all categorical groups of the clinical parameters and B cell variables (B). Comparisons between B cell populations and continuous clinical variables in asthma patients and healthy controls (C). B cell subsets are presented as percentage of $CD19^+$ B cells. Coefficient estimates, p-values and adjusted p-values after multiple test corrections are shown. GINA, Global Initiative for Asthma; BDR, bronchodilator response; OCS, oral corticosteroids; BMI, Body Mass Index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; IgE, Immunoglobulin E; T1 B cell, Transitional 1 B cells; T2 B cell, Transitional 2 B cells.

Table S4. Linear Model

B cell variable	Clinical variable	Term	estimate	standard error	p-value	q-value of clinical variable
T1 B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	-0.0895	0.0589	0.1300	0.1911
T1 B cell [%]	Blood neutrophils [1000/µl]	Age	0.0094	0.0078	0.2338	0.1911
T1 B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	-1.0294	0.3386	0.0027	0.1911
T1 B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	1.2838	0.5063	0.0121	0.1911
T1 B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	0.0247	0.0199	0.2169	0.2236
T1 B cell [%]	BMI [Kg/m^2]	Age	0.0095	0.0078	0.2246	0.2236
T1 B cell [%]	BMI [Kg/m^2]	Regular OCS	-1.3554	0.2920	< 0,001	0.2236
T1 B cell [%]	BMI [Kg/m^2]	(Intercept)	0.2408	0.6594	0.7154	0.2236
T1 B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	-0.4878	0.4163	0.2433	0.2236
T1 B cell [%]	Sputum inflammation	Neutrophilic inflammation	-0.7629	0.3689	0.0404	0.2236
T1 B cell [%]	Sputum inflammation	Eosinophilic inflammation	-0.6300	0.4545	0.1679	0.2236
T1 B cell [%]	Sputum inflammation	Age	0.0181	0.0094	0.0576	0.2236
T1 B cell [%]	Sputum inflammation	Regular OCS	-1.1920	0.3437	< 0,001	0.2236
T1 B cell [%]	Sputum inflammation	(Intercept)	0.9811	0.5011	0.0522	0.2236
T1 B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.0883	0.0887	0.3209	0.2498
T1 B cell [%]	FEV_1/FVC [z-score]	Age	0.0099	0.0079	0.2104	0.2498
T1 B cell [%]	FEV_1/FVC [z-score]	Regular OCS	-1.3447	0.3009	< 0,001	0.2498
T1 B cell [%]	FEV_1/FVC [z-score]	(Intercept)	0.7540	0.4375	0.0867	0.2498
T1 B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	0.9784	1.0534	0.3543	0.2498
T1 B cell [%]	R5-R20 [kPa/l/s]	Age	0.0086	0.0079	0.2831	0.2498
T1 B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	-1.3445	0.2949	< 0,001	0.2498
T1 B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	0.8485	0.4213	0.0456	0.2498
T1 B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	-0.3583	0.3784	0.3450	0.2498
T1 B cell [%]	Blood eosinophils [1000/µl]	Age	0.0109	0.0078	0.1638	0.2498
T1 B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	-1.2686	0.2909	< 0,001	0.2498
T1 B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	0.9538	0.4343	0.0294	0.2498
T1 B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	0.0623	0.0814	0.4451	0.2789
T1 B cell [%]	AX [kPa/l/s]	Age	0.0101	0.0079	0.2064	0.2789
T1 B cell [%]	AX [kPa/l/s]	Regular OCS	-1.3438	0.3050	< 0,001	0.2789
T1 B cell [%]	AX [kPa/l/s]	(Intercept)	0.8308	0.4248	0.0522	0.2789
T1 B cell [%]	Gender	Female	-0.1652	0.2249	0.4635	0.2806

T1 B cell [%]	Gender	Age	0.0098	0.0078	0.2075	0.2806
T1 B cell [%]	Gender	Regular OCS	-1.2957	0.2882	< 0,001	0.2806
T1 B cell [%]	Gender	(Intercept)	0.9810	0.4431	0.0282	0.2806
T1 B cell [%]	GINA control status	Uncontrolled	0.2066	0.3129	0.5102	0.3057
T1 B cell [%]	GINA control status	Partly controlled	0.0238	0.3217	0.9411	0.3057
T1 B cell [%]	GINA control status	Age	0.0113	0.0093	0.2256	0.3057
T1 B cell [%]	GINA control status	Regular OCS	-1.3192	0.3141	< 0,001	0.3057
T1 B cell [%]	GINA control status	(Intercept)	0.7046	0.5190	0.1767	0.3057
T1 B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	-0.0431	0.1060	0.6848	0.3057
T1 B cell [%]	FEF_{25-75} [z-score]	Age	0.0115	0.0091	0.2076	0.3057
T1 B cell [%]	FEF_{25-75} [z-score]	Regular OCS	-1.3750	0.3367	< 0,001	0.3057
T1 B cell [%]	FEF_{25-75} [z-score]	(Intercept)	0.7702	0.5182	0.1395	0.3057
T1 B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	-0.0396	0.0821	0.6306	0.3057
T1 B cell [%]	FEV_1 [z-score]	Age	0.0104	0.0079	0.1881	0.3057
T1 B cell [%]	FEV_1 [z-score]	Regular OCS	-1.3212	0.3075	< 0,001	0.3057
T1 B cell [%]	FEV_1 [z-score]	(Intercept)	0.8164	0.4358	0.0628	0.3057
T1 B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	-0.1081	0.4664	0.8170	0.3057
T1 B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	0.1838	0.4413	0.6778	0.3057
T1 B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	-0.0984	0.4589	0.8305	0.3057
T1 B cell [%]	Age at asthma diagnosis [yrs]	Age	0.0156	0.0104	0.1370	0.3057
T1 B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	-1.2188	0.3057	< 0,001	0.3057
T1 B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	0.5174	0.6078	0.3960	0.3057
T1 B cell [%]	Asthma severity	Healthy	0.0500	0.4191	0.9051	0.3057
T1 B cell [%]	Asthma severity	Mild-moderate asthma	-0.1888	0.3435	0.5833	0.3057
T1 B cell [%]	Asthma severity	Age	0.0098	0.0078	0.2111	0.3057
T1 B cell [%]	Asthma severity	Regular OCS	-1.4001	0.3975	< 0,001	0.3057
T1 B cell [%]	Asthma severity	(Intercept)	1.0036	0.5290	0.0595	0.3057
T1 B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	0.0133	0.0314	0.6732	0.3057
T1 B cell [%]	Specific IgE [kU/l]	Age	0.0106	0.0078	0.1765	0.3057
T1 B cell [%]	Specific IgE [kU/l]	Regular OCS	-1.2765	0.2905	< 0,001	0.3057
T1 B cell [%]	Specific IgE [kU/l]	(Intercept)	0.8190	0.4384	0.0634	0.3057
T1 B cell [%]	Smoking status	Current or former smokers ≥10PY	0.0638	0.2669	0.8114	0.3099
T1 B cell [%]	Smoking status	Age	0.0099	0.0078	0.2084	0.3099
T1 B cell [%]	Smoking status	Regular OCS	-1.2959	0.2893	< 0,001	0.3099
T1 B cell [%]	Smoking status	(Intercept)	0.8735	0.4189	0.0385	0.3099

T1 B cell [%]	Positive BDR [yes/no]	No	-0.0614	0.2970	0.8364	0.3133
T1 B cell [%]	Positive BDR [yes/no]	Age	0.0098	0.0079	0.2194	0.3133
T1 B cell [%]	Positive BDR [yes/no]	Regular OCS	-1.2798	0.2975	< 0,001	0.3133
T1 B cell [%]	Positive BDR [yes/no]	(Intercept)	0.9409	0.4881	0.0556	0.3133
T1 B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	0.0061	0.0500	0.9031	0.3222
T1 B cell [%]	Severe exacerbations [n]	Age	0.0108	0.0081	0.1854	0.3222
T1 B cell [%]	Severe exacerbations [n]	Regular OCS	-1.3173	0.3506	< 0,001	0.3222
T1 B cell [%]	Severe exacerbations [n]	(Intercept)	0.8345	0.4360	0.0573	0.3222
T2 B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	-0.2527	0.1372	0.0672	0.1486
T2 B cell [%]	Blood neutrophils [1000/µl]	Age	0.0072	0.0183	0.6925	0.1486
T2 B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	-3.0242	0.7890	< 0,001	0.1486
T2 B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	5.8595	1.1798	< 0,001	0.1486
T2 B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	-1.1171	0.8828	0.2074	0.2236
T2 B cell [%]	Blood eosinophils [1000/µl]	Age	0.0117	0.0182	0.5214	0.2236
T2 B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	-3.6897	0.6786	< 0,001	0.2236
T2 B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	4.9588	1.0130	< 0,001	0.2236
T2 B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	0.0496	0.0465	0.2879	0.2485
T2 B cell [%]	BMI [Kg/m^2]	Age	0.0087	0.0181	0.6305	0.2485
T2 B cell [%]	BMI [Kg/m^2]	Regular OCS	-3.9042	0.6829	< 0,001	0.2485
T2 B cell [%]	BMI [Kg/m^2]	(Intercept)	3.4012	1.5424	0.0288	0.2485
T2 B cell [%]	Gender	Female	-0.4578	0.5252	0.3846	0.2598
T2 B cell [%]	Gender	Age	0.0092	0.0181	0.6110	0.2598
T2 B cell [%]	Gender	Regular OCS	-3.7875	0.6729	< 0,001	0.2598
T2 B cell [%]	Gender	(Intercept)	4.9720	1.0346	< 0,001	0.2598
T2 B cell [%]	Asthma severity	Healthy	0.9182	0.9767	0.3485	0.2789
T2 B cell [%]	Asthma severity	Mild-moderate asthma	-0.0236	0.8005	0.9765	0.2789
T2 B cell [%]	Asthma severity	Age	0.0106	0.0182	0.5611	0.2789
T2 B cell [%]	Asthma severity	Regular OCS	-3.6177	0.9261	< 0,001	0.2789
T2 B cell [%]	Asthma severity	(Intercept)	4.4936	1.2326	< 0,001	0.2789
T2 B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.1112	0.2071	0.5920	0.3057
T2 B cell [%]	FEV_1/FVC [z-score]	Age	0.0103	0.0183	0.5751	0.3057
T2 B cell [%]	FEV_1/FVC [z-score]	Regular OCS	-3.7892	0.7025	< 0,001	0.3057
T2 B cell [%]	FEV_1/FVC [z-score]	(Intercept)	4.4694	1.0216	< 0,001	0.3057

T2 B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	0.6856	2.4647	0.7812	0.3057
T2 B cell [%]	R5-R20 [kPa/l/s]	Age	0.0088	0.0186	0.6384	0.3057
T2 B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	-3.8038	0.6901	< 0,001	0.3057
T2 B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	4.6668	0.9858	< 0,001	0.3057
T2 B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	-0.3185	0.9726	0.7438	0.3057
T2 B cell [%]	Sputum inflammation	Neutrophilic inflammation	-0.9722	0.8617	0.2611	0.3057
T2 B cell [%]	Sputum inflammation	Eosinophilic inflammation	-0.8894	1.0617	0.4036	0.3057
T2 B cell [%]	Sputum inflammation	Age	0.0222	0.0221	0.3163	0.3057
T2 B cell [%]	Sputum inflammation	Regular OCS	-3.8080	0.8028	< 0,001	0.3057
T2 B cell [%]	Sputum inflammation	(Intercept)	4.7118	1.1707	< 0,001	0.3057
T2 B cell [%]	Positive BDR [yes/no]	No	0.2476	0.6914	0.7208	0.3057
T2 B cell [%]	Positive BDR [yes/no]	Age	0.0101	0.0185	0.5843	0.3057
T2 B cell [%]	Positive BDR [yes/no]	Regular OCS	-3.7002	0.6928	< 0,001	0.3057
T2 B cell [%]	Positive BDR [yes/no]	(Intercept)	4.4641	1.1365	< 0,001	0.3057
T2 B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	-0.5321	1.0462	0.6118	0.3057
T2 B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	0.2902	0.9900	0.7698	0.3057
T2 B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	-0.2558	1.0294	0.8041	0.3057
T2 B cell [%]	Age at asthma diagnosis [yrs]	Age	0.0215	0.0233	0.3572	0.3057
T2 B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	-3.4605	0.6857	< 0,001	0.3057
T2 B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	3.9519	1.3633	0.0043	0.3057
T2 B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	0.0388	0.0734	0.5981	0.3057
T2 B cell [%]	Specific IgE [kU/l]	Age	0.0116	0.0183	0.5285	0.3057
T2 B cell [%]	Specific IgE [kU/l]	Regular OCS	-3.7322	0.6784	< 0,001	0.3057
T2 B cell [%]	Specific IgE [kU/l]	(Intercept)	4.5150	1.0238	< 0,001	0.3057
T2 B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	0.0412	0.1903	0.8289	0.3133
T2 B cell [%]	AX [kPa/l/s]	Age	0.0114	0.0186	0.5404	0.3133
T2 B cell [%]	AX [kPa/l/s]	Regular OCS	-3.7989	0.7129	< 0,001	0.3133
T2 B cell [%]	AX [kPa/l/s]	(Intercept)	4.5938	0.9930	< 0,001	0.3133
T2 B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	0.0306	0.1914	0.8730	0.3201
T2 B cell [%]	FEV_1 [z-score]	Age	0.0107	0.0183	0.5592	0.3201
T2 B cell [%]	FEV_1 [z-score]	Regular OCS	-3.6712	0.7168	< 0,001	0.3201
T2 B cell [%]	FEV_1 [z-score]	(Intercept)	4.6463	1.0161	< 0,001	0.3201
T2 B cell [%]	GINA control status	Uncontrolled	0.3042	0.7029	0.6658	0.3222

T2 B cell [%]	GINA control status	Partly controlled	0.2026	0.7226	0.7796	0.3222
T2 B cell [%]	GINA control status	Age	0.0089	0.0208	0.6708	0.3222
T2 B cell [%]	GINA control status	Regular OCS	-3.6603	0.7055	< 0,001	0.3222
T2 B cell [%]	GINA control status	(Intercept)	4.4022	1.1659	< 0,001	0.3222
T2 B cell [%]	Smoking status	Current or former smokers ≥10PY	-0.0516	0.6237	0.9341	0.3294
T2 B cell [%]	Smoking status	Age	0.0104	0.0183	0.5709	0.3294
T2 B cell [%]	Smoking status	Regular OCS	-3.7705	0.6759	< 0,001	0.3294
T2 B cell [%]	Smoking status	(Intercept)	4.6749	0.9789	< 0,001	0.3294
T2 B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	0.0145	0.2421	0.9523	0.3339
T2 B cell [%]	FEF_{25-75} [z-score]	Age	0.0152	0.0208	0.4663	0.3339
T2 B cell [%]	FEF_{25-75} [z-score]	Regular OCS	-4.1197	0.7688	< 0,001	0.3339
T2 B cell [%]	FEF_{25-75} [z-score]	(Intercept)	4.5948	1.1835	< 0,001	0.3339
T2 B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	0.0028	0.1149	0.9806	0.3420
T2 B cell [%]	Severe exacerbations [n]	Age	0.0109	0.0187	0.5626	0.3420
T2 B cell [%]	Severe exacerbations [n]	Regular OCS	-3.7785	0.8064	< 0,001	0.3420
T2 B cell [%]	Severe exacerbations [n]	(Intercept)	4.6275	1.0028	< 0,001	0.3420
Naive B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	2.3927	1.0318	0.0218	0.0867
Naive B cell [%]	FEF_{25-75} [z-score]	Age	0.0209	0.0888	0.8141	0.0867
Naive B cell [%]	FEF_{25-75} [z-score]	Regular OCS	-10.4268	3.2761	0.0018	0.0867
Naive B cell [%]	FEF_{25-75} [z-score]	(Intercept)	63.0731	5.0429	< 0,001	0.0867
Naive B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	1.9338	0.8880	0.0308	0.0998
Naive B cell [%]	FEV_1/FVC [z-score]	Age	-0.0411	0.0786	0.6017	0.0998
Naive B cell [%]	FEV_1/FVC [z-score]	Regular OCS	-10.5614	3.0113	< 0,001	0.0998
Naive B cell [%]	FEV_1/FVC [z-score]	(Intercept)	66.9550	4.3793	< 0,001	0.0998
Naive B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	-0.9436	0.5007	0.0613	0.1486
Naive B cell [%]	Severe exacerbations [n]	Age	-0.0213	0.0815	0.7941	0.1486
Naive B cell [%]	Severe exacerbations [n]	Regular OCS	-9.1389	3.5133	0.0101	0.1486
Naive B cell [%]	Severe exacerbations [n]	(Intercept)	64.6066	4.3689	< 0,001	0.1486
Naive B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	1.4899	0.8234	0.0722	0.1517
Naive B cell [%]	FEV_1 [z-score]	Age	-0.0541	0.0789	0.4934	0.1517
Naive B cell [%]	FEV_1 [z-score]	Regular OCS	-10.3899	3.0834	0.0009	0.1517

Naive B cell [%]	FEV_1 [z-score]	(Intercept)	66.3529	4.3711	< 0,001	0.1517
Naive B cell [%]	Asthma severity	Healthy	0.8976	4.2176	0.8317	0.1911
Naive B cell [%]	Asthma severity	Mild-moderate asthma	6.0546	3.4569	0.0817	0.1911
Naive B cell [%]	Asthma severity	Age	-0.0321	0.0787	0.6838	0.1911
Naive B cell [%]	Asthma severity	Regular OCS	-7.9827	3.9994	0.0475	0.1911
Naive B cell [%]	Asthma severity	(Intercept)	59.7485	5.3227	< 0,001	0.1911
Naive B cell [%]	GINA control status	Uncontrolled	-1.9738	3.1423	0.5309	0.2485
Naive B cell [%]	GINA control status	Partly controlled	2.8943	3.2306	0.3718	0.2485
Naive B cell [%]	GINA control status	Age	-0.0666	0.0931	0.4752	0.2485
Naive B cell [%]	GINA control status	Regular OCS	-11.7167	3.1539	< 0,001	0.2485
Naive B cell [%]	GINA control status	(Intercept)	66.0265	5.2122	< 0,001	0.2485
Naive B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	-10.9645	10.7168	0.3077	0.2485
Naive B cell [%]	R5-R20 [kPa/l/s]	Age	-0.0292	0.0808	0.7185	0.2485
Naive B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	-11.3776	3.0006	< 0,001	0.2485
Naive B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	64.9111	4.2864	< 0,001	0.2485
Naive B cell [%]	Gender	Female	2.2382	2.2858	0.3289	0.2498
Naive B cell [%]	Gender	Age	-0.0402	0.0790	0.6116	0.2498
Naive B cell [%]	Gender	Regular OCS	-11.8856	2.9288	< 0,001	0.2498
Naive B cell [%]	Gender	(Intercept)	63.0004	4.5033	< 0,001	0.2498
Naive B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	-0.7091	0.8096	0.3824	0.2598
Naive B cell [%]	AX [kPa/l/s]	Age	-0.0411	0.0790	0.6035	0.2598
Naive B cell [%]	AX [kPa/l/s]	Regular OCS	-9.5916	3.0337	0.0019	0.2598
Naive B cell [%]	AX [kPa/l/s]	(Intercept)	64.8139	4.2253	< 0,001	0.2598
Naive B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	0.1694	0.2029	0.4048	0.2655
Naive B cell [%]	BMI [Kg/m^2]	Age	-0.0498	0.0791	0.5299	0.2655
Naive B cell [%]	BMI [Kg/m^2]	Regular OCS	-12.3926	2.9780	< 0,001	0.2655
Naive B cell [%]	BMI [Kg/m^2]	(Intercept)	60.1038	6.7260	< 0,001	0.2655
Naive B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	4.5755	4.7550	0.3376	0.2789
Naive B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	-0.3365	4.4997	0.9405	0.2789

Naive B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	-0.5301	4.6787	0.9100	0.2789
Naive B cell [%]	Age at asthma diagnosis [yrs]	Age	-0.1494	0.1060	0.1611	0.2789
Naive B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	-13.4080	3.1167	< 0,001	0.2789
Naive B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	69.7230	6.1964	< 0,001	0.2789
Naive B cell [%]	Smoking status	Current or former smokers ≥10PY	-1.3329	2.7145	0.6240	0.3057
Naive B cell [%]	Smoking status	Age	-0.0393	0.0798	0.6233	0.3057
Naive B cell [%]	Smoking status	Regular OCS	-11.8459	2.9418	< 0,001	0.3057
Naive B cell [%]	Smoking status	(Intercept)	64.4585	4.2605	< 0,001	0.3057
Naive B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	0.4986	4.0879	0.9031	0.3057
Naive B cell [%]	Sputum inflammation	Neutrophilic inflammation	3.4855	3.6216	0.3375	0.3057
Naive B cell [%]	Sputum inflammation	Eosinophilic inflammation	2.1627	4.4624	0.6287	0.3057
Naive B cell [%]	Sputum inflammation	Age	-0.0862	0.0928	0.3542	0.3057
Naive B cell [%]	Sputum inflammation	Regular OCS	-10.2722	3.3742	0.0028	0.3057
Naive B cell [%]	Sputum inflammation	(Intercept)	64.8153	4.9204	< 0,001	0.3057
Naive B cell [%]	Positive BDR [yes/no]	No	-1.0860	3.0022	0.7180	0.3057
Naive B cell [%]	Positive BDR [yes/no]	Age	-0.0487	0.0802	0.5443	0.3057
Naive B cell [%]	Positive BDR [yes/no]	Regular OCS	-12.0144	3.0080	< 0,001	0.3057
Naive B cell [%]	Positive BDR [yes/no]	(Intercept)	65.2296	4.9346	< 0,001	0.3057
Naive B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	0.1184	0.3198	0.7116	0.3057
Naive B cell [%]	Specific IgE [kU/l]	Age	-0.0406	0.0798	0.6115	0.3057
Naive B cell [%]	Specific IgE [kU/l]	Regular OCS	-11.8204	2.9557	< 0,001	0.3057
Naive B cell [%]	Specific IgE [kU/l]	(Intercept)	63.9659	4.4607	< 0,001	0.3057
Naive B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	-0.1278	0.6020	0.8321	0.3133
Naive B cell [%]	Blood neutrophils [1000/µl]	Age	-0.0556	0.0802	0.4892	0.3133
Naive B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	-11.4050	3.4631	0.0012	0.3133
Naive B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	65.4260	5.1781	< 0,001	0.3133
Naive B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	-0.5269	3.8548	0.8914	0.3222
Naive B cell [%]	Blood eosinophils [1000/µl]	Age	-0.0533	0.0797	0.5043	0.3222
Naive B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	-11.7450	2.9631	< 0,001	0.3222

Naive B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	64.9595	4.4238	< 0,001	0.3222
$CD27^{+}IgM^{+}$ B cell [%]	Smoking status	Current or former smokers ≥10PY	-2.9017	1.2028	0.0169	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Smoking status	Age	0.0643	0.0354	0.0708	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Smoking status	Regular OCS	4.6126	1.3035	< 0,001	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Smoking status	(Intercept)	4.9944	1.8878	0.0089	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Asthma severity	Healthy	-4.0344	1.8796	0.0332	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Asthma severity	Mild-moderate asthma	-4.3587	1.5406	0.0052	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Asthma severity	Age	0.0413	0.0351	0.2407	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Asthma severity	Regular OCS	0.8988	1.7824	0.6147	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	Asthma severity	(Intercept)	9.1042	2.3721	< 0,001	0.0867
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.8005	0.3950	0.0443	0.1293
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1/FVC [z-score]	Age	0.0404	0.0350	0.2499	0.1293
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1/FVC [z-score]	Regular OCS	3.2786	1.3397	0.0154	0.1293
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1/FVC [z-score]	(Intercept)	4.4543	1.9483	0.0235	0.1293
$CD27^{+}IgM^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	-2.1871	2.1952	0.3208	0.1486
$CD27^{+}IgM^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	1.7603	2.0773	0.3982	0.1486
$CD27^{+}IgM^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	-1.0040	2.1599	0.6428	0.1486
$CD27^{+}IgM^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age	0.0873	0.0489	0.0766	0.1486
$CD27^{+}IgM^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	4.7298	1.4388	0.0013	0.1486
$CD27^{+}IgM^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	3.4903	2.8606	0.2244	0.1486
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	-0.6590	0.3657	0.0733	0.1517
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1 [z-score]	Age	0.0459	0.0350	0.1919	0.1517
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1 [z-score]	Regular OCS	3.1611	1.3694	0.0222	0.1517
$CD27^{+}IgM^{+}$ B cell [%]	FEV_1 [z-score]	(Intercept)	4.6517	1.9412	0.0177	0.1517
$CD27^{+}IgM^{+}$ B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	-0.8087	0.4800	0.0942	0.1832
$CD27^{+}IgM^{+}$ B cell [%]	FEF_{25-75} [z-score]	Age	0.0277	0.0413	0.5040	0.1832
$CD27^{+}IgM^{+}$ B cell [%]	FEF_{25-75} [z-score]	Regular OCS	3.2168	1.5240	0.0365	0.1832
$CD27^{+}IgM^{+}$ B cell [%]	FEF_{25-75} [z-score]	(Intercept)	5.5200	2.3460	0.0200	0.1832
$CD27^{+}IgM^{+}$ B cell [%]	Gender	Female	-1.4925	1.0257	0.1475	0.1911

$CD27^+IgM^+$ B cell [%]	Gender	Age	0.0491	0.0354	0.1679	0.1911
$CD27^+IgM^+$ B cell [%]	Gender	Regular OCS	4.3448	1.3142	0.0012	0.1911
$CD27^+IgM^+$ B cell [%]	Gender	(Intercept)	5.9532	2.0207	0.0037	0.1911
$CD27^+IgM^+$ B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	0.3547	0.2703	0.1912	0.2152
$CD27^+IgM^+$ B cell [%]	Blood neutrophils [1000/µl]	Age	0.0589	0.0360	0.1036	0.2152
$CD27^+IgM^+$ B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	3.2879	1.5549	0.0359	0.2152
$CD27^+IgM^+$ B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	3.2165	2.3250	0.1683	0.2152
$CD27^+IgM^+$ B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	-0.0944	0.0913	0.3025	0.2485
$CD27^+IgM^+$ B cell [%]	BMI [Kg/m^2]	Age	0.0549	0.0356	0.1244	0.2485
$CD27^+IgM^+$ B cell [%]	BMI [Kg/m^2]	Regular OCS	4.6342	1.3393	< 0,001	0.2485
$CD27^+IgM^+$ B cell [%]	BMI [Kg/m^2]	(Intercept)	7.4069	3.0249	0.0153	0.2485
$CD27^+IgM^+$ B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	1.6242	1.7350	0.3505	0.2498
$CD27^+IgM^+$ B cell [%]	Blood eosinophils [1000/µl]	Age	0.0526	0.0359	0.1445	0.2498
$CD27^+IgM^+$ B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	4.2171	1.3336	0.0019	0.2498
$CD27^+IgM^+$ B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	4.4650	1.9910	0.0262	0.2498
$CD27^+IgM^+$ B cell [%]	GINA control status	Uncontrolled	1.8207	1.4749	0.2191	0.2655
$CD27^+IgM^+$ B cell [%]	GINA control status	Partly controlled	0.2847	1.5163	0.8513	0.2655
$CD27^+IgM^+$ B cell [%]	GINA control status	Age	0.0615	0.0437	0.1612	0.2655
$CD27^+IgM^+$ B cell [%]	GINA control status	Regular OCS	3.7032	1.4804	0.0135	0.2655
$CD27^+IgM^+$ B cell [%]	GINA control status	(Intercept)	3.9327	2.4465	0.1101	0.2655
$CD27^+IgM^+$ B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	-0.1461	0.2282	0.5228	0.2995
$CD27^+IgM^+$ B cell [%]	Severe exacerbations [n]	Age	0.0489	0.0371	0.1902	0.2995
$CD27^+IgM^+$ B cell [%]	Severe exacerbations [n]	Regular OCS	4.9878	1.6010	0.0022	0.2995
$CD27^+IgM^+$ B cell [%]	Severe exacerbations [n]	(Intercept)	5.2456	1.9909	0.0092	0.2995
$CD27^+IgM^+$ B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	2.3100	4.8426	0.6340	0.3057
$CD27^+IgM^+$ B cell [%]	R5-R20 [kPa/l/s]	Age	0.0488	0.0365	0.1833	0.3057
$CD27^+IgM^+$ B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	4.2756	1.3559	0.0019	0.3057
$CD27^+IgM^+$ B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	4.8834	1.9369	0.0126	0.3057
$CD27^+IgM^+$ B cell [%]	Positive BDR [yes/no]	No	0.5789	1.3347	0.6650	0.3057

$CD27^{+}IgM^{+}$ B cell [%]	Positive BDR [yes/no]	Age	0.0451	0.0356	0.2078	0.3057
$CD27^{+}IgM^{+}$ B cell [%]	Positive BDR [yes/no]	Regular OCS	3.8976	1.3372	0.0040	0.3057
$CD27^{+}IgM^{+}$ B cell [%]	Positive BDR [yes/no]	(Intercept)	4.9684	2.1937	0.0248	0.3057
$CD27^{+}IgM^{+}$ B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	-0.0882	0.1439	0.5409	0.3057
$CD27^{+}IgM^{+}$ B cell [%]	Specific IgE [kU/l]	Age	0.0490	0.0359	0.1738	0.3057
$CD27^{+}IgM^{+}$ B cell [%]	Specific IgE [kU/l]	Regular OCS	4.2913	1.3298	0.0015	0.3057
$CD27^{+}IgM^{+}$ B cell [%]	Specific IgE [kU/l]	(Intercept)	5.3472	2.0069	0.0084	0.3057
$CD27^{+}IgM^{+}$ B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	0.0915	0.3742	0.8070	0.3099
$CD27^{+}IgM^{+}$ B cell [%]	AX [kPa/l/s]	Age	0.0546	0.0365	0.1366	0.3099
$CD27^{+}IgM^{+}$ B cell [%]	AX [kPa/l/s]	Regular OCS	4.4656	1.4021	0.0017	0.3099
$CD27^{+}IgM^{+}$ B cell [%]	AX [kPa/l/s]	(Intercept)	4.7903	1.9528	0.0152	0.3099
$CD27^{+}IgM^{+}$ B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	0.1465	1.6863	0.9309	0.3133
$CD27^{+}IgM^{+}$ B cell [%]	Sputum inflammation	Neutrophilic inflammation	-0.0249	1.4940	0.9867	0.3133
$CD27^{+}IgM^{+}$ B cell [%]	Sputum inflammation	Eosinophilic inflammation	1.2882	1.8408	0.4852	0.3133
$CD27^{+}IgM^{+}$ B cell [%]	Sputum inflammation	Age	0.0671	0.0383	0.0819	0.3133
$CD27^{+}IgM^{+}$ B cell [%]	Sputum inflammation	Regular OCS	2.7278	1.3919	0.0520	0.3133
$CD27^{+}IgM^{+}$ B cell [%]	Sputum inflammation	(Intercept)	4.2282	2.0298	0.0390	0.3133
$CD27^{-}IgG^{+}$ B cell [%]	Gender	Female	0.8336	0.5961	0.1638	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Gender	Age	-0.0308	0.0206	0.1369	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Gender	Regular OCS	2.5984	0.7638	0.0008	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Gender	(Intercept)	5.4657	1.1744	< 0,001	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	0.1946	0.1324	0.1435	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Severe exacerbations [n]	Age	-0.0329	0.0216	0.1293	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Severe exacerbations [n]	Regular OCS	1.8538	0.9289	0.0476	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Severe exacerbations [n]	(Intercept)	5.8556	1.1551	< 0,001	0.1911
$CD27^{-}IgG^{+}$ B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	1.2171	0.8163	0.1382	0.2319
$CD27^{-}IgG^{+}$ B cell [%]	Sputum inflammation	Neutrophilic inflammation	0.0234	0.7232	0.9742	0.2319
$CD27^{-}IgG^{+}$ B cell [%]	Sputum inflammation	Eosinophilic inflammation	0.0645	0.8911	0.9424	0.2319
$CD27^{-}IgG^{+}$ B cell [%]	Sputum inflammation	Age	-0.0386	0.0185	0.0388	0.2319

$CD27^-IgG^+$ B cell [%]	Sputum inflammation	Regular OCS	1.8176	0.6738	0.0078	0.2319
$CD27^-IgG^+$ B cell [%]	Sputum inflammation	(Intercept)	5.8244	0.9825	< 0,001	0.2319
$CD27^-IgG^+$ B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	0.0975	0.0833	0.2438	0.2319
$CD27^-IgG^+$ B cell [%]	Specific IgE [kU/l]	Age	-0.0291	0.0208	0.1643	0.2319
$CD27^-IgG^+$ B cell [%]	Specific IgE [kU/l]	Regular OCS	2.6808	0.7703	< 0,001	0.2319
$CD27^-IgG^+$ B cell [%]	Specific IgE [kU/l]	(Intercept)	5.6055	1.1625	< 0,001	0.2319
$CD27^-IgG^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	-0.2620	1.2875	0.8391	0.2485
$CD27^-IgG^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	-1.2254	1.2184	0.3162	0.2485
$CD27^-IgG^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	0.5156	1.2669	0.6847	0.2485
$CD27^-IgG^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age	-0.0232	0.0287	0.4202	0.2485
$CD27^-IgG^+$ B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	2.3467	0.8439	0.0062	0.2485
$CD27^-IgG^+$ B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	6.0457	1.6778	< 0,001	0.2485
$CD27^-IgG^+$ B cell [%]	Smoking status	Current or former smokers ≥10PY	0.7014	0.7084	0.3236	0.2498
$CD27^-IgG^+$ B cell [%]	Smoking status	Age	-0.0354	0.0208	0.0906	0.2498
$CD27^-IgG^+$ B cell [%]	Smoking status	Regular OCS	2.5202	0.7677	0.0012	0.2498
$CD27^-IgG^+$ B cell [%]	Smoking status	(Intercept)	6.0045	1.1119	< 0,001	0.2498
$CD27^-IgG^+$ B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	-0.2095	0.2160	0.3336	0.2498
$CD27^-IgG^+$ B cell [%]	FEV_1 [z-score]	Age	-0.0290	0.0207	0.1626	0.2498
$CD27^-IgG^+$ B cell [%]	FEV_1 [z-score]	Regular OCS	2.4530	0.8090	0.0028	0.2498
$CD27^-IgG^+$ B cell [%]	FEV_1 [z-score]	(Intercept)	5.6451	1.1469	< 0,001	0.2498
$CD27^-IgG^+$ B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	-0.2350	0.2602	0.3680	0.2567
$CD27^-IgG^+$ B cell [%]	FEF_{25-75} [z-score]	Age	-0.0325	0.0224	0.1489	0.2567
$CD27^-IgG^+$ B cell [%]	FEF_{25-75} [z-score]	Regular OCS	2.8945	0.8263	< 0,001	0.2567
$CD27^-IgG^+$ B cell [%]	FEF_{25-75} [z-score]	(Intercept)	5.5080	1.2720	< 0,001	0.2567
$CD27^-IgG^+$ B cell [%]	Positive BDR [yes/no]	No	-0.6866	0.7828	0.3817	0.2598
$CD27^-IgG^+$ B cell [%]	Positive BDR [yes/no]	Age	-0.0287	0.0209	0.1708	0.2598
$CD27^-IgG^+$ B cell [%]	Positive BDR [yes/no]	Regular OCS	2.6121	0.7843	0.0011	0.2598
$CD27^-IgG^+$ B cell [%]	Positive BDR [yes/no]	(Intercept)	6.4225	1.2866	< 0,001	0.2598
$CD27^-IgG^+$ B cell [%]	GINA control status	Uncontrolled	-0.5666	0.8560	0.5091	0.2829

$CD27^-IgG^+$ B cell [%]	GINA control status	Partly controlled	-1.0680	0.8801	0.2269	0.2829
$CD27^-IgG^+$ B cell [%]	GINA control status	Age	-0.0273	0.0254	0.2826	0.2829
$CD27^-IgG^+$ B cell [%]	GINA control status	Regular OCS	2.4967	0.8592	0.0042	0.2829
$CD27^-IgG^+$ B cell [%]	GINA control status	(Intercept)	6.3863	1.4199	< 0,001	0.2829
$CD27^-IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	0.7161	1.0079	0.4784	0.2829
$CD27^-IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	Age	-0.0312	0.0208	0.1357	0.2829
$CD27^-IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	2.4801	0.7748	0.0016	0.2829
$CD27^-IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	5.7341	1.1567	< 0,001	0.2829
$CD27^-IgG^+$ B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	0.0202	0.0532	0.7046	0.3057
$CD27^-IgG^+$ B cell [%]	BMI [Kg/m^2]	Age	-0.0331	0.0207	0.1120	0.3057
$CD27^-IgG^+$ B cell [%]	BMI [Kg/m^2]	Regular OCS	2.5218	0.7801	0.0015	0.3057
$CD27^-IgG^+$ B cell [%]	BMI [Kg/m^2]	(Intercept)	5.4888	1.7619	0.0022	0.3057
$CD27^-IgG^+$ B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.0809	0.2345	0.7304	0.3057
$CD27^-IgG^+$ B cell [%]	FEV_1/FVC [z-score]	Age	-0.0300	0.0208	0.1507	0.3057
$CD27^-IgG^+$ B cell [%]	FEV_1/FVC [z-score]	Regular OCS	2.6219	0.7954	0.0012	0.3057
$CD27^-IgG^+$ B cell [%]	FEV_1/FVC [z-score]	(Intercept)	5.7999	1.1567	< 0,001	0.3057
$CD27^-IgG^+$ B cell [%]	Asthma severity	Healthy	-0.5258	1.1158	0.6381	0.3057
$CD27^-IgG^+$ B cell [%]	Asthma severity	Mild-moderate asthma	0.1329	0.9145	0.8846	0.3057
$CD27^-IgG^+$ B cell [%]	Asthma severity	Age	-0.0325	0.0208	0.1203	0.3057
$CD27^-IgG^+$ B cell [%]	Asthma severity	Regular OCS	2.5598	1.0580	0.0166	0.3057
$CD27^-IgG^+$ B cell [%]	Asthma severity	(Intercept)	6.0217	1.4081	< 0,001	0.3057
$CD27^-IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	0.0384	0.1576	0.8076	0.3099
$CD27^-IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	Age	-0.0303	0.0210	0.1514	0.3099
$CD27^-IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	2.4283	0.9067	0.0081	0.3099
$CD27^-IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	5.7540	1.3558	< 0,001	0.3099
$CD27^-IgG^+$ B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	0.0283	0.2174	0.8965	0.3222
$CD27^-IgG^+$ B cell [%]	AX [kPa/l/s]	Age	-0.0314	0.0212	0.1403	0.3222
$CD27^-IgG^+$ B cell [%]	AX [kPa/l/s]	Regular OCS	2.5204	0.8145	0.0023	0.3222
$CD27^-IgG^+$ B cell [%]	AX [kPa/l/s]	(Intercept)	5.9497	1.1344	< 0,001	0.3222

$CD27^-IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	-0.3273	2.8095	0.9074	0.3222
$CD27^-IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	Age	-0.0316	0.0212	0.1377	0.3222
$CD27^-IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	2.5814	0.7866	0.0013	0.3222
$CD27^-IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	6.0050	1.1237	< 0,001	0.3222
$CD27^+IgG^+$ B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	-0.6210	0.2627	0.0194	0.0867
$CD27^+IgG^+$ B cell [%]	FEF_{25-75} [z-score]	Age	-0.0473	0.0226	0.0383	0.0867
$CD27^+IgG^+$ B cell [%]	FEF_{25-75} [z-score]	Regular OCS	3.2612	0.8342	< 0,001	0.0867
$CD27^+IgG^+$ B cell [%]	FEF_{25-75} [z-score]	(Intercept)	7.4579	1.2841	< 0,001	0.0867
$CD27^+IgG^+$ B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	0.3090	0.1322	0.0207	0.0867
$CD27^+IgG^+$ B cell [%]	Severe exacerbations [n]	Age	-0.0338	0.0215	0.1180	0.0867
$CD27^+IgG^+$ B cell [%]	Severe exacerbations [n]	Regular OCS	2.5407	0.9277	0.0069	0.0867
$CD27^+IgG^+$ B cell [%]	Severe exacerbations [n]	(Intercept)	7.1455	1.1536	< 0,001	0.0867
$CD27^+IgG^+$ B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.5226	0.2334	0.0264	0.0943
$CD27^+IgG^+$ B cell [%]	FEV_1/FVC [z-score]	Age	-0.0336	0.0207	0.1055	0.0943
$CD27^+IgG^+$ B cell [%]	FEV_1/FVC [z-score]	Regular OCS	3.3803	0.7915	< 0,001	0.0943
$CD27^+IgG^+$ B cell [%]	FEV_1/FVC [z-score]	(Intercept)	6.7053	1.1511	< 0,001	0.0943
$CD27^+IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	0.3203	0.1576	0.0437	0.1293
$CD27^+IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	Age	-0.0290	0.0210	0.1689	0.1293
$CD27^+IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	2.6756	0.9066	0.0036	0.1293
$CD27^+IgG^+$ B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	5.9128	1.3556	< 0,001	0.1293
$CD27^+IgG^+$ B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	0.3869	0.2078	0.0644	0.1486
$CD27^+IgG^+$ B cell [%]	AX [kPa/l/s]	Age	-0.0396	0.0203	0.0527	0.1486
$CD27^+IgG^+$ B cell [%]	AX [kPa/l/s]	Regular OCS	3.1957	0.7788	< 0,001	0.1486
$CD27^+IgG^+$ B cell [%]	AX [kPa/l/s]	(Intercept)	7.3447	1.0846	< 0,001	0.1486
$CD27^+IgG^+$ B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	-0.3766	0.2168	0.0842	0.1688
$CD27^+IgG^+$ B cell [%]	FEV_1 [z-score]	Age	-0.0302	0.0208	0.1479	0.1688
$CD27^+IgG^+$ B cell [%]	FEV_1 [z-score]	Regular OCS	3.3626	0.8117	< 0,001	0.1688
$CD27^+IgG^+$ B cell [%]	FEV_1 [z-score]	(Intercept)	6.8999	1.1507	< 0,001	0.1688
$CD27^+IgG^+$ B cell [%]	GINA control status	Uncontrolled	0.7011	0.8553	0.4137	0.1911

$CD27^+IgG^+$ B cell [%]	GINA control status	Partly controlled	-0.9630	0.8793	0.2753	0.1911
$CD27^+IgG^+$ B cell [%]	GINA control status	Age	-0.0334	0.0253	0.1888	0.1911
$CD27^+IgG^+$ B cell [%]	GINA control status	Regular OCS	3.3448	0.8585	< 0,001	0.1911
$CD27^+IgG^+$ B cell [%]	GINA control status	(Intercept)	7.5305	1.4187	< 0,001	0.1911
$CD27^+IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	1.4526	1.0151	0.1543	0.1911
$CD27^+IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	Age	-0.0347	0.0210	0.0999	0.1911
$CD27^+IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	3.5159	0.7803	< 0,001	0.1911
$CD27^+IgG^+$ B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	7.0440	1.1649	< 0,001	0.1911
$CD27^+IgG^+$ B cell [%]	Positive BDR [yes/no]	No	1.1038	0.7859	0.1620	0.1911
$CD27^+IgG^+$ B cell [%]	Positive BDR [yes/no]	Age	-0.0335	0.0210	0.1119	0.1911
$CD27^+IgG^+$ B cell [%]	Positive BDR [yes/no]	Regular OCS	3.9100	0.7874	< 0,001	0.1911
$CD27^+IgG^+$ B cell [%]	Positive BDR [yes/no]	(Intercept)	6.5577	1.2917	< 0,001	0.1911
$CD27^+IgG^+$ B cell [%]	Asthma severity	Healthy	-1.4580	1.1172	0.1936	0.1911
$CD27^+IgG^+$ B cell [%]	Asthma severity	Mild-moderate asthma	-1.7651	0.9157	0.0556	0.1911
$CD27^+IgG^+$ B cell [%]	Asthma severity	Age	-0.0384	0.0208	0.0671	0.1911
$CD27^+IgG^+$ B cell [%]	Asthma severity	Regular OCS	2.2708	1.0594	0.0335	0.1911
$CD27^+IgG^+$ B cell [%]	Asthma severity	(Intercept)	9.0993	1.4099	< 0,001	0.1911
$CD27^+IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	3.4495	2.7707	0.2148	0.2236
$CD27^+IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	Age	-0.0386	0.0209	0.0662	0.2236
$CD27^+IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	3.5191	0.7758	< 0,001	0.2236
$CD27^+IgG^+$ B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	7.2540	1.1082	< 0,001	0.2236
$CD27^+IgG^+$ B cell [%]	Smoking status	Current or former smokers ≥10PY	0.8653	0.7148	0.2277	0.2248
$CD27^+IgG^+$ B cell [%]	Smoking status	Age	-0.0377	0.0210	0.0745	0.2248
$CD27^+IgG^+$ B cell [%]	Smoking status	Regular OCS	3.5834	0.7746	< 0,001	0.2248
$CD27^+IgG^+$ B cell [%]	Smoking status	(Intercept)	7.4657	1.1219	< 0,001	0.2248
$CD27^+IgG^+$ B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	-0.0280	0.0537	0.6032	0.3057
$CD27^+IgG^+$ B cell [%]	BMI [Kg/m^2]	Age	-0.0333	0.0209	0.1137	0.3057
$CD27^+IgG^+$ B cell [%]	BMI [Kg/m^2]	Regular OCS	3.7237	0.7879	< 0,001	0.3057
$CD27^+IgG^+$ B cell [%]	BMI [Kg/m^2]	(Intercept)	8.1865	1.7796	< 0,001	0.3057

$CD27^{+}IgG^{+}$ B cell [%]	Gender	Female	-0.1869	0.6055	0.7579	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Gender	Age	-0.0345	0.0209	0.1011	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Gender	Regular OCS	3.6453	0.7759	< 0,001	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Gender	(Intercept)	7.5902	1.1930	< 0,001	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	1.3453	1.0386	0.1973	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Sputum inflammation	Neutrophilic inflammation	0.9445	0.9202	0.3064	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Sputum inflammation	Eosinophilic inflammation	1.4293	1.1338	0.2095	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Sputum inflammation	Age	-0.0380	0.0236	0.1088	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Sputum inflammation	Regular OCS	2.9737	0.8573	< 0,001	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Sputum inflammation	(Intercept)	6.7164	1.2501	< 0,001	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	-1.6312	1.3059	0.2137	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	-1.3866	1.2358	0.2637	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	-1.0804	1.2849	0.4018	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Age	-0.0224	0.0291	0.4440	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	3.6771	0.8559	< 0,001	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	8.1087	1.7017	< 0,001	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	0.0276	0.0845	0.7443	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Specific IgE [kU/l]	Age	-0.0331	0.0211	0.1183	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Specific IgE [kU/l]	Regular OCS	3.6807	0.7811	< 0,001	0.3057
$CD27^{+}IgG^{+}$ B cell [%]	Specific IgE [kU/l]	(Intercept)	7.3551	1.1789	< 0,001	0.3057
$CD27^{-}IgA^{+}$ B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	0.2231	0.0677	0.0012	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	Severe exacerbations [n]	Age	0.0003	0.0110	0.9751	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	Severe exacerbations [n]	Regular OCS	0.6130	0.4749	0.1986	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	Severe exacerbations [n]	(Intercept)	2.0971	0.5905	< 0,001	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	0.3390	0.1107	0.0026	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	AX [kPa/l/s]	Age	-0.0027	0.0108	0.8026	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	AX [kPa/l/s]	Regular OCS	0.9965	0.4147	0.0174	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	AX [kPa/l/s]	(Intercept)	2.1729	0.5775	< 0,001	0.0257
$CD27^{-}IgA^{+}$ B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	4.2238	1.4484	0.0040	0.0323

$CD27^-IgA^+$ B cell [%]	R5-R20 [kPa/l/s]	Age	-0.0039	0.0109	0.7184	0.0323
$CD27^-IgA^+$ B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	1.1522	0.4055	0.0050	0.0323
$CD27^-IgA^+$ B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	2.0842	0.5793	< 0,001	0.0323
$CD27^-IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	0.2117	0.0814	0.0102	0.0725
$CD27^-IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	Age	0.0068	0.0108	0.5306	0.0725
$CD27^-IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	0.7203	0.4685	0.1261	0.0725
$CD27^-IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	1.1604	0.7005	0.0995	0.0725
$CD27^-IgA^+$ B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	-0.2703	0.1123	0.0171	0.0867
$CD27^-IgA^+$ B cell [%]	FEV_1 [z-score]	Age	0.0048	0.0108	0.6588	0.0867
$CD27^-IgA^+$ B cell [%]	FEV_1 [z-score]	Regular OCS	1.1466	0.4203	0.0070	0.0867
$CD27^-IgA^+$ B cell [%]	FEV_1 [z-score]	(Intercept)	1.8405	0.5959	0.0024	0.0867
$CD27^-IgA^+$ B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.2794	0.1218	0.0230	0.0867
$CD27^-IgA^+$ B cell [%]	FEV_1/FVC [z-score]	Age	0.0027	0.0108	0.8009	0.0867
$CD27^-IgA^+$ B cell [%]	FEV_1/FVC [z-score]	Regular OCS	1.2319	0.4129	0.0033	0.0867
$CD27^-IgA^+$ B cell [%]	FEV_1/FVC [z-score]	(Intercept)	1.8209	0.6005	0.0028	0.0867
$CD27^-IgA^+$ B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	-0.2555	0.1173	0.0311	0.0998
$CD27^-IgA^+$ B cell [%]	FEF_{25-75} [z-score]	Age	0.0092	0.0101	0.3634	0.0998
$CD27^-IgA^+$ B cell [%]	FEF_{25-75} [z-score]	Regular OCS	1.2576	0.3726	0.0010	0.0998
$CD27^-IgA^+$ B cell [%]	FEF_{25-75} [z-score]	(Intercept)	1.4104	0.5735	0.0151	0.0998
$CD27^-IgA^+$ B cell [%]	Positive BDR [yes/no]	No	-0.5837	0.4107	0.1571	0.1911
$CD27^-IgA^+$ B cell [%]	Positive BDR [yes/no]	Age	0.0045	0.0110	0.6845	0.1911
$CD27^-IgA^+$ B cell [%]	Positive BDR [yes/no]	Regular OCS	1.3685	0.4115	0.0011	0.1911
$CD27^-IgA^+$ B cell [%]	Positive BDR [yes/no]	(Intercept)	2.6451	0.6751	< 0,001	0.1911
$CD27^-IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	-0.5482	0.6735	0.4170	0.1911
$CD27^-IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	-0.7741	0.6373	0.2266	0.1911
$CD27^-IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	0.3699	0.6627	0.5776	0.1911
$CD27^-IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age	0.0084	0.0150	0.5759	0.1911
$CD27^-IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	1.4151	0.4415	0.0017	0.1911
$CD27^-IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	2.2673	0.8777	0.0108	0.1911

$CD27^-IgA^+$ B cell [%]	Smoking status	Current or former smokers ≥10PY	0.4816	0.3728	0.1981	0.2192
$CD27^-IgA^+$ B cell [%]	Smoking status	Age	0.0004	0.0110	0.9714	0.2192
$CD27^-IgA^+$ B cell [%]	Smoking status	Regular OCS	1.3459	0.4040	0.0011	0.2192
$CD27^-IgA^+$ B cell [%]	Smoking status	(Intercept)	2.2293	0.5851	< 0,001	0.2192
$CD27^-IgA^+$ B cell [%]	GINA control status	Uncontrolled	0.3552	0.4498	0.4310	0.2485
$CD27^-IgA^+$ B cell [%]	GINA control status	Partly controlled	-0.3233	0.4624	0.4855	0.2485
$CD27^-IgA^+$ B cell [%]	GINA control status	Age	-0.0015	0.0133	0.9083	0.2485
$CD27^-IgA^+$ B cell [%]	GINA control status	Regular OCS	1.2717	0.4514	0.0055	0.2485
$CD27^-IgA^+$ B cell [%]	GINA control status	(Intercept)	2.4281	0.7460	0.0014	0.2485
$CD27^-IgA^+$ B cell [%]	Gender	Female	0.3214	0.3151	0.3092	0.2485
$CD27^-IgA^+$ B cell [%]	Gender	Age	0.0031	0.0109	0.7782	0.2485
$CD27^-IgA^+$ B cell [%]	Gender	Regular OCS	1.3925	0.4038	< 0,001	0.2485
$CD27^-IgA^+$ B cell [%]	Gender	(Intercept)	2.0223	0.6208	0.0014	0.2485
$CD27^-IgA^+$ B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	0.0189	0.0280	0.5012	0.2897
$CD27^-IgA^+$ B cell [%]	BMI [Kg/m^2]	Age	0.0018	0.0109	0.8657	0.2897
$CD27^-IgA^+$ B cell [%]	BMI [Kg/m^2]	Regular OCS	1.3339	0.4109	0.0014	0.2897
$CD27^-IgA^+$ B cell [%]	BMI [Kg/m^2]	(Intercept)	1.7465	0.9281	0.0616	0.2897
$CD27^-IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	-0.2386	0.5314	0.6539	0.3057
$CD27^-IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	Age	0.0037	0.0110	0.7365	0.3057
$CD27^-IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	1.3841	0.4084	< 0,001	0.3057
$CD27^-IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	2.2524	0.6098	< 0,001	0.3057
$CD27^-IgA^+$ B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	0.4412	0.4858	0.3654	0.3057
$CD27^-IgA^+$ B cell [%]	Sputum inflammation	Neutrophilic inflammation	0.0913	0.4304	0.8323	0.3057
$CD27^-IgA^+$ B cell [%]	Sputum inflammation	Eosinophilic inflammation	0.2322	0.5303	0.6622	0.3057
$CD27^-IgA^+$ B cell [%]	Sputum inflammation	Age	0.0092	0.0110	0.4048	0.3057
$CD27^-IgA^+$ B cell [%]	Sputum inflammation	Regular OCS	1.3279	0.4010	0.0012	0.3057
$CD27^-IgA^+$ B cell [%]	Sputum inflammation	(Intercept)	1.5617	0.5848	0.0084	0.3057
$CD27^-IgA^+$ B cell [%]	Asthma severity	Healthy	-0.3043	0.5883	0.6057	0.3057
$CD27^-IgA^+$ B cell [%]	Asthma severity	Mild-moderate asthma	-0.3575	0.4822	0.4595	0.3057

$CD27^{-}IgA^{+}$ B cell [%]	Asthma severity	Age	0.0015	0.0110	0.8898	0.3057
$CD27^{-}IgA^{+}$ B cell [%]	Asthma severity	Regular OCS	1.1021	0.5579	0.0498	0.3057
$CD27^{-}IgA^{+}$ B cell [%]	Asthma severity	(Intercept)	2.5632	0.7425	< 0,001	0.3057
$CD27^{-}IgA^{+}$ B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	0.0113	0.0441	0.7974	0.3099
$CD27^{-}IgA^{+}$ B cell [%]	Specific IgE [kU/l]	Age	0.0028	0.0110	0.7993	0.3099
$CD27^{-}IgA^{+}$ B cell [%]	Specific IgE [kU/l]	Regular OCS	1.3956	0.4077	< 0,001	0.3099
$CD27^{-}IgA^{+}$ B cell [%]	Specific IgE [kU/l]	(Intercept)	2.1843	0.6152	< 0,001	0.3099
$CD27^{+}IgA^{+}$ B cell [%]	AX [kPa/l/s]	AX [kPa/l/s]	0.8862	0.1666	< 0,001	< 0,001
$CD27^{+}IgA^{+}$ B cell [%]	AX [kPa/l/s]	Age	0.0339	0.0163	0.0389	< 0,001
$CD27^{+}IgA^{+}$ B cell [%]	AX [kPa/l/s]	Regular OCS	2.0013	0.6242	0.0016	< 0,001
$CD27^{+}IgA^{+}$ B cell [%]	AX [kPa/l/s]	(Intercept)	1.3579	0.8694	0.1202	< 0,001
$CD27^{+}IgA^{+}$ B cell [%]	R5-R20 [kPa/l/s]	R5-R20 [kPa/l/s]	9.1168	2.2403	< 0,001	0.0023
$CD27^{+}IgA^{+}$ B cell [%]	R5-R20 [kPa/l/s]	Age	0.0312	0.0169	0.0661	0.0023
$CD27^{+}IgA^{+}$ B cell [%]	R5-R20 [kPa/l/s]	Regular OCS	2.1557	0.6272	< 0,001	0.0023
$CD27^{+}IgA^{+}$ B cell [%]	R5-R20 [kPa/l/s]	(Intercept)	1.3074	0.8961	0.1464	0.0023
$CD27^{+}IgA^{+}$ B cell [%]	FEF_{25-75} [z-score]	FEF_{25-75} [z-score]	-0.6829	0.2245	0.0028	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEF_{25-75} [z-score]	Age	0.0456	0.0193	0.0197	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEF_{25-75} [z-score]	Regular OCS	2.1538	0.7129	0.0030	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEF_{25-75} [z-score]	(Intercept)	0.7640	1.0974	0.4874	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1 [z-score]	FEV_1 [z-score]	-0.5408	0.1770	0.0026	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1 [z-score]	Age	0.0487	0.0170	0.0046	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1 [z-score]	Regular OCS	2.1366	0.6629	0.0015	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1 [z-score]	(Intercept)	0.9018	0.9397	0.3386	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1/FVC [z-score]	FEV_1/FVC [z-score]	-0.5967	0.1915	0.0022	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1/FVC [z-score]	Age	0.0444	0.0170	0.0096	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1/FVC [z-score]	Regular OCS	2.2786	0.6494	< 0,001	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	FEV_1/FVC [z-score]	(Intercept)	0.8151	0.9445	0.3894	0.0257
$CD27^{+}IgA^{+}$ B cell [%]	Severe exacerbations [n]	Severe exacerbations [n]	0.2055	0.1108	0.0654	0.1486
$CD27^{+}IgA^{+}$ B cell [%]	Severe exacerbations [n]	Age	0.0461	0.0180	0.0116	0.1486

$CD27^+IgA^+$ B cell [%]	Severe exacerbations [n]	Regular OCS	1.8701	0.7772	0.0172	0.1486
$CD27^+IgA^+$ B cell [%]	Severe exacerbations [n]	(Intercept)	1.4009	0.9664	0.1491	0.1486
$CD27^+IgA^+$ B cell [%]	GINA control status	Uncontrolled	1.2692	0.7055	0.0741	0.1911
$CD27^+IgA^+$ B cell [%]	GINA control status	Partly controlled	0.0509	0.7253	0.9442	0.1911
$CD27^+IgA^+$ B cell [%]	GINA control status	Age	0.0435	0.0209	0.0393	0.1911
$CD27^+IgA^+$ B cell [%]	GINA control status	Regular OCS	2.2324	0.7081	0.0020	0.1911
$CD27^+IgA^+$ B cell [%]	GINA control status	(Intercept)	1.3364	1.1702	0.2553	0.1911
$CD27^+IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	Blood neutrophils [1000/µl]	0.1846	0.1315	0.1621	0.1911
$CD27^+IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	Age	0.0485	0.0175	0.0062	0.1911
$CD27^+IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	Regular OCS	2.0513	0.7562	0.0074	0.1911
$CD27^+IgA^+$ B cell [%]	Blood neutrophils [1000/µl]	(Intercept)	0.7317	1.1307	0.5184	0.1911
$CD27^+IgA^+$ B cell [%]	Sputum inflammation	Mixed granulocytic inflammation	0.8608	0.7054	0.2244	0.1911
$CD27^+IgA^+$ B cell [%]	Sputum inflammation	Neutrophilic inflammation	0.7197	0.6249	0.2514	0.1911
$CD27^+IgA^+$ B cell [%]	Sputum inflammation	Eosinophilic inflammation	1.7744	0.7700	0.0226	0.1911
$CD27^+IgA^+$ B cell [%]	Sputum inflammation	Age	0.0461	0.0160	0.0046	0.1911
$CD27^+IgA^+$ B cell [%]	Sputum inflammation	Regular OCS	1.3807	0.5822	0.0191	0.1911
$CD27^+IgA^+$ B cell [%]	Sputum inflammation	(Intercept)	0.7724	0.8491	0.3645	0.1911
$CD27^+IgA^+$ B cell [%]	BMI [Kg/m^2]	BMI [Kg/m^2]	0.0613	0.0443	0.1682	0.1927
$CD27^+IgA^+$ B cell [%]	BMI [Kg/m^2]	Age	0.0430	0.0173	0.0137	0.1927
$CD27^+IgA^+$ B cell [%]	BMI [Kg/m^2]	Regular OCS	2.4660	0.6504	< 0,001	0.1927
$CD27^+IgA^+$ B cell [%]	BMI [Kg/m^2]	(Intercept)	0.0842	1.4689	0.9544	0.1927
$CD27^+IgA^+$ B cell [%]	Smoking status	Current or former smokers ≥10PY	0.6101	0.5935	0.3054	0.2485
$CD27^+IgA^+$ B cell [%]	Smoking status	Age	0.0423	0.0174	0.0164	0.2485
$CD27^+IgA^+$ B cell [%]	Smoking status	Regular OCS	2.5791	0.6432	< 0,001	0.2485
$CD27^+IgA^+$ B cell [%]	Smoking status	(Intercept)	1.6564	0.9315	0.0772	0.2485
$CD27^+IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis >40yrs	-0.9775	1.0730	0.3638	0.2498
$CD27^+IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 18-40yrs	-0.2012	1.0153	0.8432	0.2498
$CD27^+IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age at diagnosis 6-18yrs	0.6061	1.0557	0.5668	0.2498
$CD27^+IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Age	0.0666	0.0239	0.0061	0.2498

$CD27^+IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	Regular OCS	2.7632	0.7033	< 0,001	0.2498
$CD27^+IgA^+$ B cell [%]	Age at asthma diagnosis [yrs]	(Intercept)	0.7322	1.3982	0.6013	0.2498
$CD27^+IgA^+$ B cell [%]	Positive BDR [yes/no]	No	-0.4830	0.6568	0.4632	0.2806
$CD27^+IgA^+$ B cell [%]	Positive BDR [yes/no]	Age	0.0466	0.0175	0.0086	0.2806
$CD27^+IgA^+$ B cell [%]	Positive BDR [yes/no]	Regular OCS	2.6827	0.6581	< 0,001	0.2806
$CD27^+IgA^+$ B cell [%]	Positive BDR [yes/no]	(Intercept)	1.9943	1.0796	0.0665	0.2806
$CD27^+IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	Blood eosinophils [1000/µl]	-0.5909	0.8453	0.4855	0.2832
$CD27^+IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	Age	0.0460	0.0175	0.0092	0.2832
$CD27^+IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	Regular OCS	2.6647	0.6498	< 0,001	0.2832
$CD27^+IgA^+$ B cell [%]	Blood eosinophils [1000/µl]	(Intercept)	1.7939	0.9701	0.0662	0.2832
$CD27^+IgA^+$ B cell [%]	Gender	Female	0.1434	0.5022	0.7756	0.3057
$CD27^+IgA^+$ B cell [%]	Gender	Age	0.0451	0.0173	0.0101	0.3057
$CD27^+IgA^+$ B cell [%]	Gender	Regular OCS	2.6305	0.6435	< 0,001	0.3057
$CD27^+IgA^+$ B cell [%]	Gender	(Intercept)	1.5654	0.9895	0.1155	0.3057
$CD27^+IgA^+$ B cell [%]	Asthma severity	Healthy	-0.6272	0.9349	0.5032	0.3057
$CD27^+IgA^+$ B cell [%]	Asthma severity	Mild-moderate asthma	-0.5799	0.7663	0.4502	0.3057
$CD27^+IgA^+$ B cell [%]	Asthma severity	Age	0.0433	0.0174	0.0139	0.3057
$CD27^+IgA^+$ B cell [%]	Asthma severity	Regular OCS	2.1454	0.8865	0.0166	0.3057
$CD27^+IgA^+$ B cell [%]	Asthma severity	(Intercept)	2.2263	1.1798	0.0609	0.3057
$CD27^+IgA^+$ B cell [%]	Specific IgE [kU/l]	Specific IgE [kU/l]	0.0285	0.0701	0.6843	0.3057
$CD27^+IgA^+$ B cell [%]	Specific IgE [kU/l]	Age	0.0458	0.0175	0.0095	0.3057
$CD27^+IgA^+$ B cell [%]	Specific IgE [kU/l]	Regular OCS	2.6575	0.6477	< 0,001	0.3057
$CD27^+IgA^+$ B cell [%]	Specific IgE [kU/l]	(Intercept)	1.5410	0.9776	0.1168	0.3057

TABLE S4. Linear Model. Linear models describing B cell subpopulations as a function of clinical characteristics with oral corticosteroids and age as confounders. Coefficient estimates, standard error, and p-value are given for each term in the model. P-values for the clinical variables were corrected for multiple tests (q-value). BMI, Body Mass Index; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz–resistance at 20 Hz; FEF_{25-75}, forced expiratory flow

at 25% - 75% of FVC; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BDR, bronchodilator response; PY, pack-years.

Table S5. Clinical characteristics of patients with versus without SAD

Clinical variable	Patients with SAD (n=63)	Patients without SAD (n= 89)	p-value
Age [yrs]	58.9 (48.90, 66.9)	50.9 (42.7, 57.4)	0.002
BMI [Kg/m^2]	27.4 (24.5, 31.3)	27.0 (24.38, 30.46)	0.367
Adult onset asthma, n	42 (67%)	59 (66%)	0.992
Female, n	28 (44%)	56 (63%)	0.036
Current or former smokers ≥10PY, n	21 (33%)	18 (20%)	0.102
Atopy, blood and sputum differential counts			
Atopy, n	35 (56%)	53 (62%)	0.582
Blood eosinophil granulocytes [1000/µl]	0.29 (0.16, 0.58)	0.30 (0.14, 0.48)	1
Blood neutrophil granulocytes [1000/µl]	4.56 (3.34, 6.71)	4.25 (3.37, 5.31)	0.349
Sputum eosinophil granulocytes [%]	3.20 (0.80, 15.70)	1.35 (0.33, 4.38)	0.031
Sputum neutrophil granulocytes [%]	56.70 (33.30, 76.10)	55.10 (30.90, 69.80)	0.548
Asthma severity			
Mild-moderate asthma, n	27 (43%)	64 (72%)	0.001
Severe asthma, n	36 (57%)	25 (28%)	0.001
Asthma control questionnaire (ACQ)	2.0 (1.0, 3.3)	1.1 (0.6, 2.3)	<0.001
Asthma quality of life questionnaire (AQLQ)	4.94 (4.02, 5.97)	5.66 (4.46, 6.28)	0.046
Patients with ≥ 1 severe exacerbation, n	40 (64%)	40 (45%)	0.037
GINA control status			
Controlled, n	12 (19%)	36 (41%)	0.004
Partly controlled, n	18 (29%)	28 (32%)	0.004
Uncontrolled, n	33 (52%)	25 (28%)	0.004
Lung function			
Patients with R5-R20 > ULN	63 (100%)	0 (0%)	<0.001
Patients with AX > ULN	56 (90%)	14 (16%)	<0.001
FEV_1 [z-score]	-2.43 (-3.17, -1.70)	-0.98 (-1.69, -0.06)	<0.001
FEV_1/FVC [z-score]	-2.67 (-3.52, -1.74)	-1.26 (-1.89, -0.55)	<0.001
FEF_{25-75} [z-score]	-2.72 (-3.15, -1.58)	-1.24 (-1.91, -0.47)	<0.001
FeNO [ppb]	30.0 (16.5, 44.5)	25.5 (15.0, 41.8)	0.557
Medication			
ICS (Fluticasone-equivalent) [µg/d]	670 (510)	430 (440)	0.001
LTRA, n	11 (18%)	13 (15%)	0.803
LABA, n	56 (89%)	71 (80%)	0.204

LAMA, n	21 (33%)	14 (16%)	0.019
Oral corticosteroids, n	20 (32%)	16 (18%)	0.076
Omalizumab, n	2 (3%)	3 (3%)	1
Mepolizumab, n	1 (2%)	1 (1%)	1

TABLE S5. Clinical characteristics of patients with versus without SAD. Data is presented as median (25%, 75% IQR), and number (%). Yrs, years, n, number of patients; BMI, Body Mass Index; PY, pack-years; GINA, Global Initiative for Asthma; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality Of Life Questionnaire; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s]; AX, reactance area [kPa/l/s]; ULN, upper limit of normal; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV1/FVC, FEV1 as % of FVC; FEF25-75, forced expiratory flow at 25% - 75% of FVC; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; LTRA, leukotriene antagonist; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonist.

TABLE S6. Regression model for SAD defined by R5-R20

	Estimate	Standard Error	p-value	95% CI Lower Bound	95% CI Upper Bound
Age [yrs]	0.031	0.016	0.046	1.002	1.066
Gender (female)	-0.674	0.393	0.086	0.233	1.094
Sputum eosinophils [%]	0.016	0.011	0.134	0.995	1.039

TABLE S6. Regression model for SAD defined by R5-R20. Result of stepwise multivariate regression model including asthma patients with severe and mild-moderate asthma (n=121). The dependent variable is SAD defined by the 95th centile of R5-R20. A stepwise-forward regression was calculated to find the best model using AIC. The table shows the variables with best model fit (sputum eosinophils [%], gender, and age). Variables not selected by best model fit are not shown (regular OCS intake (yes/ no), blood eosinophils [1000/µl], sum of sIgE, sum of 36 allergen-specific Immunoglobulin E [kU/l], FeNO [ppb], BMI [Kg/m^2], smoking [pack-years], and CD27$^+$IgA$^+$ memory B cells [%]).

TABLE S7. Correlations between exacerbation frequency and clinical parameters and IgA^+ memory B cells

Clinical variable	Variable	estimate	adjusted p-value
Exacerbations [no]	$CD27^-IgA^+$ B cell [%]	0.351	< 0.001
Exacerbations [no]	Sputum eosinophils [%]	0.32	0.005
Exacerbations [no]	Blood neutrophils [1000/µl]	0.32	0.003
Exacerbations [no]	$CD27^+IgA^+$ B cell [%]	0.26	0.012
Exacerbations [no]	AX [kPa/l/s]	0.239	0.025
Exacerbations [no]	ICS (Fluticasone-equivalent) [µg/d]	0.22	0.037
Exacerbations [no]	R5-R20 [kPa/l/s]	0.219	0.038
Exacerbations [no]	Blood eosinophils [1000/µl]	0.119	0.275
Exacerbations [no]	BMI [Kg/m^2]	0.088	0.423
Exacerbations [no]	FeNO [ppb]	0.084	0.448
Exacerbations [no]	Disease Duration [yrs]	0.005	0.953
Exacerbations [no]	Age [yrs]	-0.03	0.815
Exacerbations [no]	Smoking [py]	-0.054	0.658
Exacerbations [no]	OCS [mg/d]	-0.065	0.814
Exacerbations [no]	Sputum neutrophils [%]	-0.097	0.423
Exacerbations [no]	FEV_1/FVC [z-score]	-0.241	0.023
Exacerbations [no]	Specific IgE [kU/l]	-0.242	0.021
Exacerbations [no]	FEV_1 [z-score]	-0.27	0.01
Exacerbations [no]	FEF_{25-75} [z-score]	-0.32	0.008

TABLE S7. Correlations between exacerbation frequency and clinical parameters and IgA+ memory B cells. Estimates and adjusted p-values after multiple test corrections are shown. No, number; BMI, Body Mass Index; yrs, years; PY, pack-years; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV1/FVC, FEV1 as % of FVC; FEF25-75, forced expiratory flow at 25% - 75% of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; ICS, inhaled corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s].

TABLE S8. Correlations between Asthma Control Questionnaire (ACQ-7) and clinical parameters and IgA$^+$ memory B cells

Clinical variable	Variable	estimate	adjusted p-value
ACQ 7 [point sum]	AX [kPa/l/s]	0.433	< 0.001
ACQ 7 [point sum]	R5-R20 [kPa/l/s]	0.432	< 0.001
ACQ 7 [point sum]	Blood neutrophils [1000/µl]	0.383	< 0.001
ACQ 7 [point sum]	ICS (Fluticasone-equivalent) [µg/d]	0.312	0.004
ACQ 7 [point sum]	Sputum eosinophils [%]	0.303	0.008
ACQ 7 [point sum]	CD27$^+$IgA$^+$ B cell [%]	0.221	0.037
ACQ 7 [point sum]	FeNO [ppb]	0.213	0.046
ACQ 7 [point sum]	CD27$^-$IgA$^+$ B cell [%]	0.208	0.049
ACQ 7 [point sum]	Blood eosinophils [1000/µl]	0.197	0.065
ACQ 7 [point sum]	Disease Duration [yrs]	0.165	0.12
ACQ 7 [point sum]	Age [yrs]	0.162	0.123
ACQ 7 [point sum]	BMI [Kg/m^2]	0.154	0.144
ACQ 7 [point sum]	Sputum neutrophils [%]	0.029	0.831
ACQ 7 [point sum]	Smoking [py]	-0.053	0.658
ACQ 7 [point sum]	Specific IgE [kU/l]	-0.18	0.088
ACQ 7 [point sum]	OCS [mg/d]	-0.193	0.405
ACQ 7 [point sum]	FEV_1/FVC [z-score]	-0.439	< 0.001
ACQ 7 [point sum]	FEV_1 [z-score]	-0.521	< 0.001
ACQ 7 [point sum]	FEF_{25-75} [z-score]	-0.535	< 0.001

TABLE S8. Correlations between Asthma Control Questionnaire (ACQ-7) and clinical parameters and IgA$^+$ memory B cells. Estimates and adjusted p-values after multiple test corrections are shown. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; BMI, Body Mass Index; yrs, years; PY, pack-years; ICS, inhaled corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s].

TABLE S9. Correlations between Asthma Quality Of Life Questionnaire (AQLQ) and clinical parameters and IgA$^+$ memory B cells

Clinical variable	Variable	estimate	adjusted p-value
AQLQ [score]	FEF_{25-75} [z-score]	0.313	0.009
AQLQ [score]	FEV_1 [z-score]	0.290	0.008
AQLQ [score]	FEV_1/FVC [z-score]	0.188	0.085
AQLQ [score]	Specific IgE [kU/l]	0.182	0.09
AQLQ [score]	OCS [mg/d]	0.041	0.847
AQLQ [score]	Smoking [py]	0.023	0.847
AQLQ [score]	Sputum neutrophils [%]	-0.022	0.847
AQLQ [score]	Disease Duration [yrs]	-0.044	0.735
AQLQ [score]	FeNO [ppb]	-0.095	0.418
AQLQ [score]	Sputum eosinophils [%]	-0.111	0.378
AQLQ [score]	BMI [Kg/m^2]	-0.127	0.257
AQLQ [score]	Age [yrs]	-0.156	0.144
AQLQ [score]	Blood eosinophils [1000/µl]	-0.169	0.12
AQLQ [score]	CD27$^-$IgA$^+$ B cell [%]	-0.196	0.069
AQLQ [score]	ICS (Fluticasone-equivalent) [µg/d]	-0.200	0.065
AQLQ [score]	CD27$^+$IgA$^+$ B cell [%]	-0.278	0.009
AQLQ [score]	Blood neutrophils [1000/µl]	-0.292	0.008
AQLQ [score]	AX [kPa/l/s]	-0.295	0.008
AQLQ [score]	R5-R20 [kPa/l/s]	-0.310	0.005

TABLE S9. Correlations between Asthma Quality Of Life Questionnaire (AQLQ) and clinical parameters and IgA$^+$ memory B cells. Estimates and adjusted p-values after multiple test corrections are shown. FEF_{25-75}, forced expiratory flow at 25% - 75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_1/FVC, FEV_1 as % of FVC; IgE, Immunoglobulin E; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; BMI, Body Mass Index; yrs, years; PY, pack-years; ICS, inhaled corticosteroids; AX, reactance area [kPa/l/s]; R5–R20, resistance at 5 Hz – resistance at 20 Hz [kPa/l/s].