Interactive Pathways of Key Prognostic Factors in Severe Asthma: A Bayesian Network Comparison of Clinical Trials & Real-World Data

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Aim and Methods

Rationale

Risk predictors for severe asthma may interact differently in clinical trials versus real-world settings, affecting clinical risk prediction validity.

Aim

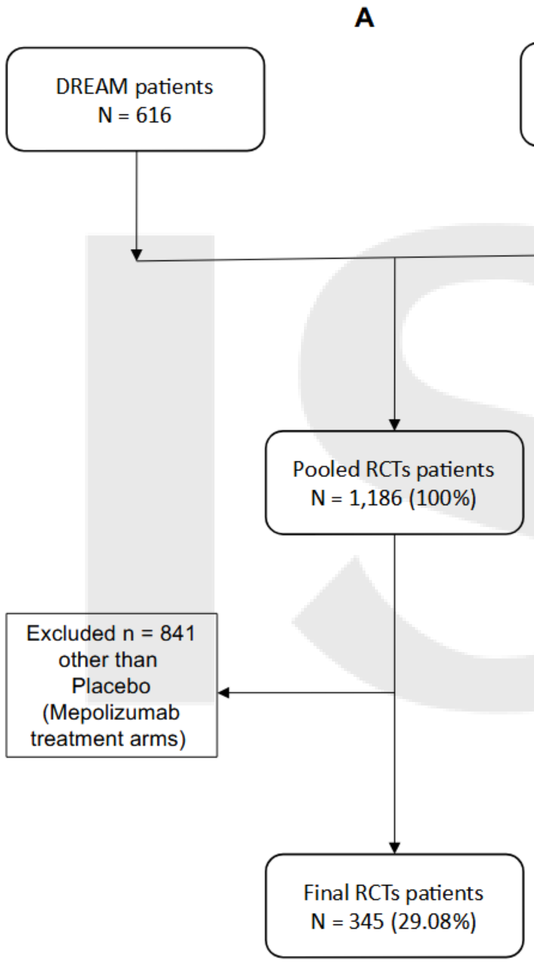
To compare the essential interactive pathways of key risk factors leading to severe asthma exacerbations across randomised controlled trials (RCTs) and real-world data (RWD).

Methods

- **Data sources:** Two RCTs (DREAM and MENSA) and RWD from the International Severe Asthma Registry (ISAR).
- **Study population:** RCT placebo-arm patients (>12 years) with ≤1 year follow-up, and ISAR severe asthma patients ≥18 years not receiving biologics at baseline.
- **Outcome:** Severe asthma exacerbations within 365 days, categorized as 0, 1, or ≥2 events.
- **Statistical analyses:** A Bayesian network model combing expert knowledge and machine learning algorithms identified key predictors and pathways, with external validation across RCT and ISAR datasets.

ISAR: International Severe Asthma Registry, RCT: Randomised Controlled Trial, DREAM: Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma, MENSA: Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma

Patient Selection Flowcharts



A

DREAM patients
N = 616

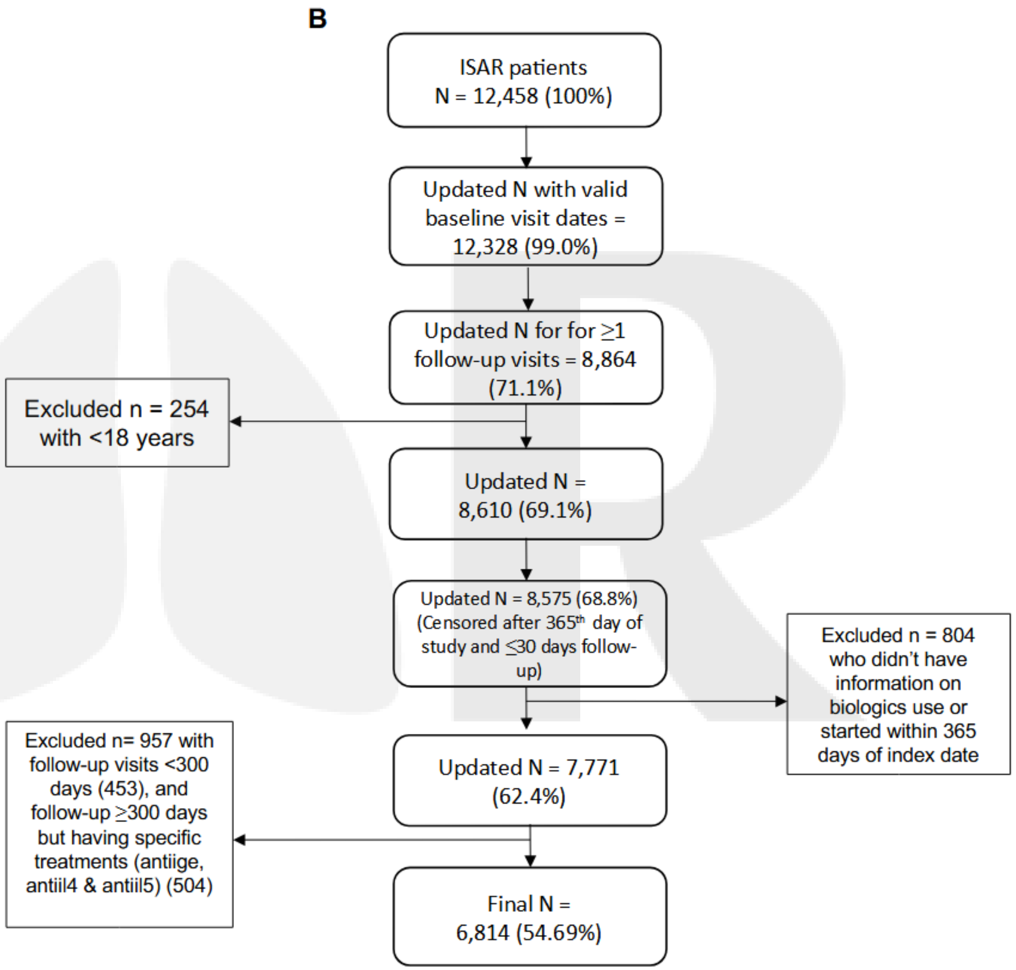
MENSA patients
N = 570

Pooled RCTs patients
N = 1,186 (100%)

Excluded n = 841 other than Placebo (Mepolizumab treatment arms)

Final RCTs patients
N = 345 (29.08%)

Flow diagram of RCTs



B

ISAR patients
N = 12,458 (100%)

Updated N with valid baseline visit dates = 12,328 (99.0%)

Updated N for for ≥1 follow-up visits = 8,864 (71.1%)

Excluded n = 254 with <18 years

Updated N =
8,610 (69.1%)

Updated N = 8,575 (68.8%) (Censored after 365th day of study and ≤30 days follow-up)

Excluded n = 804 who didn't have information on biologics use or started within 365 days of index date

Updated N = 7,771 (62.4%)

Excluded n= 957 with follow-up visits <300 days (453), and follow-up ≥300 days but having specific treatments (antiige, antiil4 & antiil5) (504)

Final N =
6,814 (54.69%)

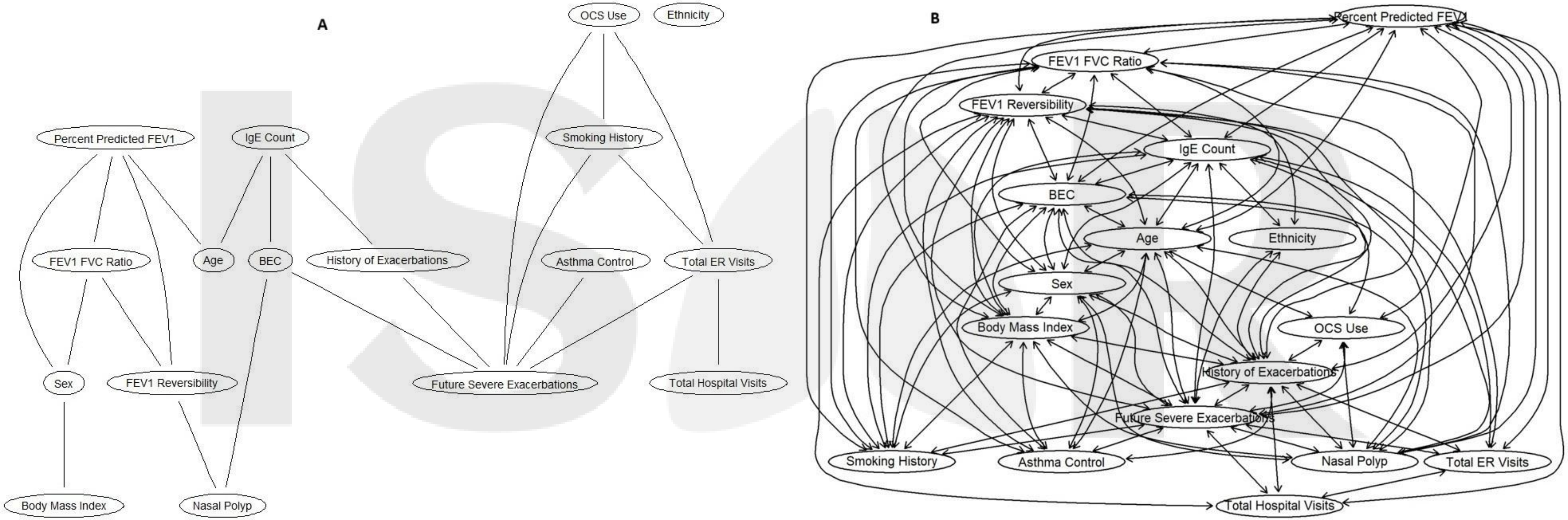
Flow diagram of ISAR cohort

ISAR: International Severe Asthma Registry, RCT: Randomised Controlled Trial, DREAM: Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma, MENSA: Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma

Comparison of the local interactive network of 16 core predictors

Structure plot showing parents and children among predictors for RCTs (A) and ISAR (B).

Of note: FeNO was unavailable in RCTs



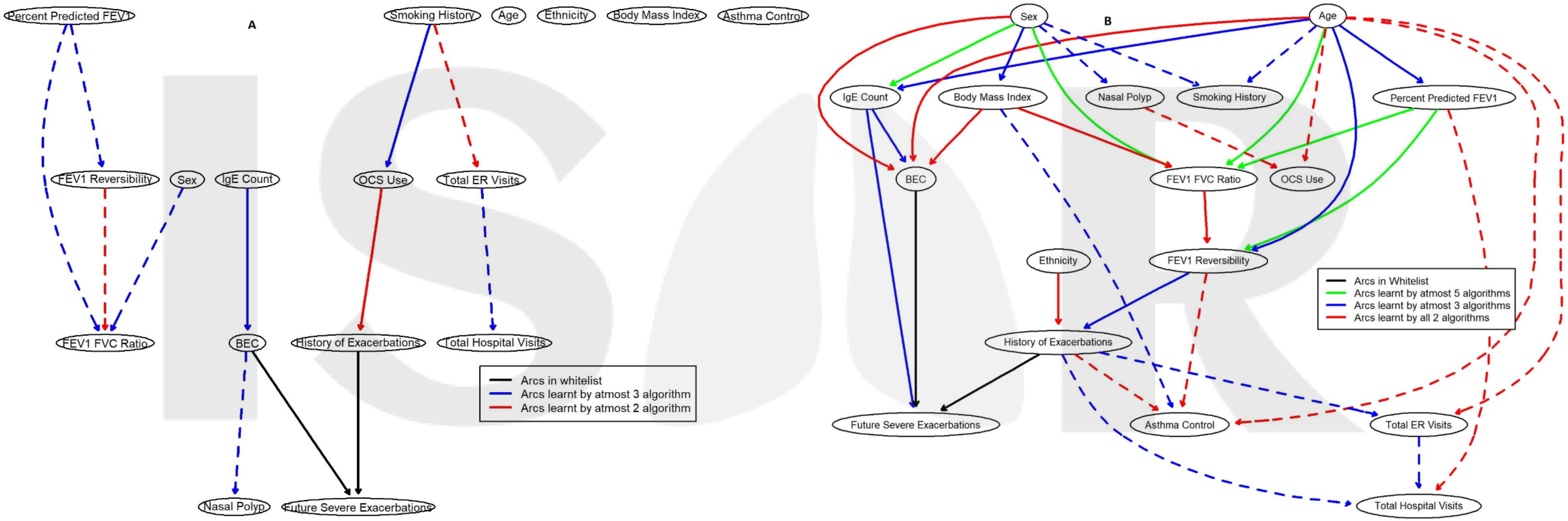
RCTs: 44 arcs; key connected nodes included ER visits, % predicted FEV_1, IgE, OCS use, FEV_1 reversibility, prior severe exacerbations, and smoking. 6 predictors (BEC, prior exacerbations, asthma control, OCS use, smoking, ER visits) directly predicted 12-month severe exacerbations.

ISAR: 170 arcs identified; highly connected nodes included prior exacerbations, % predicted FEV_1, sex, BMI, age, BEC, lung function measures, IgE, smoking, and nasal polyps. 15 variables directly predicted 12-month severe exacerbations.

OCS: Oral Corticosteroids, BEC: Blood Eosinophil Count, IgE: Immunoglobulin E, FEV1: Forced Expiratory Volume 1 second, FVC: Forced Vital Capacity, ISAR: International Severe Asthma Registry, RCT: Randomised Controlled Trial, SAE: Severe Asthma Exacerbation, ER: Emergency Room, FeNO: Fractional Exhaled Nitric Oxide

Comparison of Machine Learning-selected core prediction pathways

Bayesian network from combined 5 machine learning algorithms for RCTs (A) and ISAR (B). Bold lines: direct prediction pathways toward the outcome; dotted lines: prediction pathways without direct impact.



RCT Bayesian network:

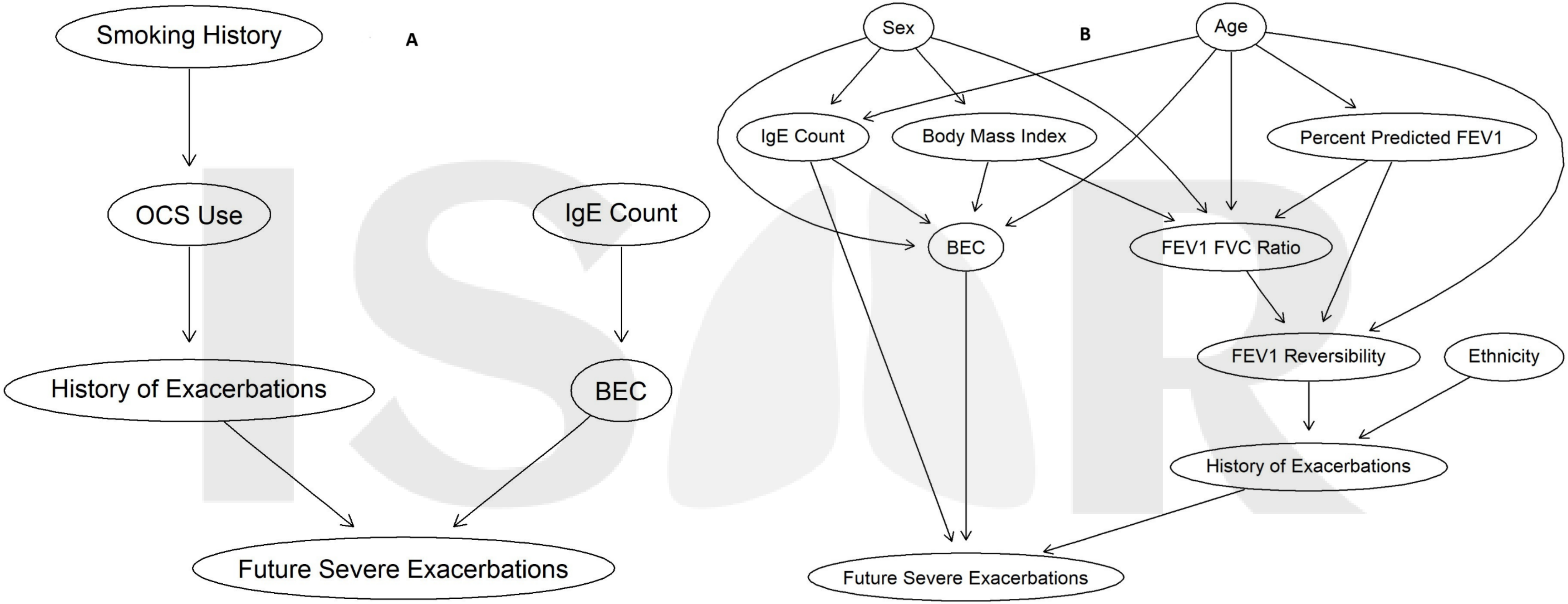
- Two key pathways to severe exacerbations: **IgE → BEC → future SAEs** and **history of SAEs → future SAEs**; smoking influenced risk indirectly via **OCS use and prior exacerbations**.

ISAR Bayesian network:

- Same **two core pathways**, but with **more complex upstream interactions**, where **age and sex influenced IgE/BEC and lung function**, which then affected prior exacerbations..

OCS: Oral Corticosteroids, BEC: Blood Eosinophil Count, IgE: Immunoglobulin E, FEV1: Forced Expiratory Volume 1 second, FVC: Forced Vital Capacity, ISAR: International Severe Asthma Registry, RCT: Randomised Controlled Trial, SAE: Severe Asthma Exacerbation, ER: Emergency Room

Final Bayesian Networks learned under RCTs (A) and ISAR (B) settings.



Final RCT network:

- Simplified model confirmed **two main drivers of SAEs: IgE–BEC pathway and prior exacerbation history**, with limited influence from demographics or lung function.

Final ISAR network:

- Final model retained **the same core pathways**, while showing broader upstream influences from **age, sex, ethnicity, and lung function** shaping exacerbation risk.

OCS: Oral Corticosteroids, BEC: Blood Eosinophil Count, IgE: Immunoglobulin E, FEV1: Forced Expiratory Volume 1 second, FVC: Forced Vital Capacity, ISAR: International Severe Asthma Registry, RCT: Randomised Controlled Trial

Performance of RCTs-derived and ISAR-derived BN models

External validation (Tested RCTs-Bayesian Network [BN] in ISAR population and ISAR-BN in RCTs population)

Performance Metrices	**RCTs-derived BN in the ISAR cohort**		**ISAR-derived BN in the RCT cohort**	
	Adaptive Synthetic Cases	Original cases	Adaptive Synthetic Cases	Original cases
AUC	0.67	0.68	0.62	0.50
Specificity	0.74	0.76	0.71	0.67
Precision	0.50	0.49	0.41	0.83
Recall	0.50	0.50	0.42	0.33
F1-score	0.49	0.47	0.40	0.91
Accuracy	0.62	0.63	0.56	0.50

RCTs: randomized control trials; ISAR: International Severe Asthma Registry; BN: Bayesian network; AUC: area under the ROC curve, which plots the true positive rate against the false positive rate; Specificity: measures the proportion of true negatives correctly identified by the model; Precision: indicates the proportion of true positives among all positive predictions made by the model; Recall: measures the proportion of true positives correctly identified among all actual positive instances.; F1-score: Represents the harmonic mean of precision and recall and provides a balance between precision and recall; Accuracy: indicates the proportion of correct predictions made by the model among all predictions.

Note: The ranges for these metrics vary from 0 to 1, where higher values indicate better performance.

Findings

- **RCT-derived Prediction Pathway Model:** Showed consistent external validity in RWD datasets (AUC ≈ 0.67–0.68), indicating good transferability from RCT to real-world settings.

- **ISAR-derived Prediction Pathway Model:** Demonstrated weaker transferability to RCT data (AUC: 0.62 synthetic; 0.50 original), suggesting RWD relationships may not generalize to controlled trial environments.

Conclusions

- **Consistent core predictors:** Across both RCT and real-world data, **blood eosinophil count (modulated by IgE level)** and **prior exacerbation history** formed two main downstream pathways predicting future severe asthma exacerbations.

- **Greater complexity in RWD:** While predictive performance was comparable, the **ISAR network revealed more complex upstream interactions and additional risk factors** not captured in RCT-modelled pathways.

- **Complementary value of RWD:** Findings highlight the importance of **integrating RWD with RCT evidence to validate prediction mechanisms and uncover broader risk patterns**. Combining both data sources may support more personalized and adaptable risk prediction and management strategies for severe asthma.

- **Limitation:** FeNO was unavailable in the RCT data, despite it was a core downstream predictor of severe exacerbations in ISAR data.

ISAR: International Severe Asthma Registry, RCT: Randomised Controlled Trial, RWD: Real-World Data, FeNO: Fractional exhaled Nitric Oxide, IgE: Immunoglobulin E