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Supplementary appendix

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INFLAMMATORY AND CLINICAL RISK FACTORS FOR ASTHMA ATTACKS: A PATIENT-LEVEL META-ANALYSIS OF CONTROL ARMS OF 22 RANDOMISED TRIALS

ORACLE2 (The OxfoRd Asthma attaCk risk scaLE meta-analysis)

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1. Supplementary Methods

1.1. PubMed Medline search details

PubMed Search URL

https://pubmed.ncbi.nlm.nih.gov/?term=asthma+exacerbations&filter=pubt.randomizedcontrolledtrial&filter=dates.1993%2F1%2F1-2021%2F4%2F1&filter=hum_ani.humans&filter=lang.english&filter=lang.french&filter=age.adolescent&filter=age.alladult&filter=age.youngadult&filter=age.adult&filter=age.middleagedaged&filter=age.middleaged&filter=age.aged&filter=age.80andover&sort=date

PubMed Search details
Date of query: 2021-04-06
Search: asthma exacerbations Filters: Randomized Controlled Trial, Humans, English, French, Adolescent: 13-18 years, Adult: 19+ years, Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged + Aged: 45+ years, Middle Aged: 45-64 years, Aged: 65+ years, 80 and over: 80+ years, from 1993/1/1 - 2021/4/1 Sort by: Most Recent
((("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "asthmas"[All Fields] OR "asthma s"[All Fields]) AND ("exacerbate"[All Fields] OR "exacerbated"[All Fields] OR "exacerbates"[All Fields] OR "exacerbating"[All Fields] OR "exacerbation"[All Fields] OR "exacerbations"[All Fields] OR "exacerbator"[All Fields] OR "exacerbators"[All Fields])) AND ((randomizedcontrolledtrial[Filter]) AND (humans[Filter]) AND (1993/1/31:2021/4/1[pdat]) AND (english[Filter] OR french[Filter]) AND (adolescent[Filter] OR alladult[Filter] OR youngadult[Filter] OR adult[Filter] OR middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))

1.2. Data dictionary supplied to data providers

For initial data extraction from the data providers, the following data dictionary was provided (Table S1). Modified treatment step definitions supplied for this study (Table S2). Inhaled corticosteroid (ICS)-dose strength was judged according to the following table, retained from the 2021 GINA guidelines (Table S3).

1.3. Initial data analysis (IDA) of individual participant data received

Definitions
Body mass index (BMI) at baseline was measured by dividing a person's weight in kilograms by the square of the height in meters. According to the WHO (World Health Organization) criteria, the following categories were defined for BMI: BMI $\leq$ 19 (underweight), 19 < BMI $\leq$ 25 (normal weight), 25 < BMI $\leq$ 30 (overweight or pre-obesity), 30 < BMI $\leq$ 35 (obesity class I), 35 < BMI $\leq$ 40 (obesity class II), 40 < BMI (obesity class III).

Severe asthma attacks were defined as the number of acute asthma episodes requiring $\geq$ 3 days of systemic corticosteroids.

Data cleaning and screening

For data cleaning purposes, we reviewed the minimum and maximum values of all baseline variables. We found that variables blood eosinophil count had values of 0 cells/L in 48 cases and FeNO 0 ppb in 1 case. Since these variables must be log-transformed for the analysis, 0 was replaced by the subsequent minimum value/2, as described previously. [1] In addition, we found one case with a total IgE of "<2 ng/mL" in the BENRAP2B trial. This value was replaced by 1 ng/mL. With respect to maximum values, the value of the outcome variable was coded as 9999 if no severe asthma attacks occurred during follow-up in three trials (PACT, QUEST and DRI12544; total of 272 cases). This was recoded to 0 severe asthma attacks during follow-up. Finally, for STRATOS, we received FEV_1 reversibility % expressed as a decimal (0.1 meaning 10%); for CAPTAIN, we encountered a similar issue with adherence in trial. These values were multiplied by 100 to yield percentages. Subsequently, several variables were recoded into new variables, as described in Table S5.

During data cleaning and screening, we observed that the criteria for ICS dose (high, medium, low or none) were not applied homogenously across the included studies. One explanation is that the studies were conducted in different years, resulting in the application of different tables for ICS dosage categorization at data entry. Due to these discrepancies in criteria for ICS dosage categorization, we mainly used treatment step.

Data distribution and patterns of missing data

Regarding data distribution, age, FEV_1% pre-bronchodilator, FEV_1% reversibility and ACQ-5 were reasonably normally distributed, whereas the distribution of BMI, BEC, FeNO, total IgE, SABA actuations per day in- and pre-trial appeared left-skewed and of adherence pre- and in-trial and follow-up duration right-skewed. The associations between continuous variables in the dataset were assessed using a correlation matrix with complete pairs.

We assessed the extent and patterns of missing data using the *Hmisc* and *naniar* packages in R, particularly using the `naclus` function for cluster analysis methods and the `gg_miss_upset` function to plot the pattern of missingness. In addition, Table S6 displays the proportion of missing values per variable per study. The clustering analyses and patterns are shown in supplementary Figures S1-S5. Figure S1 illustrates how variables associate in terms of missingness; it shows the proportion of missing values in common in a tree structure. As displayed in left panel of Figure S2, the fraction of missing values differed substantially per variable. Variables including enrolled trial, age and sex had (close to) 0% missing values, whereas variables including previous intubation or ICU admittance and adherence pre-trial had >60% missing observation. Of all variables, the main variables used in the analyses had relatively few missing values, with FEV_1% pre-bronchodilator having the most missing observations (8.7% missing), followed by 8.2% missing in FeNO, 7.0% missing in ACQ-5 score and 1.2% missing in BEC. Treatment step, attack history, follow-up duration and number of attacks during follow-up had no missing observations across the dataset (Figure S3 left panel). In most cases, only one variable ha a missing value per observation, but 216 observations ACQ-5 score and FeNO were jointly missing (Figure S4). Lastly, Figure S5 illustrates the proportion of completely (or systematically) and partially missing values per variable. In total, 26.7% of the missingness in the dataset were systematically missing by study (meaning, completely missing in certain studies), leaving 0.9% to be partially missing (meaning, missing in a certain proportion of patients within a study).

Membership concordance (*c*-)statistic

As a summary measure of similarity between studies, a membership model was performed using a multinomial logistic regression with study membership as the outcome. We included the baseline predictor variables of model 2 as covariates:

lrm(study ~ attack history + FEV_1% preBD + ACQ score + BEC + FeNO, data=data)

Smaller studies (n < 100) were combined for this specific analysis. The *c*-statistic of the membership model can be calculated by comparing the predicted probabilities for patients from one study with the predicted probabilities of patients not included in that study. The *c*--statistic has the discriminative ability to separate a specific study from all other studies, where a high *c*-statistic reflects substantial differences in baseline characteristic and outcome. The studies and *c*-statistics are summarized in Table S7. Some studies are quite different from others, with *c*-statistics > 0.9 (Novel_START, 0.95; PRACTICAL, 0.94). Some studies are quite different from others, with *c*-statistics > 0.9 (Novel_START, 0.95; PRACTICAL, 0.94).

Overall investigator assessment of the internal validity of provided covariates

Authors IDP and SC performed an evaluation of the overall internal validity of the provided covariates' IPD according to their degree of standardisation across trials and degree of completeness in reporting. The evaluation was informed by discussion with co-authors (principal investigators on the included studies) and data providers. The assessment focused on covariates that were indicated as candidate predictors for the prediction model.[2] Results of the assessment are shown in Table S8.

1.4. Multiple imputation

Two types of missing values could be described in this dataset: partially missing values (assumed to represent a missing at random (MAR) mechanism and thus imputed for all regression analyses) and systematically missing values (imputed only for multivariable regression analyses). Partially missing values were missing in a certain proportion of participants within a study, but not completely missing in each study, whereas systematically missing values were completely missing in certain studies. The latter was due to the nature of this IPD dataset (composed of multiple randomized clinical trials) and the coherent variability in study design and collected data. In line with statistical recommendations[3], we created a completed dataset with m=10 imputations in which the systematically missing values were put back to missing. This was performed per trial as follows: first, the missing values in the non-imputed dataset were replaced with a numeric value that did not occur in this original dataset, e.g. 8888, if the variable was 100% missing in a certain trial; second, this value of 8888 was used as a reference for the imputed dataset, in which a imputed value was put back to NA if the corresponding observation was 8888 in the original dataset. This method ensured that the missing at random values were imputed, but the missing not at random values remained missing for univariable analyses.

Missing variable data were multiply imputed using Multiple Imputation by Chained Equation (with the *mice* package in R [R Core Team (2023). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/]).[4,5] Prior to imputing the missing covariates, three steps were taken. First, all continuous variables were truncated to the 99% percentile to limit the influence of extreme observations using `winsorize` in R. Second, variables FeNO, BEC and total IgE were log-transformed with a base-

10 logarithm, and follow-up duration was log-transformed with a natural logarithm. Third, variables age, BMI and pack years were singly imputed. As explained in Table S5, we received the data for age, BMI and pack years as either continuous or categorical variables, depending on the trial. We created four columns per variable, namely the continuous and categorial value, and the corresponding minimum and maximum value of the category. Using an indicator variable for completely missing values (no continuous value or categorical value) and semi-missing values (only a categorical value), we imputed the completely missing values with predictive mean matching and imputed the semi-missing values using post-processing methods to squeeze the imputed value within the given category, e.g. between 20 and 30 years old. This squeezing method has been described previously by Stef van Buuren.[6] Whether the squeeze function was successful was assessed using the minimal and maximal values of the category, as well as by visual inspection of the distribution of the observed vs. imputed values. After singly imputing age, BMI and pack years separately, the complete variables were used in the multiple imputation model of the covariates.

The multiple imputation resulted in a total of 10 imputed datasets. Each imputed dataset was created with 30 iterations across the covariates. Imputation for continuous covariates was performed with predictive mean matching (pmm); for binary covariates this was logistic regression (logreg) and polytomous logistic regression (polyreg) for nominal covariates. The imputation models included all patient, disease and treatment characteristics, which were measured at baseline, as well as follow-up duration and the outcome (number of severe asthma attacks during follow-up). Region, previous intubation or ICU admittance, psychiatric disease, eczema, previous nasal polypectomy, adherence pre-trial, SABA actuations per day, FEV_1% post-bronchodilator, FVC pre- and post-bronchodilator and prescription of SABA, LABA, ICS, maintenance OCS, montelukast, theophylline and intranasal steroids were used as auxiliary variables in the imputation model. No interactions were included in the imputation model. The imputation procedure showed good convergence. Results across the multiply imputed datasets were combined using the Rubin rule.[5,7] After multiple imputation, we computed the new variable FEV_1/forced vital capacity ratio by dividing the FEV1 prebronchodilator in L by the FVC prebronchodilator in L.

1.5. Statistical analysis

Patient, disease and treatment characteristics were reported using the (geometric) mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables; frequencies and proportions were used for categorical variables. The primary endpoint of this study was the number of severe asthma attacks to occur during follow-up. Two models were fit using a negative binomial regression. Model 1 was a univariable model adjusted for log-transformed observation duration (days) as an offset variable and enrolled trial as a factor variable. Model 2 was a multivariable model adjusted for log-transformed observation duration as an offset variable and enrolled trial as a factor variable, treatment step (1-5), baseline pre-bronchodilator FEV_1 (%), baseline ACQ-5 score, history of severe asthma attacks within 1 year prior to the enrolled trial (yes/no), and log-transformed baseline biomarkers FeNO (ppb) and BEC ($x10^9$/L). Most of these covariates were described previously by Loymans *et al.* as the core set of predictors for a prediction model assessing future risk of severe asthma attacks in adult patients with asthma[8]. We visualised the rate ratios and the corresponding 95% CI of both models with forest plots using the *forestploter* package in R.[9] The Nagelkerke R^2 was

calculated for each predictor in model 2 using the *fmsb* package in R by taking the mean of the R^2 in each of the 10 imputed datasets.

In addition to the main covariates included in the multivariable model, we examined: age; sex (female); body mass index (BMI); number of hospitalisations for asthma in past 12 months; smoking status (ex or current); pack years; allergic rhinitis (yes/no); ; airborne allergic sensitisation (defined as positive skin-prick testing or serum specific IgE); chronic rhinosinusitis (yes/no); nasal polyposis (yes/no); adherence in trial to ICS (defined as the % of taken doses of ICS reported compared to prescription); FEV_1% reversibility postbronchodilator (per 10%); and $\log_{10}$(IgE). These variables were analysed one by one by adding into the model, adjusted for log-transformed observation duration (days) as an offset variable and enrolled trial as a factor variable (the univariable model 1) and additionally adjusted for treatment step (1-5), baseline pre-bronchodilator FEV_1 (%), baseline ACQ-5 score, history of severe asthma attacks within 1 year prior to the enrolled trial (yes/no), and log-transformed baseline biomarkers FeNO (ppb) and BEC ($x10^9$/L) (the multivariable model 2), and subsequently taking it out of the model before analysing the next variable. For example:

Model 1

Number of attacks during follow-up ~
Age +
offset(log(follow-up duration) +
as.factor(study)

Number of attacks during follow-up ~
BMI +
offset(log(follow-up duration) +
as.factor(study)

Model 2

Number of attacks during follow-up ~
Age +
offset(log(follow-up duration) +
as.factor(study) +
Treatment step +
FEV1% prebronchodilator +
Any attack in the past 12 months +
ACQ-5 mean score +
BEC +
FeNO

Number of attacks during follow-up ~
BMI +
offset(log(follow-up duration) +
as.factor(study) +
Treatment step +
FEV1% prebronchodilator +

Any attack in the past 12 months +
ACQ-5 mean score +
BEC +
FeNO

We also fit a negative binomial regression model including all covariates of interest (Figure S13).

In addition to the primary analysis, we performed the negative binomial regression analyses of the type-2 biomarkers with standardized independent variables using the 25/75 percentile scaling (Figure S9). This scaling method uses the 25th and 75th percentile value of the predictor to give it a more clinically meaningful interpretation as it compares an individual in the middle of the upper half of the predictor's distribution to an individual in the middle of the lower half.

To verify to robustness of our results, we performed two sensitivity analyses: 1) excluding the open-label trials (Novel START and PRACTICAL) and 2) excluding the trials with some risk of bias (LUTE and VERSE). The forest plots can be found in Figure S11 and S12.

The impact of baseline biomarkers FeNO and BEC, and their interaction, on the annualised severe asthma attack rate was also assessed by means of a spline curve. We allowed for a potential flexible non-linear effect of baseline BEC by using restricted cubic splines with three internal knots. Three curves were fit based on predefined baseline FeNO value: 1) 25 < ppb, 2) 25 ≤ ppb <50, 3) ≥50 ppb. This model was adjusted for the same variables as those described above for model 2, and included an interaction term for BEC*FeNO. The effects of using different cut points for FeNO (20, 35, 40, 50 ppb) on subgroup prevalence and prognostic value were also explored, as shown in Figure S16.

For the combined effects of biomarkers BEC and FeNO on the annualised asthma attack rate risk, we performed 9 negative binomial regression analyses using a dummy variable for one of the 9 different FeNO and BEC combinations (i.e., low-low, low-mid, low-high, mid-low, mid-mid, mid-high, high-low, high-mid, high-high), adjusted for the offset of the linear predictors of model 2. The corresponding rate ratios are shown in a 3×3 matrix in Table S11. Again, multiple cut points for FeNO were explored. We repeated these analyses for the combined effects of FEV_1 % pre- and postbronchodilator on the annualised asthma attack rate risk (Table S12). In addition, we performed negative binomial regression analyses for the combined effects of BEC and FeNO using the low-low category as the reference (Table S11).

2. Supplementary Figures

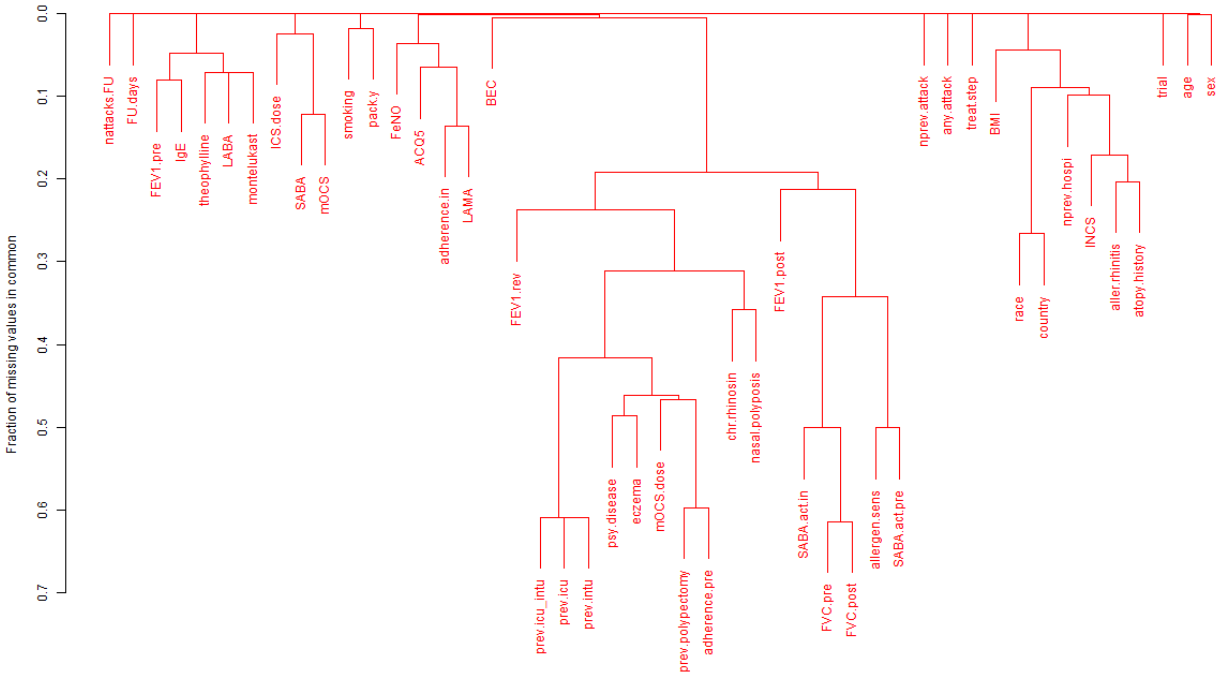


FIGURE S1. Fraction of missing values in common.
Variables that have the most missing values in common are 1) Previous intubation and previous ICU admittance, 2) previous polypectomy and adherence pre-trial, 3) FVC pre-bronchodilator and FVC post-bronchodilator.

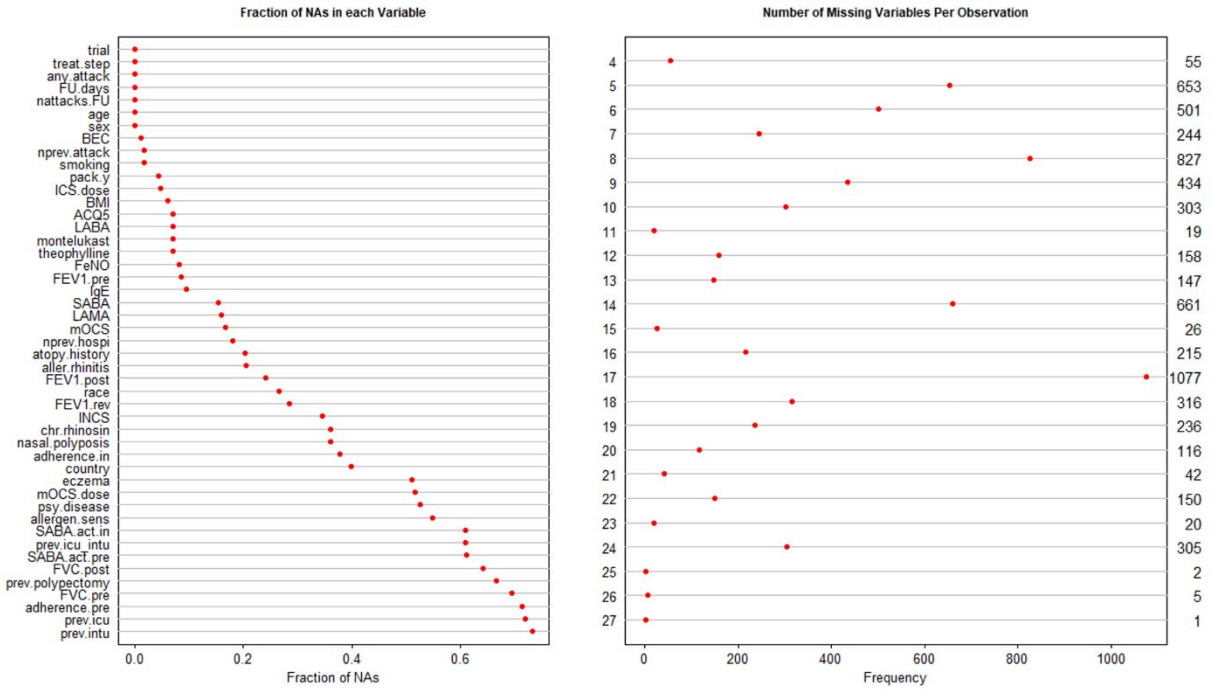


FIGURE S2. Fraction of missing values in each variable (left panel) and the number of missing variables per observation (right panel).

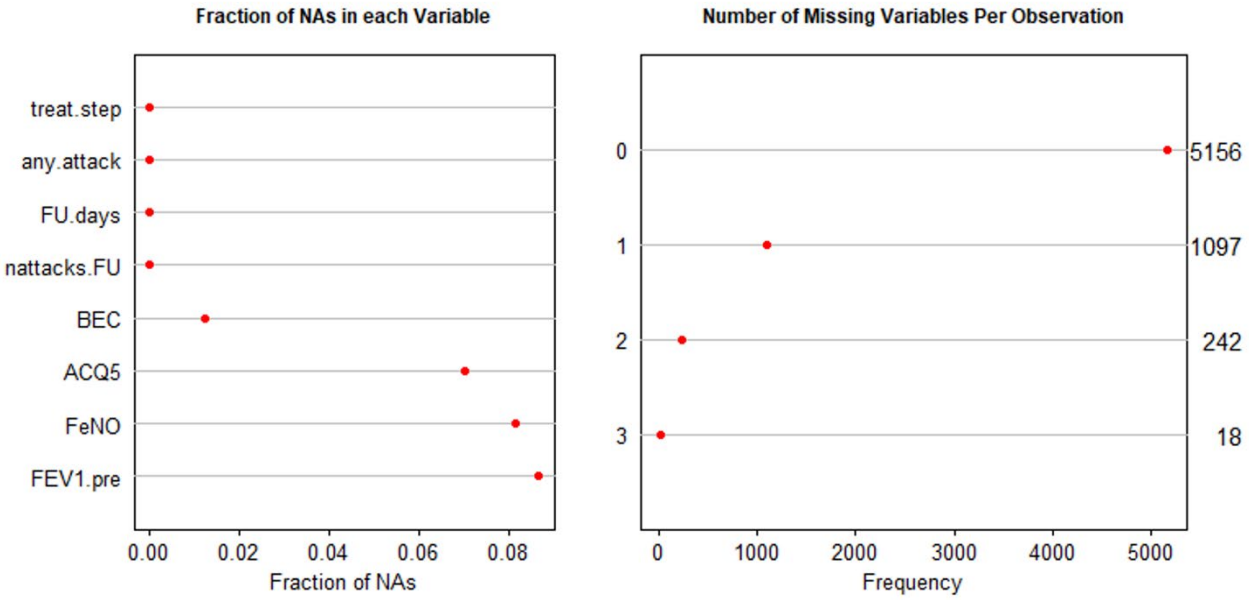


FIGURE S3. Fraction of missing values in the main variables (left panel) and the number of missing variables per observation (right panel).

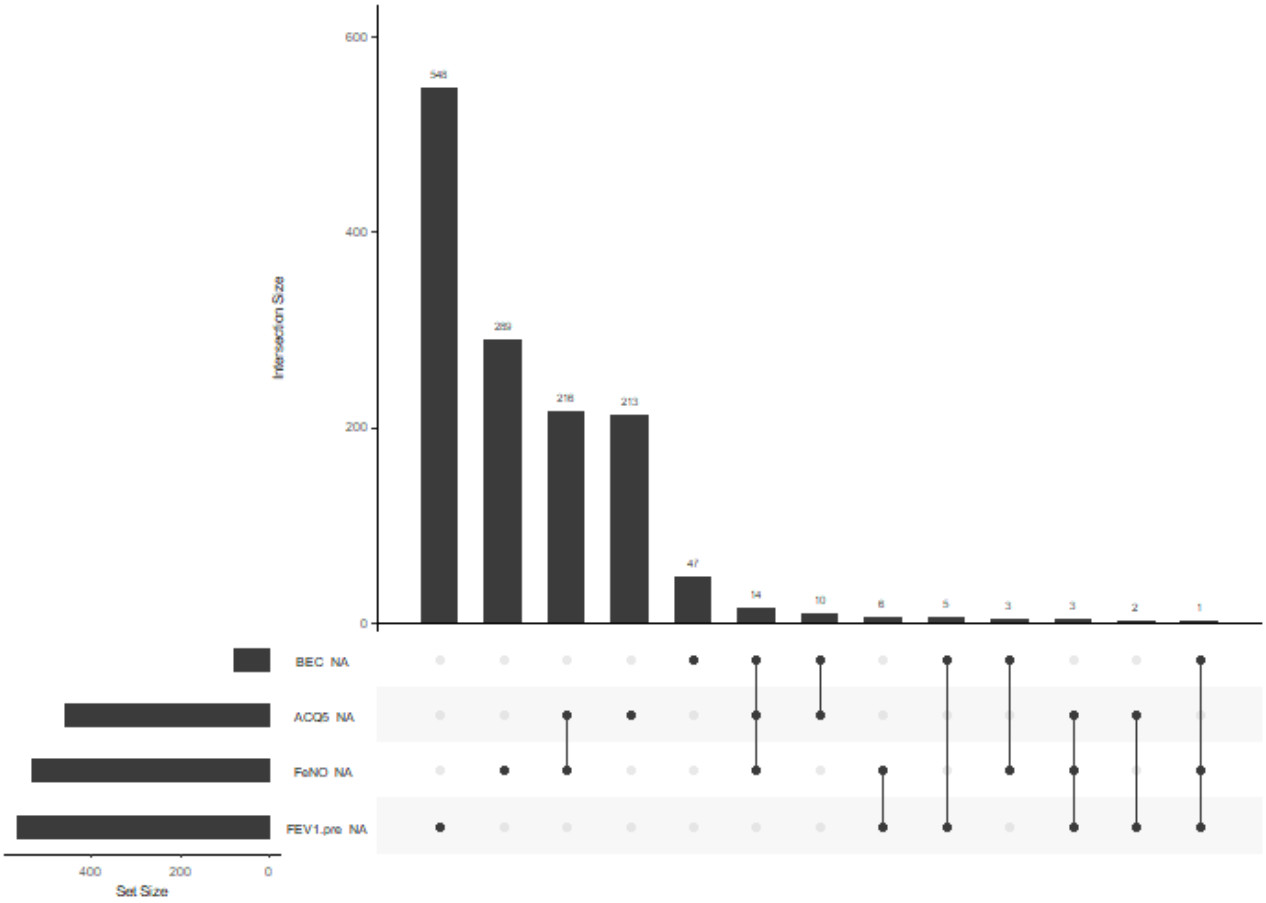


FIGURE S4. UpSet plot visualising the most commonly occurring combinations of missing values in the main variables.

The bar chart in the bottom-left hand corner of the plot shows the prevalence of missing values per variable, while the main bar chart shows the number of observations with a specific combination of missing values (defined by the black dots under it). For example, 80 observations had missing values in variable BEC (either as only missing value, or in combination with other variables), while 47 observations had missing values in *only* BEC.

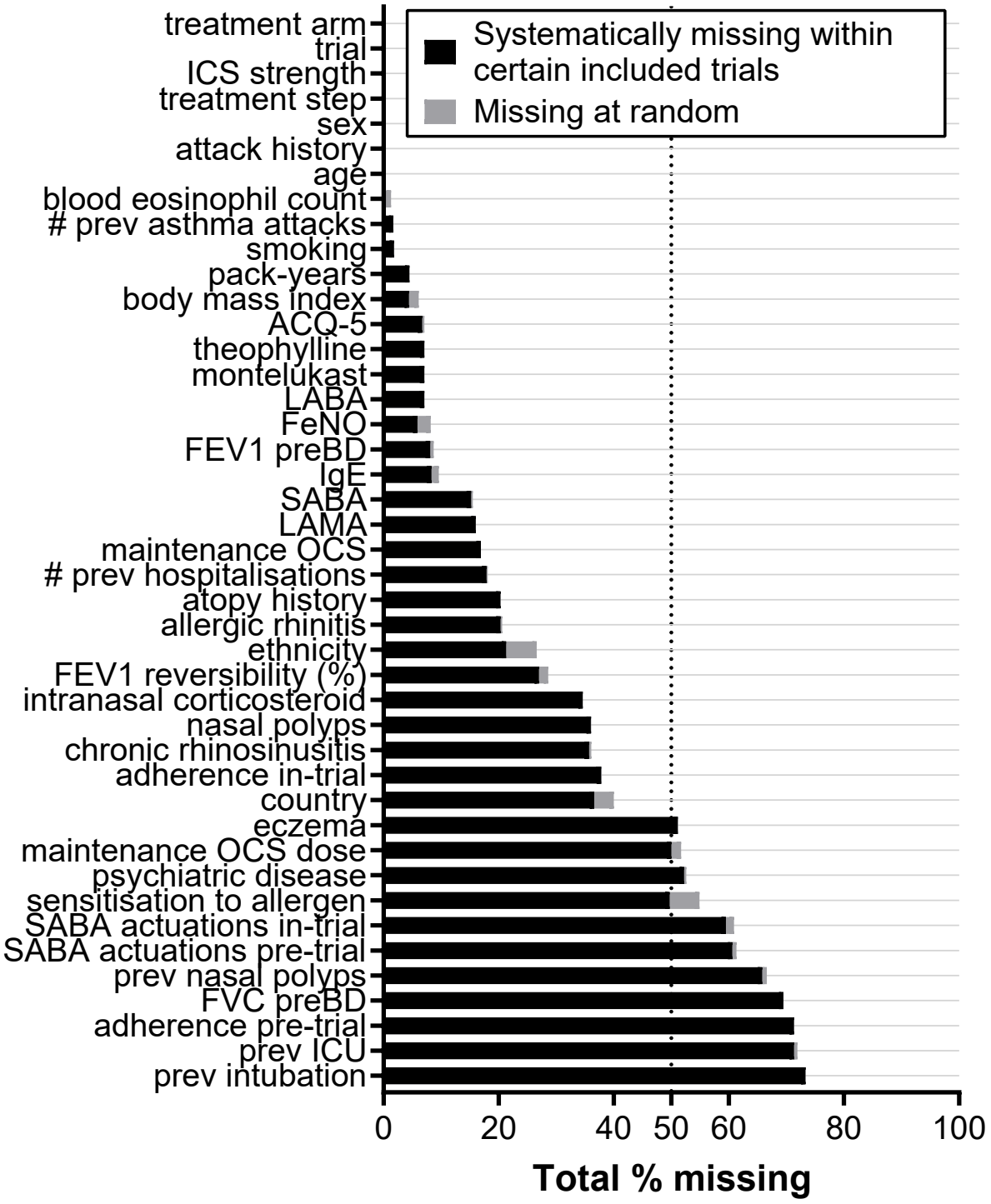


FIGURE S5. Proportion of missing values per variable.

Black bars represent the systematically missing values; grey bars represent the partially missing values, which are assumed to be missing at random. For example, the missing values in blood eosinophil count are all partially missing, whereas the missing values in the number of previous asthma attacks and smoking are completely missing in a certain study due to study design.

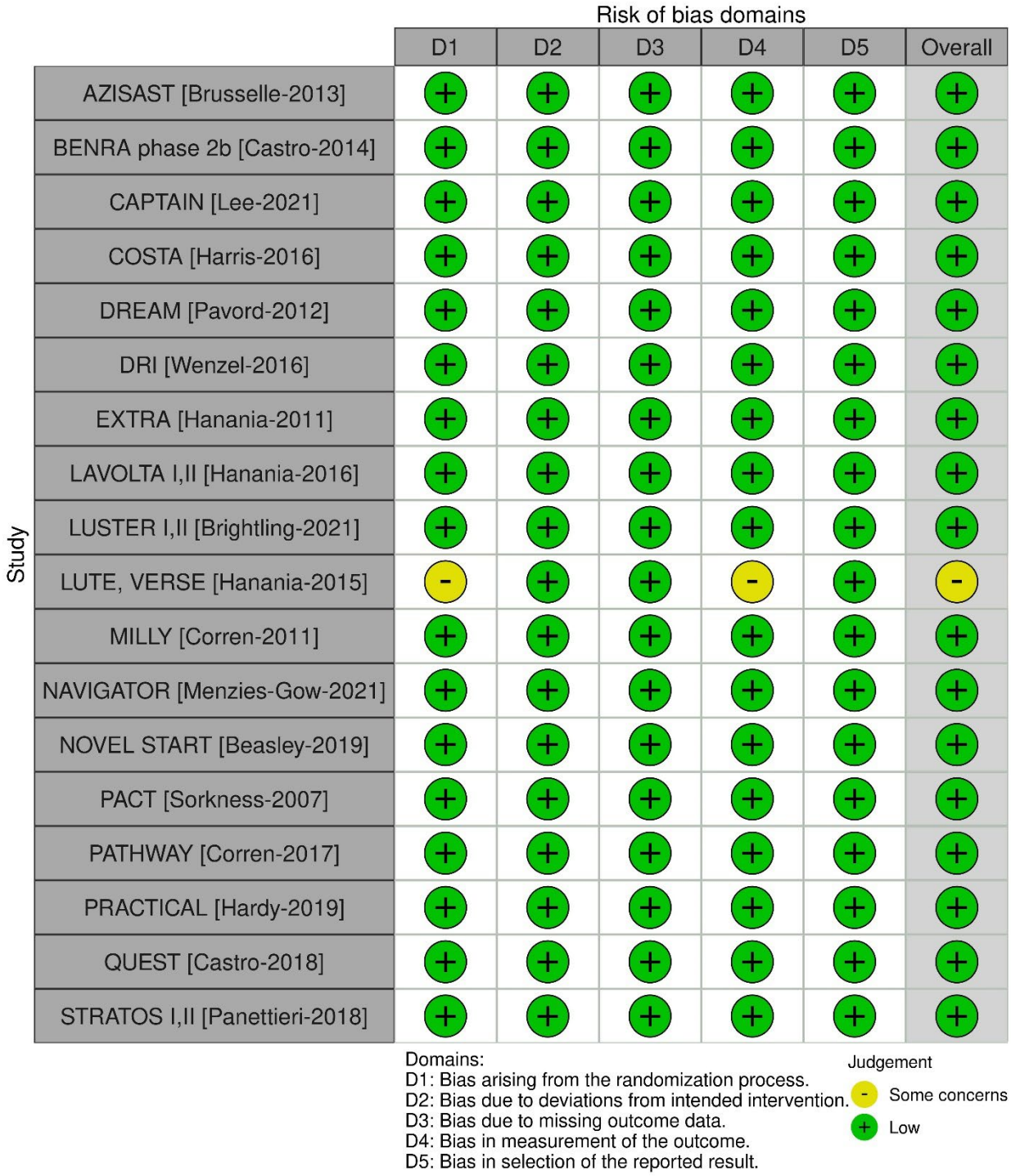


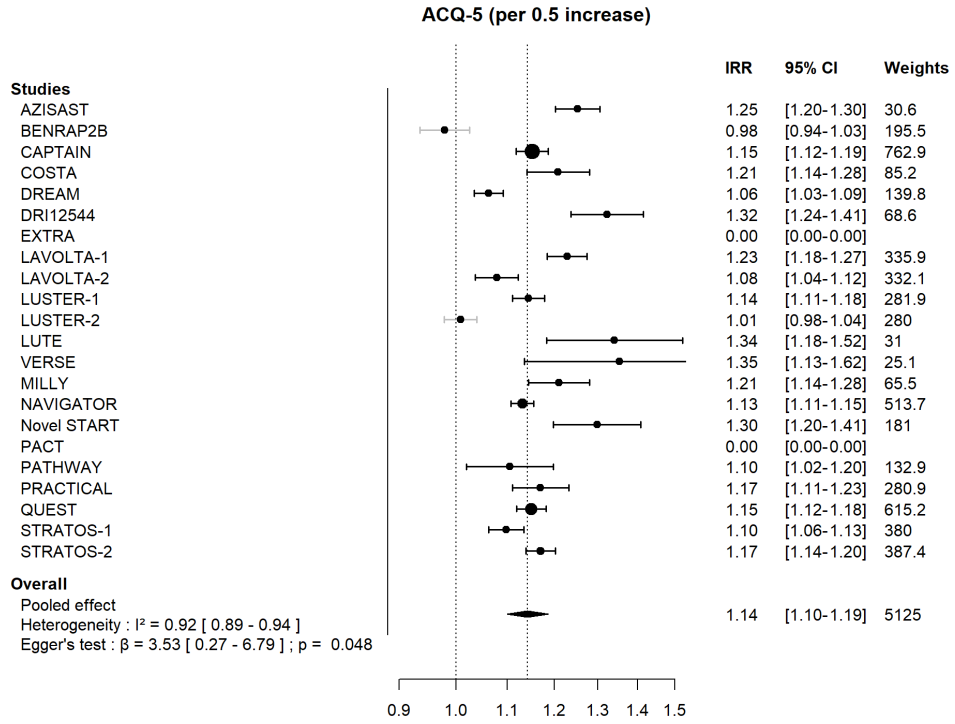
FIGURE S6. Risk of bias assessment – Traffic light plot for the studies that provided control arm individual participant data.

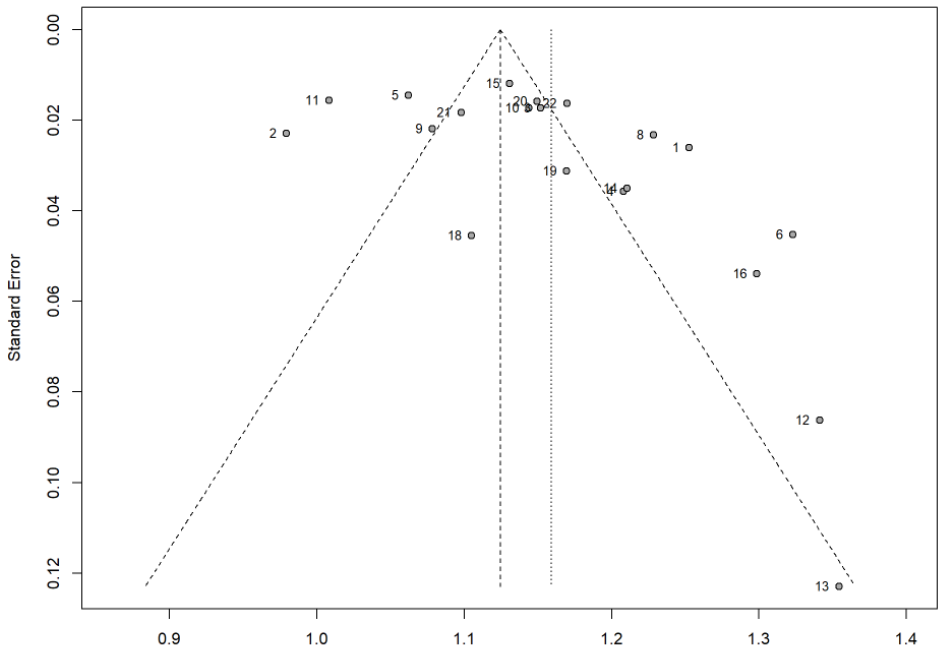
The risk of bias was assessed for the outcome variable of asthma exacerbations for RCTs that contributed individual participant data for their control arm population. The assessment and graphical outputs were done using the Cochrane Collaboration tool for assessing the risk of bias in randomised trials (RoB2).[10] Full results of the RoB2 analysis are available on GitHub.

FIGURE S7. Forest plots of the associations between predictors at baseline and future severe asthma attacks (univariable, model 1), disaggregated per predictor and stratified by study, accompanied by a funnel plot per analysis.

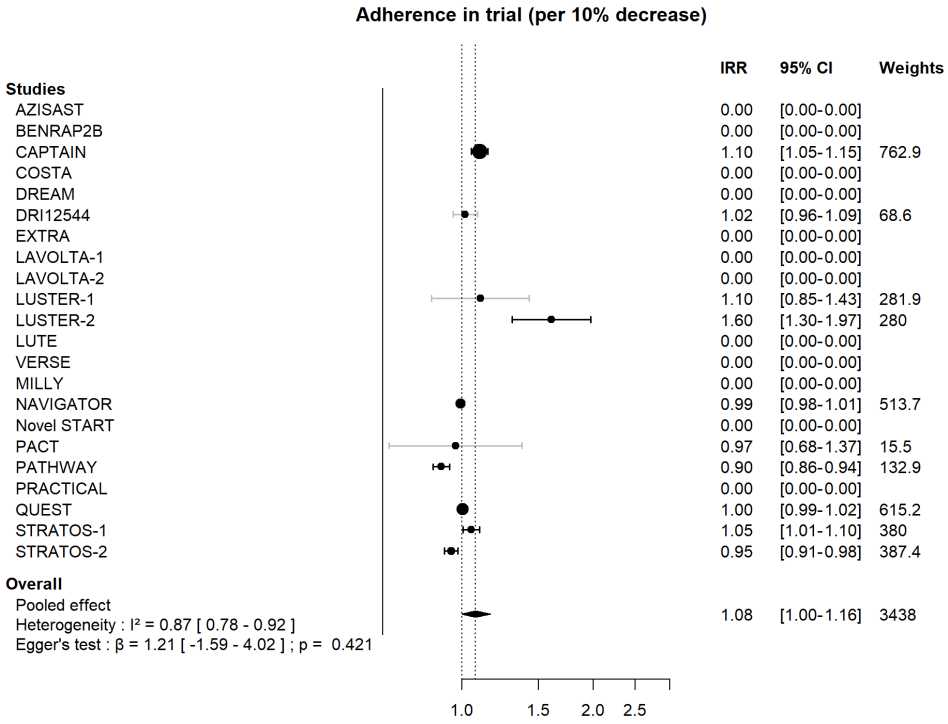
ACQ-5, Asthma Control Questionnaire (5-items); CI, confidence interval; IRR, Incidence Rate Ratio. Weights are person*years of follow-up.

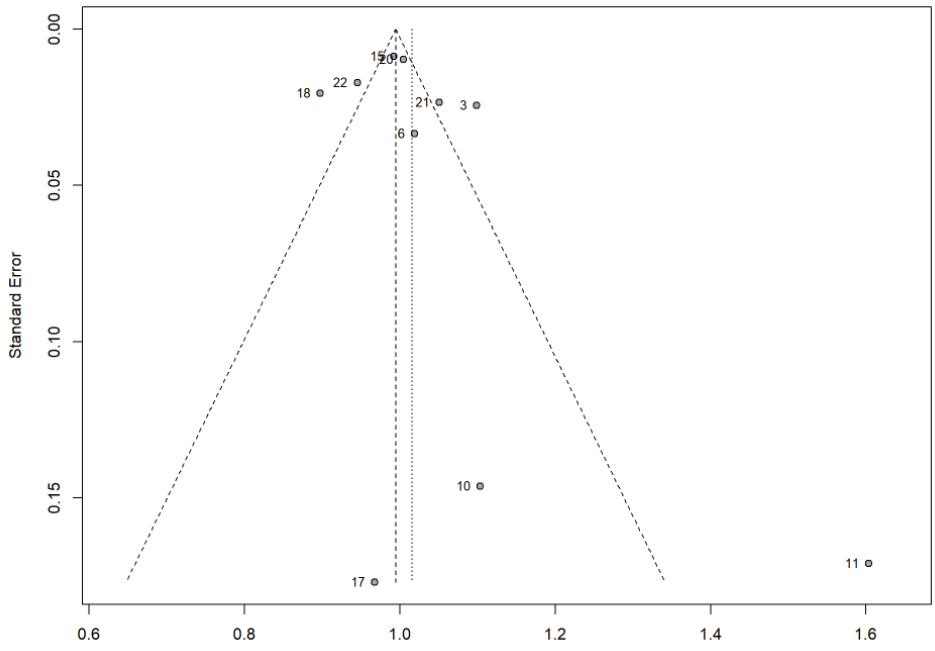
A- ACQ-5





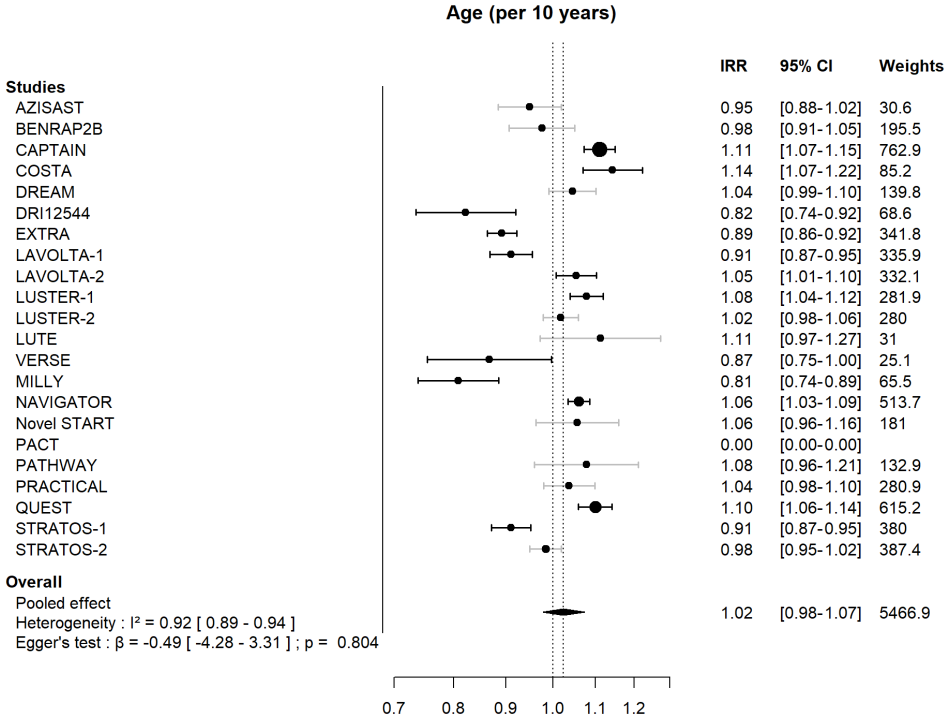
B- Adherence in trial

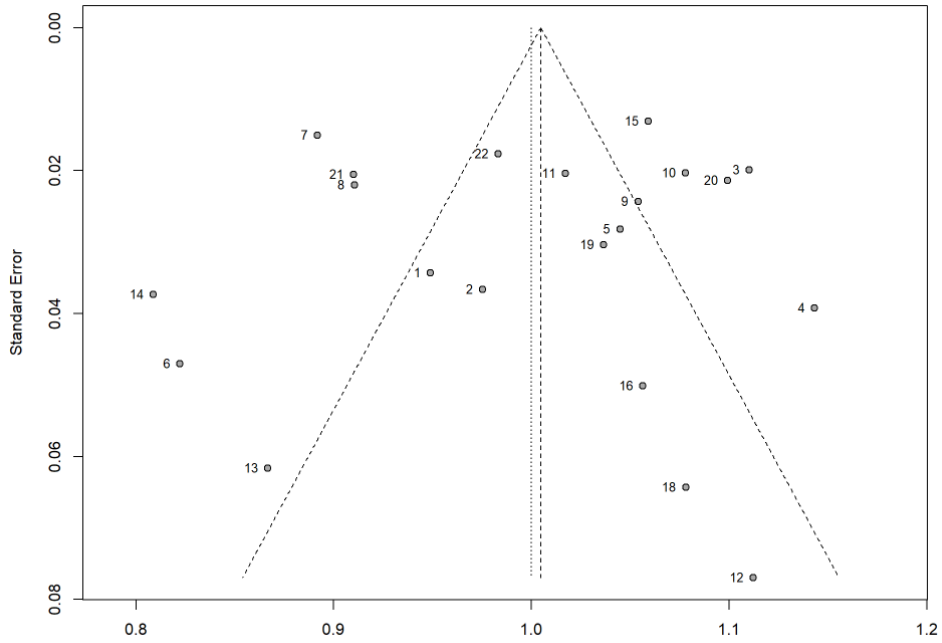




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

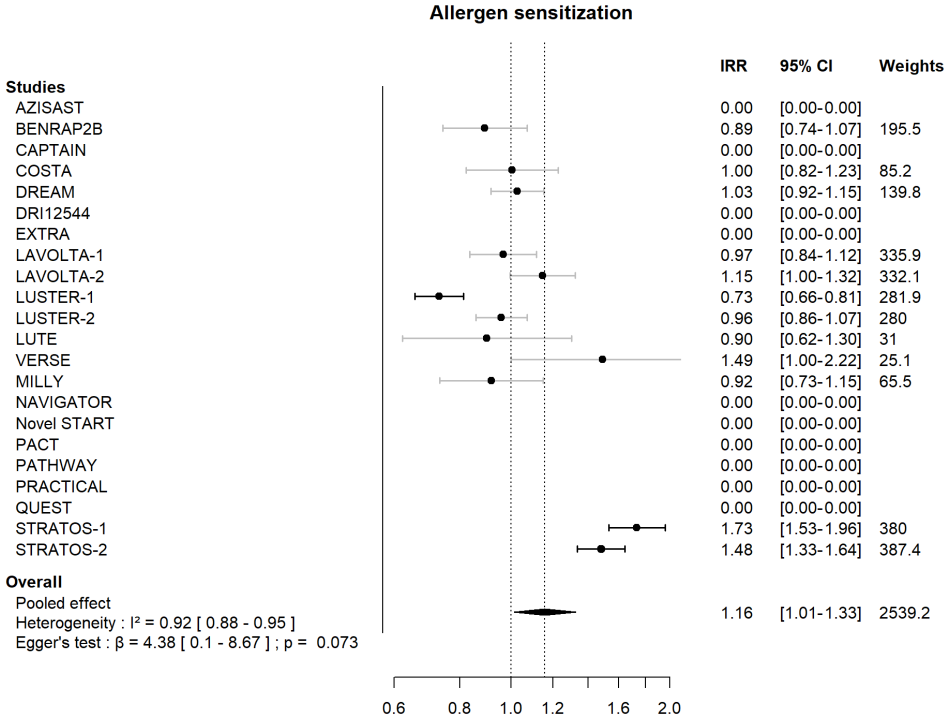
C- Age

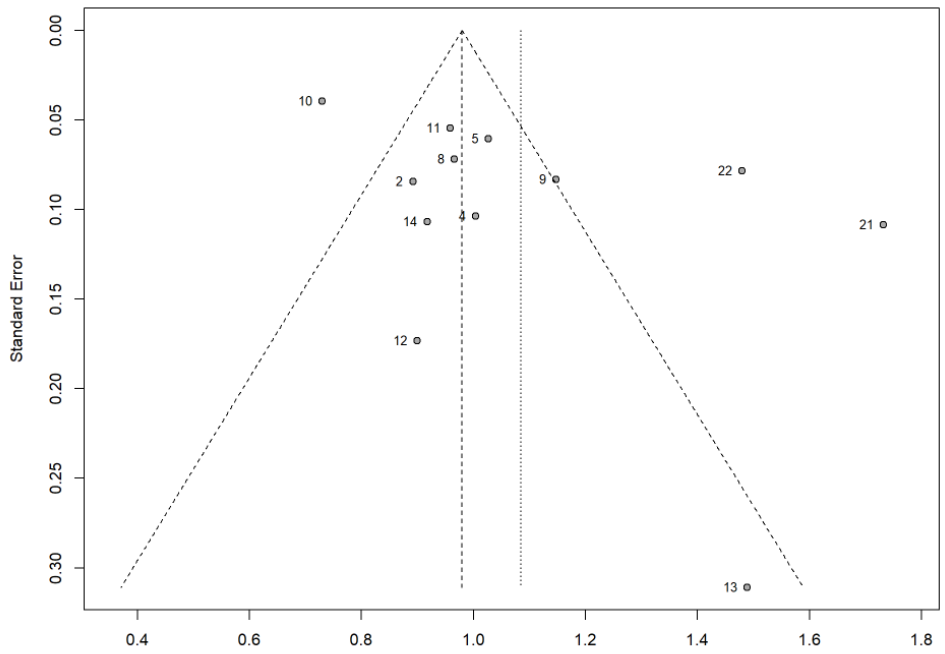




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

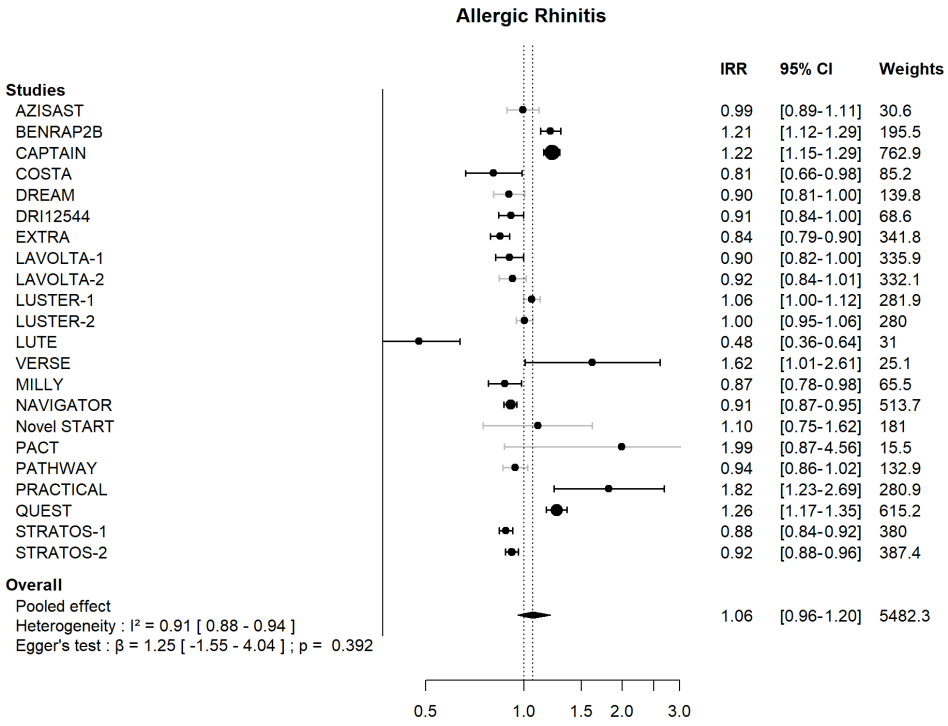
D- Airborne allergen sensitisation

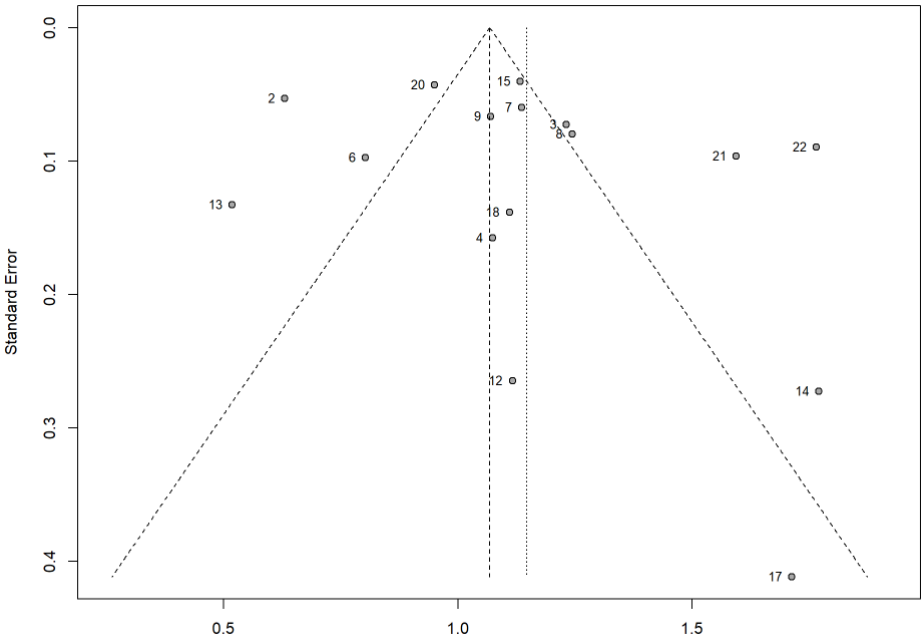




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

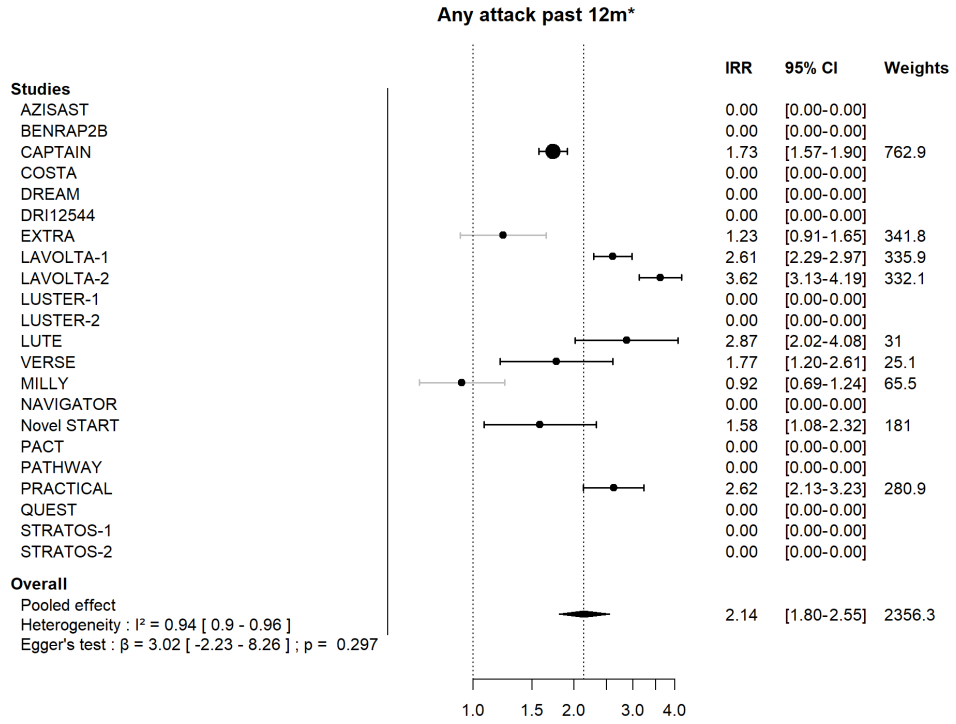
E- Allergic rhinitis

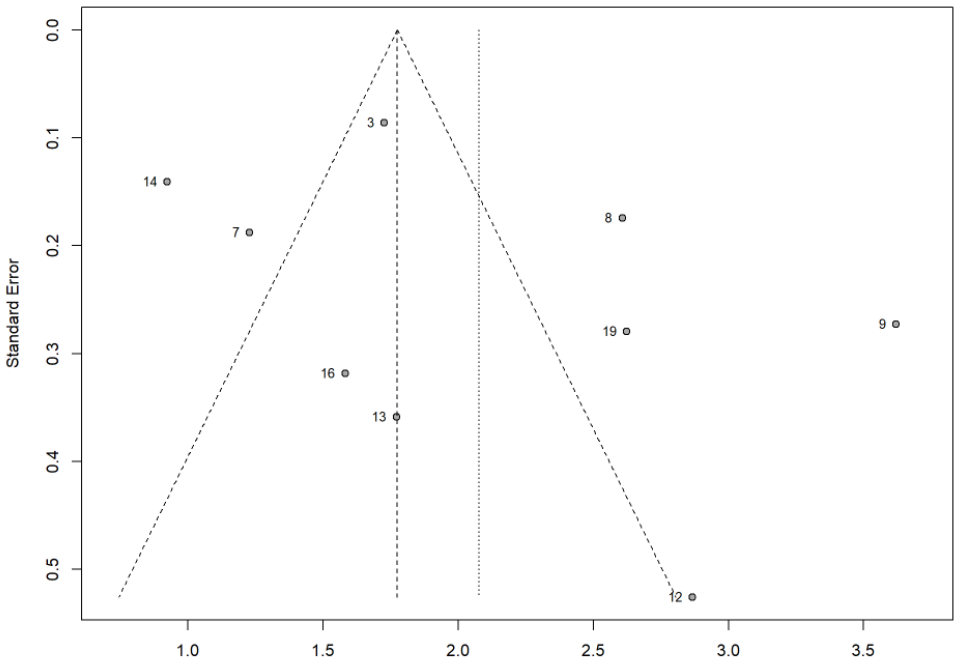




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

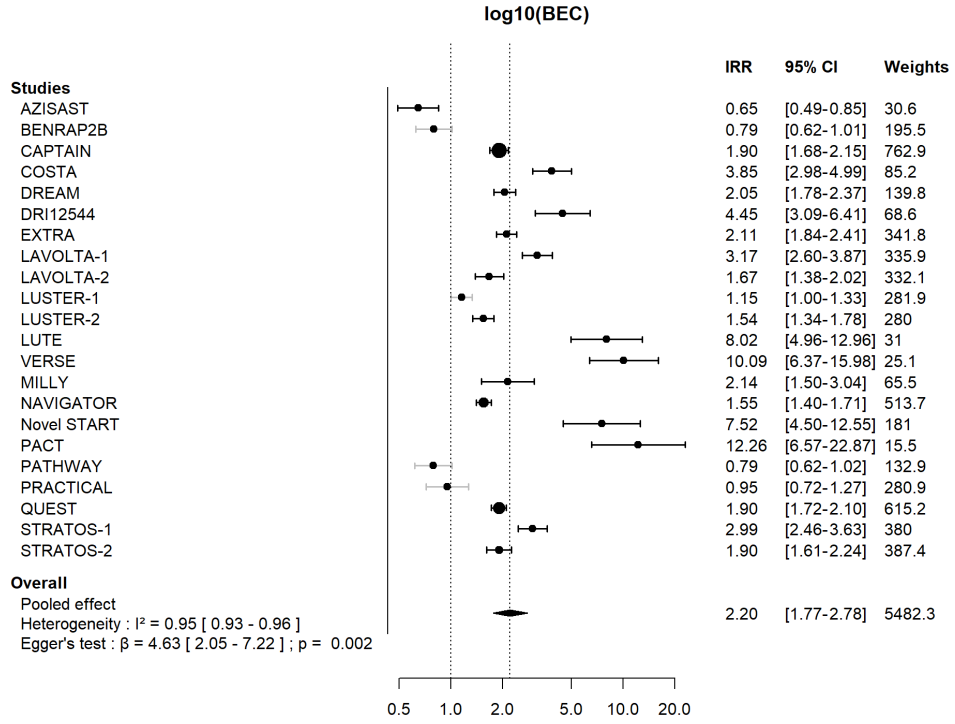
F- Any attack in past 12 months

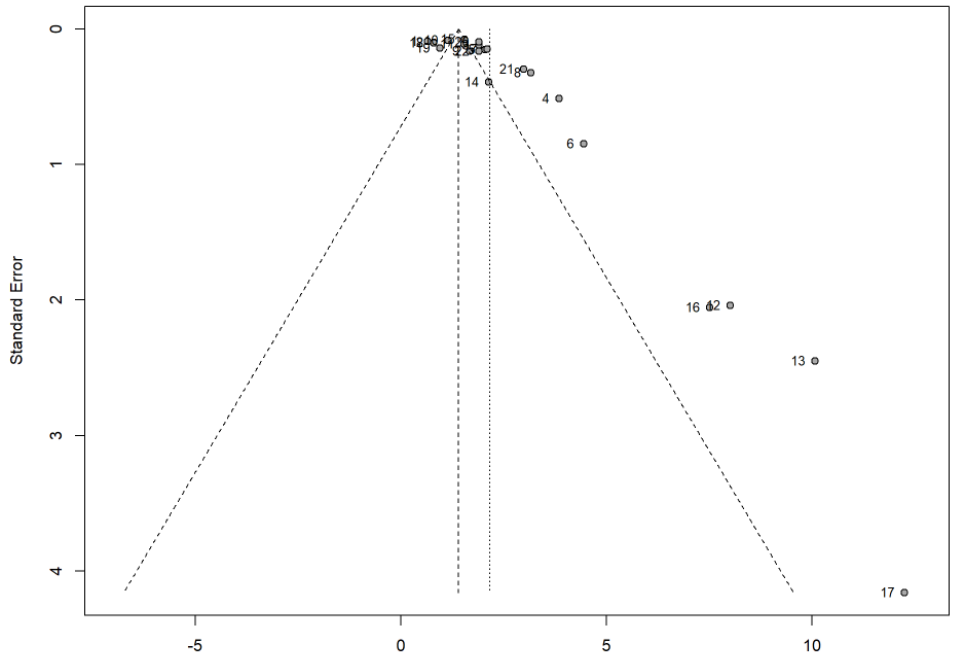




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

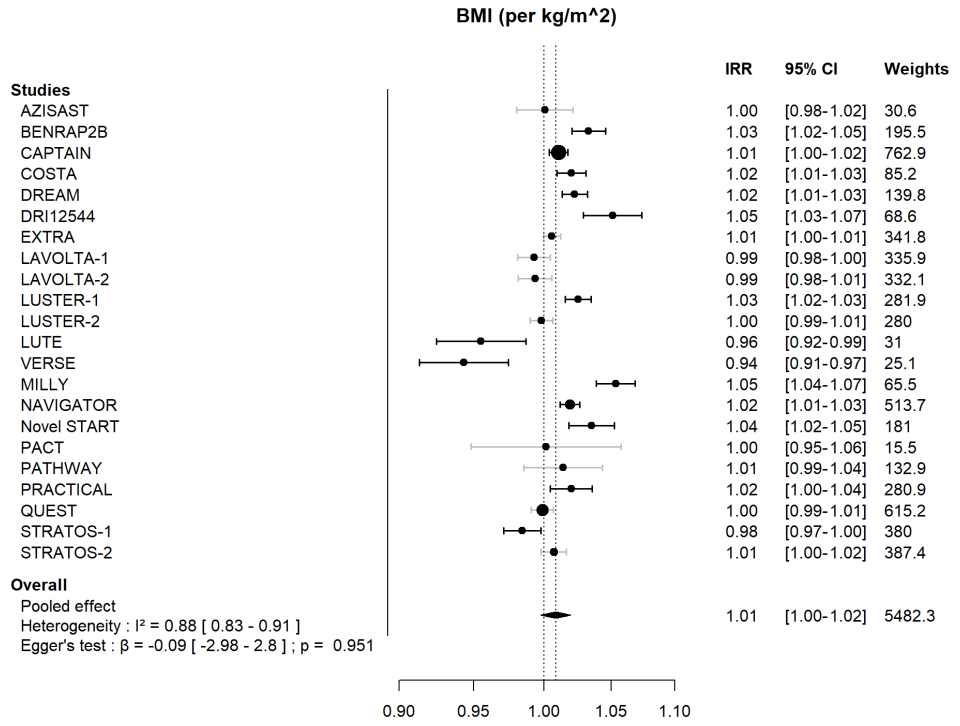
G- Blood eosinophil count (BEC)

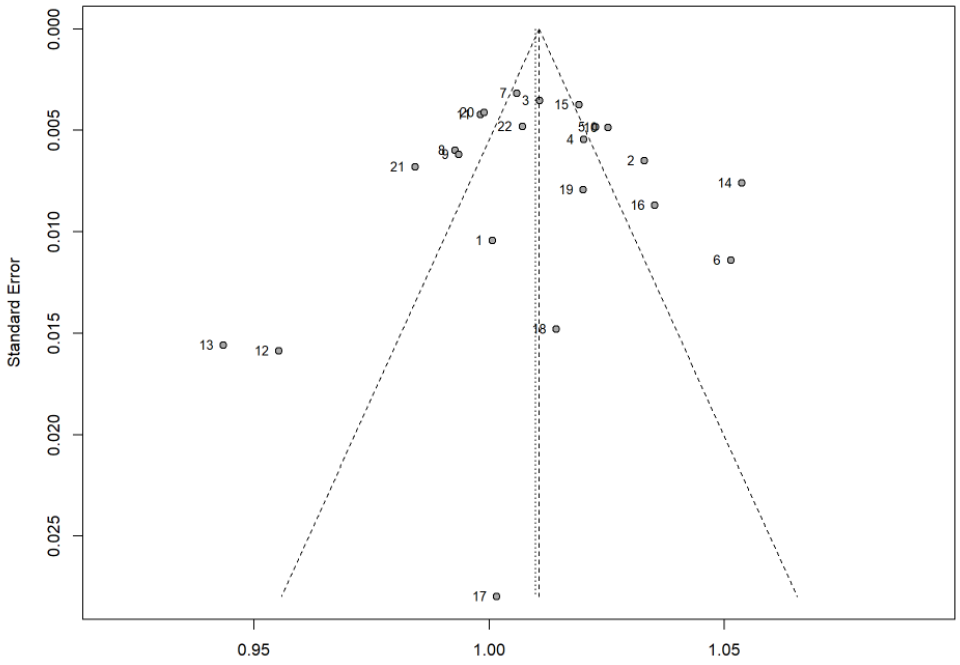




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

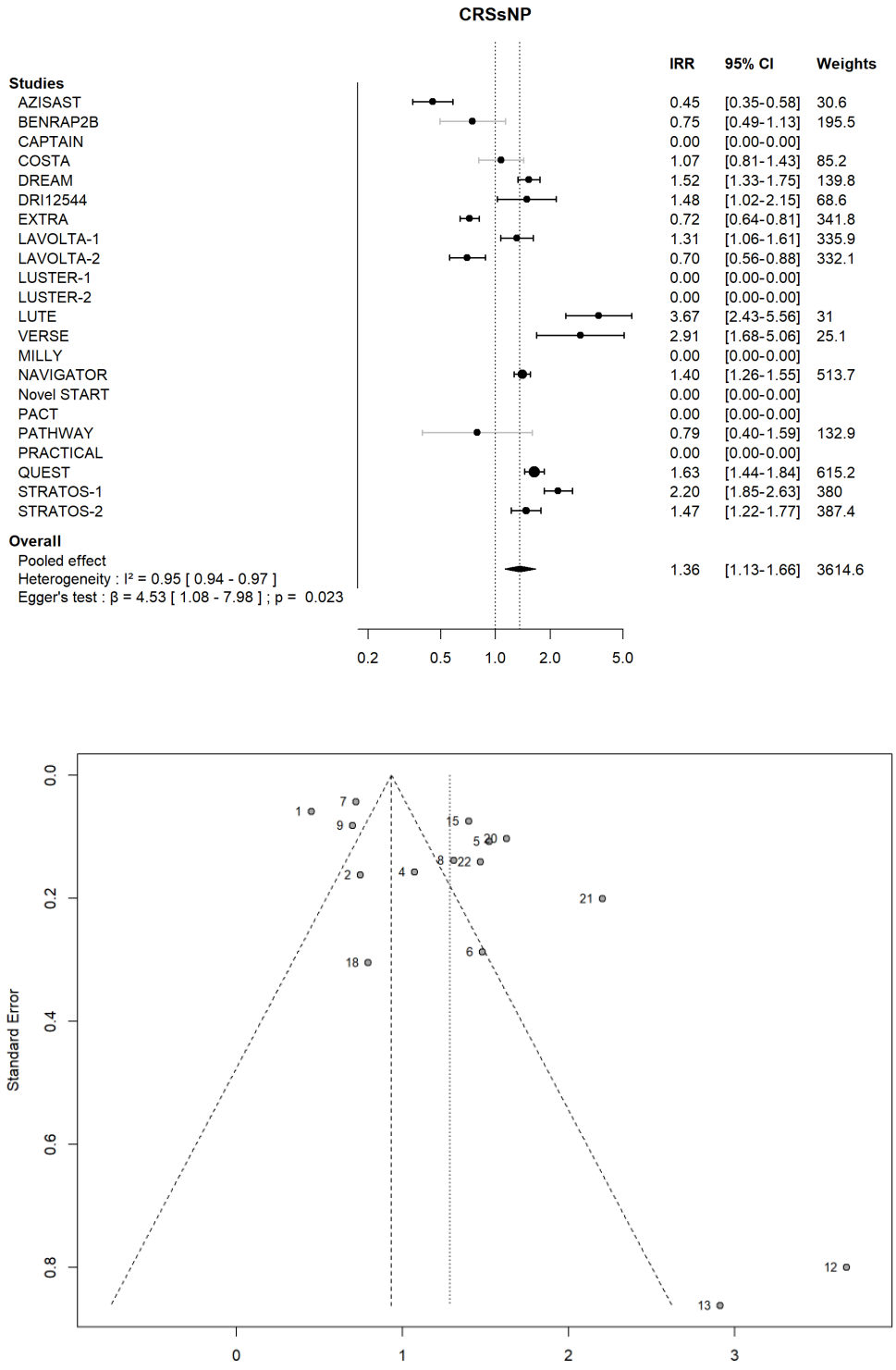
H- Body mass index (BMI)





(Figure S7, univariable forest plots and funnel plot per trial - Continued)

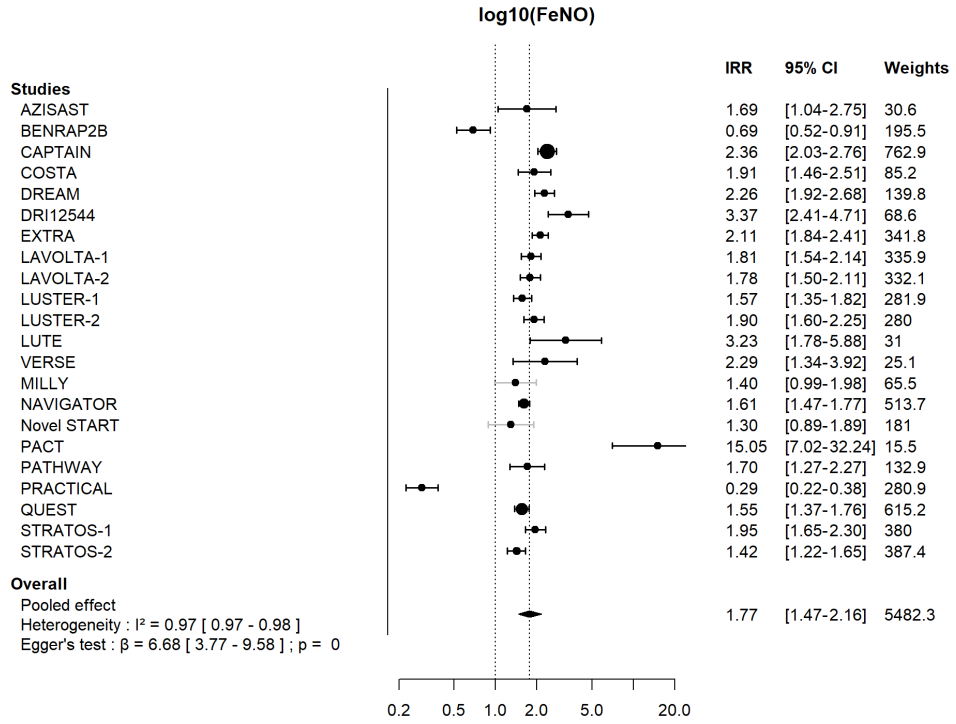
I- Chronic rhinosinusitis without polyposis (CRSsNP)

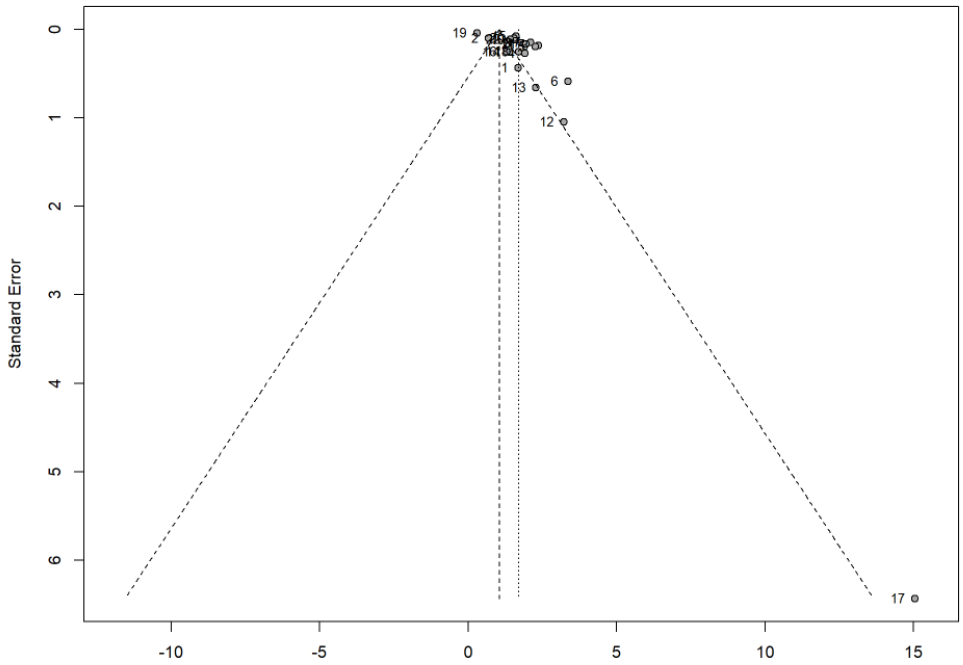


(Figure S7, univariable forest plots and funnel plot per trial - Continued)

(Figure S7, univariable forest plots per trial - Continued)

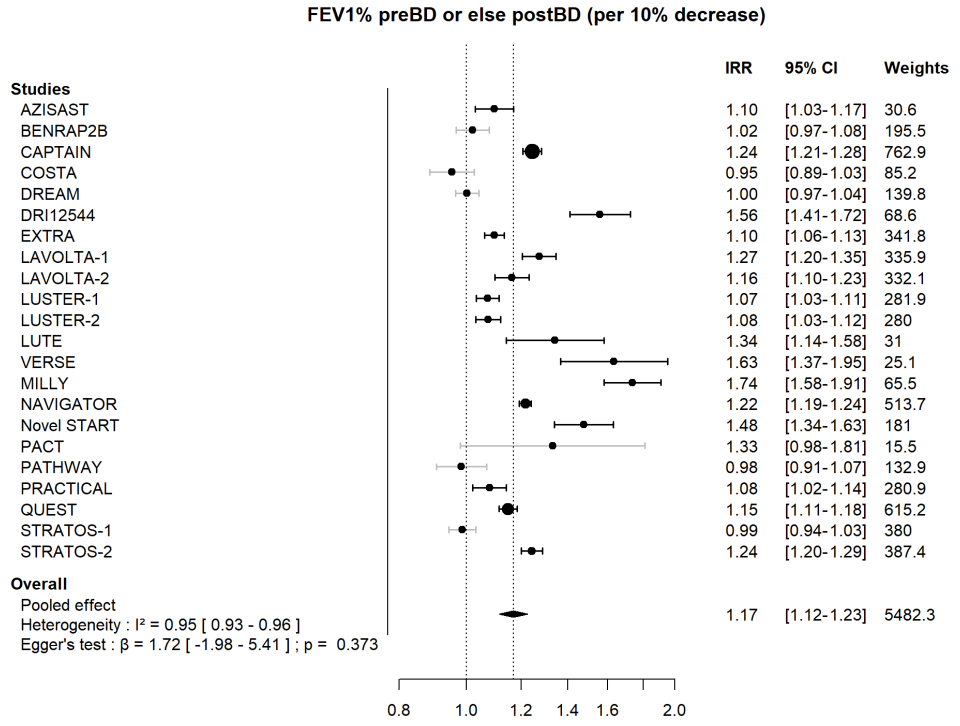
J- Fractional exhaled nitric oxide (FeNO)

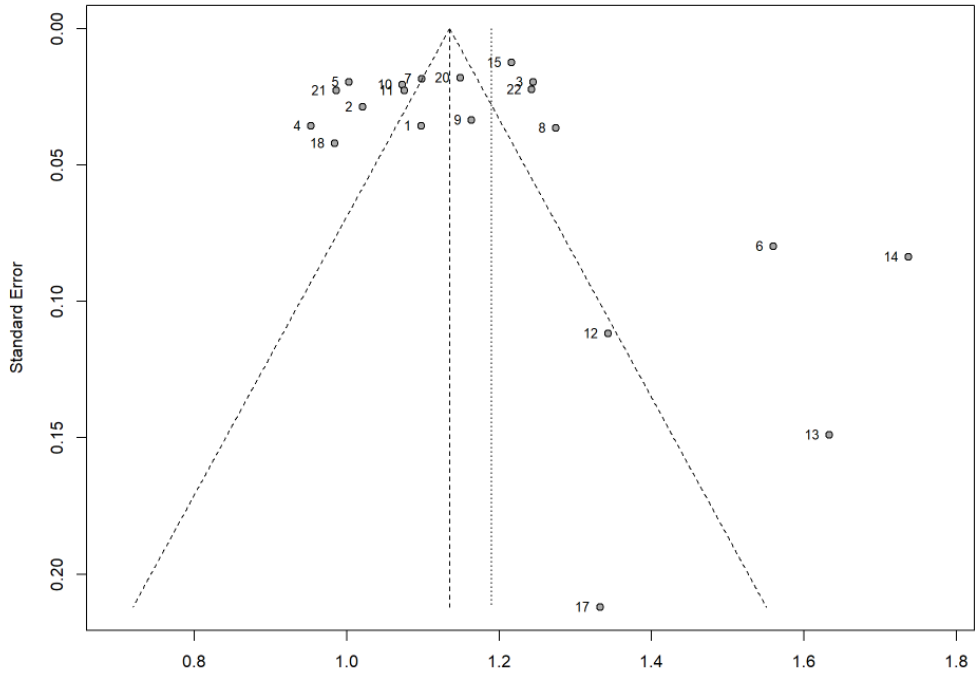




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

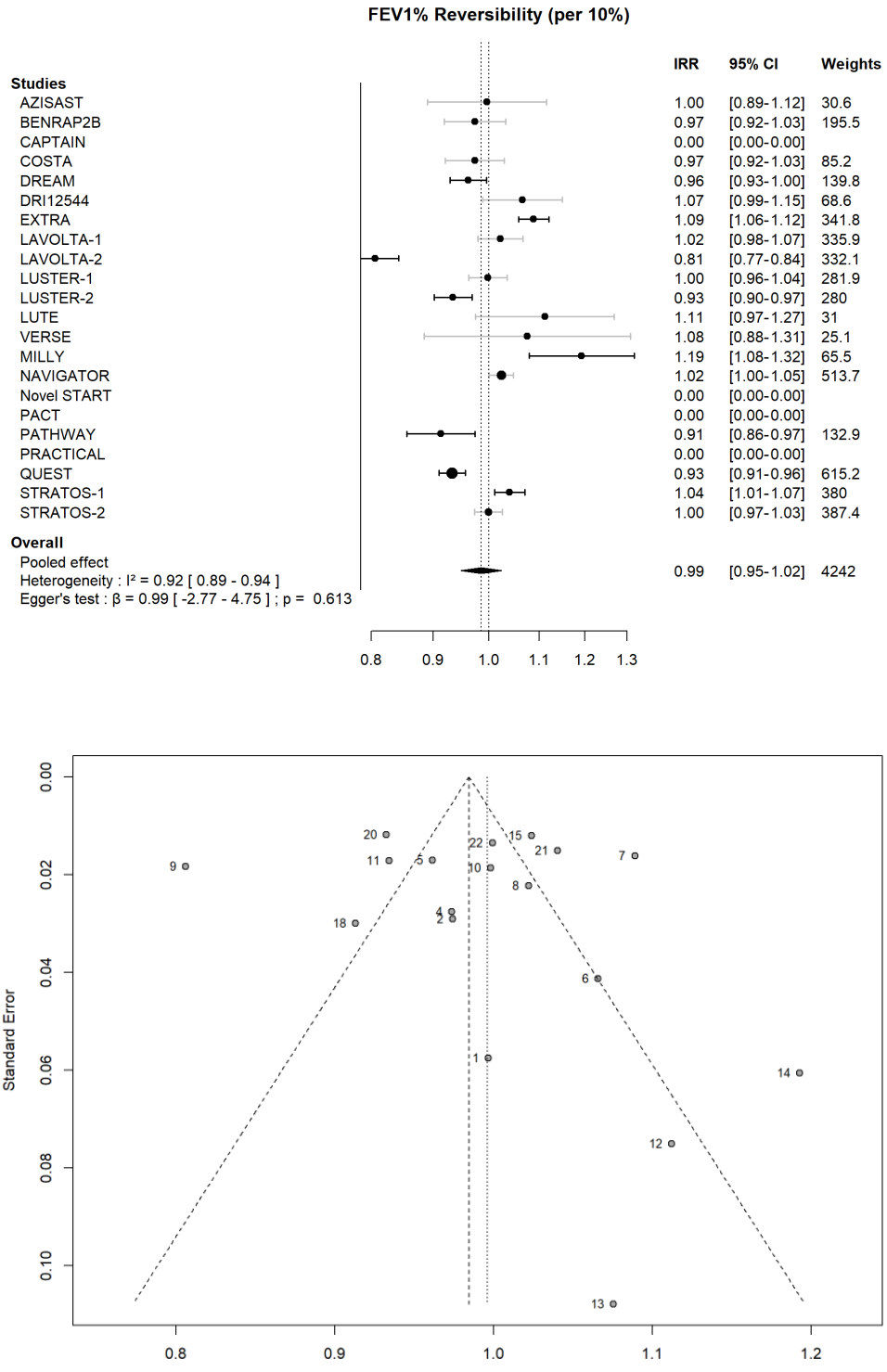
K- Forced expiratory volume in 1st second (FEV1) % predicted, prebronchodilator





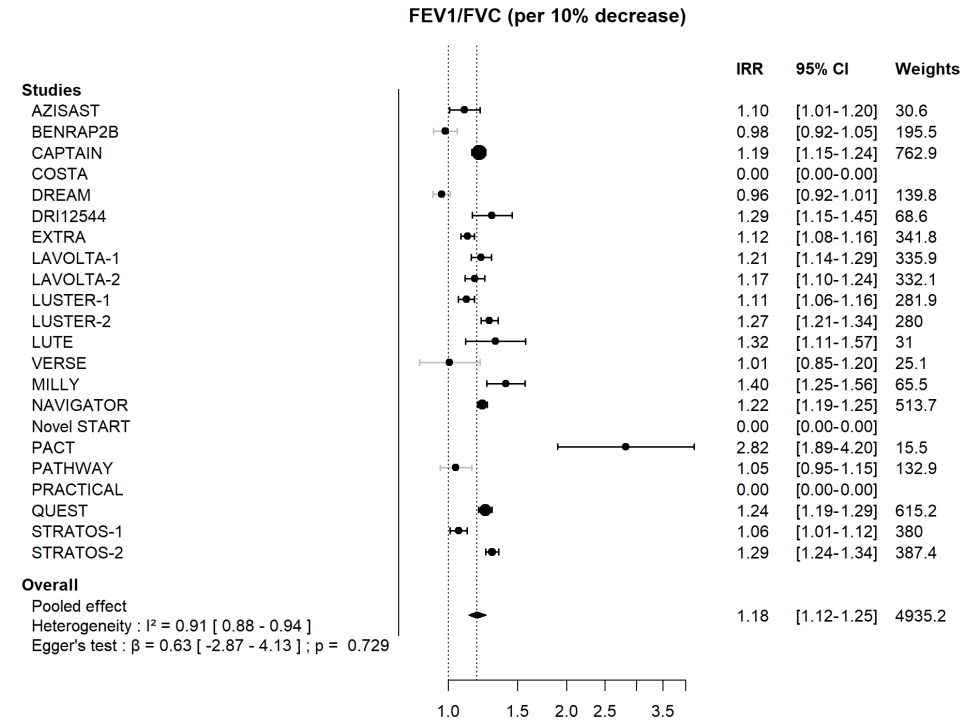
(Figure S7, univariable forest plots and funnel plot per trial - Continued)

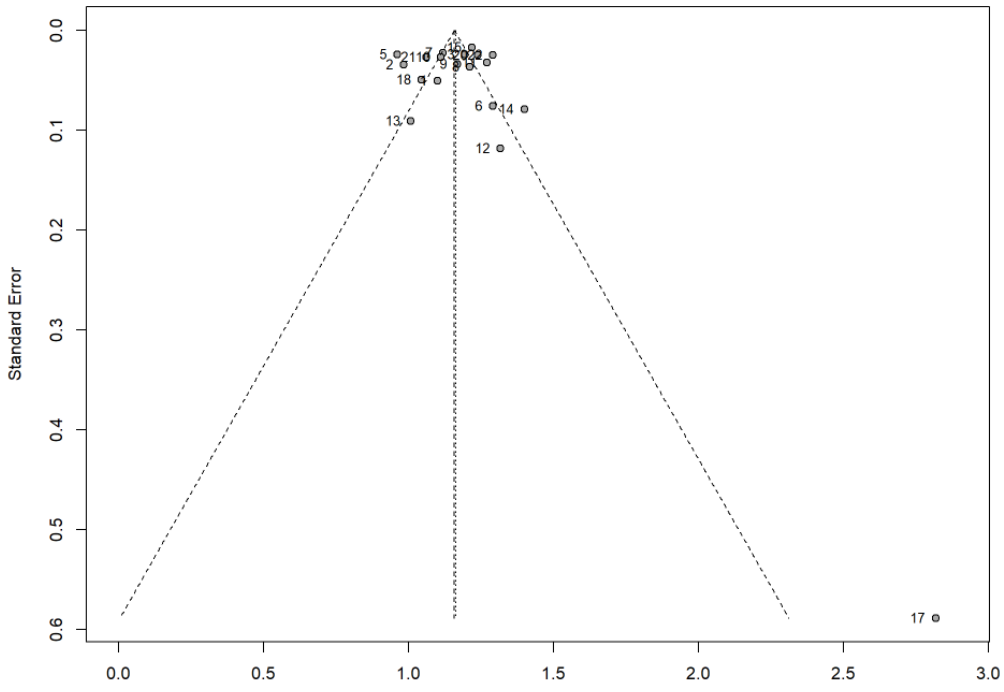
L- Forced expiratory volume in 1st second (FEV1) reversibility (%)



(Figure S7, univariable forest plots and funnel plot per trial - Continued)

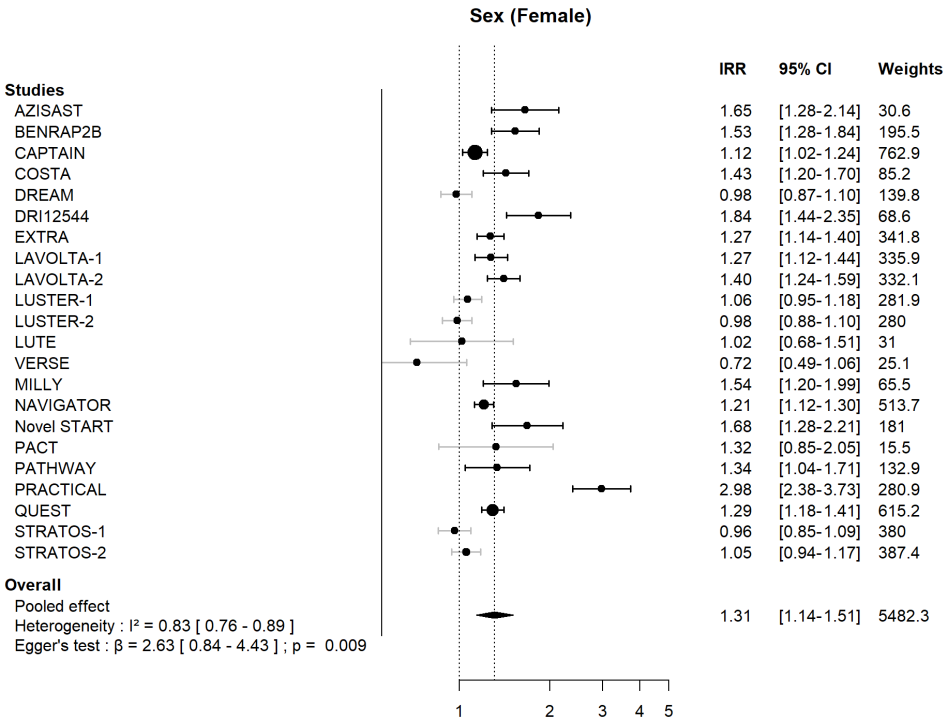
M- Forced expiratory volume in 1st second (FEV1 / forced vital capacity (FVC) ratio

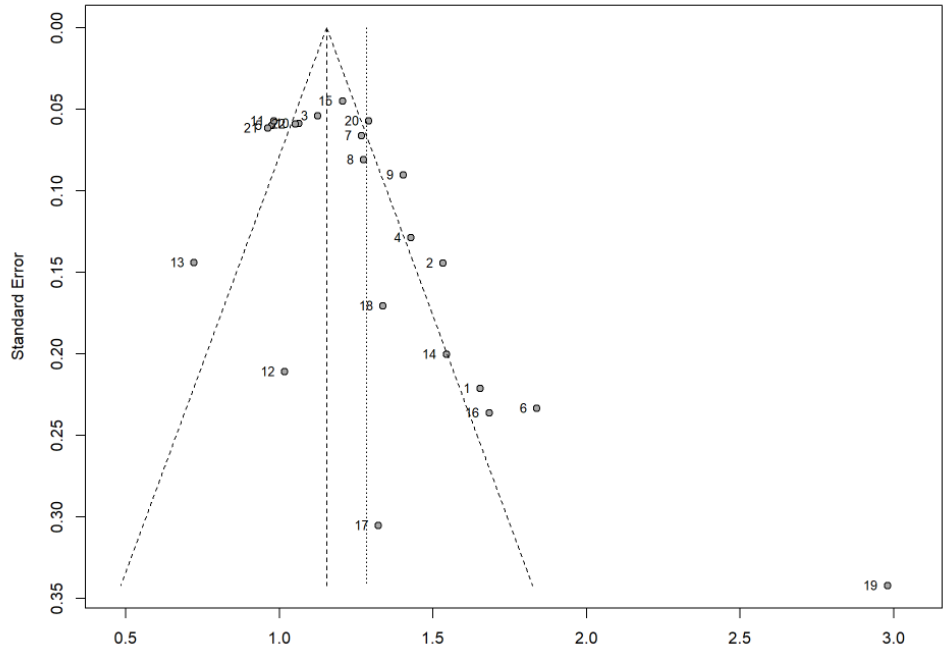




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

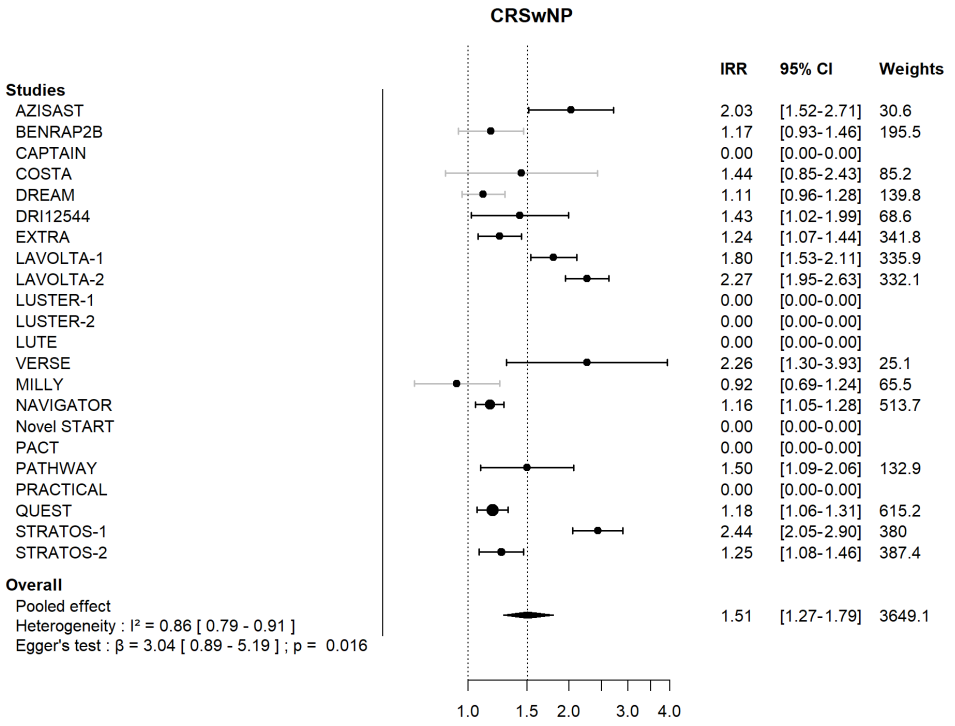
N- Sex

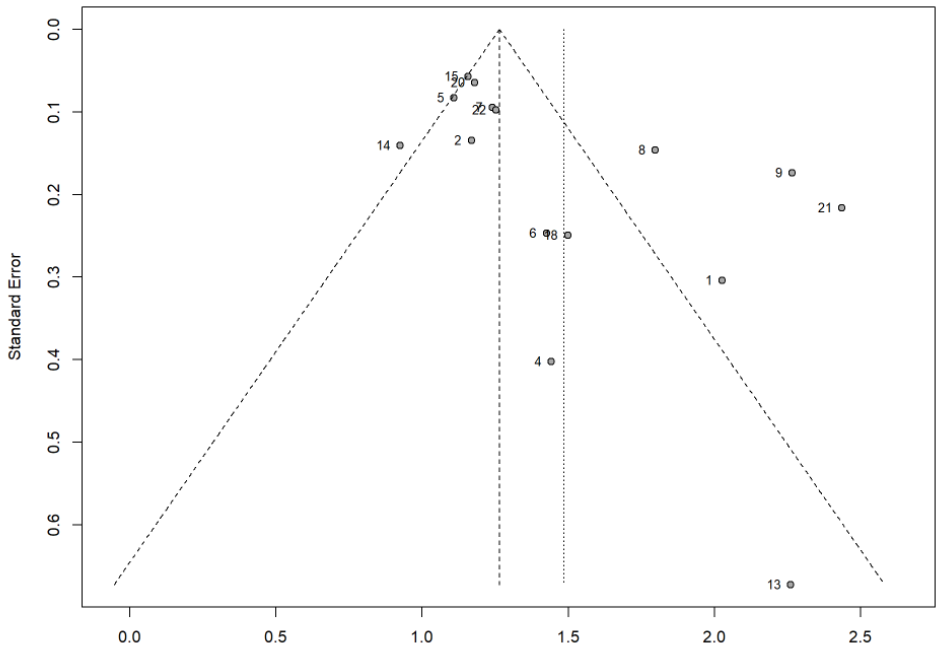




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

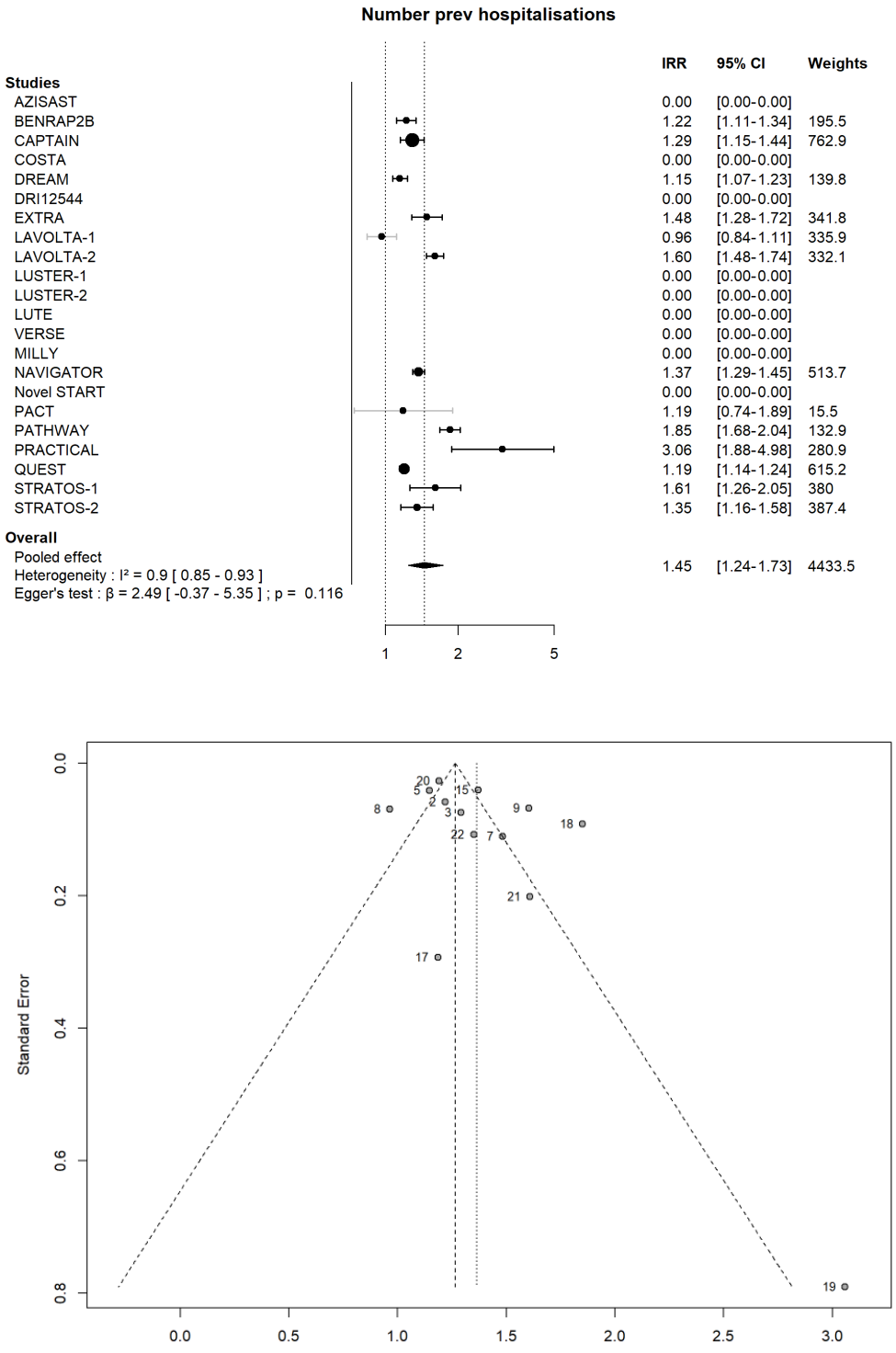
O- Chronic rhinosinusitis with nasal polyposis (CRSwNP)





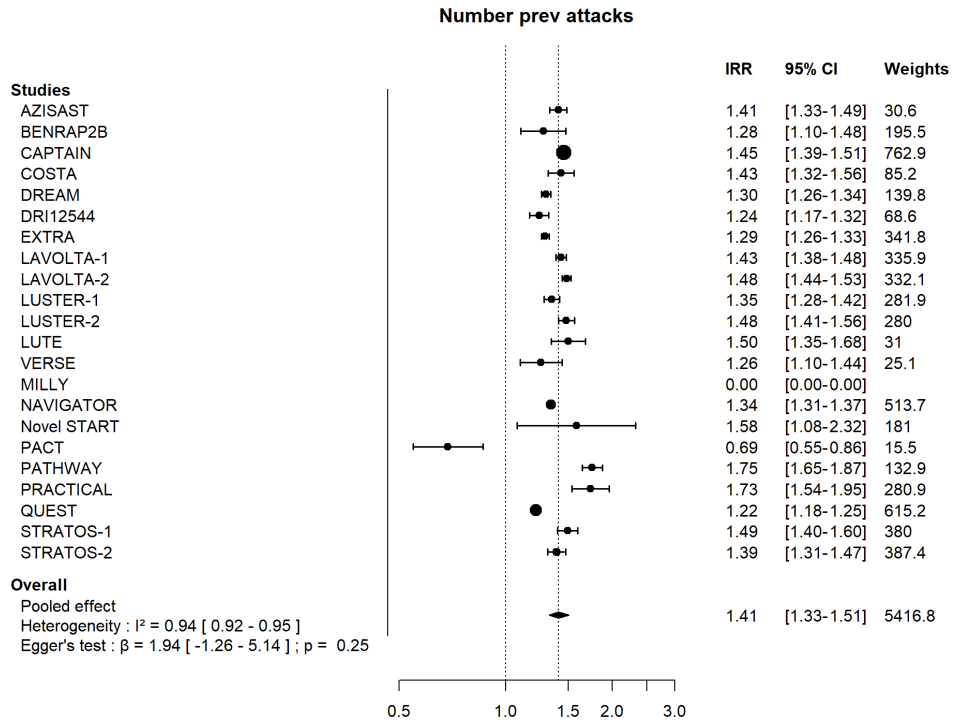
(Figure S7, univariable forest plots and funnel plot per trial - Continued)

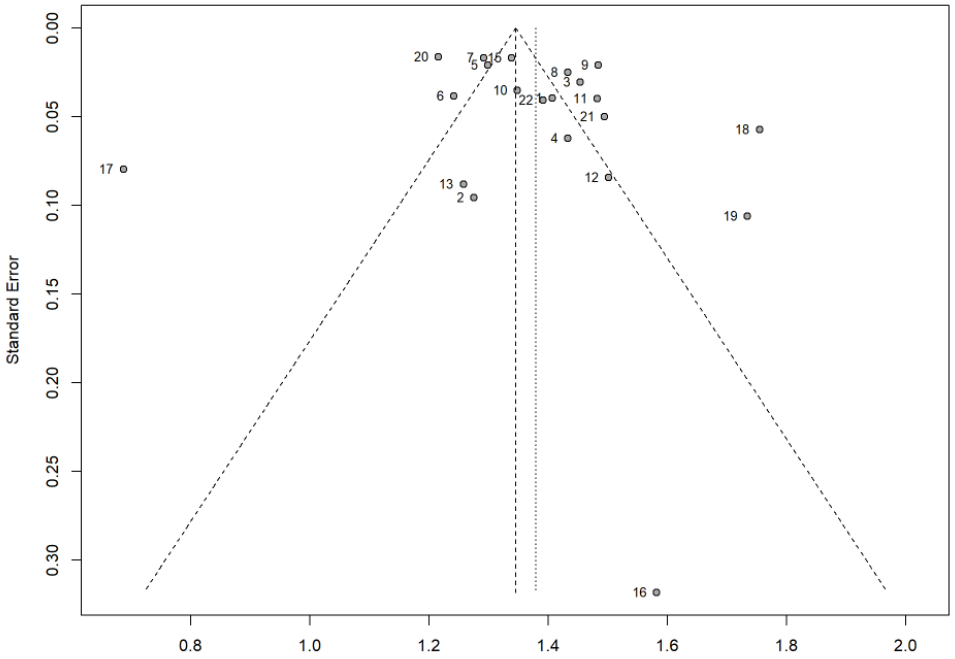
P- Number of previous asthma hospitalisations for asthma attacks in past 12 months



(Figure S7, univariable forest plots and funnel plot per trial - Continued)

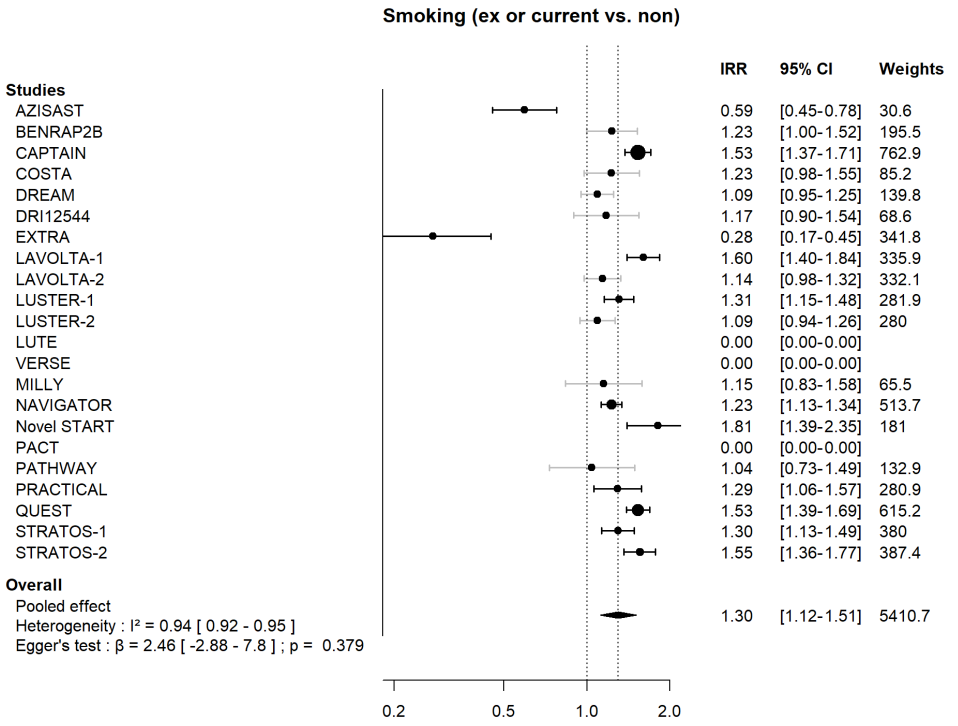
Q- Number of previous severe asthma attacks in past 12 months

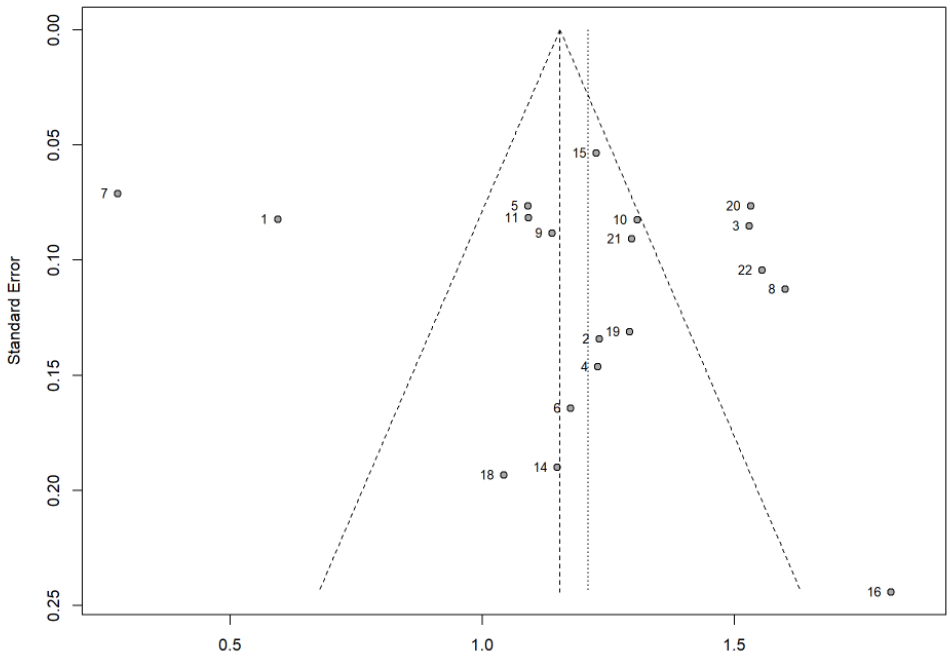




(Figure S7, univariable forest plots and funnel plot per trial - Continued)

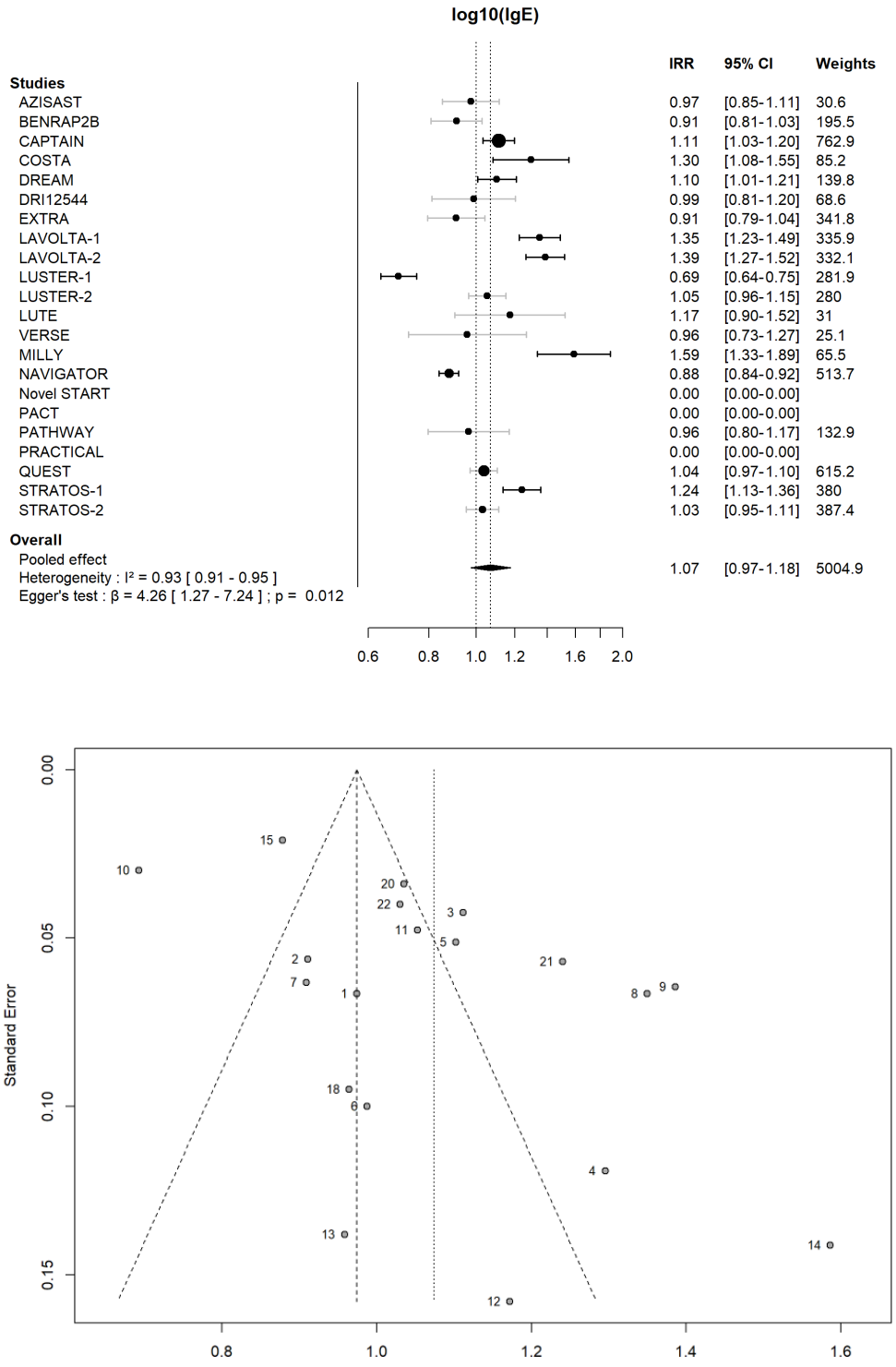
R- Smoking history





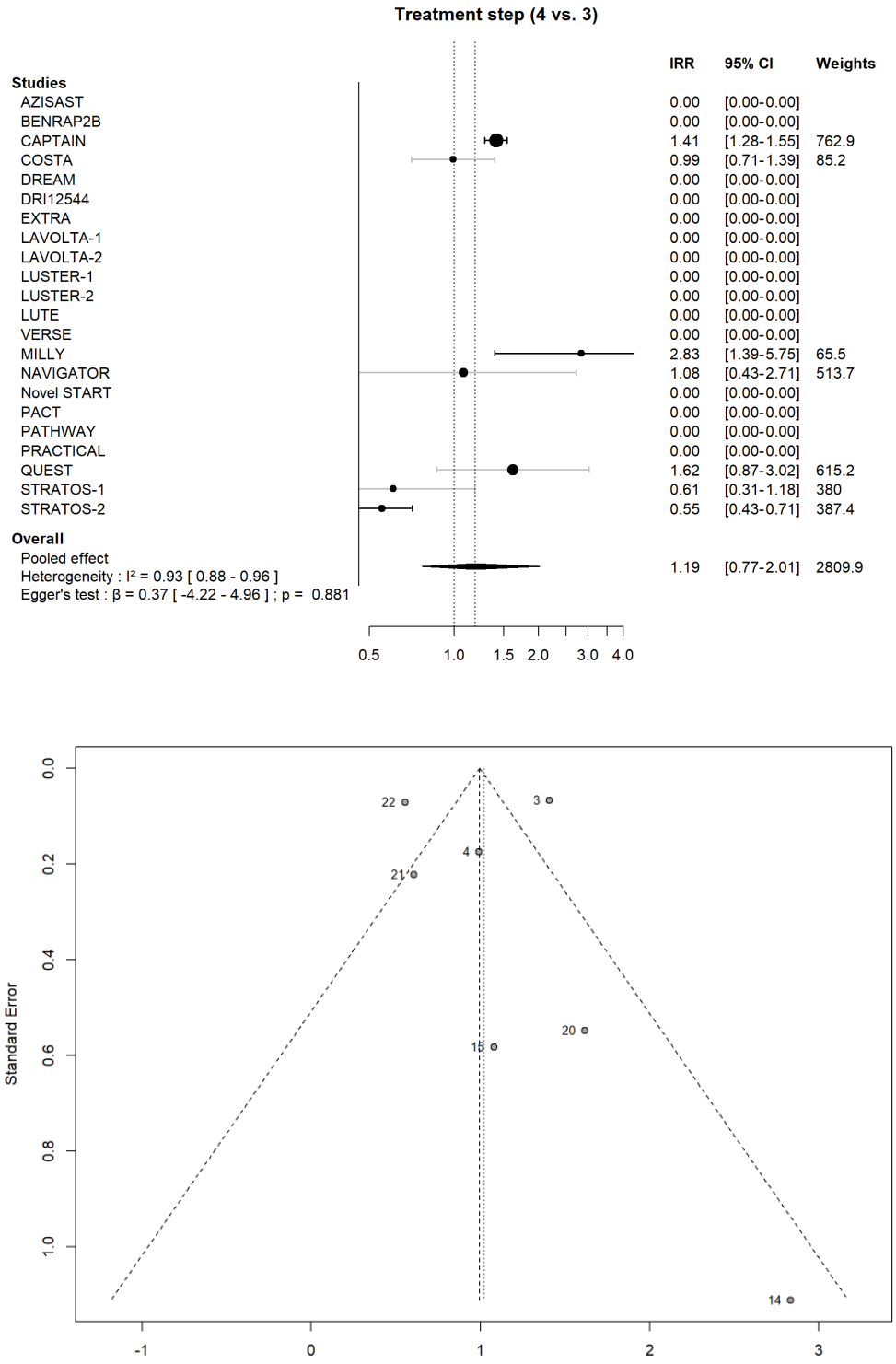
(Figure S7, univariable forest plots and funnel plot per trial - Continued)

S- Total serum immunoglobulin E (IgE)



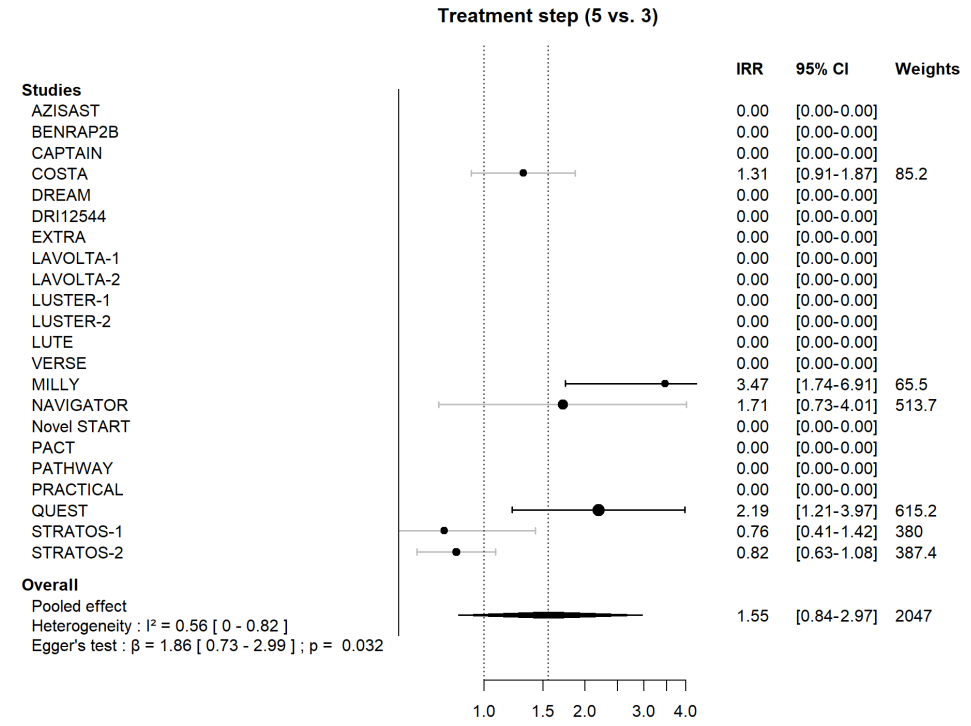
(Figure S7, univariable forest plots and funnel plot per trial - Continued)

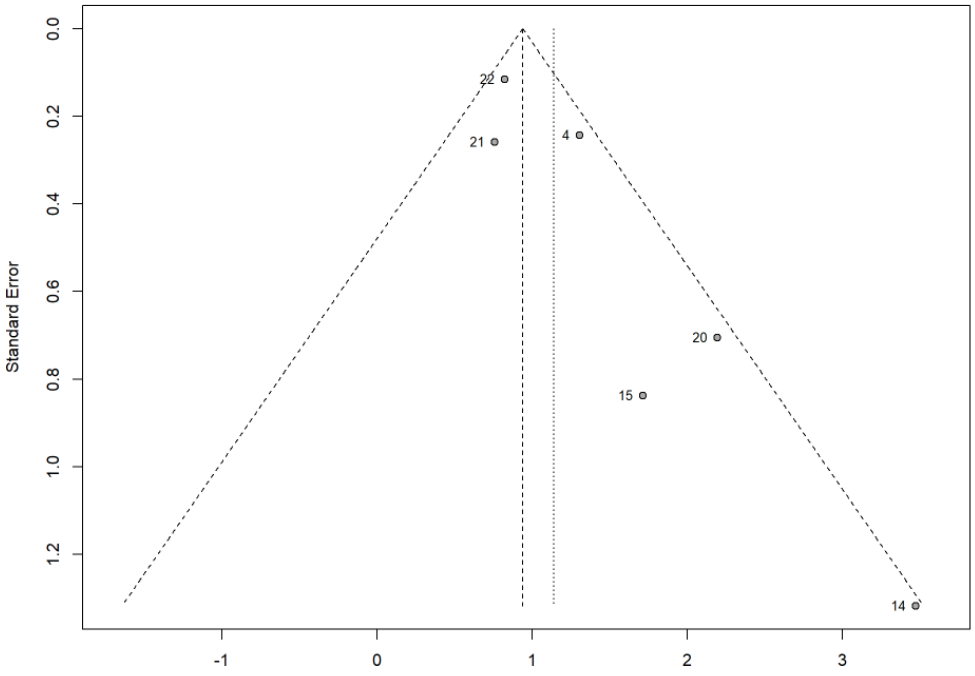
T- Treatment step (4 vs 3)



(Figure S7, univariable forest plots and funnel plot per trial - Continued)

U- Treatment step (5 vs 3)





(Figure S7, univariable forest plots and funnel plot per trial - Continued)

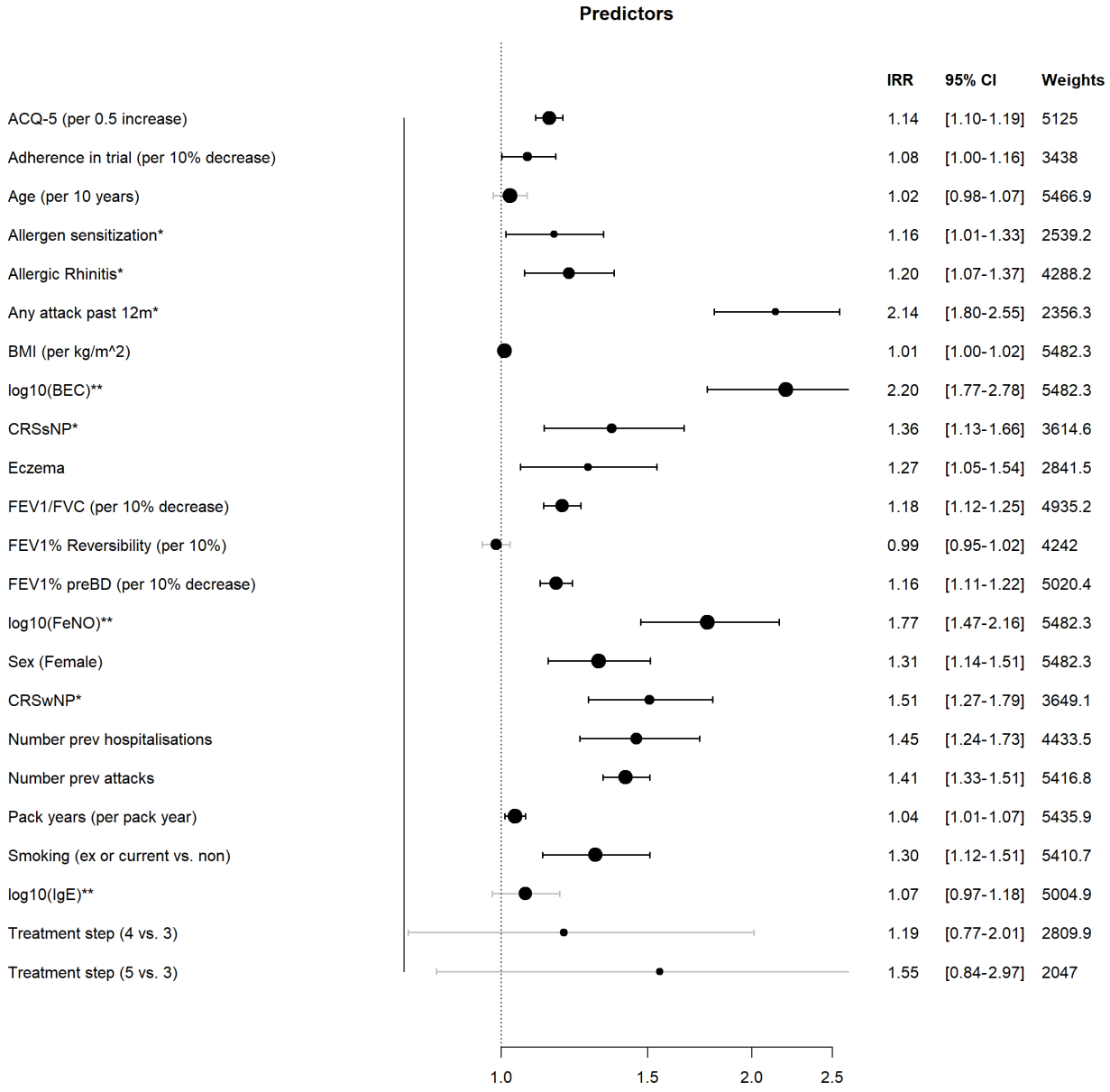


FIGURE S8. Forest plot of the associations between predictors at baseline and future severe asthma attacks (univariable, derived per trial), weighted by the trial's person-years.

All predictors are adjusted for the offset of follow-up duration. ACQ-5, Asthma Control Questionnaire (5-items); BEC, blood eosinophil count; BMI, body mass index; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyps; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IRR, Incidence Rate Ratio.

* Dichotomous variable (yes/no)

** Per 10-fold increase

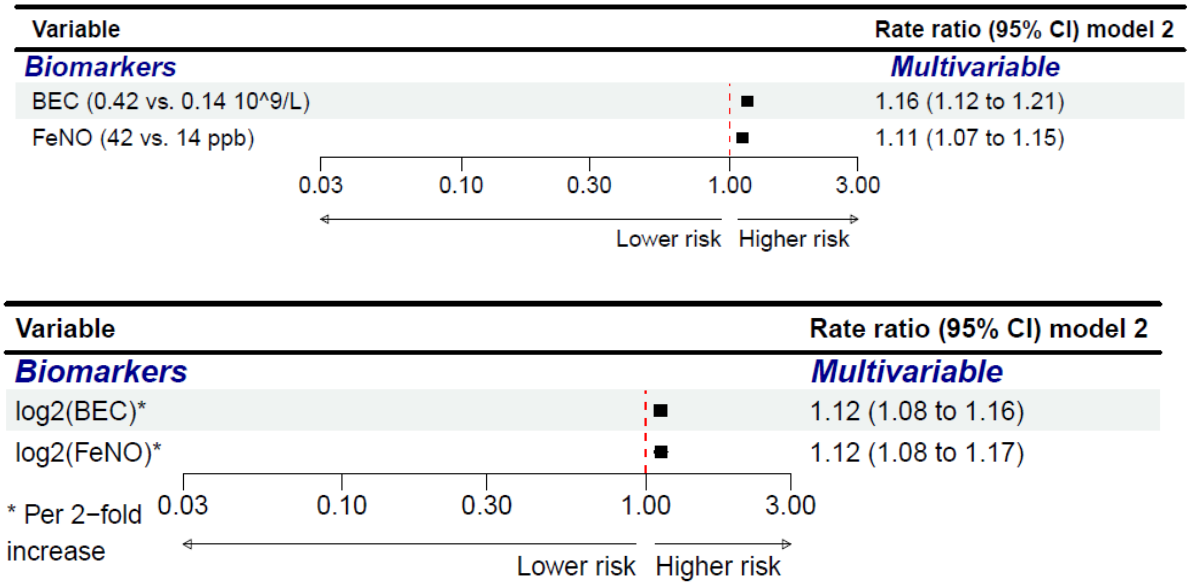


FIGURE S9. Forest plots of the associations between biomarkers BEC and FeNO at baseline and future severe asthma attacks, standardised by 25/75 percentile scaling and per 2-fold increase.

Rate ratios correspond to the multivariable model (model 2), adjusted for study as a factor, offset follow-up duration, treatment step (1-5), attack history (yes/no), FEV_1% pre-bronchodilator and mean ACQ-5 symptom score, with 95% CI. BEC, blood eosinophil count; CI, confidence interval; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

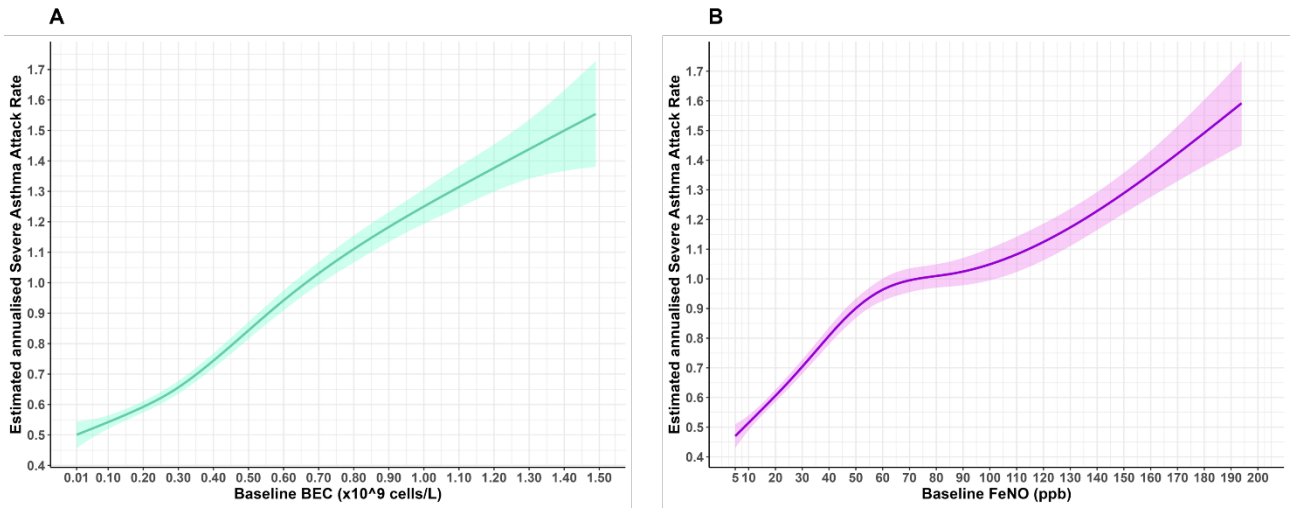


FIGURE S10. Spline plots of BEC (A) and FeNO (B) on a linear scale, and the estimated annualised severe asthma attack rate. Analyses adjusted according to the multivariable model (mode 2). BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

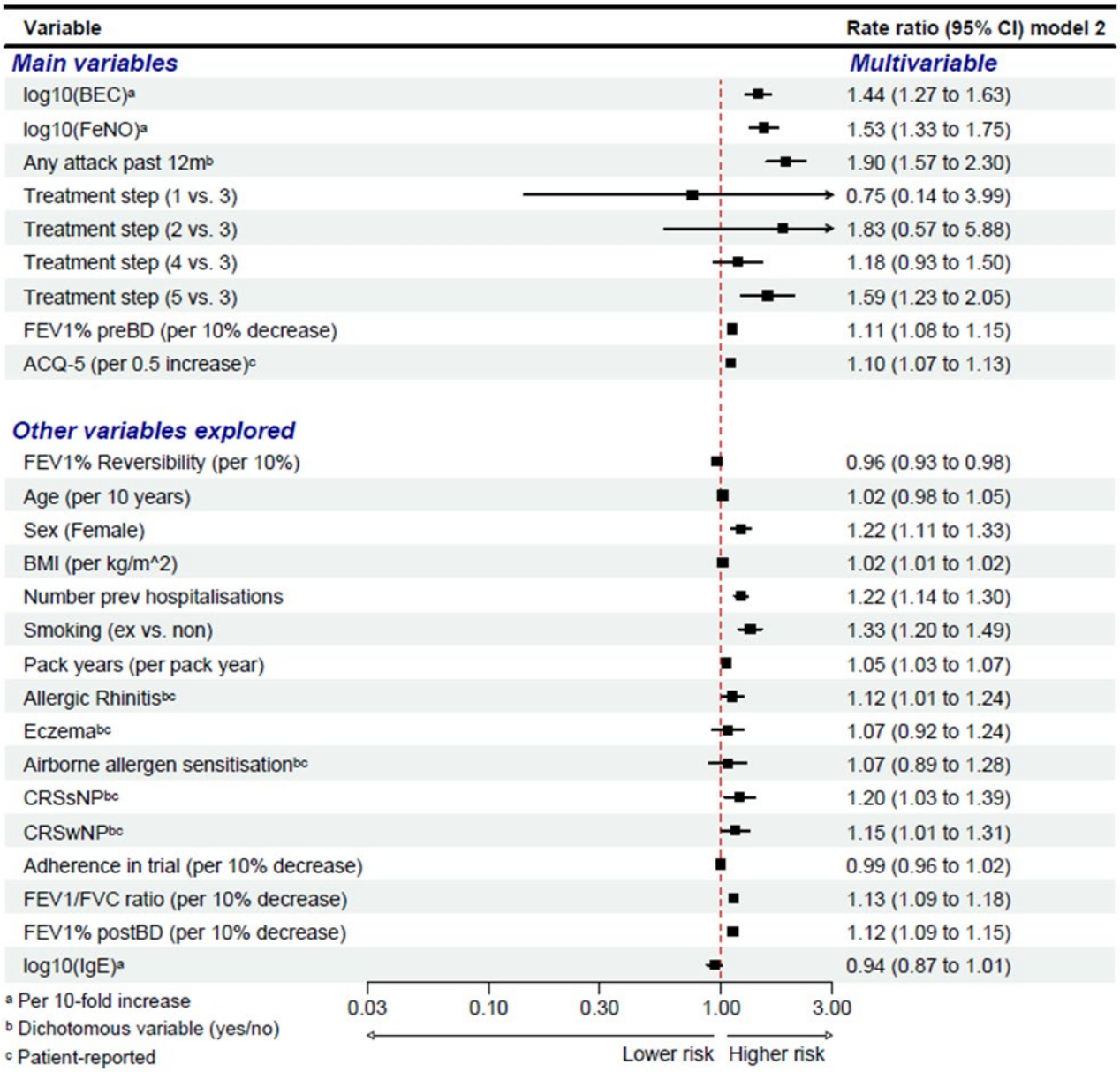


FIGURE S11. Sensitivity analysis - Associations between baseline characteristics and number of severe asthma attacks during follow-up in the double-blind trials (n=5,988)(2 open-label trials excluded)

Baseline characteristics are categorized as main variable or other variable. Rate ratios correspond to multivariable model (model 2), with a 95% CI. Model 2 was adjusted for study as a factor, offset log-transformed follow-up duration, asthma attack in the past year (yes *vs* no), asthma severity (treatment step 1 to 5), FEV1% pre-bronchodilator, ACQ-5 symptom score, BEC and FeNO. There were no current smokers in this sensitivity analysis. ACQ, Asthma Control Questionnaire; BD, bronchodilator; BEC, blood eosinophil count; BMI, body mass index; CI, confidence interval; CRSsNP, chronic rhinosinusitis without Nasal Polyposis; CRSwNP, chronic rhinosinusitis with Nasal Polyposis; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E.

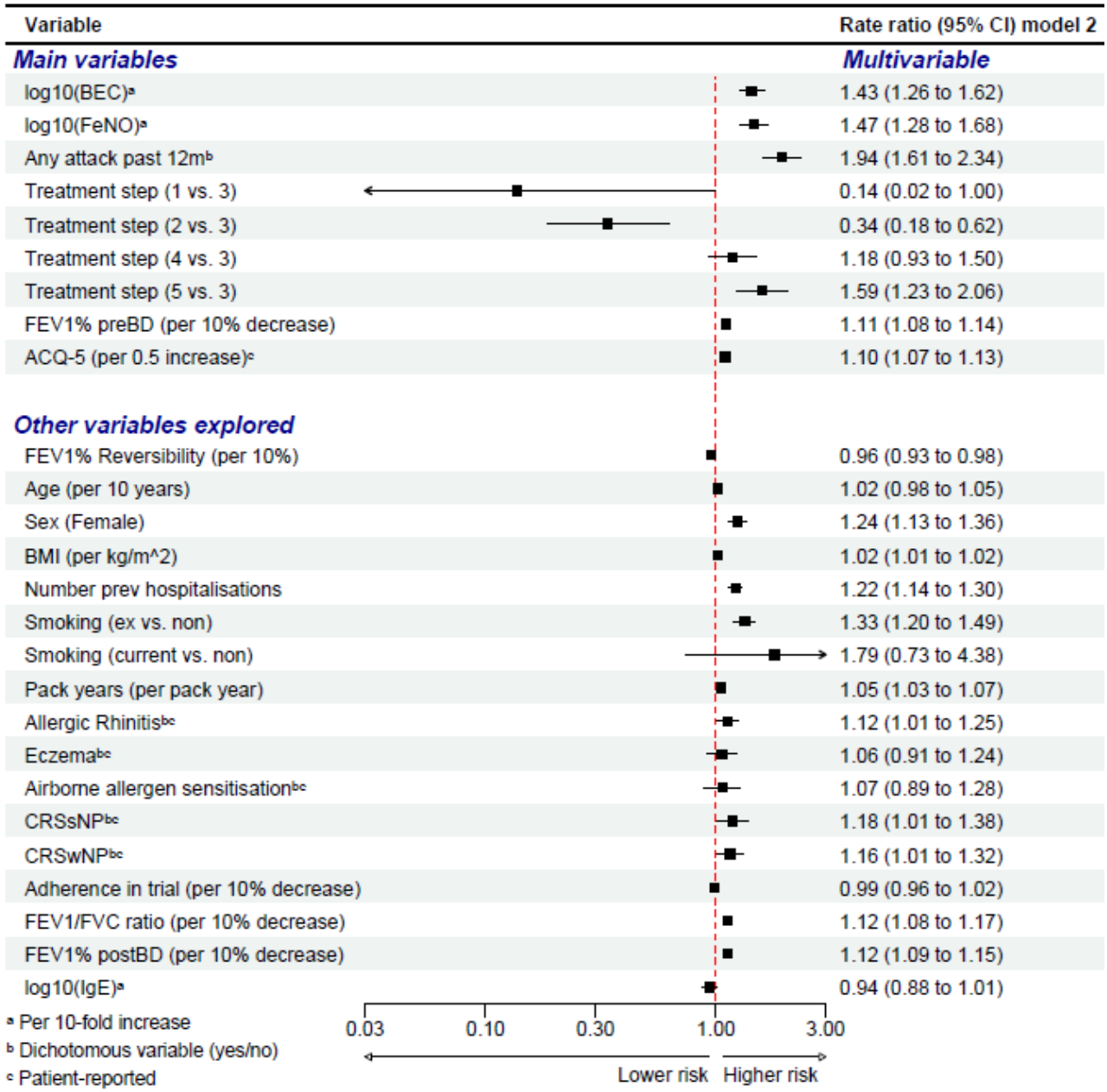


FIGURE S12. Sensitivity analysis - Associations between baseline characteristics and number of severe asthma attacks during follow-up in the trials with low risk of bias (n=6,397)(2 potentially biased trials excluded).

Baseline characteristics are categorized as main variable or other variable. Rate ratios correspond to multivariable model (model 2), with a 95% CI. Model 2 was adjusted for study as a factor, offset log-transformed follow-up duration, asthma attack in the past year (yes *vs* no), asthma severity (treatment step 1 to 5), FEV1% pre-bronchodilator, ACQ-5 symptom score, BEC and FeNO. ACQ, Asthma Control Questionnaire; BD, bronchodilator; BEC, blood eosinophil count; BMI, body mass index; CI, confidence interval; CRSsNP, chronic rhinosinusitis without Nasal Polyposis; CRSwNP, chronic rhinosinusitis with Nasal Polyposis; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E.

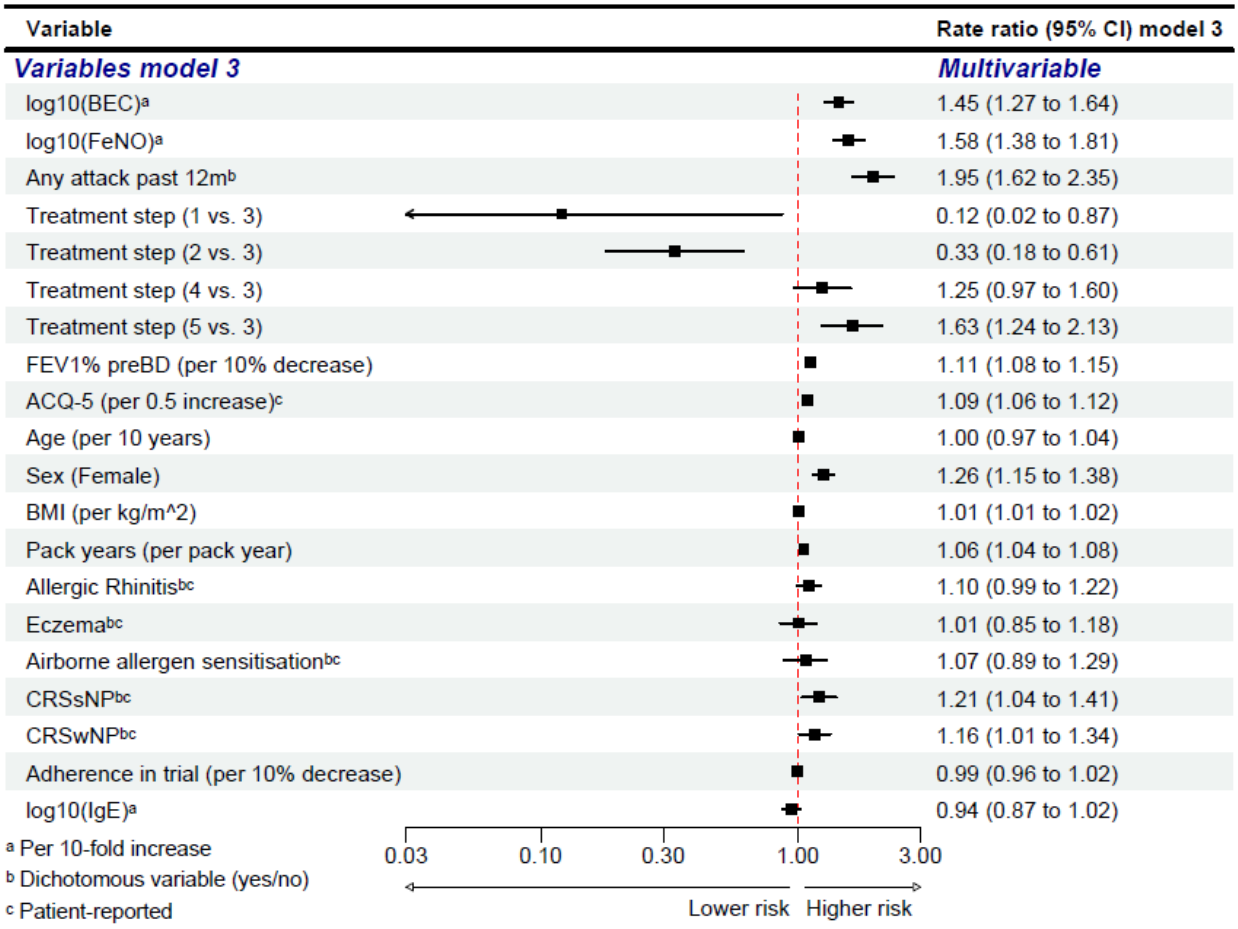


FIGURE S13. Forest plots of the associations between prognostic factors at baseline and future severe asthma attacks, adjusted for all covariates listed in the forest plot (model 3).

Rate ratios correspond to the fully adjusted multivariable model (model 3) with 95% CI. ACQ, Asthma Control Questionnaire; BEC, blood eosinophil count; BMI, body mass index; CI, confidence interval; CRSsNP, chronic rhinosinusitis without Nasal Polyposis; CRSwNP, chronic rhinosinusitis with Nasal Polyposis; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E.

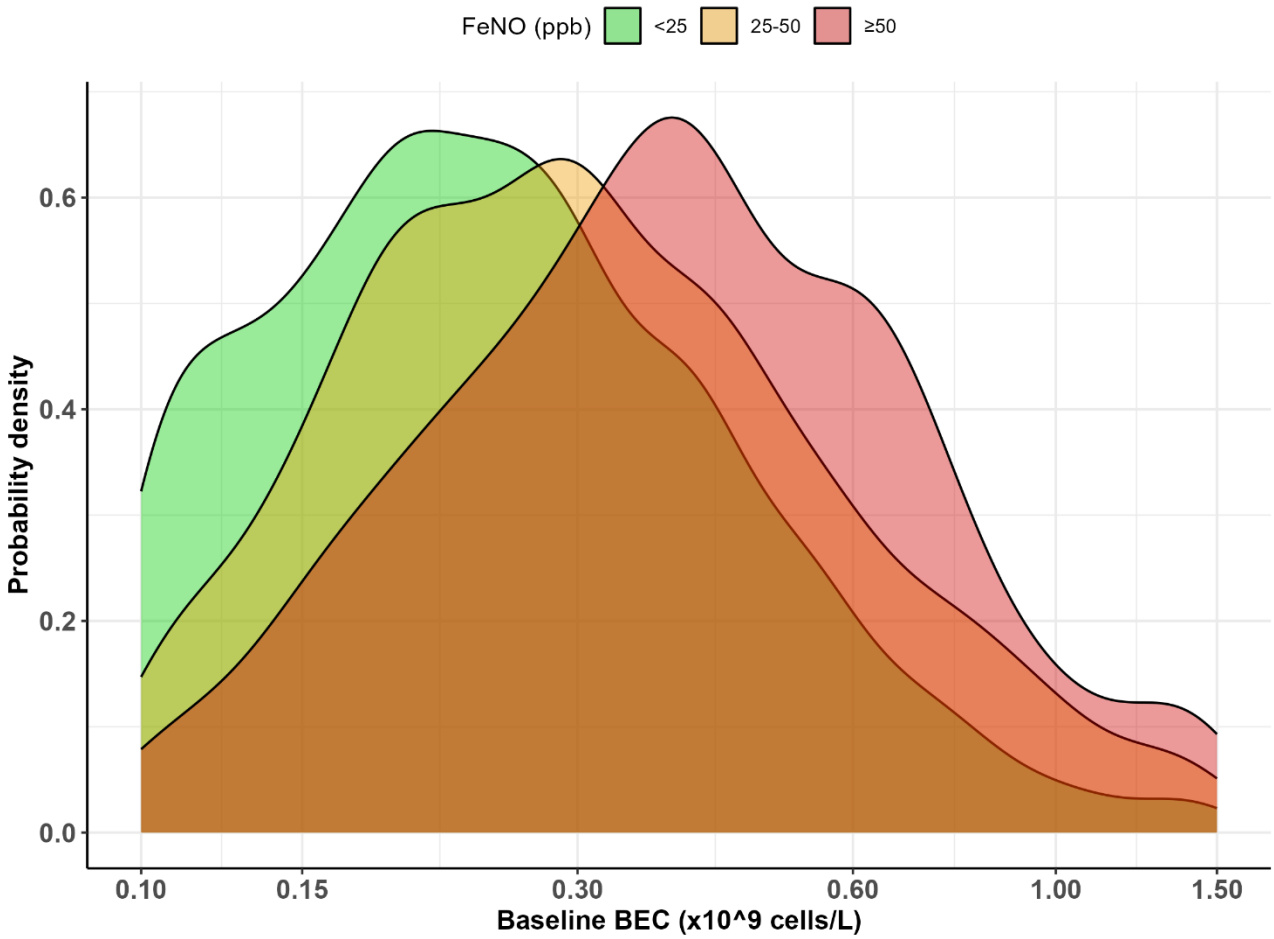


FIGURE S14. Density plot of BEC and FeNO, restricting the study population to trials that did not select according to biomarkers.

Included trials for this analysis: Novel START, PRACTICAL, CAPTAIN, Dupilumab phase 2b, LAVOLTA 1-2, LUTE-VERSE, MILLY, PACT, QUEST, STRATOS 1-2**.** The Y-axis shows the probability density (meaning, how likely it is that a certain value of BEC is observed within a FeNO group). BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

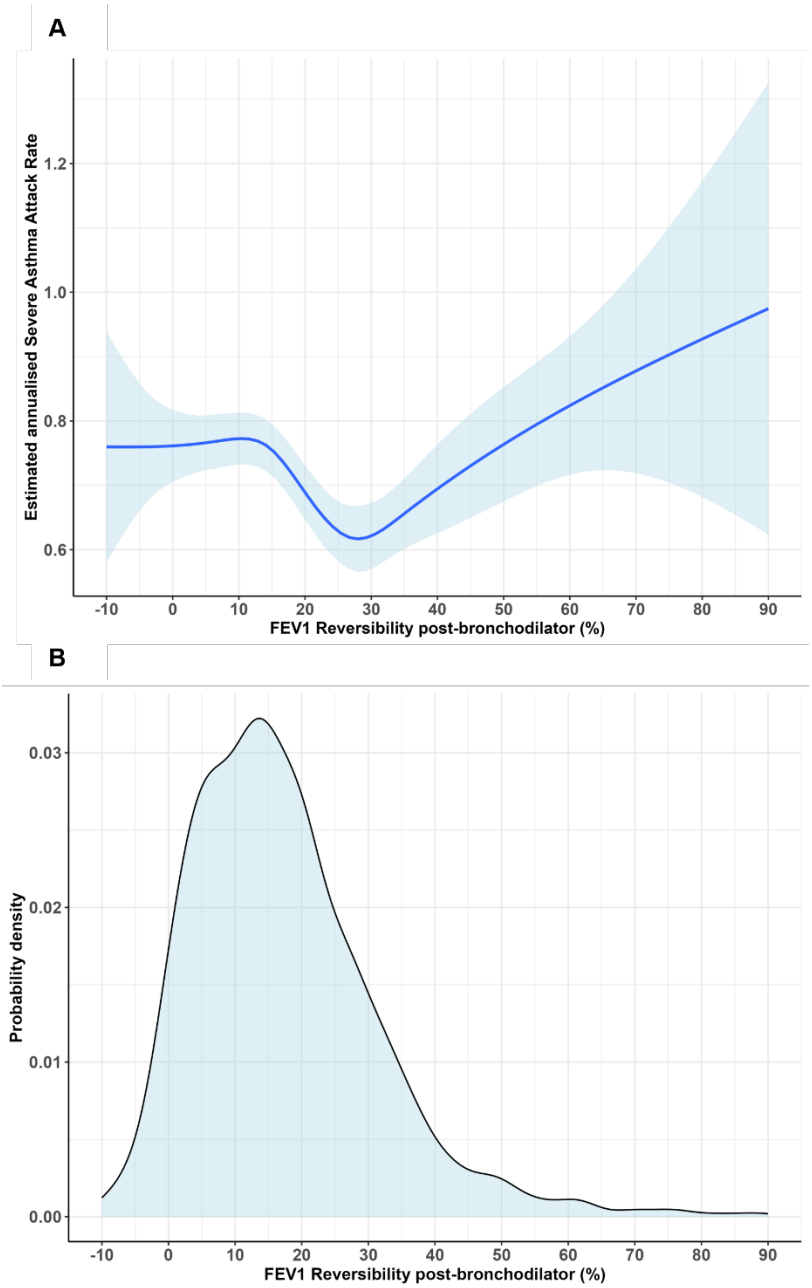


FIGURE S15. Spline plot (A) and density plot (B) for FEV1% reversibility, restricting the study population to trials that did not require FEV1% reversibility at baseline visit.

Included trials for this analysis were: Benralizumab phase 2b, COSTA, DREAM, EXTRA, Novel START, PACT, PATHWAY, PRACTICAL. B) The Y-axis shows the probability density (meaning, how likely it is that a certain value of FEV1% reversibility is observed in the study population). Analyses adjusted according to the multivariable model (mode 2). FEV1, forced expiratory volume in the first second.

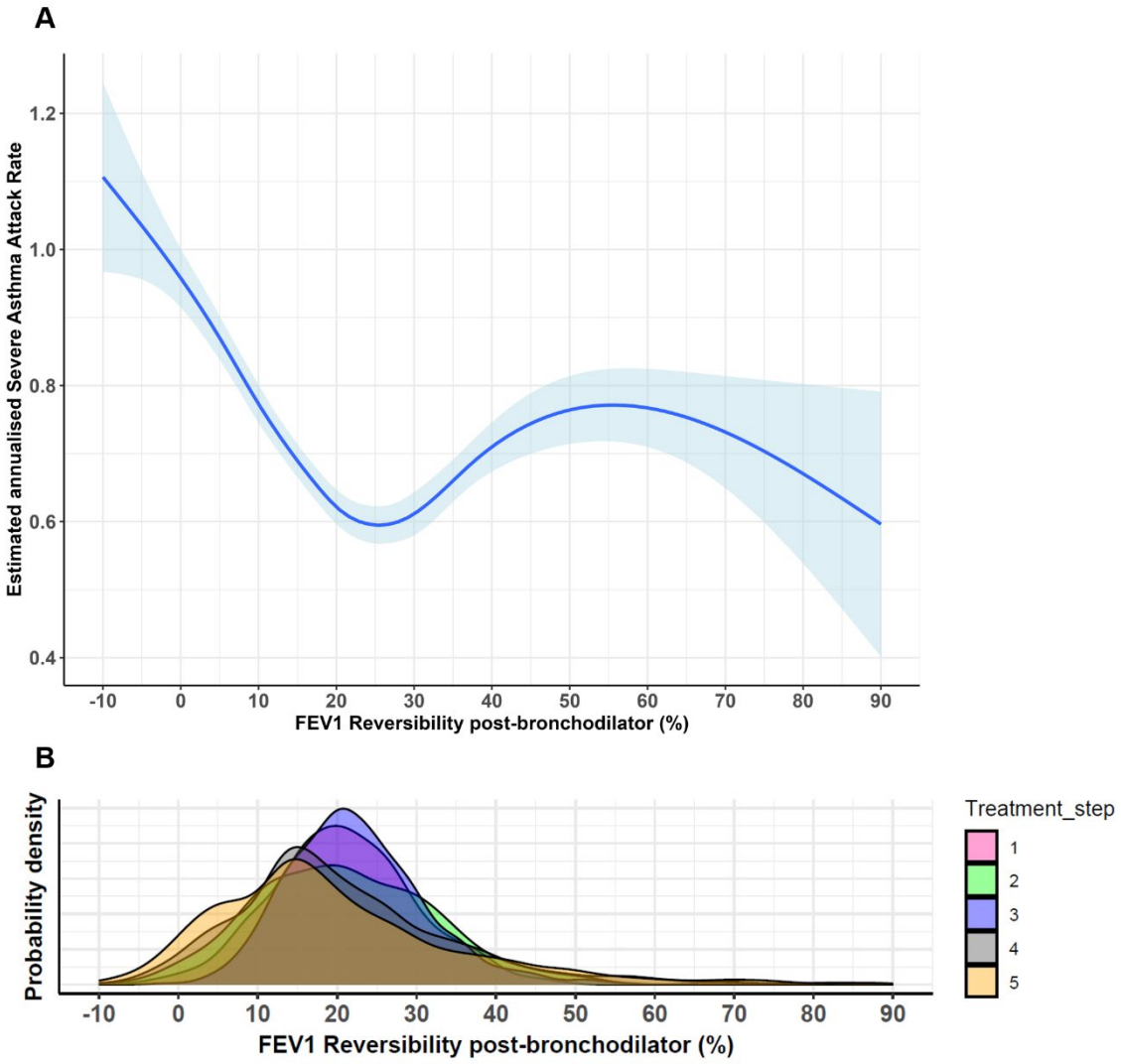


FIGURE S16. Spline plot (A) and density plot (B) for FEV1% reversibility, with the probability density by treatment step (1 to 5).

B) The Y-axis shows the probability density (meaning, how likely it is that a certain value of FEV1% reversibility is observed in the study population). Analyses adjusted according to the multivariable model (mode 2). FEV1, forced expiratory volume in the first second.

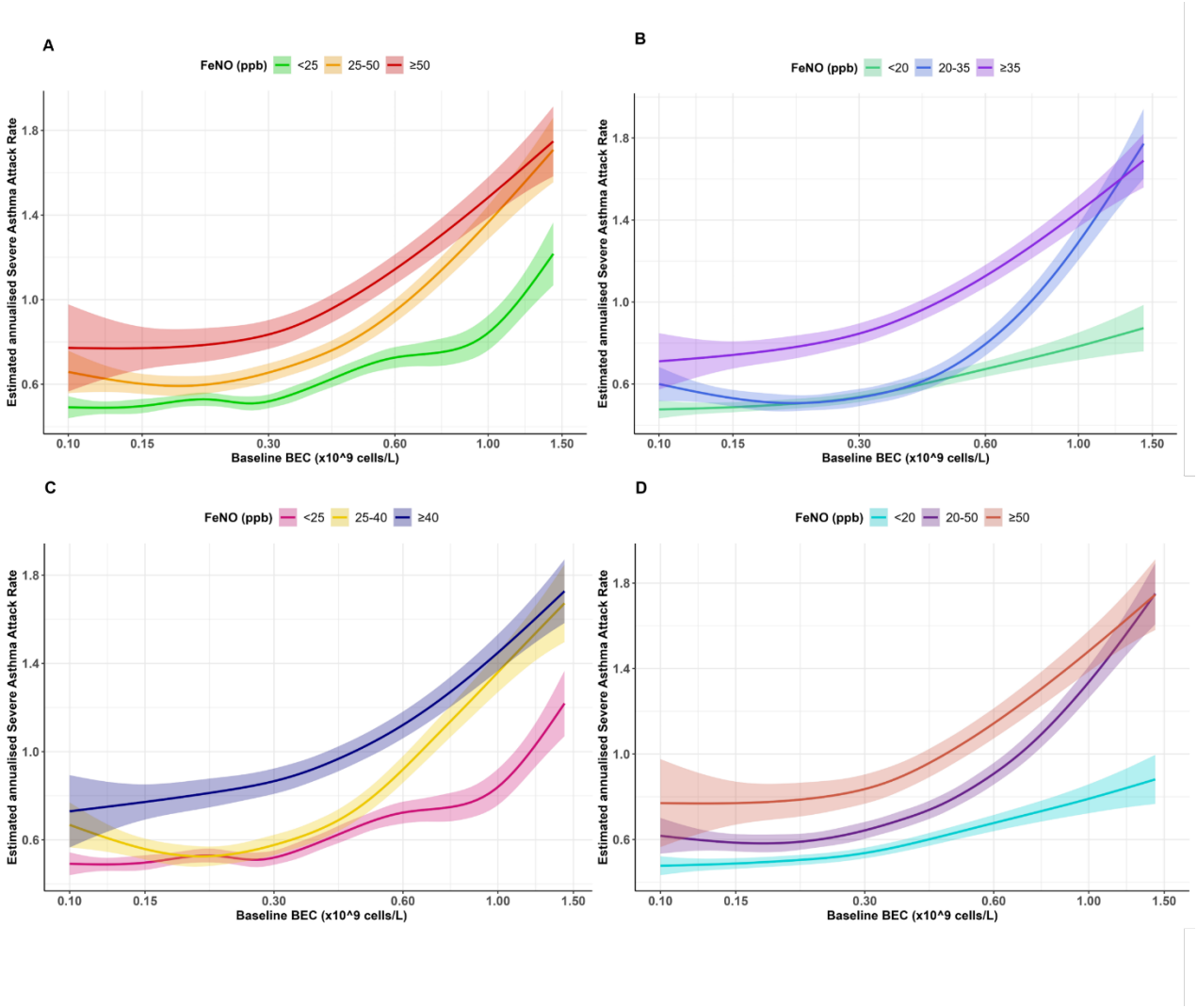


FIGURE S17. Spline plots BEC and estimated annualised severe asthma attack rate with different FeNO cut-off values.

A) FeNO < 25 ppb (green), 25 ≤ ppb < 50 (orange) and ≥ 50 ppb (red);
B) FeNO < 20 ppb (green), 20 ≤ ppb < 35 (blue) and ≥ 35 ppb (purple);
C) FeNO < 25 ppb (pink), 25 ≤ ppb < 40 (yellow) and ≥ 40 ppb (dark blue);
D) FeNO < 20 ppb (light blue), 20 ≤ ppb < 50 (purple) and ≥ 50 ppb (red)

Analyses adjusted for key variables.
BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

3. Supplementary Tables

TABLE S1. Data dictionary supplied to data providers for data extraction

Variable name **red variables are mandatory**	**Description**	**Value labels**
Sequential_number	Sequential number in excel spreadsheet - for data compilation	
Subject_ID	Anonymised subject ID in your trial - for data tracking if audit / question	
Enrolled_Trial_name	Acroynm, short title of trial, or encoded trial ID	
Treatment_arm	Arm the patient was randomised to	E.g. 'placebo' , 'placebo 1.8mL', 'Albuterol', 'BUD400_Saba_Prn 'montelukast'
Age	Age at baseline	
Gender_0Female_1Male	Gender	Enter as 0 (female) or 1 (male)
BMI	in kg/m^2; include one decimal	
Ethnicity	I have not coded anything here as terms will vary. Examples are caucasian, african american, …	
Country	Country in which the patient was randomised to the trial	
Treatment_step	Mandatory entry. See 'TABLE S2' and 'TABLE S3'	1,2,3,4,5
Any_severe_attack_ previous_12m_0no_1yes	Mandatory. Any severe asthma attacks in 12 months previous to baseline. Severe asthma attacks are defined as acute asthma requiring ≥3 days of systemic corticosteroid therapy.	Enter 0 (if none) or 1 (if any)
Number_severe_attack _previous_12m	Enter number of severe asthma attacks in 12 months previous to baseline. A severe asthma attack is defined as acute asthma requiring ≥3 days of systemic corticosteroid therapy.	Enter 0 (if none) or (number of episodes)
Number_hospitalisations_for_ asthma_previous_12_months	Number of inpatient stays for asthma in past 12 months, excluding emergency room visits	Enter 0 (if none) or (number of episodes)
Previous_ICU_ 0no_1yes_9999notknown	Ever been into ICU for asthma	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Previous_Intubation_ 0no_1yes_9999notknown	Ever been intubated for asthma	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Smoking_0never _1ex_2current	Smoking status	Enter 0 (neversmoker), 1 (ex-smoker), 2 (current smoker)

Pack_years	Pack years;	Enter 0 (if neversmoker) or (number of packyears)
Psychiatric_disease _0no_1yes_9999notknown	See below for which diseases count	Enter 0 (if none), 1 (if any), or 9999 (unknown)
Psy_disease_type _0none_1depressionORanxiety _2psychosis_ 3nontobaccosubstanceabuse_ 4other_9999notknown	Please code which psychiatric disease the patient has	Enter 0 (none), 1 (depression or anxiety), 2 (psychosis e.g. schizophrenia), 3 (substance abuse, excluding tobacco), 4 (other; no need to detail), or 9999 (unknown)
Atopy_history_0no_ 1yes_9999notknown	Atopy includes self-reported hayfever/allergic rhinitis, eczema, food allergies;	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Eczema_0no_ 1yes_9999notknown	Self-reported eczema	Enter 0 (no) or 1 (yes) or 9999 (unknown)
AllergicRhinitis__ 0no_1yes_9999notknown	Self-reported allergic rhinitis (unimportant if it is perennial or seasonal)	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Airborne_allergen_ sensitisation_on_testing_ 0no_1yes_9999notknown	Objective airborne allergy on testing (either self-reported or conducted within the trial)	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Chronic_Rhinosinusitis_ 0no_1yes_9999notknown	Self-reported chronic rhinosinusitis	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Nasal_polyposis_ 0no_1yes_9999notknown	Self-reported nasal polyps	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Previous_nasal_polypectomy _0no_1yes_9999notknown	Self-reported previous nasal polypectomy	Enter 0 (no) or 1 (yes) or 9999 (unknown)
Adherence_PreTrial_quantity	This is intentionally vague; please complete the "PLEASE FILL supplementary info" sheet so that I understand what was entered here. Example could be the % doses taken during the run-in period, or % adherence in diary	(See description)
Adherence_PreTrial_quality	This is intentionally vague; please complete the "PLEASE FILL supplementary info" sheet so that I understand what was entered here. "Quality" was added as a different cell in case adherence was loosely defined; we usually use an adherence to ICS pickups ≥70% as adherent.	(See description)

Adherence_InTrial_quantity	This is intentionally vague; please complete the "PLEASE FILL supplementary info" sheet so that I understand what was entered here. Example could be the % doses taken during trial, or % adherence in diary	(See description)
Adherence_InTrial_quality	This is intentionally vague; please complete the "PLEASE FILL supplementary info" sheet so that I understand what was entered here.	(See description)
SABA_actuations_ per_day_average_PreTrial	SABA average actuations per day pre-trial (either self-reported or during run-in period)	
SABA_prescribed__ 0no_1yes	SABA on medication profile during conduct of the trial	
SABA_actuations_ per_day_average_InTrial	SABA average actuations per day during trial (either self-reported or during run-in period)	
Any_ICS_ prescribed_0no_1yes	Any ICS on medication profile during conduct of the trial	
ICS_TYPE	ICS type during conduct of the trial.	See right table. If multiple ICS inhalers, please only include the main one
ICS_Dose_ PER_DAY	Total daily dosing of ICS during conduct of the trial	If on multiple ICS inhalers, please correct the total ICS dosage to include the overall total daily equidosing for specified inhaler type (see 'TABLE 4') -->
LABA_prescribed _0no_1yes	LABA on medication profile during conduct of the trial	Enter 0 (no) or 1 (yes)
LAMA_prescribed __0no_1yes	LAMA on medication profile during conduct of the trial	Enter 0 (no) or 1 (yes)
maintenance_OCS_ prescribed__0no_1yes	Maintenance oral glucocorticosteroids on medication profile at baseline	Enter 0 (no) or 1 (yes)
Mainteance_OCS_dose	Maintenance oral glucocorticosteroids daily average dose on medication profile at baseline	Enter 0 (if none) or (daily dose)
Montelukast_prescribed __0no_1yes	Montelukast on medication profile during conduct of the trial	Enter 0 (no) or 1 (yes)
Theophylline_prescribed __0no_1yes	Theophylline on medication profile during conduct of the trial	Enter 0 (no) or 1 (yes)
Intranasal_seroid_prescribed __0no_1yes	Intransal steroids prescribed on medication profile during conduct of the trial	Enter 0 (no) or 1 (yes) or 9999 (unknown)
FEV1_predicted_L	FEV_1 predicted value (in litres)	
FVC_predicted_L	FVC predicted value (in litres)	

FEV1_preBD_L _Baseline	FEV_1 pre bronchodilator value at baseline (in litres)	
FEV1_preBD_PCT _Baseline	FEV_1 pre bronchodilator value at baseline (in PCT predicted)	
FVC_preBD_L _Baseline	FVC pre bronchodilator value at baseline (in litres)	
FVC_preBD_PCT _Baseline	FVC pre bronchodilator value at baseline (in PCT predicted)	
FEV1_postBD_L _Baseline	FEV_1 post bronchodilator value at baseline (in litres)	
FEV1_postBD_PCT _Baseline	FEV_1 post bronchodilator value at baseline (in PCT predicted)	
FVC_postBD_L _Baseline	FVC post bronchodilator value at baseline (in litres)	
FVC_postBD_PCT _Baseline	FVC post bronchodilator value at baseline (in PCT predicted)	
FEV1_PCT_ reversibility_postBD	change in FEV_1 post-bronchodilator (calculated as (FEV_1 post BD minus FEV_1 preBD in litres) divided by FEV_1 preBD in litres): if not measured at baseline, can be historical within 12 months	
ACQ_baseline_score_mean	Mean baseline score for the ACQ used during trial; please complete the "PLEASE FILL supplementary info" sheet so that I understand which score was entered here	ACQ 5
ACQ_score_items1-7	If possible, segment the items of the ACQ score (as different trials used diffent versions)	
ACT_baseline_score	Baseline ACT score (if completed)	
Blood_Eos_baseline_ x10_9_cells_per_L	Mandatory entry. Baseline blood eosinophil count ($x10^9$ cells/L)	
FeNO_baseline_ppb	Mandatory entry. Baseline FeNO value (ppb)	
Total_IgE	Total IgE (in IU/mL)	
Follow_up_duration_days	Mandatory entry. Days of follow-up while patient under treatment arm	
Number_severe_asthma_ attacks_during_followup	Mandatory entry. Severe asthma attacks are defined as acute asthma requiring ≥3 days of systemic corticosteroid therapy.	
End-FollowUp_Reason	End of follow-up reason. 0, follow-up period completed. 1, lost to follow-up. 2, withdrawal from study. 3. death. 4. other	

TABLE S2. Modified treatment step definitions for this study

Treatment step	Definition
Step 1	As-needed short-acting beta2-agonist
Step 2	Daily low dose ICS or As-needed low dose inhaled corticosteroid (ICS)-formoterol Daily leukotriene receptor agonist
Step 3	Daily low dose ICS + an additional controller therapy
Step 4	Any medium dose ICS-containing regimen
Step 5	Any high dose ICS-containing regimen or Any maintenance systemic corticosteroid use (defined as use of systemic corticosteroids for ≥50% of the previous year)

Modified from GINA 2017 and 2023 (Global Initiative for Asthma (GINA), 2023) guidelines.

TABLE S3. Low, medium and high daily metered doses of inhaled corticosteroids in adults and adolescents (12 years and older)

Inhaled corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate CFC-propellent MDI	200-500	>500-1000	>1000
Beclomethasone dipropionate extrafine particle MDI or DPI	100-200	>200-400	>400
Budesonide	200-400	>400-800	>800
Fluticasone dipropionate	100-250	>250-500	>500
Fluticasone furoate	100	100	200
Ciclesonide	80-160	>160-320	>320
Mometasone furoate	200-400	200-400	>400

Adapted from (Global Initiative for Asthma (GINA), 2023). CFC, chlorofluorocarbon; DPI, dry powder inhaler; MDI, multidose inhaler.

TABLE S4. Reports reviewed for eligibility, source, and reason for exclusion

#	Report	Source	Exclusion reason
1	A. Basu; A. Dalal; G. W. Canonica; M. Forshag; S. W. Yancey; S. Nagar; C. F. Bell (2017) Economic analysis of the phase III MENSA study evaluating mepolizumab for severe asthma with eosinophilic phenotype.Expert Rev Pharmacoecon Outcomes Res.10.1080/14737167.2017.1298444	PubMed (NLM)	Irrelevant post-hoc analysis
2	A. C. Pinto Bezerra Soter; T. F. Bezerra; R. Pezato; T. R. Teles Abdo; R. M. Pilan; F. R. Pinna; P. Gevaert; T. van Zele; C. Bachert; R. L. Voegels (2017) Prospective open-label evaluation of long-term low-dose doxycycline for difficult-to-treat chronic rhinosinusitis with nasal polyps.Rhinology.10.4193/Rhin15.291	PubMed (NLM)	study population not outpatient asthma
3	A. D. Smith; J. O. Cowan; K. P. Brassett; G. P. Herbison; D. R. Taylor (2005) Use of exhaled nitric oxide measurements to guide treatment in chronic asthma.N Engl J Med.10.1056/NEJMoa043596	PubMed (NLM)	Not a RCT with fixed treatment control arm
4	A. Di Franco; E. Bacci; M. L. Bartoli; S. Cianchetti; F. L. Dente; M. Taccola; B. Vagaggini; M. Zingoni; P. L. Paggiaro (2006) Inhaled fluticasone propionate is effective as well as oral prednisone in reducing sputum eosinophilia during exacerbations of asthma which do not require hospitalization.Pulm Pharmacol Ther.10.1016/j.pupt.2005.09.003	PubMed (NLM)	Duration < 24 weeks
5	A. França-Pinto; F. A. Mendes; R. M. de Carvalho-Pinto; R. C. Agondi; A. Cukier; R. Stelmach; B. M. Saraiva-Romanholo; J. Kalil; M. A. Martins; P. Giavina-Bianchi; C. R. Carvalho (2015) Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial.Thorax.10.1136/thoraxjnl-2014-206070	PubMed (NLM)	Duration < 24 weeks
6	A. G. Ayars; L. C. Altman; S. Potter-Perigo; K. Radford; T. N. Wight; P. Nair (2013) Sputum hyaluronan and versican in severe eosinophilic asthma.Int Arch Allergy Immunol.10.1159/000343031	PubMed (NLM)	Not a RCT with fixed treatment control arm
7	A. L. Voskamp; A. Gillman; K. Symons; A. Sandrini; J. M. Rolland; R. E. O'Hehir; J. A. Douglass (2015) Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis.J Allergy Clin Immunol Pract.10.1016/j.jaip.2014.12.008	PubMed (NLM)	study population not outpatient asthma
8	A. M. Salem; A. O. Bamosa; H. O. Qutub; R. K. Gupta; A. Badar; A. Elnour; M. N. Afzal (2017) Effect of Nigella sativa supplementation on lung function and inflammatory mediatorsin partly controlled asthma: a randomized controlled trial.Ann Saudi Med.10.5144/0256-4947.2017.64	PubMed (NLM)	Duration < 24 weeks
9	A. M. Zandsteeg; P. Hirmann; H. R. Pasma; J. P. Yska; A. ten Brinke (2009) Effect of $MgSO_4$ on FEV_1 in stable severe asthma patients with chronic airflow limitation.Magnes Res.10.1684/mrh.2009.0184	PubMed (NLM)	Not a RCT with fixed treatment control arm
10	A. P. Baptist; W. Hao; P. X. Song; L. Carpenter; J. Steinberg; L. J. Cardozo (2020) A behavioral intervention can decrease asthma exacerbations in older adults.Ann Allergy Asthma Immunol.10.1016/j.anai.2019.12.015	PubMed (NLM)	Not a RCT with fixed treatment control arm
11	A. P. Pietropaoli; M. W. Frampton; R. W. Hyde; P. E. Morrow; G. Oberdörster; C. Cox; D. M. Speers; L. M. Frasier; D. C. Chalupa; L. S. Huang; M. J. Utell (2004) Pulmonary function, diffusing capacity, and inflammation in healthy and asthmatic subjects exposed to ultrafine particles.Inhal Toxicol.10.1080/08958370490443079	PubMed (NLM)	Not a RCT with fixed treatment control arm
12	A. Papi; D. Dokic; W. Tzimas; I. Mészáros; A. Olech-Cudzik; Z. Koroknai; K. McAulay; S. Mersmann; P. S. Dalvi; T. Overend (2017) Fluticasone propionate/formoterol for COPD management: a randomized controlled trial.Int J Chron Obstruct Pulmon Dis.10.2147/copd.S136527	PubMed (NLM)	study population not outpatient asthma
13	A. R. Martineau; B. D. MacLaughlin; R. L. Hooper; N. C. Barnes; D. A. Jolliffe; C. L. Greiller; K. Kilpin; D. McLaughlin; G. Fletcher; C. A. Mein; M. Hoti; R. Walton; J. Grigg; P. M. Timms; R. K. Rajakulasingam; A. Bhowmik; M. Rowe; T. R. Venton; A. B. Choudhury; D. E. Simcock; Z. Sadique; W. R. Monteiro; C. J. Corrigan; C. M. Hawrylowicz; C. J. Griffiths (2015) Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs).Thorax.10.1136/thoraxjnl-2014-206449	PubMed (NLM)	No baseline blood eosinophil AND FeNO
14	A. Wallin; M. Sue-Chu; L. Bjermer; J. Ward; T. Sandström; A. Lindberg; B. Lundbäck; R. Djukanović; S. Holgate; S. Wilson (2003) Effect of inhaled	PubMed (NLM)	Duration < 24 weeks

	fluticasone with and without salmeterol on airway inflammation in asthma.J Allergy Clin Immunol.10.1067/mai.2003.1518		
15	B. E. Chipps; I. Hirsch; F. Trudo; M. Alacqua; J. G. Zangrilli (2020) Benralizumab efficacy for patients with fixed airflow obstruction and severe, uncontrolled eosinophilic asthma.Ann Allergy Asthma Immunol.10.1016/j.anai.2019.10.006	PubMed (NLM)	Irrelevant post-hoc analysis
16	B. E. Chipps; P. Newbold; I. Hirsch; F. Trudo; M. Goldman (2018) Benralizumab efficacy by atopy status and serum immunoglobulin E for patients with severe, uncontrolled asthma.Ann Allergy Asthma Immunol.10.1016/j.anai.2018.01.030	PubMed (NLM)	Irrelevant post-hoc analysis
17	B. J. Lipworth; P. M. Short; P. A. Williamson; K. L. Clearie; T. C. Fardon; C. M. Jackson (2012) A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial.Chest.10.1378/chest.11-1748	PubMed (NLM)	Not a RCT with fixed treatment control arm
18	B. S. Berthon; P. G. Gibson; P. McElduff; L. K. MacDonald-Wicks; L. G. Wood (2015) Effects of short-term oral corticosteroid intake on dietary intake, body weight and body composition in adults with asthma - a randomized controlled trial.Clin Exp Allergy.10.1111/cea.12505	PubMed (NLM)	Duration < 24 weeks
19	B. Vagaggini; M. Taccola; S. Cianchetti; S. Carnevali; M. L. Bartoli; E. Bacci; F. L. Dente; A. Di Franco; D. Giannini; P. L. Paggiaro (2002) Ozone exposure increases eosinophilic airway response induced by previous allergen challenge.Am J Respir Crit Care Med.10.1164/rccm.2201013	PubMed (NLM)	Not a RCT with fixed treatment control arm
20	C. A. Sorkness; J. J. Wildfire; A. Calatroni; H. E. Mitchell; W. W. Busse; G. T. O'Connor; J. A. Pongracic; K. Ross; M. A. Gill; M. Kattan; W. J. Morgan; S. J. Teach; P. J. Gergen; A. H. Liu; S. J. Szefler (2013) Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents.J Allergy Clin Immunol Pract.10.1016/j.jaip.2013.01.011	PubMed (NLM)	Not a RCT with fixed treatment control arm
21	C. M. Kercsmar; D. G. Dearborn; M. Schluchter; L. Xue; H. L. Kirchner; J. Sobolewski; S. J. Greenberg; S. J. Vesper; T. Allan (2006) Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources.Environ Health Perspect.10.1289/ehp.8742	PubMed (NLM)	Not a RCT with fixed treatment control arm
22	C. M. Prazma; S. Wenzel; N. Barnes; J. A. Douglass; B. F. Hartley; H. Ortega (2014) Characterisation of an OCS-dependent severe asthma population treated with mepolizumab.Thorax.10.1136/thoraxjnl-2014-205581	PubMed (NLM)	Irrelevant post-hoc analysis
23	D. B. Peden; R. W. Setzer, Jr.; R. B. Devlin (1995) Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics.Am J Respir Crit Care Med.10.1164/ajrccm.151.5.7735583	PubMed (NLM)	Not a RCT with fixed treatment control arm
24	D. B. Price; D. Hernandez; P. Magyar; J. Fiterman; K. M. Beeh; I. G. James; S. Konstantopoulos; R. Rojas; J. A. van Noord; M. Pons; L. Gilles; J. A. Leff (2003) Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma.Thorax.10.1136/thorax.58.3.211	PubMed (NLM)	Duration < 24 weeks
25	D. E. Shaw; M. A. Berry; M. Thomas; R. H. Green; C. E. Brightling; A. J. Wardlaw; I. D. Pavord (2007) The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial.Am J Respir Crit Care Med.10.1164/rccm.200610-1427OC	PubMed (NLM)	Not a RCT with fixed treatment control arm
26	D. Hodgson; J. Anderson; C. Reynolds; G. Meakin; H. Bailey; I. Pavord; D. Shaw; T. Harrison (2015) A randomised controlled trial of small particle inhaled steroids in refractory eosinophilic asthma (SPIRA).Thorax.10.1136/thoraxjnl-2014-206481	PubMed (NLM)	Not a RCT with fixed treatment control arm
27	D. J. Jackson; M. Humbert; I. Hirsch; P. Newbold; E. Garcia Gil (2020) Ability of Serum IgE Concentration to Predict Exacerbation Risk and Benralizumab Efficacy for Patients with Severe Eosinophilic Asthma.Adv Ther.10.1007/s12325-019-01191-2	PubMed (NLM)	Irrelevant post-hoc analysis
28	D. K. Lee; C. M. Jackson; K. Haggart; B. J. Lipworth (2004) Repeated dosing effects of mediator antagonists in inhaled corticosteroid-treated atopic asthmatic patients.Chest.10.1378/chest.125.4.1372	PubMed (NLM)	Duration < 24 weeks
29	D. K. Lee; K. Haggart; G. P. Currie; C. E. Bates; B. J. Lipworth (2004) Effects of hydrofluoroalkane formulations of ciclesonide 400 microg once daily vs fluticasone 250 microg twice daily on methacholine hyper-responsiveness in mild-to-moderate persistent asthma.Br J Clin Pharmacol.10.1111/j.1365-2125.2004.02108.x	PubMed (NLM)	Duration < 24 weeks

30	D. K. Lee; R. D. Gray; A. M. Wilson; F. M. Robb; P. C. Soutar; B. J. Lipworth (2004) Single and short-term dosing effects of levocetirizine on adenosine monophosphate bronchoprovocation in atopic asthma.Br J Clin Pharmacol.10.1111/j.1365-2125.2004.02110.x	PubMed (NLM)	Duration < 24 weeks
31	D. Ledford; W. Busse; B. Trzaskoma; T. A. Omachi; K. Rosén; B. E. Chipps; A. T. Luskin; P. G. Solari (2017) A randomized multicenter study evaluating Xolair persistence of response after long-term therapy.J Allergy Clin Immunol.10.1016/j.jaci.2016.08.054	PubMed (NLM)	Not a RCT with fixed treatment control arm
32	D. R. Taylor; G. I. Town; G. P. Herbison; D. Boothman-Burrell; E. M. Flannery; B. Hancox; E. Harré; K. Laubscher; V. Linscott; C. M. Ramsay; G. Richards (1998) Asthma control during long-term treatment with regular inhaled salbutamol and salmeterol.Thorax.10.1136/thx.53.9.744	PubMed (NLM)	No baseline blood eosinophil AND FeNO
33	D. R. Taylor; M. R. Sears; G. P. Herbison; E. M. Flannery; C. G. Print; D. C. Lake; D. M. Yates; M. K. Lucas; Q. Li (1993) Regular inhaled beta agonist in asthma: effects on exacerbations and lung function.Thorax.10.1136/thx.48.2.134	PubMed (NLM)	No baseline blood eosinophil AND FeNO
34	E. A. Pawlak; T. L. Noah; H. Zhou; C. Chehrazi; C. Robinette; D. Diaz-Sanchez; L. Müller; I. Jaspers (2016) Diesel exposure suppresses natural killer cell function and resolution of eosinophil inflammation: a randomized controlled trial of exposure in allergic rhinitics.Part Fibre Toxicol.10.1186/s12989-016-0135-7	PubMed (NLM)	study population not outpatient asthma
35	E. Bacci; M. Latorre; S. Cianchetti; M. Bartoli; F. Costa; A. Di Franco; L. Malagrinò; F. Novelli; B. Vagaggini; F. L. Dente; P. Paggiaro (2012) Transient sputum eosinophilia may occur over time in non-eosinophilic asthma and this is not prevented by salmeterol.Respirology.10.1111/j.1440-1843.2012.02242.x	PubMed (NLM)	Not a RCT with fixed treatment control arm
36	E. Bathoorn; D. J. Slebos; D. S. Postma; G. H. Koeter; A. J. van Oosterhout; M. van der Toorn; H. M. Boezen; H. A. Kerstjens (2007) Anti-inflammatory effects of inhaled carbon monoxide in patients with COPD: a pilot study.Eur Respir J.10.1183/09031936.00163206	PubMed (NLM)	study population not outpatient asthma
37	E. Bathoorn; J. J. Liesker; D. S. Postma; M. Boorsma; E. Bondesson; G. H. Koëter; H. F. Kauffman; A. J. van Oosterhout; H. A. Kerstjens (2008) Anti-inflammatory effects of combined budesonide/formoterol in COPD exacerbations.Copd.10.1080/15412550802363360	PubMed (NLM)	study population not outpatient asthma
38	E. C. Matsui; H. A. Sampson; H. T. Bahnson; R. S. Gruchalla; J. A. Pongracic; S. J. Teach; P. J. Gergen; G. R. Bloomberg; J. F. Chmiel; A. H. Liu; M. Kattan; C. A. Sorkness; S. F. Steinbach; R. E. Story; C. M. Visness (2010) Allergen-specific IgE as a biomarker of exposure plus sensitization in inner-city adolescents with asthma.Allergy.10.1111/j.1398-9995.2010.02412.x	PubMed (NLM)	Not a RCT with fixed treatment control arm
39	E. Forno; T. Wang; Q. Yan; J. Brehm; E. Acosta-Perez; A. Colon-Semidey; M. Alvarez; N. Boutaoui; M. M. Cloutier; J. F. Alcorn; G. Canino; W. Chen; J. C. Celedón (2017) A Multiomics Approach to Identify Genes Associated with Childhood Asthma Risk and Morbidity.Am J Respir Cell Mol Biol.10.1165/rcmb.2017-0002OC	PubMed (NLM)	Not a RCT with fixed treatment control arm
40	E. H. Bel; S. E. Wenzel; P. J. Thompson; C. M. Prazma; O. N. Keene; S. W. Yancey; H. G. Ortega; I. D. Pavord (2014) Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.N Engl J Med.10.1056/NEJMoa1403291	PubMed (NLM)	Not a RCT with fixed treatment control arm
41	E. H. De Boever; C. Ashman; A. P. Cahn; N. W. Locantore; P. Overend; I. J. Pouliquen; A. P. Serone; T. J. Wright; M. M. Jenkins; I. S. Panesar; S. S. Thiagarajah; S. E. Wenzel (2014) Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial.J Allergy Clin Immunol.10.1016/j.jaci.2014.01.002	PubMed (NLM)	Duration < 24 weeks
42	E. J. Peirsman; T. J. Carvelli; P. Y. Hage; L. S. Hanssens; L. Pattyn; M. M. Raes; K. A. Sauer; F. Vermeulen; K. N. Desager (2014) Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial.Pediatr Pulmonol.10.1002/ppul.22873	PubMed (NLM)	Not a RCT with fixed treatment control arm
43	E. M. Erin; B. R. Leaker; G. C. Nicholson; A. J. Tan; L. M. Green; H. Neighbour; A. S. Zacharasiewicz; J. Turner; E. S. Barnathan; O. M. Kon; P. J. Barnes; T. T. Hansel (2006) The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma.Am J Respir Crit Care Med.10.1164/rccm.200601-072OC	PubMed (NLM)	Duration < 24 weeks

44	E. R. Bleecker; J. M. FitzGerald; P. Chanez; A. Papi; S. F. Weinstein; P. Barker; S. Sproule; G. Gilmartin; M. Aurivillius; V. Werkström; M. Goldman (2016) Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β(2)-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial.Lancet.10.1016/s0140-6736(16)31324-1	PubMed (NLM)	No baseline blood eosinophil AND FeNO
45	E. R. Bleecker; M. E. Wechsler; J. M. FitzGerald; A. Menzies-Gow; Y. Wu; I. Hirsch; M. Goldman; P. Newbold; J. G. Zangrilli (2018) Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma.Eur Respir J.10.1183/13993003.00936-2018	PubMed (NLM)	Irrelevant post-hoc analysis
46	F. A. Mendes; F. M. Almeida; A. Cukier; R. Stelmach; W. Jacob-Filho; M. A. Martins; C. R. Carvalho (2011) Effects of aerobic training on airway inflammation in asthmatic patients.Med Sci Sports Exerc.10.1249/MSS.0b013e3181ed0ea3	PubMed (NLM)	Duration < 24 weeks
47	F. C. Albers; A. Papi; C. Taillé; D. J. Bratton; E. S. Bradford; S. W. Yancey; N. Kwon (2019) Mepolizumab reduces exacerbations in patients with severe eosinophilic asthma, irrespective of body weight/body mass index: meta-analysis of MENSA and MUSCA.Respir Res.10.1186/s12931-019-1134-7	PubMed (NLM)	Irrelevant post-hoc analysis
48	G. Chupp; N. L. Lugogo; J. N. Kline; G. T. Ferguson; I. Hirsch; M. Goldman; J. G. Zangrilli; F. Trudo (2019) Rapid onset of effect of benralizumab on morning peak expiratory flow in severe, uncontrolled asthma.Ann Allergy Asthma Immunol.10.1016/j.anai.2019.02.016	PubMed (NLM)	Irrelevant post-hoc analysis
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54	H. A. Boushey; C. A. Sorkness; T. S. King; S. D. Sullivan; J. V. Fahy; S. C. Lazarus; V. M. Chinchilli; T. J. Craig; E. A. Dimango; A. Deykin; J. K. Fagan; J. E. Fish; J. G. Ford; M. Kraft; R. F. Lemanske, Jr.; F. T. Leone; R. J. Martin; E. A. Mauger; G. R. Pesola; S. P. Peters; N. J. Rollings; S. J. Szefler; M. E. Wechsler; E. Israel (2005) Daily versus as-needed corticosteroids for mild persistent asthma.N Engl J Med.10.1056/NEJMoa042552	PubMed (NLM)	No baseline blood eosinophil AND FeNO
55	H. G. Ortega; M. C. Liu; I. D. Pavord; G. G. Brusselle; J. M. FitzGerald; A. Chetta; M. Humbert; L. E. Katz; O. N. Keene; S. W. Yancey; P. Chanez (2014) Mepolizumab treatment in patients with severe eosinophilic asthma.N Engl J Med.10.1056/NEJMoa1403290	PubMed (NLM)	No baseline blood eosinophil AND FeNO
56	H. G. Ortega; S. W. Yancey; B. Mayer; N. B. Gunsoy; O. N. Keene; E. R. Bleecker; C. E. Brightling; I. D. Pavord (2016) Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies.Lancet Respir Med.10.1016/s2213-2600(16)30031-5	PubMed (NLM)	Irrelevant post-hoc analysis
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84	J. de Kluijver; C. E. Evertse; J. K. Sont; J. A. Schrumpf; C. J. van Zeijl-van der Ham; C. R. Dick; K. F. Rabe; P. S. Hiemstra; P. J. Sterk (2003) Are rhinovirus-induced airway responses in asthma aggravated by chronic allergen exposure?.Am J Respir Crit Care Med.10.1164/rccm.200212-1520OC	PubMed (NLM)	Not a RCT with fixed treatment control arm
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98	K. Maneechotesuwan; J. Assawabhumi; K. Rattanasaengloet; T. Suthamsmai; S. Pipopsuthipaiboon; S. Udompunturak (2014) Comparison between the effects of generic and original salmeterol/fluticasone combination (SFC) treatment on airway inflammation in stable asthmatic patients.J Med Assoc Thai.	PubMed (NLM)	Duration < 24 weeks
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103	K. Pike; A. Selby; S. Price; J. Warner; G. Connett; J. Legg; J. S. Lucas; S. Peters; H. Buckley; K. Magier; K. Foote; K. Drew; R. Morris; N. Lancaster; G. Roberts (2013) Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial.Clin Respir J.10.1111/j.1752-699X.2012.00306.x	PubMed (NLM)	Not a RCT with fixed treatment control arm
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109	L. G. Heaney; J. Busby; C. E. Hanratty; R. Djukanovic; A. Woodcock; S. M. Walker; T. C. Hardman; J. R. Arron; D. F. Choy; P. Bradding; C. E. Brightling; R. Chaudhuri; D. C. Cowan; A. H. Mansur; S. J. Fowler; R. M. Niven; P. H. Howarth; J. L. Lordan; A. Menzies-Gow; T. W. Harrison; D. S. Robinson; C. T. J. Holweg; J. G. Matthews; I. D. Pavord (2021) Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial.Lancet Respir Med.10.1016/s2213-2600(20)30397-0	PubMed (NLM)	Not a RCT with fixed treatment control arm
110	L. J. Meltzer; A. Faino; S. J. Szefler; M. Strand; E. W. Gelfand; D. W. Beebe (2015) Experimentally manipulated sleep duration in adolescents with asthma: Feasibility and preliminary findings.Pediatr Pulmonol.10.1002/ppul.23179	PubMed (NLM)	Not a RCT with fixed treatment control arm
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112	L. M. Nelsen; M. Vernon; H. Ortega; S. M. Cockle; S. W. Yancey; G. Brusselle; F. C. Albers; P. W. Jones (2017) Evaluation of the psychometric properties of the St George's Respiratory Questionnaire in patients with severe asthma.Respir Med.10.1016/j.rmed.2017.04.015	PubMed (NLM)	study population not outpatient asthma
113	L. Mitchiguian Hotta; U. Cardinalli Adler; A. de Toledo Cesar; E. Z. Martinez; M. M. P. Demarzo (2018) Homeopathy for Perennial Asthma in Adolescents: Pilot Feasibility Study Testing a Randomised Withdrawal Design.Homeopathy.10.1055/s-0038-1637009	PubMed (NLM)	Not a RCT with fixed treatment control arm
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117	M. Bafadhel; S. Peterson; M. A. De Blas; P. M. Calverley; S. I. Rennard; K. Richter; M. Fagerås (2018) Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials.Lancet Respir Med.10.1016/s2213-2600(18)30006-7	PubMed (NLM)	study population not outpatient asthma
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120	M. Castro; J. Zangrilli; M. E. Wechsler; E. D. Bateman; G. G. Brusselle; P. Bardin; K. Murphy; J. F. Maspero; C. O'Brien; S. Korn (2015) Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials.Lancet Respir Med.10.1016/s2213-2600(15)00042-9	PubMed (NLM)	No baseline blood eosinophil AND FeNO
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133	M. M. Kelly; T. M. O'Connor; R. Leigh; J. Otis; C. Gwozd; G. M. Gauvreau; J. Gauldie; P. M. O'Byrne (2010) Effects of budesonide and formoterol on allergen-induced airway responses, inflammation, and airway remodeling in asthma.J Allergy Clin Immunol.10.1016/j.jaci.2009.09.011	PubMed (NLM)	Not a RCT with fixed treatment control arm
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137	M. W. Pijnenburg; E. M. Bakker; W. C. Hop; J. C. De Jongste (2005) Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial.Am J Respir Crit Care Med.10.1164/rccm.200503-458OC	PubMed (NLM)	Not a RCT with fixed treatment control arm
138	N. A. Molfino; P. Kuna; J. A. Leff; C. K. Oh; D. Singh; M. Chernow; B. Sutton; G. Yarranton (2016) Phase 2, randomised placebo-controlled trial to evaluate the efficacy and safety of an anti-GM-CSF antibody (KB003) in patients with inadequately controlled asthma.BMJ Open.10.1136/bmjopen-2015-007709	PubMed (NLM)	Duration < 24 weeks
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141	N. Lazarinis; J. Bood; C. Gomez; J. Kolmert; A. S. Lantz; P. Gyllfors; A. Davis; C. E. Wheelock; S. E. Dahlén; B. Dahlén (2018) Leukotriene E(4) induces airflow obstruction and mast cell activation through the cysteinyl leukotriene type 1 receptor.J Allergy Clin Immunol.10.1016/j.jaci.2018.02.024	PubMed (NLM)	Duration < 24 weeks
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147	P. Flood-Page; C. Swenson; I. Faiferman; J. Matthews; M. Williams; L. Brannick; D. Robinson; S. Wenzel; W. Busse; T. T. Hansel; N. C. Barnes (2007) A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma.Am J Respir Crit Care Med.10.1164/rccm.200701-085OC	PubMed (NLM)	Duration < 24 weeks
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153	P. Nair; M. M. Pizzichini; M. Kjarsgaard; M. D. Inman; A. Efthimiadis; E. Pizzichini; F. E. Hargreave; P. M. O'Byrne (2009) Mepolizumab for prednisone-dependent asthma with sputum eosinophilia.N Engl J Med.10.1056/NEJMoa0805435	PubMed (NLM)	Not a RCT with fixed treatment control arm
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155	P. W. Heymann; T. A. E. Platts-Mills; J. A. Woodfolk; L. Borish; D. D. Murphy; H. T. Carper; M. R. Conaway; J. W. Steinke; L. Muehling; W. Gerald Teague; J. L. Kennedy; A. M. Irani; M. D. McGraw; S. V. Early; L. M. Wheatley; A. P. Adams; R. B. Turner (2020) Understanding the asthmatic response to an experimental rhinovirus infection: Exploring the effects of blocking IgE.J Allergy Clin Immunol.10.1016/j.jaci.2020.01.035	PubMed (NLM)	Not a RCT with fixed treatment control arm
156	R. A. McIvor; E. Pizzichini; M. O. Turner; P. Hussack; F. E. Hargreave; M. R. Sears (1998) Potential masking effects of salmeterol on airway inflammation in asthma.Am J Respir Crit Care Med.10.1164/ajrccm.158.3.9802069	PubMed (NLM)	Not a RCT with fixed treatment control arm
157	R. Djukanović; S. J. Wilson; M. Kraft; N. N. Jarjour; M. Steel; K. F. Chung; W. Bao; A. Fowler-Taylor; J. Matthews; W. W. Busse; S. T. Holgate; J. V. Fahy (2004) Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma.Am J Respir Crit Care Med.10.1164/rccm.200312-1651OC	PubMed (NLM)	Duration < 24 weeks
158	R. H. Green; C. E. Brightling; S. McKenna; B. Hargadon; D. Parker; P. Bradding; A. J. Wardlaw; I. D. Pavord (2002) Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial.Lancet.10.1016/s0140-6736(02)11679-5	PubMed (NLM)	Not a RCT with fixed treatment control arm
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	J. K. Sont; G. Ter Riet (2016) Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable prediction model.Thorax.10.1136/thoraxjnl-2015-208138		
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162	R. S. Gruchalla; H. A. Sampson; E. Matsui; G. David; P. J. Gergen; A. Calatroni; M. Brown; A. H. Liu; G. R. Bloomberg; J. F. Chmiel; R. Kumar; C. Lamm; E. Smartt; C. A. Sorkness; S. F. Steinbach; K. D. Stone; S. J. Szefler; W. W. Busse (2009) Asthma morbidity among inner-city adolescents receiving guidelines-based therapy: role of predictors in the setting of high adherence.J Allergy Clin Immunol.10.1016/j.jaci.2009.05.036	PubMed (NLM)	Not a RCT with fixed treatment control arm
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164	S. C. Lazarus; H. A. Boushey; J. V. Fahy; V. M. Chinchilli; R. F. Lemanske, Jr.; C. A. Sorkness; M. Kraft; J. E. Fish; S. P. Peters; T. Craig; J. M. Drazen; J. G. Ford; E. Israel; R. J. Martin; E. A. Mauger; S. A. Nachman; J. D. Spahn; S. J. Szefler (2001) Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial.Jama.10.1001/jama.285.20.2583	PubMed (NLM)	No baseline blood eosinophil AND FeNO
165	S. F. Weinstein; R. K. Katial; P. Bardin; S. Korn; M. McDonald; M. Garin; E. D. Bateman; F. C. L. Hoyte; M. Germinaro (2019) Effects of Reslizumab on Asthma Outcomes in a Subgroup of Eosinophilic Asthma Patients with Self-Reported Chronic Rhinosinusitis with Nasal Polyps.J Allergy Clin Immunol Pract.10.1016/j.jaip.2018.08.021	PubMed (NLM)	No baseline blood eosinophil AND FeNO
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167	S. H. Lee; J. H. Lee; H. I. Yoon; H. Y. Park; T. H. Kim; K. H. Yoo; Y. M. Oh; K. S. Jung; S. D. Lee; S. W. Lee (2019) Change in inhaled corticosteroid treatment and COPD exacerbations: an analysis of real-world data from the KOLD/KOCOSS cohorts.Respir Res.10.1186/s12931-019-1029-7	PubMed (NLM)	study population not outpatient asthma
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169	S. Hashimoto; A. T. Brinke; A. C. Roldaan; I. H. van Veen; G. M. Möller; J. K. Sont; E. J. Weersink; J. S. van der Zee; G. J. Braunstahl; A. H. Zwinderman; P. J. Sterk; E. H. Bel (2011) Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial.Thorax.10.1136/thx.2010.153411	PubMed (NLM)	Not a RCT with fixed treatment control arm
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171	S. J. Ioannides; M. Williams; S. Jefferies; K. Perrin; M. Weatherall; R. Siebers; J. Crane; M. Patel; J. Travers; P. Shirtcliffe; R. Beasley (2014) Randomised placebo-controlled study of the effect of paracetamol on asthma severity in adults.BMJ Open.10.1136/bmjopen-2013-004324	PubMed (NLM)	Duration < 24 weeks
172	S. J. Szefler; C. Vogelberg; J. A. Bernstein; S. Goldstein; L. Mansfield; L. Zaremba-Pechmann; M. Engel; E. Hamelmann (2019) Tiotropium Is	PubMed (NLM)	No baseline blood eosinophil AND FeNO

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174	S. J. Szefler; R. J. Martin; T. S. King; H. A. Boushey; R. M. Cherniack; V. M. Chinchilli; T. J. Craig; M. Dolovich; J. M. Drazen; J. K. Fagan; J. V. Fahy; J. E. Fish; J. G. Ford; E. Israel; J. Kiley; M. Kraft; S. C. Lazarus; R. F. Lemanske, Jr.; E. Mauger; S. P. Peters; C. A. Sorkness (2002) Significant variability in response to inhaled corticosteroids for persistent asthma.J Allergy Clin Immunol.10.1067/mai.2002.122635	PubMed (NLM)	No baseline blood eosinophil AND FeNO
175	S. Khatri; W. Moore; P. G. Gibson; R. Leigh; A. Bourdin; J. Maspero; M. Barros; R. Buhl; P. Howarth; F. C. Albers; E. S. Bradford; M. Gilson; R. G. Price; S. W. Yancey; H. Ortega (2019) Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma.J Allergy Clin Immunol.10.1016/j.jaci.2018.09.033	PubMed (NLM)	Irrelevant post-hoc analysis
176	S. Pascoe; N. Barnes; G. Brusselle; C. Compton; G. J. Criner; M. T. Dransfield; D. M. G. Halpin; M. K. Han; B. Hartley; P. Lange; S. Lettis; D. A. Lipson; D. A. Lomas; F. J. Martinez; A. Papi; N. Roche; R. J. P. van der Valk; R. Wise; D. Singh (2019) Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial.Lancet Respir Med.10.1016/s2213-2600(19)30190-0	PubMed (NLM)	study population not outpatient asthma
177	S. Raeisi; A. Fakharian; F. Ghorbani; H. R. Jamaati; M. S. Mirenayat (2019) Value and Safety of High Flow Oxygenation in the Treatment of Inpatient Asthma: A Randomized, Double-blind, Pilot Study.Iran J Allergy Asthma Immunol.10.18502/ijaai.v18i6.2174	PubMed (NLM)	study population not outpatient asthma
178	S. Suissa; S. Dell'Aniello; P. Ernst (2018) Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study.Lancet Respir Med.10.1016/s2213-2600(18)30368-0	PubMed (NLM)	study population not outpatient asthma
179	S. Wenzel; L. Ford; D. Pearlman; S. Spector; L. Sher; F. Skobieranda; L. Wang; S. Kirkesseli; R. Rocklin; B. Bock; J. Hamilton; J. E. Ming; A. Radin; N. Stahl; G. D. Yancopoulos; N. Graham; G. Pirozzi (2013) Dupilumab in persistent asthma with elevated eosinophil levels.N Engl J Med.10.1056/NEJMoa1304048	PubMed (NLM)	Not a RCT with fixed treatment control arm
180	T. B. Casale; E. D. Bateman; M. Vandewalker; J. C. Virchow; H. Schmidt; M. Engel; P. Moroni-Zentgraf; H. A. M. Kerstjens (2018) Tiotropium Respimat Add-on Is Efficacious in Symptomatic Asthma, Independent of T2 Phenotype.J Allergy Clin Immunol Pract.10.1016/j.jaip.2017.08.037	PubMed (NLM)	No baseline blood eosinophil AND FeNO
181	T. F. Reiss; P. Chervinsky; R. J. Dockhorn; S. Shingo; B. Seidenberg; T. B. Edwards (1998) Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group.Arch Intern Med.10.1001/archinte.158.11.1213	PubMed (NLM)	Duration < 24 weeks
182	T. Higaki; M. Okano; S. Makihara; T. Fujiwara; T. Haruna; Y. Noda; S. Kariya; K. Nishizaki (2012) Early interventional treatment with intranasal corticosteroids compared with postonset treatment in pollinosis.Ann Allergy Asthma Immunol.10.1016/j.anai.2012.08.016	PubMed (NLM)	study population not outpatient asthma
183	T. Horiguchi; R. Kondo; J. Miyazaki; K. Fukumokto; H. Torigoe (2004) Clinical evaluation of a transdermal therapeutic system of the beta2-agonist tulobuterol in patients with mild or moderate persistent bronchial asthma.Arzneimittelforschung.10.1055/s-0031-1296971	PubMed (NLM)	No baseline blood eosinophil AND FeNO
184	T. L. Staton; J. R. Arron; J. Olsson; C. T. J. Holweg; J. G. Matthews; D. F. Choy (2017) Seasonal variability of severe asthma exacerbations and clinical benefit from lebrikizumab.J Allergy Clin Immunol.10.1016/j.jaci.2017.01.028	PubMed (NLM)	No baseline blood eosinophil AND FeNO
185	T. L. Staton; K. Peng; R. Owen; D. F. Choy; C. R. Cabanski; A. Fong; F. Brunstein; K. R. Alatsis; H. Chen (2019) A phase I, randomized, observer-blinded, single and multiple ascending-dose study to investigate the safety,	PubMed (NLM)	Duration < 24 weeks

	pharmacokinetics, and immunogenicity of BITS7201A, a bispecific antibody targeting IL-13 and IL-17, in healthy volunteers.BMC Pulm Med.10.1186/s12890-018-0763-9		
186	T. Morphew; H. W. Shin; S. Marchese; N. Pires-Barracosa; S. P. Galant (2019) Phenotypes favoring fractional exhaled nitric oxide discordance vs guideline-based uncontrolled asthma.Ann Allergy Asthma Immunol.10.1016/j.anai.2019.05.008	PubMed (NLM)	Not a RCT with fixed treatment control arm
187	T. Ritz; C. A. Werchan; J. L. Kroll; D. Rosenfield (2019) Beetroot juice supplementation for the prevention of cold symptoms associated with stress: A proof-of-concept study.Physiol Behav.10.1016/j.physbeh.2019.01.015	PubMed (NLM)	study population not outpatient asthma
188	T. Shimoda; H. Odajima; A. Okamasa; M. Kawase; M. Komatsubara; B. Mayer; S. Yancey; H. Ortega (2017) Efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma.Allergol Int.10.1016/j.alit.2016.11.006	PubMed (NLM)	Irrelevant post-hoc analysis
189	T. W. Harrison; P. Chanez; F. Menzella; G. W. Canonica; R. Louis; B. G. Cosio; N. L. Lugogo; A. Mohan; A. Burden; L. McDermott; E. Garcia Gil; J. G. Zangrilli (2021) Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial.Lancet Respir Med.10.1016/s2213-2600(20)30414-8	PubMed (NLM)	No baseline blood eosinophil AND FeNO
190	V. E. Murphy; M. E. Jensen; J. Mattes; M. J. Hensley; W. B. Giles; M. J. Peek; A. Bisits; L. K. Callaway; K. McCaffery; H. L. Barrett; P. B. Colditz; S. K. Seeho; J. Attia; A. Searles; C. Doran; H. Powell; P. G. Gibson (2016) The Breathing for Life Trial: a randomised controlled trial of fractional exhaled nitric oxide (FENO)-based management of asthma during pregnancy and its impact on perinatal outcomes and infant and childhood respiratory health.BMC Pregnancy Childbirth.10.1186/s12884-016-0890-3	PubMed (NLM)	Not a RCT with fixed treatment control arm
191	V. Ezratty; M. Bonay; C. Neukirch; G. Orset-Guillossou; M. Dehoux; S. Koscielny; P. A. Cabanes; J. Lambrozo; M. Aubier (2007) Effect of formaldehyde on asthmatic response to inhaled allergen challenge.Environ Health Perspect.10.1289/ehp.9414	PubMed (NLM)	Not a RCT with fixed treatment control arm
192	V. Kalinauskaite-Zukauske; A. Januskevicius; I. Janulaityte; S. Miliauskas; K. Malakauskas (2019) Expression of eosinophil β chain-signaling cytokines receptors, outer-membrane integrins, and type 2 inflammation biomarkers in severe non-allergic eosinophilic asthma.BMC Pulm Med.10.1186/s12890-019-0904-9	PubMed (NLM)	Not a RCT with fixed treatment control arm
193	W. W. Busse; E. R. Bleecker; J. M. FitzGerald; G. T. Ferguson; P. Barker; S. Sproule; R. F. Olsson; U. J. Martin; M. Goldman (2019) Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial.Lancet Respir Med.10.1016/s2213-2600(18)30406-5	PubMed (NLM)	Irrelevant post-hoc analysis
194	W. W. Busse; J. F. Maspero; Y. Lu; J. Corren; N. A. Hanania; B. E. Chipps; C. H. Katelaris; J. M. FitzGerald; S. Quirce; L. B. Ford; M. S. Rice; S. Kamat; A. H. Khan; A. Jagerschmidt; S. Harel; P. Rowe; G. Pirozzi; N. Amin; M. Ruddy; N. M. H. Graham; A. Teper (2020) Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis.Ann Allergy Asthma Immunol.10.1016/j.anai.2020.05.026	PubMed (NLM)	Irrelevant post-hoc analysis
195	X. Puéchal; C. Pagnoux; G. Baron; T. Quémeneur; A. Néel; C. Agard; F. Lifermann; E. Liozon; M. Ruivard; P. Godmer; N. Limal; A. Mékinian; T. Papo; A. M. Ruppert; A. Bourgarit; B. Bienvenu; L. Geffray; J. L. Saraux; E. Diot; B. Crestani; X. Delbrel; L. Sailler; P. Cohen; V. Le Guern; B. Terrier; M. Groh; C. Le Jeunne; L. Mouthon; P. Ravaud; L. Guillevin (2017) Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.Arthritis Rheumatol.10.1002/art.40205	PubMed (NLM)	study population not outpatient asthma
196	X. Shi; D. J. Buysse; L. M. Ritterband; S. M. Sereika; P. J. Strollo; S. E. Wenzel; F. S. Luyster (2019) Solving insomnia electronically: Sleep treatment for asthma (SIESTA): A study protocol for a randomized controlled trial.Contemp Clin Trials.10.1016/j.cct.2019.02.011	PubMed (NLM)	Not a RCT with fixed treatment control arm

197	Y. L. Chia; L. Yan; B. Yu; B. Wang; P. Barker; M. Goldman; L. Roskos (2019) Relationship Between Benralizumab Exposure and Efficacy for Patients With Severe Eosinophilic Asthma.Clin Pharmacol Ther.10.1002/cpt.1371	PubMed (NLM)	Irrelevant post-hoc analysis
198	Y. S. Sabogal Piñeros; S. M. Bal; M. A. van de Pol; B. S. Dierdorp; T. Dekker; A. Dijkhuis; P. Brinkman; K. F. van der Sluijs; A. H. Zwinderman; C. J. Majoor; P. I. Bonta; L. Ravanetti; P. J. Sterk; R. Lutter (2019) Anti-IL-5 in Mild Asthma Alters Rhinovirus-induced Macrophage, B-Cell, and Neutrophil Responses (MATERIAL). A Placebo-controlled, Double-Blind Study.Am J Respir Crit Care Med.10.1164/rccm.201803-0461OC	PubMed (NLM)	Duration < 24 weeks
199	Y. S. Wasfi; C. Villarán; B. de Tilleghem Cle; S. S. Smugar; W. D. Hanley; T. F. Reiss; B. A. Knorr (2012) The efficacy and tolerability of MK-0633, a 5-lipoxygenase inhibitor, in chronic asthma.Respir Med.10.1016/j.rmed.2011.08.019	PubMed (NLM)	No baseline blood eosinophil AND FeNO
200	Z. Yildirim; T. Ozlu; Y. Bulbul; H. Bayram (2004) Addition of montelukast versus double dose of inhaled budesonide in moderate persistent asthma.Respirology.10.1111/j.1440-1843.2004.00555.x	PubMed (NLM)	No baseline blood eosinophil AND FeNO

TABLE S5. Recoding of new variables based on old variables if a predefined condition is met.

New variable	Old variable(s)	Condition
Age category*	Age	Age was categorized per 5 years (except the first category), From 0 < x <= 10 to 85 < x <= 90 years
Age continuous*	Age	Age continuous = Age, if Age = continuous value, other = NA
Age minimum	Age category	Minimal age of the corresponding category
Age maximum	Age category	Maximum age of the corresponding category
BMI category*	BMI	BMI was categorized per 5 kg/m^2, from 0 < x <= 19 to 40 < x kg/m^2
BMI continuous*	BMI	BMI continuous = BMI, if BMI = continuous value, other = NA
BMI minimum	BMI category	Minimal BMI of the corresponding category
BMI maximum	BMI category	Maximum BMI of the corresponding category
Pack years category*	Pack years	Pack years was categorised in three groups: 1) 0 cigarettes per day 2) <10 cigarettes per day 3) >=10 cigarettes per day
Pack years continuous*	Pack years; Smoking	Pack years continuous = Pack years, if Pack years = continuous value, other = NA; Pack years continuous = 0, if Smoking = non-smoker
Pack years minimum	Pack years category	Minimal Pack years of the corresponding category; 0.001 was the minimum for "<10 cigarettes per day"
Pack years maximum	Pack years category	Maximum Pack years of the corresponding category; 20 was the maximum for ">=10 cigarettes per day"
Any attack or hospitalisation in previous 12 months	Number of severe asthma attacks in previous 12 months; Number of hospitalisations in previous 12 months	Any attack or hospitalisation in previous 12 months = yes, if Number of severe asthma attacks in previous 12 months > 0 OR Number of hospitalisations in previous 12 months > 0
Region	Country	Region = Europe, if Country = Italy; United Kingdom; Belgium; Poland; Romania; Hungary; Czech Republic; Belarus; Ukraine; Spain; Slovakia; Russia; France; Serbia; Bulgaria; Germany; Netherlands; Latvia; Lithuania; Europe Region = Asia,

		if Country = Japan; Korea; Israel; Turkey; Vietnam; South Korea; Asia Region = North America if Country = United States; Canada; Mexico; North America Region = South America if Country = Argentina; Chile; Peru; Brazil; South America Region = Oceania if Country = Australia, New Zealand; Oceania Region = South Africa if Country = South Africa
Previous ICU or intubation	Previous ICU; previous intubation	Previous ICU or intubation = yes, if previous ICU OR previous intubation = yes
FEV_1 postbronchodilator reversibility	FEV_1 postbronchodilator reversibility	Enrolled trial = STRATOS 1 or STRATOS 2, FEV_1 postbronchodilator reversibility * 100 for percentages
Adherence in trial	Adherence in trial	Enrolled trial = CAPTIAN, Adherence in trial * 100 for percentages
Chronic rhinosinusitis with nasal polyposis (CRSwNP)	Chronic rhinosinusitis with history of nasal polyposis or nasal polypectomy	CRSwNP=Yes If Nasal_polyposis=Yes or Previous nasal polypectomy = Yes CRSwNP=No If Nasal polyposis=No and Previous nasal polypectomy =No
Chronic rhinosinusitis without nasal polyposis (CRSsNP)	Chronic rhinosinusitis without history of nasal polyposis or nasal polypectomy	CRSsNP= Yes If Chronic rhinosinusitis =Yes and CRSwNP=No CRSsNP= No If Chronic rhinosinusitis =No or CRSwNP=Yes

* We received variables Age, BMI and Pack years as continuous and categorical variables, depending on the trial. This was dealt with during the imputation process, as described in the Supplementary Initial Data Analysis section.

TABLE S6. Proportion of missing data in each study.

	AZISAST	BENRAP2B	CAPTAIN	COSTA	DREAM	DRI12544	EXTRA	LAVOLTA1	LAVOLTA2	LUSTER1	LUSTER2
N	*54*	*211*	*1218*	*145*	*155*	*155*	*420*	*362*	*354*	*298*	*287*
Age	0	0	0	0	0	0	0	0	0	0	0
Sex	0	0	0	0	0	0	0	0	0	0	0
Ethnicity	0	60.7	0	0	0	0	0	0	0	100	100
Region	0	0	0	0	0	100	0	0	0	100	100
BEC	0	0	2.5	0	0	0	5.7	0	0	0	0
FeNO	0	0	7.8	0	2.6	9.0	54.8	0.3	0.6	22.1	31.0
Total IgE	0	0	0.9	0	0	0.6	0.2	0	0	2.3	3.1
BMI	0	0	0	0	0	0	0.2	0	0	0	100
FEV_1%	0	0	0.8	0	0	0	0.7	0	0	4.0	3.5
FEV_1% reversibility	1.9	0.9	100	0	23.2	0	3.6	0	0	8.1	5.6
Previous ICU or intubation	0	0	100	0	0	100	0.2	0	0	100	100
Allergy testing positive	100	0	100	11.7	0	100	0.2	42.8	45.2	0	1.0
Eczema	100	0	100	0	100	100	0	0	0	100	100
Allergic rhinitis	100	0	0	0	100	2.6	0	0	0	100	100
Chronic rhinosinusitis without nasal polyps	3.7	0	100	0	0	2.6	0	0	0	100	100
Chronic rhinosinusitis with nasal polyposis	0	0.5	100	0	0	2.6	0	0	0	100	100
Previous nasal polypectomy	100	14.7	100	0	100	100	0	100	100	100	100
ACQ-5	1.9	0	0.4	0.7	1.3	0	100	0	0.6	0.3	1.0
Smoking	0	0	0	0	0	0	0	0	0	0	0
Psychiatric disease	100	0.5	100	0	0	100	1.7	0	0	100	100

On ICS	0	0	0	0	0	0	0	0	0	0	0
On SABA	100	0	0	100	0	100	0	0	0	0	4.5
SABA actuations/day in trial	100	8.1	100	100	100	100	1.0	100	100	2.0	4.5
SABA actuations/day pretrial	100	100	100	100	100	0	100	100	100	15.1	14.6
On mOCS	0	0	0	0	0	100	0	0	0	0	0
On intranasal ICS	0	100	0	100	0	100	0	0	0	100	100
Adherence pre-trial	100	100	100	100	100	100	100	100	100	100	100
Adherence in-trial	100	100	0.6	100	100	0	100	100	100	0	0
Attack history	0	0	0	0	0	0	0	0	0	0	0

TABLE S6 (continued)

	LUTE	**MILLY**	**NAVIGA-TOR**	**Novel_START**	**PACT**	**PATHWAY**	**PRACTI-CAL**	**QUEST**	**STRATOS 1**	**STRATOS 2**	**VERSE**
N	*66*	*112*	*517*	*218*	*16*	*133*	*307*	*634*	*388*	*413*	*50*
Age	0	0	0	0	0	2.3	0	0	0	0	0
Sex	0	0	0	0	0	2.3	0	0	0	0	0
Ethnicity	0	0	35.0	0	0	27.8	0	0	100	100	0
Region	0	0	35.0	0	0	27.8	0	100	100	100	0
BEC	0	0	0	1.8	0	5.3	0.3	0.2	1.8	0.5	0
FeNO	3.0	1.8	0.8	0	6.3	0.8	0	1.7	0.5	1.5	4.0
Total IgE	0	0	0	100	100	0	100	0.6	1.3	1.5	0
BMI	0	0	0	0	0	2.3	0	0	1.5	23.0	0
FEV_1%	0	0	0	100	0	0	100	0	0.8	0.5	0
FEV_1% reversibility	1.5	0	0	100	100	0	100	0	0.8	0.5	0
Previous ICU or intubation	100	100	0	0	0	29.3	100	100	100	100	100
Allergy testing positive	0	0	100	100	6.3	100	100	100	0	0	0

Eczema	0	0	0	100	0	2.3	100	100	0	0	0
Allergic rhinitis	0	0	0	100	0	13.5	100	0	0	0	0
Chronic rhinosinusitis without nasal polyps	0	0	0	100	100	16	100	0	0	0	0
Chronic rhinosinusitis with nasal polyposis	0	0	0	100	100	2.3	100	0	0	0	0
Previous nasal polypectomy	100	100	0	100	100	13.5	100	100	0	0	100
ACQ-5	1.5	0.9	0	0.5	100	0	0	0	0.5	0	4.0
Smoking	100	0	0	0	0	0	0	0	0	0.2	100
Psychiatric disease	0	0	0	100	100	13.5	100	100	0	0	0
On ICS	0	0	0	0	0	0	0	0	0	0	0
On SABA	0	0	0	0	0	0	0	100	0	0	0
SABA actuations/day in trial	0	1.8	100	100	0	100	0	100	0	0.2	0
SABA actuations/day pretrial	0	0	100	0	0	100	100	0	0	0.2	0
On mOCS	0	0	0	0	0	0	100	100	0	0	0
On intranasal ICS	0	0	0	100	0	0	100	100	0	0	0
Adherence pre-trial	0	100	0	100	100	3.0	0.3	100	0	0.2	0
Adherence in-trial	100	100	0	100	0	0.8	100	0.6	0	0.2	100
Attack history	0	100	0	0	0	0	0	0.2	0	0	0

TABLE S7. Membership model and discriminative ability (*c*-statistic) per study

No.	Name study	Membership *c*-statistic
1-4	AZISAST, LUTE, PACT, VERSE *(combined)*	0.71
5	BENRAP2B	0.70
6	CAPTAIN	0.80
7	COSTA	0.67
8	DREAM	0.69
9	DRI12544	0.64
10	EXTRA	0.62
11	LAVOLTA 1	0.68
12	LAVOLTA 2	0.67
13	LUSTER 1	0.69
14	LUSTER 2	0.70
15	MILLY	0.58
16	NAVIGATOR	0.67
17	Novel START	0.95
18	PATHWAY	0.65
19	PRACTICAL	0.94
20	QUEST	0.62
21	STRATOS 1	0.66
22	STRATOS 2	0.64
Mean ± standard deviation		0.70 ± 0.09

TABLE S8. Internal validity of supplied IPD per variable

High	Moderate	Low
Blood eosinophils (baseline)	Geographical region	Adherence in trial
FeNO (baseline)	Ethnicity / race	
IgE (baseline)	Chronic rhinosinusitis without nasal polyposis history	
Age	Chronic rhinosinusitis with nasal polyposis history	
BMI	Allergic rhinitis history	
Sex	Eczema history	**Missing > 50%**
ACQ-5	Number of previous hospitalisations	Intubated for asthma on history
FEV_1% (pre & postBD)	Smoking history	ICU for asthma on history
FEV_1% reversibility	Pack years	Adherence pre-randomisation
Number of attacks past 12m	ICS dose class (low, med, high)	FVC preBD
Treatment step	mOCS	Objective allergy test +
	Intranasal corticosteroids	Psychiatric disease history
	LAMA	mOCS dose at baseline
	SABA	Previous nasal polypectomy
	LABA	SABA actuations/d pre-randomisation
	Montelukast	SABA actuations/d during trial
	Theophylline	Eczema history

ACQ-5, asthma control questionnaire (5-items); BD, bronchodilator; BMI, body mass index; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1st second; ICS, inhaled corticosteroids; ICU, intensive care unit; IgE, immunoglobulin E; LABA, long-acting beta-2-agonist; LAMA, long-acting anti-muscarinic; mOCS, maintenance oral corticosteroids; SABA, ac1 short acting beta2 agonist.

TABLE S9. Additional study-level information for the trials that provided individual participant data*

Trial(s) reported [registration no.]	Study design	Key inclusion criteria	Reversibility inclusion criteria	Recruitment biomarker targets	Investigator blinding to biomarkers	Endpoints
AZISAST[12] **(AZIthromycin in Severe ASThma)** [NCT00760838]	Randomised, placebo-controlled double-blind parallel-group	• Age 18–75 • GINA step 4 or 5 • High doses of ICS/LABA • At least 2 severe asthma exacerbations or LRTI requiring antibiotics within the previous 12 months	Historical, 1 of: i) postBD reversibility FEV1; ii) BPT test positive; iii) PEF variability	All patients: FeNO level below the upper limit of normal according to gender, atopic status, and smoking history[13]	-	Primary • Severe asthma exacerbations and/or LRTI requiring antibiotics Secondary • FEV1, PEF, AQLQ and ACQ
Benralizumab phase 2b[14] [NCT01238861]	Randomised, placebo-controlled, double-blind, parallel-group dose-ranging	• Aged 18–75 • Medium-dose high-dose ICS/LABA for at least 1 year • History of two to six severe exacerbations in the past year • FEV1 40%-90%, reversibility • ACQ-6 score of 1.5 or higher	Past 36 months, 1 of: i) postBD reversibility, FEV1 or FVC, 200 mL and 12%; ii) BPT test positive;	-	Patients, site personnel, and sponsor blinded to eosinophil counts post-randomization	Primary • Severe asthma annual exacerbation rate in eosinophilic individuals Secondary • Change from baseline in FEV1, ACQ-6, overall symptom score, and AQLQ
CAPTAIN[15] **(Clinical Study in Asthma Patients Receiving Triple Therapy in a Single Inhaler)** [NCT02924688]	Randomised, double-blind, parallel-group, phase 3A	• Aged ≥18 years • ACQ-6 ≥1.5 • ICS/LABA (>250 µg per day fluticasone or equivalent) for at least 12 consecutive weeks • Documented health-care contact or temporary change in asthma therapy for acute asthma within 1 year • FEV1 30%-85%, reversibility	Baseline, all patients: postBD reversibility, FEV1, 200 mL and 12%;	-	-	Primary • Change from baseline in FEV1 Secondary • Annualised rate of moderate and/or severe asthma exacerbations
COSTA[16] [NCT01582503]	Randomised, placebo-controlled double-blind, parallel-group, phase 2	• Aged 18–75 years • FEV1 40–80 %, reversibility • Daily use of ICS (≥400 µg/day total daily dose of FP) and second controller for 3 months • ACQ-5 ≥1.5 • History of at least one severe asthma exacerbation in the 18 months prior	Past 24 months, 1 of: i) postBD reversibility, FEV1 or FVC, 12%; ii) BPT test positive;	All patients: At least one positive aero-allergen or a total serum IgE ≥75 IU/mL	-	Primary outcome • Annualised rate of severe asthma exacerbations Secondary outcomes • FEV1 and the change in asthma symptoms

…Trial	Design	Key inclusion criteria	Reversibility	Biomarker target	Biom blinding	Endpoints
DREAM[17] **(Dose Ranging Efficacy And safety with Mepolizumab)** [NCT01000506]	Randomised, placebo-controlled, double-blind, parallel-group, dose-ranging	• Age 12–74 years • History of two or more severe exacerbations • FEV1 <80% • At least 880 µg fluticasone propionate/day, with or without OCS.	Past 12 months, 1 of: i) postBD reversibility FEV1; 12% and 200 mL ii) BPT test positive; iii) FEV1 inter-visit variability, 20% iii) PEF diurnal variability, 20%	All patients, past 12 months, 1 of: i) sputum eosinophil count ≥3%, ii) FENO ≥50 ppb, iii) blood eosinophil ≥0·3×10⁹/L.	Patients, site personnel, and sponsor blinded to eosinophil counts post-randomization	Primary outcome • Rate of severe clinically significant asthma exacerbations Secondary outcomes • Rate of exacerbations, blood and sputum eosinophil counts, FEV1, AQLQ and ACQ
Dupilumab phase 2b[18] [NCT01854047]	Randomised, placebo-controlled, double-blind, parallel-group, dose-ranging	• Adults (aged ≥18 years) • Treatment with medium-to-high-dose ICS/LABA at least 1 month • FEV1 of 40–80% • ACQ-5 ≥ 1·5 • At least one severe asthma exacerbation	Baseline, all patients: postBD reversibility, FEV1, 200 mL and 12%;	-	-	Primary endpoint • Change in FEV1 in patients with baseline blood eosinophil ≥300 Secondary endpoints • Change from baseline in FEV1; annualised severe asthma exacerbation rate; ACQ-5, AQLQ, FeNO
EXTRA[19] [NCT00314574]	Randomised, placebo-controlled double-blind, parallel-group,	• Aged 12 to 75 years • History of severe allergic asthma for at least 1 year • FEV1 of 40-80% • Asthma was not well-controlled despite treatment with high-dose ICS/LABA with or without other controllers (including OCS), based on NAEPP guidelines.	No reversibility criteria: "Physician-diagnosed asthma"	All patients, past 12 months: At least one positive aero-allergen or a total serum IgE 30-<700 IU/mL	-	Primary end point • Rate of severe asthma exacerbations Secondary end points • Change in total asthma symptom severity score (TASS), change in mean puffs per day of albuterol; and change AQLQ
LAVOLTA I, II[20] [NCT01867125, NCT01868061]	Randomised, placebo-controlled, double-blind, parallel-group, replicate, phase 3,	• Aged 18–75 years • FEV1 40–80% • ICS (500–2000 µg per day fluticasone propionate or equivalent) for at least 6 months and at least one additional controller medication. • ACQ-5 ≥1·5	Baseline, all patients: postBD reversibility, FEV1, 12%;	-	Patients, site personnel, and sponsor blinded to eosinophil counts, FeNO, and periostin post-randomization	Primary endpoint • Rate of severe asthma exacerbations in biomarker-high Secondary endpoints • Absolute changeFEV1; time to first asthma exacerbation; AQLQ, ACQ-5

…Trial	Design	Key inclusion criteria	Reversibility	Biomarker target	Biom blinding	Endpoints
LUSTER I, II[21] [NCT02555683, NCT02563067]	Randomised, placebo-controlled, double-blind, parallel-group, replicate, phase 3	• Aged 12 years or older • Uncontrolled asthma on dual/triple asthma therapy with medium/high dose ICS with up to two controllers with or without OCS • History of two or more asthma exacerbations within the previous 12 months. • FEV1 ≤80%	Past 24 months, 1 of: i) postBD reversibility, FEV1 or FVC, 200 mL and 12%; ii) BPT test positive;	• 2/3 : blood eosinophil count ≥0·25×10⁹/L • 1/3 : blood eosinophil count <0·25×10⁹/L.	-	Primary endpoint • Number of moderate to severe asthma exacerbations per patient year both in patients with high blood eosinophil counts (≥250 cells/μL) and in all patients Secondary endpoints • Change from baseline in FEV1, ACQ-5, AQLQ
LUTE, VERSE[22] [NCT01545440, NCT01545453]	Randomised, placebo-controlled double-blind, replicate studies, phase IIb. Amended protocol and early termination	• Patients aged 18–75 years • Daily use of 500–2000 μg/day of fluticasone and a second asthma controller medication ≥12 months • FEV1 40–80% • ACQ-5 ≥1.5	Baseline, all patients: postBD reversibility, FEV1, 12%;	-	Patients, physicians and site staff were blinded to FeNO and periostin	Primary endpoint • Rate of severe asthma exacerbations Secondary endpoints • Change in FEV1 from baseline, time to first exacerbation, AQLQ
MILLY[23] [NCT00930163]	Randomised, placebo-controlled double-blind, parallel-group	• Age 18-65 years • For at least 6 months of ICS (≥200 and ≤1000 μg of inhaled fluticasone propionate daily) • ACQ5 ≥1.5 • FEV1 40%-80%,	Baseline, all patients: postBD reversibility, FEV1, 12%;	-	-	Primary outcome • Relative change in FEV1 Secondary outcomes • Rates of moderate and severe exacerbations, PEF, ACQ5, ACDD, and use of rescue medication
NAVIGATOR[24] [NCT03347279]	Randomised, placebo-controlled double-blind parallel-group, phase 3	• Age 12-80 years • Medium/high-dose ICS for at least 12 months and at least one additional controller, with or without oral glucocorticoids, for at least 3 months before • FEV1 <80% • At least two exacerbations in the 12 months before	Baseline, all patients: postBD reversibility, FEV1, 200 mL and 12%;	• 50% : blood eosinophil count ≥0·3×10⁹/L • 50% : blood eosinophil count <0·3×10⁹/L.	Patients, physicians and site staff were blinded to FeNO	Primary endpoint • Rate of severe asthma exacerbations Secondary endpoints • Change in FEV1 from baseline, time to first exacerbation, AQLQ

…Trial	Design	Key inclusion criteria	Reversibility	Biomarker target	Biom blinding	Endpoints
NOVEL START[25] [ACTRN12615000999538]	Randomised, open-label, controlled parallel group trial	• Age 18 to 75 years • SABA as the sole asthma therapy in the previous 3 months on at least two occasions, but on an average of two or fewer occasions per day in the previous 4 weeks	No reversibility criteria: "Self-reported asthma"	-	-	Primary outcome • Annualised rate of asthma severe/moderate exacerbations Secondary outcomes • Number of exacerbations, number of severe exacerbations, ACQ-5, FeNO, oral prednisone use
PACT[26] [NCT00272506]	Randomised, placebo-controlled, double-blind, parallel group	• Age 6-14 years • FEV1 ≥70% predicted • Mild-moderate persistent asthma	No reversibility criteria: all patients required positive BPT at visit 2	-	-	Primary outcome • Percent of asthma control days Secondary analyses • Percent of episode-free days, number of severe exacerbations and time to the first exacerbation, ACQ
PATHWAY[27] [NCT02054130]	Randomised, placebo-controlled double-blind, parallel group	• Age 18 to 75 • Asthma not well controlled despite treatment with medium/high dose LABA/ICS at least 6 months • At least two severe asthma exacerbations • FEV1 40%-80% • ACQ-6 ≥1.5	Past 12 months, all patients: postBD reversibility, FEV1, 200 mL and 12%;	• ≥50% : blood eosinophil count	-	Primary endpoint • Annualised rate of severe asthma exacerbations Secondary endpoints • Changes FEV1, ACQ-6, AQLQ, asthma symptom score, and FVC, annualized rate of exacerbations, time to the first exacerbation

…Trial	Design	Key inclusion criteria	Reversibility	Biomarker target	Biom blinding	Endpoints
PRACTICAL[28] [ACTRN12616000377437]	Randomised, open-label, controlled parallel-group, pragmatic trial	• Aged 18 to 75 • SABA reliever alone in the past 12 weeks, symptoms or need for SABA on ≥2 occasions in the past 4 weeks, or a history of a severe asthma exacerbation in the past 52 weeks • SABA reliever with low/moderate doses of ICS in the past 12 weeks, partly or well controlled or uncontrolled asthma with poor adherence	No reversibility criteria: "Self-reported asthma"	-	-	Primary outcome • Number of severe asthma exacerbations per patient per year Secondary outcomes • Proportion of patients with a least one severe exacerbation; time to first exacerbation; ACQ-5, FEV1, FeNO
QUEST[29] [NCT02414854]	Randomised, placebo-controlled, double-blind, parallel-group, phase 3	• Age 12 years or older • Medium/high-dose ICS/LABA plus up to 2 controllers • FEV1 80% or less, reversibility • ACQ-5 ≥1.5 • Severe asthma exacerbation in the previous year	Baseline, all patients: postBD reversibility, FEV1, 200 mL and 12%;	-	-	Primary efficacy end points • Annualised rate of severe exacerbation events and the absolute change from baseline in the FEV1 Secondary end points • Percentage change from baseline in the FEV1
STRATOS I, II[30] [NCT02161757, NCT02194699]	Randomised, placebo-controlled, double-blind, parallel-group, replicate trials, phase 3	• Aged 12–75 years • Medium/high dose ICS/LABA for at least 3 months • Additional controller medications if required • ≥2 severe asthma exacerbation in the previous year	Baseline, all patients: postBD reversibility, FEV1, 200 mL and 12%;	-	-	Primary endpoint • Annualised severe asthma exacerbation rate Secondary endpoints • FEV1, ACQ-6, AQLQ, time to first exacerbation; proportion of participants with one or more exacerbations

*Benralizumab phase 2a removed from the table, as did not provide individual participant data. BD, bronchodilator; BPT, bronchial provocation test; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; FEV_1, forced expiratory volume in 1st second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; PEF, peak expiratory flow.

TABLE S10. Baseline characteristics of analysed participant data, per trial, before imputation

	Total (N=6513)	AZISAST (N=54)	BENRAP2B (N=211)	CAPTAIN (N=1218)	COSTA (N=145)	DREAM (N=155)	DRI12544 (N=155)	EXTRA (N=420)
Demographics								
Age (years)	50 (39 - 59)	53 (36 - 60)	..	54 (44 - 63)	47 (38 - 58)	47 (39 - 55)	..	46 (36 - 56)
In categories	2448 (38%)	0 (0%)	211 (100%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	0 (0%)
Missing	3 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sex (female)	4140/6510 (64%)	38/54 (70%)	146/211 (69%)	764/1218 (63%)	84/145 (58%)	97/155 (63%)	102/155 (66%)	294/420 (70%)
Missing	3 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Body Mass Index (kg/m2)	27·9 (24·5 - 32·3)	25·7 (22·7 - 28·3)	..	28·1 (24·8 - 32·5)	28·1 (25·3 - 31·3)	26·4 (24·1 - 31·1)	..	30·4 (26·3 - 36·1)
In categories	2342 (36%)	0 (0%)	206 (98%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	0 (0%)
Missing	397 (6%)	0 (0%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Smoking history								
Never smoked	5197 (80%)	39 (72%)	174 (82%)	990 (81%)	123 (85%)	121 (78%)	123 (79%)	410 (98%)
Former smoker	1161 (18%)	15 (28%)	37 (18%)	228 (19%)	22 (15%)	34 (22%)	32 (21%)	10 (2%)
Current smoker	38 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	117 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity								
American Indian or Alaska Native	14 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Asian	502 (8%)	0 (0%)	0 (0%)	169 (14%)	3 (2%)	8 (5%)	25 (16%)	0 (0%)
Black or African American	267 (4%)	0 (0%)	0 (0%)	58 (5%)	3 (2%)	6 (4%)	7 (5%)	85 (20%)
Maori	32 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiple	8 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian or other Pacific Islander	13 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Other	120 (2%)	0 (0%)	0 (0%)	8 (1%)	13 (9%)	0 (0%)	5 (3%)	17 (4%)
White	3825 (59%)	54 (100%)	83 (39%)	983 (81%)	122 (84%)	140 (90%)	118 (76%)	318 (76%)
Missing	1732 (26.6%)	0 (0%)	128 (60.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Region								
Asia	344 (5%)	0 (0%)	..	140 (11%)	2 (1%)	6 (4%)	..	0 (0%)
Europe	1475 (23%)	54 (100%)	..	699 (57%)	76 (52%)	105 (68%)	..	0 (0%)
North America	1244 (19%)	0 (0%)	..	238 (20%)	38 (26%)	25 (16%)	..	420 (100%)
Oceania	520 (8%)	0 (0%)	..	7 (1%)	2 (1%)	6 (4%)	..	0 (0%)
South Africa	88 (1%)	0 (0%)	..	31 (3%)	0 (0%)	0 (0%)	..	0 (0%)
South America	238 (4%)	0 (0%)	..	103 (8%)	27 (19%)	13 (8%)	..	0 (0%)
Missing	2604 (40%)	0 (0%)	211 (100%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	0 (0%)

Comorbidities								
Any of: Allergic rhinitis, Eczema, and/or Food allergy	2540/4008 (63%)	38/54 (70%)	142/211 (67%)	..	47/145 (32%)	..	118/151 (78%)	323/420 (77%)
Missing	2505 (39%)	0 (0%)	0 (0%)	1218 (100%)	0 (0%)	155 (100%)	4 (3%)	0 (0%)
Airborne allergen sensitisation	1721/2940 (59%)	..	58/211 (27%)	..	103/128 (80%)	81/155 (52%)	..	418/419 (100%)
Missing	3573 (55%)	54 (100%)	0 (0%)	1218 (100%)	17 (12%)	0 (0%)	155 (100%)	1 (0%)
Eczema	330/3184 (10%)	..	24/211 (11%)	..	13/145 (9%)	..	..	33/420 (8%)
Missing	3329 (51%)	54 (100%)	0 (0%)	1218 (100%)	0 (0%)	155 (100%)	155 (100%)	0 (0%)
Allergic rhinitis	2501/5172 (48%)	..	141/211 (67%)	215/1218 (18%)	14/145 (10%)	..	102/151 (68%)	296/420 (70%)
Missing	1341 (21%)	54 (100%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	4 (3%)	0 (0%)
Chronic rhinosinusitis without nasal polyps	439 / 4 141 (11%)	18 / 52 (35%)	11 / 210 (5·2%)	..	14 / 145 (9·7%)	29 / 155 (19%)	13 / 151 (8·6%)	88 / 420 (21%)
Missing	2372 (36%)	2 (4%)	0 (0%)	1218 (100%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)
Chronic rhinosinusits with nasal polyposis	598 / 4 161 (14%)	6/54 (11%)	29 / 210 (14%)	..	4/145 (3%)	28/155 (18%)	18/151 (12%)	39/420 (9%)
Missing	2352 (36%)	0 (0%)	1 (0%)	1218 (100%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)
Psychiatric disease	420/3300 (13%)	..	32/210 (15%)	..	16/145 (11%)	18/155 (12%)	..	124/413 (30%)
Missing	3213 (49%)	54 (100%)	1 (0%)	1218 (100%)	0 (0%)	0 (0%)	155 (100%)	7 (2%)
Baseline Asthma medication								
Treatment step								
Step 1	226 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Step 2	315 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Step 3	859 (13%)	0 (0%)	0 (0%)	817 (67%)	11 (8%)	0 (0%)	0 (0%)	0 (0%)
Step 4	2555 (39%)	0 (0%)	118 (56%)	401 (33%)	68 (47%)	0 (0%)	78 (50%)	0 (0%)
Step 5	2558 (39%)	54 (100%)	93 (44%)	0 (0%)	66 (46%)	155 (100%)	77 (50%)	420 (100%)
ICS Dose								
None	218 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Low	1592 (24%)	0 (0%)	4 (2%)	1218 (100%)	11 (8%)	0 (0%)	0 (0%)	1 (0%)
Medium	1400 (21%)	0 (0%)	113 (54%)	0 (0%)	68 (47%)	0 (0%)	78 (50%)	5 (1%)
High	3303 (51%)	54 (100%)	94 (45%)	0 (0%)	66 (46%)	155 (100%)	77 (50%)	414 (99%)
On SABA	3725/5506 (68%)	..	201/211 (95%)	275/1218 (23%)	..	114/155 (74%)	..	415/420 (99%)
Missing	1007 (16%)	54 (100%)	0 (0%)	0 (0%)	145 (100%)	0 (0%)	155 (100%)	0 (0%)
On LABA	5743/6205 (93%)	54/54 (100%)	211/211 (100%)	1218/1218 (100%)	140/145 (97%)	150/155 (97%)	..	420/420 (100%)
Missing	462 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	0 (0%)
On LAMA	1197/5476 (22%)	16/38 (30%)	3/211 (1%)	811/1218 (67%)	5/145 (3%)	..	..	..
Missing	1037 (16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	155 (100%)	420 (100%)
On Montelukast	1250/6051 (21%)	27/54 (50%)	15/211 (7%)	47/1218 (4%)	38/145 (26%)	43/155 (28%)	..	202/420 (48%)
Missing	462 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	0 (0%)
On mOCS	261/5417 (5%)	3/54 (6%)	7/211 (3%)	49/1218 (4%)	14/145 (10%)	45/155 (29%)	..	31/420 (7%)
Missing	1096 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	155 (100%)	0 (0%)

Adherence to medication								
Adherence pre-trial	100 (85·7 - 100)	··	··	··	··	··	··	··
Missing	4645 (71%)	54 (100%)	211 (100%)	1218 (100%)	145 (100%)	155 (100%)	155 (100%)	420 (100%)
Adherence in trial	97·0 (89·1 - 99·7)	··	··	99·0 (94·0 - 100)	··	··	97·3 (90·7 - 99·4)	··
Missing	2467 (38%)	54 (100%)	211 (100%)	7 (0.6%)	145 (100%)	155 (100%)	0 (0%)	420 (100%)
Asthma symptoms and history								
ACQ-5 score	2·40 (1·80 - 3·00)	1·60 (0·80 - 2.60)	2·60 (2·10 - 3·10)	2·00 (1·60 - 2·60)	2·80 (2·35 - 3·40)	2·60 (1·80 - 3·20)	2·60 (2·00 - 3·20)	··
<1.5	929 (14%)	24 (44%)	15 (7%)	287 (24%)	0 (0%)	29 (19%)	0 (0%)	··
⩾1.5	5126 (79%)	29 (54%)	196 (93%)	926 (76%)	144 (99%)	124 (80%)	155 (100%)	··
Missing	458 (7%)	1 (2%)	0 (0%)	5 (0%)	1 (1%)	2 (1%)	0 (0%)	420 (100%)
Severe exacerbation or hospitalisation in past 12 months	5120/6400 (80%)	54/54 (100%)	211/211 (100%)	754/1218 (62%)	145/145 (100%)	155/155 (100%)	155/155 (100%)	406/420 (97%)
Missing	113 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Previous ICU or intubation	134/2545 (5%)	8/54 (15%)	20/211 (9%)	··	46/145 (32%)	7/155 (5%)	··	28/419 (7%)
Missing	3968 (61%)	0 (0%)	0 (0%)	1218 (100%)	0 (0%)	0 (0%)	155 (100%)	1 (0%)
Lung function								
FEV1%	63·9 (52·9 - 73·0)	85·5 (71·0 - 96·5)	68·0 (58·0 - 79·0)	70·2 (59·2 - 79·0)	63·1 (51·2 - 69·9)	61·4 (47·4 - 69·7)	62·0 (51·5 - 70·0)	66·0 (54·1 - 75·2)
Missing	565 (9%)	0 (0%)	0 (0%)	10 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)
FEV1/FVC ratio	64·2 (56·0 - 72·3)	70·2 (58·4 - 76·9)	65·6 (56·9 - 73·7)	65·5 (57·0 - 73·1)	··	61·4 (54·1 - 70·6)	64·3 (57·8 - 70·3)	72·6 (64·0 - 79·3)
Missing	170 (11%)	0 (0%)	0 (0%)	10 (0%)	145 (100%)	0 (0%)	0 (0%)	3 (1%)
FEV1 reversibility %	17·0 (10·0 - 27·7)	4·00 (1·00 - 9·00)	11·0 (5·00 - 20·0)	··	16·0 (10·0 - 27·0)	21·4 (15·3 - 29·3)	24·2 (17·0 - 33·6)	7·86 (2·55 - 17·7)
<12%	1438 (22%)	47 (87%)	113 (54%)	··	50 (34%)	10 (6%)	7 (5%)	255 (61%)
⩾12%	3216 (49%)	6 (11%)	96 (45%)	··	95 (66%)	109 (70%)	148 (95%)	150 (36%)
Missing	1859 (29%)	1 (2%)	2 (1%)	1218 (100%)	0 (0%)	36 (23%)	0 (0%)	15 (4%)
Inflammatory biomarkers								
Blood eosinophils (x10^9 cells/L)	0·250 (0·140 - 0·420)	0·183 (0·109 - 0·348)	0·190 (0·110 - 0·315)	0·260 (0·140 - 0·430)	0·215 (0·130 - 0·380)	0·340 (0·160 - 0·610)	0·260 (0·160 - 0·430)	0·260 (0·150 - 0·455)
Missing	80 (1%)	0 (0%)	4 (2%)	30 (2%)	0 (0%)	0 (0%)	0 (0%)	24 (6%)
FeNO (ppb)	23 (14 - 42)	18 (13 - 31)	20 (13 - 30)	19 (12 - 29)	21·5 (14 - 43)	33 (19 - 59)	29 (16 - 46)	20 (12 - 33)
Missing	532 (8%)	0 (0%)	0 (0%)	95 (8%)	0 (0%)	4 (3%)	14 (9%)	230 (55%)
Total IgE (ng/mL)	171 (64 - 434)	87·3 (26 - 627)	180 (50 - 478)	173 (66 - 425)	230 (123 - 494)	181 (76 - 505)	201 (89 - 454)	139 (72 - 246)
Missing	624 (10%)	0 (0%)	39 (18%)	11 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Follow-up in trial								
Follow-up duration (days)	363 (251 - 365)	210 (210 - 214)	365 (359 - 370)	174 (169 - 256)	225 (224 - 227)	365 (362 - 367)	168 (167 - 169)	337 (334 - 339)
Total number of follow-up years, n	5482	31	195	763	85	140	69	342
In trial severe exacerbations, n	4615	43	112	331	108	296	70	316
>=1	2268/6513 (35%)	26/54 (48%)	66/211 (31%)	223/1218 (18%)	57/145 (39%)	105/155 (68%)	38/155 (25%)	179/420 (43%)
None	4245 (65%)	28 (52%)	145 (69%)	995 (82%)	88 (61%)	50 (32%)	117 (75%)	241 (57%)

TABLE S10 (continued)

	LAVOLTA_1 (N=362)	LAVOLTA_2 (N=354)	LUSTER_1 (N=298)	LUSTER_2 (N=287)	LUTE (N=66)	MILLY (N=112)	NAVIGATOR (N=517)	Novel_START (N=218)
Demographics								
Age (years)	53 (43 - 61)	52 (39 - 59)	50 (42 - 62)	54 (44 - 59)	50·5 (43 - 59)	45 (36 - 52)	··	33 (23 - 45)
In categories	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	517 (100%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sex (female)	231/362 (64%)	219/354 (62%)	177/298 (59%)	177/287 (62%)	48/66 (73%)	75/112 (67%)	328/517 (63%)	112/218 (51%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Body Mass Index (kg/m2)	28·7 (25·1 - 32·2)	27·4 (24·5 - 31·3)	26·8 (23·6 - 31·1)	··	29·5 (25·6 - 35·6)	28·7 (25·6 - 35·4)	··	26·2 (23·0 - 30·5)
In categories	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	517 (100%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	287 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Smoking history								
Never smoked	286 (79%)	290 (82%)	232 (78%)	239 (83%)	··	96 (86%)	414 (80%)	148 (68%)
Former smoker	74 (20%)	64 (18%)	66 (22%)	48 (17%)	··	16 (14%)	103 (20%)	48 (22%)
Current smoker	2 (1%)	0 (0%)	0 (0%)	0 (0%)	··	0 (0%)	0 (0%)	22 (10%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	66 (100%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity								
American Indian or Alaska Native	2 (1%)	9 (3%)	··	··	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Asian	41 (11%)	41 (12%)	··	··	0 (0%)	1 (1%)	106 (21%)	17 (8%)
Black or African American	29 (8%)	22 (6%)	··	··	9 (14%)	16 (14%)	10 (2%)	1 (0%)
Maori	0 (0%)	0 (0%)	··	··	0 (0%)	0 (0%)	0 (0%)	12 (6%)
Multiple	1 (0%)	2 (1%)	··	··	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	··	··	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Other	3 (1%)	10 (3%)	··	··	2 (3%)	0 (0%)	10 (2%)	8 (4%)
White	286 (79%)	270 (76%)	··	··	54 (82%)	95 (85%)	210 (41%)	177 (81%)
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	181 (35.0%)	0 (0%)
Region								
Asia	47 (13%)	40 (11%)	··	··	0 (0%)	0 (0%)	102 (20%)	0 (0%)
Europe	162 (45%)	169 (48%)	··	··	0 (0%)	25 (22%)	69 (13%)	32 (15%)
North America	114 (31%)	110 (31%)	··	··	66 (100%)	87 (78%)	76 (15%)	0 (0%)
Oceania	5 (1%)	4 (1%)	··	··	0 (0%)	0 (0%)	3 (1%)	186 (85%)
South Africa	13 (4%)	12 (3%)	··	··	0 (0%)	0 (0%)	31 (6%)	0 (0%)
South America	21 (6%)	19 (5%)	··	··	0 (0%)	0 (0%)	55 (11%)	0 (0%)
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	181 (35%)	0 (0%)

Comorbidities								
Any of: Allergic rhinitis, Eczema, and/or Food allergy	247/362 (68%)	217/354 (61%)	··	··	54/66 (82%)	92/112 (82%)	269/517 (52%)	··
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Airborne allergen sensitisation	186/207 (90%)	163/194 (84%)	160/298 (54%)	156/284 (55%)	44/66 (67%)	61/112 (54%)	··	··
Missing	155 (43%)	160 (45%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)	517 (100%)	218 (100%)
Eczema	56/362 (15%)	51/354 (14%)	··	··	5/66 (8%)	19/112 (17%)	50/517 (10%)	··
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Allergic rhinitis	235/362 (65%)	207/354 (58%)	··	··	52/66 (79%)	86/112 (77%)	243/517 (47%)	··
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Chronic rhinosinusitis without nasal polyps	31 / 362 (8·6%)	31 / 354 (8·8%)	··	··	8 / 66 (12%)	0 / 112 (0%)	59 / 517 (11%)	··
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Chronic rhinosinusitis with nasal polyps	49/362 (14%)	47/354 (13%)	··	··	0/66 (0%)	93/112 (83%)	75 / 517 (15%)	··
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Psychiatric disease	44/362 (12%)	42/354 (12%)	··	··	9/66 (14%)	20/112 (18%)	68/517 (13%)	··
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Baseline Asthma medication								
Treatment step								
Step 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Step 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Step 3	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	8 (7%)	1 (0%)	0 (0%)
Step 4	203 (56%)	175 (49%)	270 (91%)	260 (91%)	40 (61%)	30 (27%)	131 (25%)	0 (0%)
Step 5	159 (44%)	179 (51%)	27 (9%)	27 (9%)	26 (39%)	74 (66%)	385 (74%)	0 (0%)
ICS Dose								
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Low	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	11 (10%)	1 (0%)	0 (0%)
Medium	0 (0%)	0 (0%)	72 (24%)	58 (20%)	49 (74%)	46 (41%)	131 (25%)	0 (0%)
High	362 (100%)	354 (100%)	225 (76%)	229 (80%)	17 (26%)	55 (49%)	385 (74%)	0 (0%)
On SABA	29/362 (8%)	28/354 (8%)	292/292 (100%)	274/274 (100%)	66/66 (100%)	108/112 (96%)	474/517 (92%)	218/218 (100%)
Missing	0 (0%)	0 (0%)	6 (2%)	13 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On LABA	357/362 (99%)	349/354 (99%)	295/298 (99%)	287/287 (100%)	63/66 (95%)	90/112 (80%)	511/517 (99%)	0/218 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On LAMA	15/362 (4%)	22/354 (6%)	28/298 (9%)	38/287 (13%)	5/66 (8%)	0/112 (0%)	140/517 (27%)	0/218 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On Montelukast	85/362 (23%)	103/354 (29%)	58/298 (19%)	74/287 (26%)	15/66 (23%)	24/112 (21%)	204/517 (39%)	0/218 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On mOCS	0/362 (0%)	0/354 (0%)	27/298 (9%)	27/287 (9%)	0/66 (0%)	0/112 (0%)	47/517 (9%)	0/218 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Adherence to medication								
Adherence pre-trial	..	..	..	..	92·2 (81·7 - 96·5)	..	100 (85·7 - 100)	..
Missing	362 (100%)	354 (100%)	298 (100%)	287 (100%)	0 (0%)	112 (100%)	0 (0%)	218 (100%)
Adherence in trial	..	..	100 (100 - 100)	100 (100 - 100)	..	..	91·2 (77·7 - 97·0)	..
Missing	362 (100%)	354 (100%)	0 (0%)	0 (0%)	66 (100%)	112 (100%)	0 (0%)	218 (100%)
Asthma symptoms and history								
ACQ-5 score	2·60 (2·00 - 3·20)	2·80 (2·20 - 3·20)	2·40 (1·80 - 2·80)	2·40 (1·80 - 3·00)	3·20 (3·00 - 3·60)	2·40 (1·80 - 3·00)	2·80 (2·40 - 3·40)	1·00 (0·60 - 1·60)
<1.5	0 (0%)	0 (0%)	44 (15%)	42 (15%)	0 (0%)	6 (5%)	0 (0%)	160 (73%)
⩾1.5	362 (100%)	352 (99%)	253 (85%)	242 (84%)	65 (98%)	105 (94%)	517 (100%)	57 (26%)
Missing	0 (0%)	2 (1%)	1 (0%)	3 (1%)	1 (2%)	1 (1%)	0 (0%)	1 (0%)
Severe exacerbation or hospitalisation in past 12 months	228/362 (63%)	225/354 (64%)	298/298 (100%)	287/287 (100%)	32/66 (48%)	..	517/517 (100%)	20/218 (9%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	112 (100%)	0 (0%)	0 (0%)
Previous ICU or intubation	10/362 (3%)	8/354 (2%)	..	..	..	..	4/517 (1%)	0/218 (0%)
Missing	0 (0%)	0 (0%)	298 (100%)	287 (100%)	66 (100%)	112 (100%)	0 (0%)	0 (0%)
Lung function								
FEV1%	61·6 (53·1 - 68·6)	61·8 (52·7 - 69·4)	61·0 (50·0 - 71·0)	57·0 (48·0 - 67·0)	61·7 (55·4 - 70·1)	68·0 (59·0 - 75·0)	64·0 (51·0 - 76·0)	..
Missing	0 (0%)	0 (0%)	12 (4%)	10 (3%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
FEV1/FVC ratio	62·5 (55·6 - 69·3)	62·2 (55·4 - 68·5)	60·0 (52·8 - 68·8)	61·3 (53·8 - 69·0)	60·9 (53·8 - 67·5)	63·3 (57·0 - 70·9)	62·6 (53·6 - 71·7)	..
Missing	0 (0%)	0 (0%)	12 (4%)	10 (3%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
FEV1 reversibility %	20·0 (15·0 - 30·0)	21·0 (16·0 - 33·0)	11·6 (5·13 - 19·2)	12·6 (5·75 - 22·0)	21·0 (15·0 - 28·0)	21·0 (16·0 - 29·0)	11·1 (4·69 - 21·6)	..
<12%	27 (7%)	27 (8%)	140 (47%)	122 (43%)	9 (14%)	5 (4%)	269 (52%)	..
⩾12%	335 (93%)	327 (92%)	134 (45%)	149 (52%)	56 (85%)	107 (96%)	248 (48%)	..
Missing	0 (0%)	0 (0%)	24 (8%)	16 (6%)	1 (2%)	0 (0%)	0 (0%)	218 (100%)
Inflammatory biomarkers								
Blood eosinophils (x10^9 cells/L)	0·230 (0·170 - 0·400)	0·240 (0·150 - 0·400)	0·325 (0·173 - 0·560)	0·300 (0·170 - 0·520)	0·290 (0·150 - 0·420)	0·220 (0·120 - 0·378)	0·250 (0·140 - 0·430)	0·250 (0·160 - 0·358)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (2%)
FeNO (ppb)	27 (15 - 50)	23 (14 - 42)	24 (14 - 47)	25 (14 - 42)	20 (14 - 33)	21 (14 - 36)	29 (16 - 57)	40 (23 - 76)
Missing	1 (0%)	2 (1%)	66 (22%)	89 (31%)	2 (3%)	2 (2%)	4 (1%)	0 (0%)
Total IgE (ng/mL)	172 (68 - 441)	174 (64 - 433)	161 (69 - 456)	186 (62 - 534)	156 (43 - 492)	232 (73 - 568)	198 (52 - 600)	..
Missing	0 (0%)	0 (0%)	7 (2%)	9 (3%)	0 (0%)	0 (0%)	0 (0%)	218 (100%)
Follow-up in trial								
Follow-up duration (days)	364 (363 - 365)	364 (362 - 365)	365 (363 - 366)	365 (363 - 367)	170 (114 - 226)	225 (222 - 226)	365 (365 - 368)	356 (299 - 358)
Total number of follow-up years, n	336	332	282	280	31	66	514	181
In trial severe exacerbations, n	282	207	277	272	21	48	855	23
>=1	133/362 (37%)	121/354 (34%)	139/298 (47%)	132/287 (46%)	15/66 (23%)	32/112 (29%)	311/517 (60%)	23/218 (11%)
None	229 (63%)	233 (66%)	159 (53%)	155 (54%)	51 (77%)	80 (71%)	206 (40%)	195 (89%)

TABLE S10 (continued)

	PACT (N=16)	PATHWAY (N=133)	PRACTICAL (N=307)	QUEST (N=634)	STRATOS_1 (N=388)	STRATOS_2 (N=413)	VERSE (N=50)
Demographics							
Age (years)	12 (12 - 13)	··	45 (29 - 59)	··	··	··	50 (41 - 61)
In categories	0 (0%)	130 (98%)	0 (0%)	634 (100%)	388 (100%)	413 (100%)	0 (0%)
Missing	0 (0%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sex (female)	5/16 (31%)	89/130 (68%)	170/307 (55%)	414/634 (65%)	255/388 (66%)	289/413 (70%)	26/50 (52%)
Missing	0 (0%)	3 (2.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Body Mass Index (kg/m2)	19·8 (18·4 - 23·4)	··	27·1 (23·9 - 30·1)	··	··	··	31·2 (27·3 - 35·2)
In categories	0 (0%)	130 (98%)	0 (0%)	634 (100%)	382 (98%)	318 (77%)	0 (0%)
Missing	0 (0%)	3 (2%)	0 (0%)	0 (0%)	6 (2%)	95 (23%)	0 (0%)
Smoking history							
Never smoked	16 (100%)	118 (89%)	216 (70%)	510 (80%)	300 (77%)	352 (85%)	··
Former smoker	0 (0%)	15 (11%)	77 (25%)	124 (20%)	88 (23%)	60 (15%)	··
Current smoker	0 (0%)	0 (0%)	14 (5%)	0 (0%)	0 (0%)	0 (0%)	··
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	50 (100%)
Ethnicity							
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	··	··	0 (0%)
Asian	0 (0%)	4 (3%)	20 (7%)	66 (10%)	··	··	1 (2%)
Black or African American	3 (19%)	2 (2%)	0 (0%)	0 (0%)	··	··	16 (32%)
Maori	0 (0%)	0 (0%)	20 (7%)	0 (0%)	··	··	0 (0%)
Multiple	1 (6%)	1 (1%)	0 (0%)	0 (0%)	··	··	1 (2%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	9 (3%)	0 (0%)	··	··	0 (0%)
Other	0 (0%)	1 (1%)	7 (2%)	34 (5%)	··	··	2 (4%)
White	12 (75%)	88 (66%)	251 (82%)	534 (84%)	··	··	30 (60%)
Missing	0 (0%)	37 (27.8%)	0 (0%)	0 (0%)	388 (100%)	413 (100%)	0 (0%)
Region							
Asia	0 (0%)	7 (5%)	0 (0%)	··	··	··	0 (0%)
Europe	0 (0%)	84 (63%)	0 (0%)	··	··	··	0 (0%)
North America	16 (100%)	4 (3%)	0 (0%)	··	··	··	50 (100%)
Oceania	0 (0%)	0 (0%)	307 (100%)	··	··	··	0 (0%)
South Africa	0 (0%)	1 (1%)	0 (0%)	··	··	··	0 (0%)
South America	0 (0%)	0 (0%)	0 (0%)	··	··	··	0 (0%)
Missing	0 (0%)	37 (28%)	0 (0%)	634 (100%)	388 (100%)	413 (100%)	0 (0%)

Comorbidities							
Any of: Allergic rhinitis, Eczema, and/or Food allergy	16/16 (100%)	44/115 (38%)	··	507/634 (80%)	189/388 (49%)	194/413 (47%)	43/50 (86%)
Missing	0 (0%)	18 (14%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Airborne allergen sensitisation	15/15 (100%)	··	··	··	118/388 (30%)	129/413 (31%)	29/50 (58%)
Missing	1 (6%)	133 (100%)	307 (100%)	634 (100%)	0 (0%)	0 (0%)	0 (0%)
Eczema	4/16 (25%)	11/130 (8%)	··	··	25/388 (6%)	31/413 (8%)	8/50 (16%)
Missing	0 (0%)	3 (2%)	307 (100%)	634 (100%)	0 (0%)	0 (0%)	0 (0%)
Allergic rhinitis	10/16 (62%)	41/115 (36%)	··	445/634 (70%)	180/388 (46%)	191/413 (46%)	43/50 (86%)
Missing	0 (0%)	18 (14%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chronic rhinosinusitis without nasal polyps	··	9/115 (8%) 3 / 112 (2·7%)	··	66 / 634 (10%)	36 / 388 (9·3%)	28 / 413 (6·8%)	4 / 50 (8·0%)
Missing	16 (100%)	21 (16%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chronic rhinosinusitis with nasal polyps	··	17/130 (13%)	··	105/634 (17%)	36/388 (9%)	47/413 (11%)	5/50 (10%)
Missing	16 (100%)	3 (2%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Psychiatric disease	··	7/115 (6%)	··	··	18/388 (5%)	16/413 (4%)	6/50 (12%)
Missing	16 (100%)	18 (14%)	307 (100%)	634 (100%)	0 (0%)	0 (0%)	0 (0%)
Baseline Asthma medication							
Treatment step							
Step 1	8 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Step 2	8 (50%)	0 (0%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Step 3	0 (0%)	0 (0%)	0 (0%)	4 (1%)	3 (1%)	14 (3%)	0 (0%)
Step 4	0 (0%)	73 (55%)	0 (0%)	294 (46%)	190 (49%)	194 (47%)	30 (60%)
Step 5	0 (0%)	60 (45%)	0 (0%)	336 (53%)	195 (50%)	205 (50%)	20 (40%)
ICS Dose							
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Low	16 (100%)	0 (0%)	307 (100%)	4 (1%)	3 (1%)	14 (3%)	1 (2%)
Medium	0 (0%)	73 (55%)	0 (0%)	294 (46%)	190 (49%)	194 (47%)	29 (58%)
High	0 (0%)	60 (45%)	0 (0%)	336 (53%)	195 (50%)	205 (50%)	20 (40%)
On SABA	16/16 (100%)	121/133 (91%)	307/307 (100%)	··	354/388 (91%)	383/413 (93%)	50/50 (100%)
Missing	0 (0%)	0 (0%)	0 (0%)	634 (100%)	0 (0%)	0 (0%)	0 (0%)
On LABA	0/16 (0%)	133/133 (100%)	··	616/634 (97%)	388/388 (100%)	413/413 (100%)	48/50 (96%)
Missing	0 (0%)	0 (0%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On LAMA	0/16 (0%)	6/133 (5%)	··	66/634 (10%)	25/388 (6%)	16/413 (4%)	1/50 (2%)
Missing	0 (0%)	0 (0%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On Montelukast	0/16 (0%)	40/133 (30%)	··	52/634 (8%)	135/388 (35%)	71/413 (17%)	17/50 (34%)
Missing	0 (0%)	0 (0%)	307 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
On mOCS	0/16 (0%)	11/133 (8%)	··	··	0/388 (0%)	0/413 (0%)	0/50 (0%)
Missing	0 (0%)	0 (0%)	307 (100%)	634 (100%)	0 (0%)	0 (0%)	0 (0%)

Adherence to medication							
Adherence pre-trial	..	100 (83·3 - 100)	50·0 (25·0 - 100)	..	92·9 (92·3 - 100)	100 (92·9 - 100)	91·5 (85·1 - 95·4)
Missing	16 (100%)	4 (3.0%)	1 (0.3%)	634 (100%)	0 (0%)	1 (0.2%)	0 (0%)
Adherence in trial	94·9 (90·7 - 98·8)	98·1 (89·5 - 99·4)	..	87·7 (71·7 - 95·6)	95·9 (90·2 - 98·6)	96·0 (89·4 - 98·6)	..
Missing	0 (0%)	1 (1%)	307 (100%)	4 (1%)	0 (0%)	1 (0%)	50 (100%)
Asthma symptoms and history							
ACQ-5 score	..	2·80 (2·40 - 3·20)	1·00 (0·400 - 1·50)	2·60 (2·20 - 3·20)	2·80 (2·20 - 3·20)	2·60 (2·00 - 3·20)	3·20 (2·80 - 3·40)
<1.5	..	7 (5%)	230 (75%)	5 (1%)	40 (10%)	40 (10%)	0 (0%)
⩾1.5	..	126 (95%)	77 (25%)	629 (99%)	346 (89%)	373 (90%)	48 (96%)
Missing	16 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	2 (4%)
Severe exacerbation or hospitalisation in past 12 months	4/16 (25%)	133/133 (100%)	37/307 (12%)	633/633 (100%)	388/388 (100%)	413/413 (100%)	25/50 (50%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Previous ICU or intubation	2/16 (12%)	1/94 (1%)	..	..	..	..	..
Missing	0 (0%)	39 (29%)	307 (100%)	634 (100%)	388 (100%)	413 (100%)	50 (100%)
Lung function							
FEV1%	98·0 (95·0 - 102)	58·5 (49·4 - 66·9)	..	60·5 (49·0 - 69·0)	61·5 (51·6 - 70·8)	61·9 (49·6 - 71·0)	64·9 (57·0 - 70·0)
Missing	0 (0%)	0 (0%)	307 (100%)	0 (0%)	3 (1%)	2 (0%)	0 (0%)
FEV1/FVC ratio	76·3 (75·7 - 85·4)	62·7 (55·7 - 70·7)	..	63·7 (55·9 - 70·7)	64·8 (55·9 - 72·8)	64·1 (56·0 - 73·7)	64·3 (54·0 - 69·6)
Missing	0 (0%)	0 (0%)	307 (100%)	0 (0%)	3 (1%)	2 (0%)	0 (0%)
FEV1 reversibility %	..	18·6 (11·0 - 29·1)	..	21·6 (14·1 - 34·3)	17·7 (9·02 - 29·4)	19·8 (12·1 - 32·5)	16·0 (13·3 - 19·8)
<12%	..	37 (28%)	..	100 (16%)	114 (29%)	99 (24%)	7 (14%)
⩾12%	..	96 (72%)	..	534 (84%)	271 (70%)	312 (76%)	43 (86%)
Missing	16 (100%)	0 (0%)	307 (100%)	0 (0%)	3 (1%)	2 (0%)	0 (0%)
Inflammatory biomarkers							
Blood eosinophils (x10^9 cells/L)	0·357 (0·190 - 0·512)	0·300 (0·162 - 0·576)	0·230 (0·140 - 0·340)	0·270 (0·140 - 0·480)	0·200 (0·120 - 0·320)	0·220 (0·140 - 0·330)	0·245 (0·148 - 0·298)
Missing	0 (0%)	7 (5%)	1 (0%)	1 (0%)	7 (2%)	2 (0%)	0 (0%)
FeNO (ppb)	55 (21 - 75)	22 (12 - 46)	27 (17 - 52)	26 (15 - 47)	20 (11 - 38)	23 (14 - 40)	17 (11 - 28)
Missing	1 (6%)	1 (1%)	0 (0%)	11 (2%)	2 (1%)	6 (1%)	2 (4%)
Total IgE (ng/mL)	..	148 (84 - 398)	..	177 (60 - 446)	166 (54 - 405)	165 (55 - 494)	144 (53 - 547)
Missing	16 (100%)	0 (0%)	307 (100%)	4 (1%)	5 (1%)	6 (1%)	0 (0%)
Follow-up in trial							
Follow-up duration (days)	360 (350 - 372)	365 (365 - 365)	364 (362 - 366)	365 (363 - 366)	365 (365 - 367)	365 (363 - 366)	170 (116 - 274)
Total number of follow-up years, n	15	133	281	615	380	387	25
In trial severe exacerbations, n	11	95	47	631	244	309	17
>=1	7/16 (44%)	41/133 (31%)	43/307 (14%)	271/634 (43%)	128/388 (33%)	168/413 (41%)	10/50 (20%)
None	9 (56%)	92 (69%)	264 (86%)	363 (57%)	260 (67%)	245 (59%)	40 (80%)

TABLE S11. Exploration of combined BEC and FeNO matrices prevalence (%) and prognostic values for a future severe asthma attack at different biomarker cutoffs

A. Pre-defined biomarker-stratified rate ratios, expressed relatively to entire study population

11.1. FeNO 25 and 50 ppb, and BEC 0.15 and 0.30×10^9 cells/L cut-points

FeNO ≥ 50 ppb	0.96 (0.71-1.28); **2.3%**	1.18 (0.98-1.43); **5.0%**	1.47 (1.30-1.66); **12.4%**
FeNO 25-<50 ppb	0.85 (0.70-1.03); **5.9%**	0.94 (0.81-1.10); **9.2%**	1.26 (1.11-1.44); **12.3%**
FeNO < 25 ppb	0.76 (0.68-0.86); **19.7%**	0.79 (0.70-0.89); **18.3%**	0.96 (0.85-1.10); **14.9%**
	BEC < 0.15 *10^9 cells/L	BEC 0.15-<0.30 *10^9 cells/L	BEC ≥ 0.30 *10^9 cells/L

B. Post hoc biomarker-stratified rate ratios, expressed relatively to entire study population:

11.2. FeNO 20 and 35 ppb cut-points

FeNO ≥ 35 ppb	0.96 (0.78-1.18); **4.6%**	1.16 (1.01-1.34); **8.9%**	1.50 (1.36-1.66); **18.3%**
FeNO 20-<35 ppb	0.78 (0.64-0.94); **6.3%**	0.87 (0.74-1.03); **8.3%**	1.13 (0.97-1.31); **9.8%**
FeNO < 20 ppb	0.77 (0.68-0.87); **17.0%**	0.76 (0.67-0.87); **15.3%**	0.91 (0.79-1.06); **11.4%**
	BEC < 0.15 *10^9 cells/L	BEC 0.15-<0.30 *10^9 cells/L	BEC ≥ 0.30 *10^9 cells/L

11.3. FeNO 25 and 40 ppb cut-points

FeNO ≥ 40 ppb	0.95 (0.75-1.21); **3.4%**	1.17 (0.99-1.37); **6.9%**	1.48 (1.33-1.65); **15.7%**
FeNO 25-<40 ppb	0.83 (0.68-1.03); **4.8%**	0.90 (0.75-1.07); **7.3%**	1.21 (1.04-1.40); **9.0%**
FeNO < 25 ppb	0.76 (0.68-0.86); **19.7%**	0.79 (0.70-0.89); **18.3%**	0.96 (0.85-1.10); **14.9%**
	BEC < 0.15 *10^9 cells/L	BEC 0.15-<0.30 *10^9 cells/L	BEC ≥ 0.30 *10^9 cells/L

11.4. FeNO 20 and 50 ppb cut-points

FeNO ≥ 50 ppb	0.96 (0.71-1.28); **2.3%**	1.18 (0.98-1.43); **5.0%**	1.47 (1.30-1.66); **12.4%**
FeNO 20-<50 ppb	0.83 (0.70-0.97); **8.7%**	0.95 (0.83-1.09); **12.2%**	1.25 (1.11-1.41); **15.8%**
FeNO < 20 ppb	0.77 (0.68-0.87); **17.0%**	0.76 (0.67-0.87); **15.3%**	0.91 (0.79-1.06); **11.4%**
	BEC < 0.15 *10^9 cells/L	BEC 0.15-<0.30 *10^9 cells/L	BEC ≥ 0.30 *10^9 cells/L

Rate ratio's (95% confidence intervals) adjusted for FEV_1% pre-bronchodilator, attack history, ACQ-5 score, treatment step (all measured at baseline), offset of the follow-up duration and study. BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

C. Post hoc biomarker-stratified rate ratios, expressed relatively to the lowest biomarker combination:

11.5. FeNO 25 ppb and BEC 0.15 $\times 10^9$ cells/L cut-points

FeNO ≥ 25 ppb	1.14 (0.94-1.38); **8.1%**	1.55 (1.37-1.75); **39.0%**
FeNO < 25 ppb	1.00 (Reference); **19.7%**	1.13 (0.99-1.28); **33.1%**
	BEC < 0.15 *10^9 cells/L	BEC ≥ 0.15 *10^9 cells/L

11.6. FeNO 25 ppb or BEC 0.15 $\times 10^9$ cells/L cut-points

FeNO < 25 ppb **AND** BEC < 0.15 *10^9 cells/L	1.00 (Reference); **19.7%**
FeNO ≥ 25 ppb **AND/OR** BEC ≥ 0.15 *10^9 cells/L	1.33 (1.18-1.49); **80.3%**

Rate ratio's (95% confidence intervals) adjusted for FEV_1% pre-bronchodilator, attack history, ACQ-5 score, treatment step (all measured at baseline), offset of the follow-up duration and study. BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

TABLE S12. Exploration of combined FEV_1% of predicted pre-bronchodilator and post-bronchodilator prevalence (%) and prognostic value for a future severe asthma attack

FEV_1% post-BD ≥ 80	0.85 (0.73-0.99); **10.5%**	0.78 (0.68-0.89); **15.7%**	0.85 (0.73-0.99); **13.3%**
FEV_1% post-BD > 70 & < 80	0.86 (0.76-0.98); **16.0%**	0.94 (0.78-1.14); **6.6%**	0.84 (0.41-1.72); **0.9%**
FEV_1% post-BD < 70	1.35 (1.24-1.47); **35.7%**	1.58 (0.95-2.61); **1.1%**	2.51 (0.69-9.10); **0.2%**
	FEV_1% pre-BD < 70	FEV_1% pre-BD > 70 & < 80	FEV_1% pre-BD ≥ 80

Rate ratio's (95% confidence intervals) adjusted for attack history, ACQ-5 score, treatment step (all measured at baseline), offset of the follow-up duration and study. BD, bronchodilator; FEV_1, forced expiratory volume in the first second.

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