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Short communication

The interplay between obesity and blood neutrophils in adult-onset asthma

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To the Editor,

Obesity is an established risk factor for the development of asthma in adults [1], often associated with a type-2 low phenotype [2]. Further, obese individuals with asthma have poorer asthma control and prognosis than non-obese individuals with asthma [2–4].

We have previously shown that severe obesity and blood neutrophils matter for both asthma control [5] and severity of adult onset asthma [6]. It is possible that not only their independent effects matter [6], but likely, the interplay between obesity and neutrophils contribute to poorer outcomes. Thus, more knowledge is needed, as good asthma control is the primary goal of asthma management.

We aimed to investigate the associations between obesity and blood neutrophils, and whether the levels of blood neutrophils influence the associations between obesity and asthma control, in adult-onset asthma.

1. Methods

Population-based samples have been recruited since 1985 within the Obstructive Lung disease In Northern Sweden (OLIN) studies. In 2019–2020, previous participants were invited to follow-ups including structured interviews, spirometry, measurements of fractional exhaled nitric oxide (FeNO), and blood sampling, in which n = 251 with asthma onset after 15 years of age participated. Data on blood cell counts were available for n = 233, and blood neutrophils were dichotomized using two thresholds (4.0 and 5.0*10^9/L, respectively [7,8]). Body Mass Index (BMI) was calculated as kg/m^2 and categorized as: underweight (<18.5), normal/healthy weight (18.5–24.99), overweight (25.0–29.99), obesity (30.0–34.99) and severe obesity (≥35). Uncontrolled asthma was defined according to ERS/ATS [9] based on at least one of a) Asthma Control Test score≤19, b) frequent severe exacerbations during the last 12 months (≥2 bursts of oral corticosteroids last 12 months), c) serious exacerbations during the last 12 months (≥1 hospitalization), or d) airflow limitation (FEV_1<80 % predicted and FEV_1/FVC < Lower Limit of Normal).

Means were compared across groups using ANOVA, while the Chi-squared test was used to compare proportions. Statistical significance was set at $p < 0.05$. Multivariable logistic regression was utilized to estimate odds ratios (OR) with 95 % confidence intervals (CI) adjusted for age, sex, pack-years of smoking and inhaled corticosteroids (ICS) dose according to Global Initiative for Asthma (GINA, 2019).

2. Results

In the total sample (n = 233), 66.1 % were women, mean age: 62.7 years, mean BMI: 29.1, and 0.0 % had underweight, 22.2 % normal weight, 41.1 % overweight, 26.2 % obesity, and 10.5 % severe obesity. The largest proportion with uncontrolled asthma (50.0 %) and lowest mean FEV_1 (83.0 %) and FVC (82.6 %) percent of predicted were observed in individuals with severe obesity. Allergic sensitization, FeNO and blood eosinophils did not differ significantly between BMI categories.

Regarding the association between BMI categories and neutrophils, mean (SD) blood neutrophils (*10^9/L) differed accordingly: 3.7 (1.7) in normal weight, 3.5 (1.4) in overweight, 3.7 (1.3) in obesity, and 5.3 (1.6) in severe obesity ($p < 0.001$). When dichotomizing blood neutrophils by different thresholds, the highest proportions were consistently seen in severe obesity, among which e.g. 83.3 % had blood neutrophils≥4.0*10^9/L compared to 31.5 % in normal weight ($p < 0.001$). The association between severe obesity and blood neutrophils≥4.0*10^9/L was significant also in the multivariable models (OR

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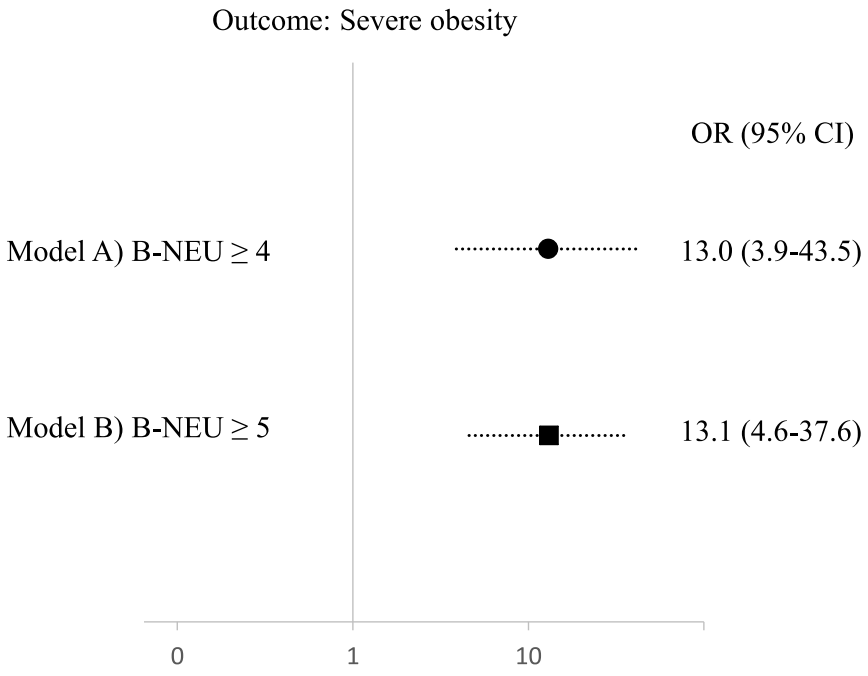

Fig. 1. Associations between severe obesity (body mass index ≥35) and levels of blood neutrophils (*10^9/L) in adult-onset asthma. Results are expressed as odds ratios (OR) with 95 % confidence intervals (CI) from two separate logistic regression models (Model A using the cut-off ≥4*10^9/L and Model B using the cut-off ≥5*10^9/L for blood neutrophil count) adjusted for age, sex, packyears of smoking and ICS dose. X-axis is presented on log scale.

13.0 (95%CI 3.9–43.5)), and the corresponding OR for neutrophils≥5.0*10^9/L was 13.1 (95%CI 4.6–37.6) (Fig. 1).

When both severe obesity and blood neutrophils≥4.0*10^9/L were included in the same multivariable model using uncontrolled asthma as outcome, the ORs for severe obesity and blood neutrophils≥4.0*10^9/L were 1.8 (95%CI 0.7–4.7) and 1.6 (95%CI 0.8–2.9), respectively. The corresponding ORs using the neutrophil cut-off ≥5.0*10^9/L were 1.4 (95%CI 0.5–3.9) for severe obesity and 2.7 (95%CI 1.3–5.8) for blood neutrophils≥5.0*10^9/L. Compared to the reference group BMI<30 and blood neutrophils<5*10^9/L, BMI≥30 with blood neutrophils≥5*10^9/L was associated with uncontrolled asthma (OR 2.8, 95%CI 1.1–7.3), while no such association was found for BMI≥30 with blood neutrophils<5*10^9/L. In the same model, blood neutrophils ≥5*10^9/L with BMI<30 was significantly associated with uncontrolled asthma (OR 4.1, 95%CI 1.5–11.3).

3. Discussion

In this population-based based study on adult-onset asthma, we found higher levels of blood neutrophils in severely obese individuals compared to individuals with normal weight. Further, the association between obesity and uncontrolled asthma was only significant in combination with increased levels of blood neutrophils.

Obesity may in itself contribute to a low-grade inflammation [10,11] and the mechanisms underlying the association include both mechanical and inflammatory effects on lungs and airways [12]. It is increasingly recognized that neutrophils actively contribute to obesity-associated inflammation and related complications [11]. Obesity may both increase the levels and alter the function of blood neutrophils [11], and here we show that the association between obesity and uncontrolled asthma differed depending on the presence or absence of higher levels of blood neutrophils. Thus, the interplay between obesity and blood neutrophils may be of importance with regards to asthma control assessed both as symptom control, lung function and exacerbation history. One potential explanation would be the effect of excess adipose tissue which neutrophils are the first cells to infiltrate. The neutrophils may thereby get activated and release inflammatory factors that recruit macrophages and other immune cells [11]. This may lead to increased pro-inflammatory cytokines of importance in asthma severity, such as interleukin-6 and tumour necrosis factor-alpha [13]. These can in turn recruit more neutrophils to the airways [14], contributing to further inflammation [15], airway narrowing and a more severe asthma [16–19], and also contribute to systemic inflammation. These immunological effects can impact the process by which neutrophils destroy invading organisms, and the affected individuals may recover less efficiently from respiratory infections and present as more symptomatic, supported by recent findings of a link between high blood neutrophils and obesity and increased use of antimicrobials [8].

Of note, although not directly measured in the target organ, i.e. the lungs, the use of blood cell counts may still be biologically plausible since the infiltrating granulocytes in the airway are bone marrow-derived cells which access the airway via the circulation [7,20]. In contrast to induced sputum, blood cell counts also offer a feasible method both in the clinics and for population-based studies.

In conclusion, the results of this population-based study on adult-onset asthma confirm a strong association between severe obesity and blood neutrophils. It also suggests that the association between obesity and uncontrolled asthma may be at least partly mediated by the levels of blood neutrophils. Our results highlight the importance of including blood neutrophils in addition to BMI in our clinical evaluation of adult-onset asthma.

CRediT authorship contribution statement

Helena Backman: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sofia Winsa Lindmark:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Linnea Hedman:** Writing – review & editing, Project administration, Methodology,

Investigation, Funding acquisition. **Hannu Kankaanranta:** Writing – review & editing. **Katja Warm:** Writing – review & editing, Data curation. **Anne Lindberg:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition. **Apostolos Bossios:** Writing – review & editing. **Eva Rönmark:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition. **Caroline Stridsman:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

None of the authors have any conflicts of interest directly related to the submitted work. HB reports personal fees for lectures from AstraZeneca, Boehringer-Ingelheim and GlaxoSmithKline outside the submitted work. AB reports a grant from AstraZeneca and lecture fees from Chiesi paid to his institution outside the submitted work. HK reports fees for lectures and/or consulting from AstraZeneca, Boehringer-Ingelheim, Chiesi, COVIS Pharma, GSK, MedScape, MSD, Novartis, Orion Pharma and Sanofi, outside the submitted work. KW reports a personal fee for lecctures from Astra Zeneca outside the submitted work. CS reports personal fees and institutional fees from AstraZeneca, Chiesi and TEVA, and fees for Advisory Board work for AstraZeneca, all outside the submitted work. AL reports personal fees for lectures at educational events from Boehringer-Ingelheim and Novartis, and for Advisory Board work from AstraZeneca, Boehringer Ingelhem, GlaxoSmithKline, and Novartis, all outside the submitted work. SWL, LH, and ER have no conflicts of interests to disclose related to the submitted work.

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References

[1] E. Ronmark, C. Andersson, L. Nystrom, B. Forsberg, B. Jarvholm, B. Lundback, Obesity increases the risk of incident asthma among adults, Eur. Respir. J. 25 (2) (2005 Feb) 282–288.

[2] Global Initiative for Asthma, Global strategy for asthma management and prevention, Available at, www.ginasthma.org/gina-reports/, 2023.

[3] H. Backman, C. Stridsman, L. Hedman, L. Ronnebjerg, B.I. Nwaru, T. Sandstrom, et al., Determinants of severe asthma - a long-term cohort study in northern Sweden, J. Asthma Allergy 15 (2022 October 10) 1429–1439.

[4] P. Ilmarinen, A. Pardo, L.E. Tuomisto, I. Vahatalo, O. Niemela, P. Nieminen, et al., Long-term prognosis of new adult-onset asthma in obese patients, Eur. Respir. J. 57 (4) (2021 Apr 1) 2001209.

[5] K. Warm, L. Hedman, C. Stridsman, A. Lindberg, E. Ronmark, H. Backman, Age-related differences in associations between uncontrolled asthma, comorbidities and biomarkers in adult-onset asthma, J. Asthma (2023 July 10) 1–9.

[6] S. Winsa-Lindmark, C. Stridsman, A. Sahlin, L. Hedman, N. Stenfors, T. Myrberg, A. Lindberg, E. Rönmark, H. Backman, Severity of adult-onset asthma - a matter of blood neutrophils and severe obesity, Respir. Med. 219 (2023 Sep 27) 107418.

[7] T. Tsiavia, J. Henny, M. Goldberg, M. Zins, N. Roche, L. Orsi, et al., Blood inflammatory phenotypes were associated with distinct clinical expressions of asthma in adults from a large population-based cohort, EBioMedicine 76 (2022 February 01) 103875.

[8] E. Flinkman, I. Vahatalo, L.E. Tuomisto, L. Lehtimaki, P. Nieminen, O. Niemela, et al., Association between blood eosinophils and neutrophils with clinical features in adult-onset asthma, J. Allergy Clin. Immunol. Pract. 11 (3) (2023 March 01) 811–821.e5.

[9] K.F. Chung, S.E. Wenzel, J.L. Brozek, A. Bush, M. Castro, P.J. Sterk, et al., International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma, Eur. Respir. J. 43 (2) (2014 Feb) 343–373.

[10] E.D. Telenga, S.W. Tideman, H.A.M. Kerstjens, N.T. Hacken, W. Timens, D. S. Postma, et al., Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response, Allergy 67 (8) (2012 August 01) 1060–1068.

[11] E. Uribe-Querol, C. Rosales, Neutrophils actively contribute to obesity-associated inflammation and pathological complications, Cells 11 (12) (2022 June 10) 1883, https://doi.org/10.3390/cells11121883.

[12] T.R. Tay, M. Hew, Comorbid "treatable traits" in difficult asthma: current evidence and clinical evaluation, Allergy 73 (7) (2018 July 01) 1369–1382.

[13] S.W. Coppack, Pro-inflammatory cytokines and adipose tissue, Proc. Nutr. Soc. 60 (3) (2001 August 01) 349–356.

[14] P.X. Liew, P. Kubes, The neutrophil's role during health and disease, Physiol. Rev. 99 (2) (2019 April 01) 1223–1248.

[15] H.A. Scott, P.G. Gibson, M.L. Garg, L.G. Wood, Airway inflammation is augmented by obesity and fatty acids in asthma, Eur. Respir. J. 38 (3) (2011 September 01) 594–602.

[16] D.E. Shaw, M.A. Berry, B. Hargadon, S. McKenna, M.J. Shelley, R.H. Green, et al., Association between neutrophilic airway inflammation and airflow limitation in adults with asthma, Chest 132 (6) (2007 Dec) 1871–1875.

[17] N. Turan, M.J. Edwards, S. Bates, D. Shaw, K.F. Chung, M.J. Loza, et al., IL-6 pathway upregulation in subgroup of severe asthma is associated with neutrophilia and poor lung function, Clin. Exp. Allergy 48 (4) (2018 Apr) 475–478.

[18] W.C. Moore, A.T. Hastie, X. Li, H. Li, W.W. Busse, N.N. Jarjour, et al., Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis, J. Allergy Clin. Immunol. 133 (6) (2014 Jun) 1557, 63.e5.

[19] M. Turrin, M. Rizzo, M. Bonato, E. Bazzan, M.G. Cosio, U. Semenzato, M. Saetta, S. Baraldo, Differences between early- and late-onset asthma: role of comorbidities in symptom control, J. Allergy Clin. Immunol. Pract. 10 (12) (2022 Dec) 3196–3203.

[20] P.G. Gibson, Tackling asthma phenotypes in community studies, Thorax 64 (5) (2009 May 01) 369–370.