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Correspondence to “The effectiveness of pollen allergen immunotherapy on allergic rhinitis over 18 years: A national cohort study in Denmark”.

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Correspondence to "The effectiveness of pollen allergen immunotherapy on allergic rhinitis over 18 years: A national cohort study in Denmark".

To the Editor,

We read with interest the publication by Bager et al.[1] The literature on long-term effectiveness in allergen immunotherapy (AIT) remains limited. The findings from Bager et al. hold promise in broadening our knowledge in this area by employing a large national cohort. We acknowledge the inherent challenges associated with conducting registry studies within respiratory allergies using Danish registries, which lead to structural limitations that warrant specialist consideration during study design. In the REACT study by Fritzsching et al.[2], which applied rigorous methodology and was preregistered on ClinicalTrials.gov, AIT showed long-term effectiveness for up to 9 years in a study population with confirmed physician diagnosis of allergic rhinitis (AR) in Germany. We would like to highlight four key factors that may have influenced the interpretability and generalisability of the outcomes in Bager et al.

Firstly, the Danish registries lack confirmed diagnosis for AR, requiring alternative methods to identify patients with AR. A commonly applied method is the use of prescription fills as a surrogate marker for a diagnosis of AR. Bager et al. refers to a validation study by Stensballe et al.[3] conducted in a paediatric cohort. The study demonstrates a low positive predictive value (PPV) of 53-65% for clinical AR diagnosis when using intranasal corticosteroids (INCS) as a proxy in children. However, the PPV in Bager et al. may be lower still due to the presence of other common conditions in adults, such as nonallergic rhinitis and chronic rhinosinusitis with or without nasal polyps, which require treatment with INCS [4, 5]. This may result in misclassification of patients and introduce bias. Furthermore, the inclusion criteria applied in the study by Bager et al. differs significantly from the validated algorithms by Stensballe et al. in terms of the heterogeneity of the study population, the duration of the baseline period, types of medication and number of required prescriptions. Another validation study by Leth-Møller et al.[6] suggests that the algorithm using ≥1 INCS yielded the lowest PPV out of 13 tested algorithms. Bager et al. uses a sensible inclusion criterion with ≥1 INCS prescription during the pollen season. However, patients with INCS prescriptions outside the pollen season are not excluded, increasing the likelihood of confounding factors, such as inclusion of polyallergic patients with AR, including perennial allergies. In addition, the study population is required to have ≥1 INCS prescription in the 3 preceding pollen seasons, meaning that patients with mild disease who are not eligible for AIT may be included.

Secondly, Rosenbaum and Rubin noted that for the propensity score to be valid, exposure to the treatment of interest had to be *strongly ignorable* as a source of risk[7]. This has only been partially achieved as there are some observed markers of severity such as hospitalisations, which are numerically greater in the treated group at baseline. Inadequate matching at baseline may consequently result in confounding by indication and affect the interpretability of the outcomes[8].

Thirdly, the authors study a very selected cohort of treated patients excluding approximately 50% of all AIT treated patients with INCS use in the three preceding pollen seasons (Bager et al. Figure 1), and thereby significantly reducing the generalisability of the outcomes.

Fourthly, using a binary "use or non-use" approach for INCS to measure the effectiveness of AIT is, in our opinion, inadequate. Clinical trials have consistently shown sustained efficacy of AIT beyond cessation of treatment, indicative of disease modification as measured by lessening symptoms and decreasing the necessity for symptomatic drugs compared with placebo[9]. However, AIT has yet to be conclusively demonstrated as a fully "curative" treatment, as suggested in the analyses conducted by Bager et al.

In conclusion, the study by Bager et al. has several methodological concerns which may influence the interpretability of the outcomes.

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[1] Bager P, Poulsen G, Wohlfahrt J, Melbye M. The effectiveness of pollen allergen immunotherapy on allergic rhinitis over 18 years: A national cohort study in Denmark. Allergy. 2024; 00: 1-14. doi:10.1111/all.16026

[2] Fritzsching B, Contoli M, Porsbjerg C, et al. Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: results from the REACT study, a retrospective cohort study. Lancet Reg Health Eur. 2022; 13:100275. doi:10.1016/j.lanepe.2021.100275

[3] Stensballe LG, Klansø L, Jensen A, Hærskjold A, Thomsen SF, Simonsen J. The validity of register data to identify children with atopic dermatitis, asthma or allergic rhinoconjunctivitis. Pediatr Allergy Immunol. 2017; 28: 535–542. https://doi.org/10.1111/pai.12743

[4] Mølgaard, E., Thomsen, S.F., Lund, T., Pedersen, L., Nolte, H. and Backer, V. (2007), Differences between allergic and nonallergic rhinitis in a large sample of adolescents and adults. Allergy, 62: 1033-1037. https://doi.org/10.1111/j.1398-9995.2007.01355.x

[5] Stevens WW, Schleimer RP, Kern RC. Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2016 Jul-Aug;4(4):565-72. doi: 10.1016/j.jaip.2016.04.012.

[6] Leth-Møller KB, Skaaby T, Madsen F, Petersen J, Linneberg A. Can we identify allergic rhinitis from administrative data: A validation study. Pharmacoepidemiol Drug Saf. 2020; 29: 1423–1431. https://doi.org/10.1002/pds.5120

[7] Rosenbaum, Paul R., and Donald B. Rubin. "The Central Role of the Propensity Score in Observational Studies for Causal Effects." Biometrika 70, no. 1 (1983): 41–55. https://doi.org/10.2307/2335942.

[8] Freemantle N, Marston L, Walters K, Wood J, Reynolds MR, Petersen I. Making inferences on treatment effects from Real World data? Propensity Scores, Confounding by Indication and other Perils for the Unwary in Observational Research. BMJ, 2013 2013;347:f6409 doi: 10.1136/bmj.f6409.

[9] Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*. 2018; 73: 765–798. https://doi.org/10.1111/all.13317