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Multiarray screening identifies plasma proteins associated with Th17 cell differentiation and viral defense in coincident asthma and obesity

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Abstract

Background: The immunological mechanisms behind the clinical association between asthma and obesity in adolescence are not fully understood. This study aimed to find new plasma protein biomarkers associated specifically with coincident asthma and obesity in adolescents.

Methods: This was a cross-sectional study in children and adolescents 10–19 years old ($N=390$). Relative plasma concentrations of 113 protein biomarkers related to inflammation and immune response were determined by proximity extension assay (Target 96; Olink, Uppsala, Sweden). Differences in protein concentrations between healthy controls ($n=84$), subjects with asthma ($n=138$), subjects with obesity ($n=107$), and subjects with both asthma and obesity (AO; $n=58$) were analyzed by ANCOVA, adjusting for age and sex, and in a separate model adjusting also for the sum of specific IgE antibody concentrations to a mix of food allergens (fx5) and aeroallergens (Phadiatop). Proteins elevated in the AO group but not in the obesity or asthma groups were considered specifically elevated in asthma and obesity.

Results: Five proteins were elevated specifically in the AO group compared to controls (here sorted from largest to smallest effect of asthma and obesity combined): CCL8, IL-33, IL-17C, FGF-23, and CLEC7A. The effects of adjusting also for specific IgE were small but IL-33, IL-17C, and FGF-23 were no longer statistically significant.

Conclusion: We identified several new potential plasma biomarkers specifically elevated in coincident asthma and obesity in adolescents. Four of the proteins, CCL8, IL-33, IL-17C, and CLEC7A, have previously been associated with viral mucosal host defense and Th17 cell differentiation.

KEYWORDS
adolescents, asthma, biomarkers, obesity, pediatric asthma, pediatric obesity

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1 | INTRODUCTION

Obesity in childhood is a risk factor both in terms of increased incidence of asthma and of a more severe asthma phenotype.[1,2] Also, the response to treatment of asthma by inhaled corticosteroids is poorer in obesity.[3] In one study, incident asthma or wheezing in the pre-school age was associated with an increased risk of developing obesity later in childhood, indicating a complex relationship between the two conditions.[4]

There are several immunological mechanisms that may link obesity and asthma in children and adolescents.[5] Obesity is often accompanied by altered immune cell composition in adipose tissue and low-grade systemic inflammation.[6] Both obesity and asthma contribute to systemic inflammation, as illustrated by the effect of both conditions on C-reactive protein concentrations.[7] Obesity-related asthma in children and adolescents is in several studies characterized by an increased T helper type 1 (Th1)/Th17 over Th2 polarization as studied by cytokine patterns and peripheral blood mononuclear cell transcription factor expression.[8–10] However, recent studies have found a somewhat mixed cytokine pattern with lower concentrations of both interleukin (IL)-8 and IL-5 and elevated IL-33 and TGF-beta, and increased eosinophil activity in children and adolescents with combined asthma and obesity.[11–13] In addition, increased leptin and decreased adiponectin in obesity affect inflammatory pathways and are of likely importance in obesity-related asthma.[14] Despite the increased knowledge regarding the immunological links between asthma to obesity over the last decade, there is still a need to further elucidate the underlying mechanisms.

The aim of the present study was to find new plasma protein biomarkers associated specifically with the combination of asthma and obesity, as opposed to biomarkers also associated with either asthma or obesity alone. To this end, we utilized two pre-selected panels with a total of 180 proteins related to inflammation and immune response in children and adolescents with and without asthma and obesity.

Key message

Obesity-related asthma is increasingly common and responds poorer to established asthma treatments. By multi-array screening of two established patient cohorts, we managed to identify new protein biomarkers specifically associated with the combination of asthma and obesity in adolescence. Our findings provide novel candidates for studies of the mechanisms behind combined asthma and obesity, which might lead to new diagnostic and treatment opportunities for this patient group.

2 | METHODS

2.1 | Study population

This was a cross-sectional study with the merger of individuals from two previously established cohorts, the Minimally Invasive Diagnostics for Asthma and Allergic Diseases (MIDAS) cohort and the Uppsala Longitudinal Study of Childhood Obesity (ULSCO).[15,16] Visits to the clinic were between April 2010 and February 2012 for subjects in the MIDAS cohort and between May 2012 and September 2020 for subjects in the ULSCO cohort. Inclusion criteria were ULSCO or MIDAS study subject aged 10–19 years old, and biobank-stored plasma samples available. Exclusion criteria were having a chronic respiratory disease other than asthma, active tuberculosis, recorded bloodborne disease, and/or syndromic obesity. With these criteria, the total study population was 387 individuals, 204 from the MIDAS cohort and 183 from the ULSCO cohort. Subjects were divided into four groups according to the presence or not of obesity and asthma. The groups are referred to as the control ($n = 84$), asthma ($n = 138$), obesity ($n = 107$), and asthma and obesity (AO; $n = 58$) groups, respectively. Obesity was defined as a body mass index standard deviation score (BMI SDS) of >2 according to the World Health Organization 2007 growth reference. Asthma was defined as physician-diagnosed asthma and having been prescribed inhaled corticosteroids and/or an oral leukotriene-receptor antagonist for at least 3 months the year before the study visit. The study was approved by the Uppsala County regional ethics committee (registration numbers 2009/349, 2010/036, and 2012/318). Written informed consent was obtained from study subjects and for study subjects under 18 years of age written informed consent was also obtained by the subjects' legal guardians.

2.2 | Biochemical analyses

Analyses were performed on biobank plasma samples, stored in −80 degrees C. IgE antibodies against a mix of food allergens (fx5) and a mix of aeroallergens (Phadiatop) were measured by ImmunoCAP (Thermo Fischer Scientific, Uppsala, Sweden). Atopy was defined by IgE-antibody concentrations of ≥0.1 kU_A/L for fx5 or Phadiatop. For the screening of proteins associated with inflammation, we selected two commercially available pre-set protein panels with a total of 180 unique proteins (Target 96 Inflammation and Immune Response; Olink, Uppsala, Sweden). Relative protein concentrations of the 180 proteins were measured by multiple proximity extension assays (Olink, Uppsala, Sweden) as described previously.[17] In brief, for each protein, there are two specific antibodies carrying complementary DNA oligonucleotides. When the antibodies bind to the target protein and thus are in proximity to one another the oligonucleotides are hybridized and subsequently extended and amplified by microfluidic real-time qPCR. The value of the quantification cycle was converted to normalized protein expression (NPX) value on a log_2-scale. Samples were randomly distributed on the plates for analysis and the person running the assay and extracting results was blinded as to which group each sample belonged. Proteins with values below

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the limit of detection were included in the analyses, using the values reported from the analytical system. Proteomic analyses were carried out in one single batch.

2.3 | Statistical analysis

One-way ANOVA with a post hoc Tukey test with all six possible group comparisons was used to test for differences in age, fx5, and Phadiatop between the four groups. To account for possible differences arising from the merger of two cohorts with different sampling procedures, we analyzed the protein biomarkers for differences between the healthy control group in the ULSCO cohort with the healthy control group in the MIDAS cohort by a one-way ANCOVA with age, sex, and BMI SDS as covariates. Only proteins that did not differ significantly between the two cohorts within the healthy controls were included in the main analysis. For proteins with outliers at least 2 NPX units higher than the second highest observation, data was analyzed with and without the presence of the outlier to evaluate whether it influenced the conclusions drawn. ANCOVA with a post hoc Tukey test was used to analyze differences in protein concentrations between the four groups, with age and sex as covariates. Additional ANCOVA models were created with specific IgE defined as the sum of the concentration of fx5 and Phadiatop (kU_A/L) added as a covariate in addition to age and sex. Adjustment for multiple testing was done on the ANCOVA *p*-values by the Benjamini-Hochberg method with a false discovery rate set to 0.1. Proteins elevated only in the AO group and not in the obesity-only or asthma-only groups were considered to be specifically elevated in coincident asthma and obesity. To obtain an effect size of how much more the proteins were elevated in the AO group compared to what would be expected from the sum of the elevations seen in the asthma-only and the obesity-only groups, we calculated the synergy effect of asthma and obesity on protein concentrations. Synergy between the effect of asthma and obesity on mean protein concentrations (MPC) was calculated as $(MPC_{AO} - MPC_{Control})/((MPC_{Asthma}\text{-}MPC_{Control})+(MBC_{Obesity}\text{-}MBC_{Control}))$ on normalized protein data for proteins significantly elevated only in the AO group compared to the control group. A *p* value <.05 was considered statistically significant. The software used for statistical analysis and graphics were Stata/BE 17.0 for Mac (StataCorp, College Station, TX, USA) and Prism 9.4.1 for Mac (GraphPad Software, San Diego, CA, USA).

3 | RESULTS

3.1 | Study population characteristics

The AO group was on average 1.4–1.5 years younger than the other study groups (Table 1). The control group had the lowest while the AO group had the highest male/female ratio. The AO group had on average 0.3 units lower BMI SDS than the O group. The AO group had lower IgE-antibody concentrations than the A group. Atopy was present in 44% of individuals in the control group, 68% in the obesity group, 78% in the AO group and was most frequent in the asthma group (87%) (Table 1).

3.2 | Biomarker panels

After removing the proteins that differed between cohorts in the healthy control group, that is, proteins where the inherent differences between cohorts were deemed to influence the results, 113 protein biomarkers were left and included in the analyses (Table S1). There were 15 biomarkers that deviated from normal distribution of residuals. Thirteen proteins were below limit of detection in >0 and <25% of cases, 10 proteins were below limit of detection in 25–75% of cases, and 29 proteins were below limit of detection in >75% of cases (Table S1). In total, 61 proteins were above limit of detection in all cases (Table S1). Since this was an exploratory study, we decided to keep all 113 proteins in further analyses.

The protein biomarkers C-C Motif Chemokine Ligand 8 (CCL8; ΔNPX 0.31 vs control, $p=.02$), C-type Lectin Domain Containing 7A (CLEC7A; ΔNPX 0.23 vs control, $p=.03$), Fibroblast Growth Factor 23 (FGF-23; ΔNPX 0.18 vs control, $p=.02$), IL-17C (ΔNPX 0.29 vs control, $p=.02$), and IL-33 (ΔNPX 0.08 vs control, $p=.04$) were significantly higher specifically in the AO group compared to controls when adjusting for age and sex (Figure 1, Table 2). There were other

TABLE 1 Combined cohort characteristics, data in mean ± SD, frequencies or median with interquartile range.

	Control ($n=87$)	Asthma ($n=138$)	Obesity ($n=107$)	Asthma and obesity ($n=58$)	*p*-Value ANOVA/chi^2
Age, years	14.7 ± 2.3[a]	14.6 ± 2.3[a]	14.6 ± 2.4[a]	13.2 ± 2.1[b]	<.001
Male, sex, *n* (%)	37 (43%)	82 (59%)	62 (58%)	41 (71%)	.014
BMI SDS	−0.2 ± 0.8[a]	0.0 ± 0.69[a]	3.1 ± 0.5[b]	2.8 ± 0.6[c]	<.001
Phadiatop* kU_A/L	0.1 (0.0–0.8)[a]	17.4 (1.0–59.4)[b]	0.2 (0.1–2.0)[a]	1.4 (0.6–25.4)[c]	<.001
Fx5* kU_A/L	0.05 (0.03–0.10)[a]	0.19 (0.07–1.6)[b]	0.07 (0.03–0.17)[a,c]	0.14 (0.04–0.76)[c]	<.001
Atopy, *n* (%)	37 (44%)	120 (87%)	73 (68%)	45 (78%)	<.001

Note: Same superscript letter = no statistically significant difference between groups in post hoc comparison. *p*-Values from ANOVA, or in case of sex and atopy from chi-squared test.

*ANOVA analysis on log-transformed data due to non-normally distributed data, non-transformed data is presented in the table.

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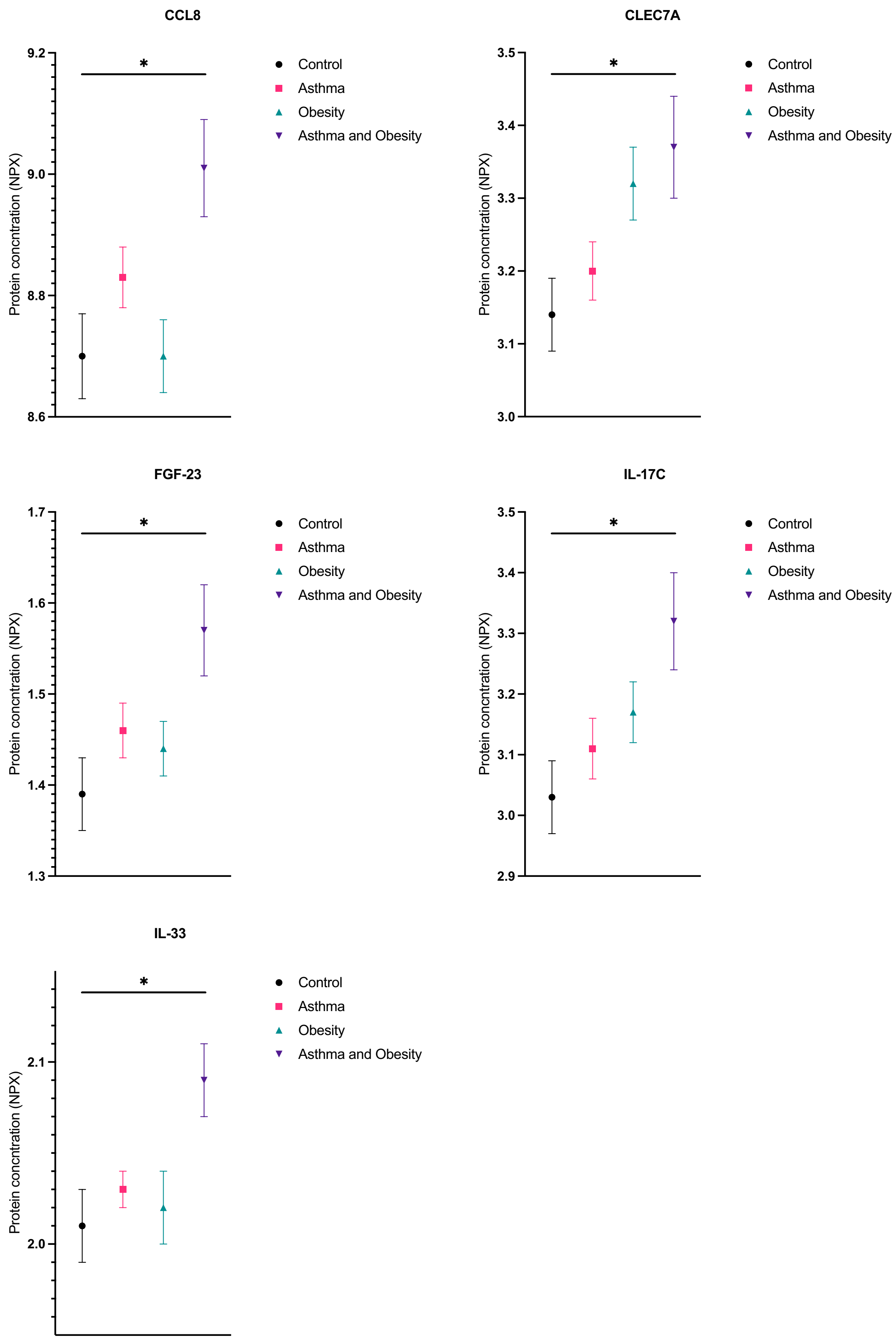

FIGURE 1 Estimated marginal means of relative concentrations of indicated protein biomarkers, adjusted for age and sex, in adolescents divided into the groups healthy control, obesity, asthma, and asthma and obesity. NPX = normalized protein expression, representing the qPCR cycle threshold converted to a $\log_2$ scale. **p* < .05 in ANCOVA with Tukey's post hoc test with age and sex as covariates. Means ± SEM.

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TABLE 2 Estimated marginal means ± SEM of protein biomarkers elevated specifically in asthma and obesity, adjusted for age and sex.

	Control	Asthma	Obesity	Asthma and Obesity	ANCOVA *p*
CCL8	8.70 ± 0.07	8.83 ± 0.05	8.70 ± 0.06	9.01 ± 0.08*‡	.01
CLEC7A	3.14 ± 0.05	3.20 ± 0.04	3.32 ± 0.05	3.37 ± 0.07*	.01
FGF-23	1.39 ± 0.04	1.46 ± 0.03	1.44 ± 0.03	1.57 ± 0.04*	.03
IL-17c	3.03 ± 0.06	3.11 ± 0.05	3.17 ± 0.05	3.32 ± 0.08*	.03
IL-33	2.01 ± 0.02	2.03 ± 0.01	2.02 ± 0.02	2.09 ± 0.02*	.05

Note: Protein biomarkers in NPX units representing the cycle threshold in a qPCR converted to a $\log_2$ scale. * and ‡ indicate significant difference from the control and obesity groups, respectively, in an ANCOVA post hoc test when including age and sex as covariates. *p* Values from the ANCOVA with age and sex as covariates.

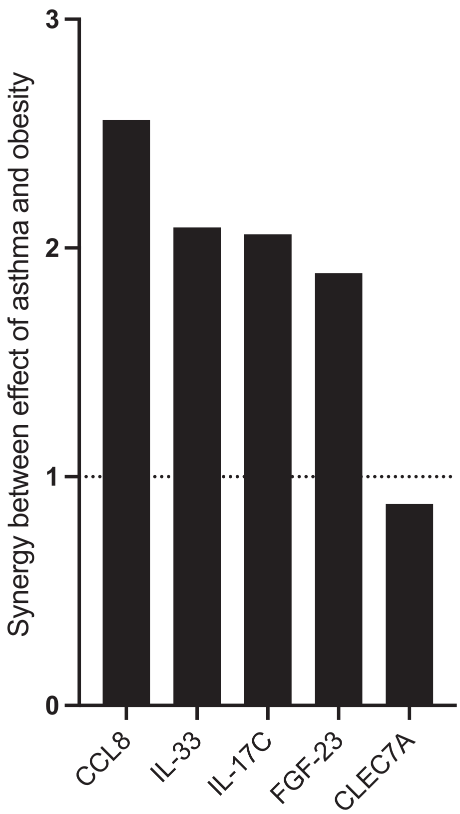

FIGURE 2 Synergy between the effect of combined asthma and obesity on the relative concentration of each indicated protein in children and adolescents. Synergy calculated from estimated marginal means adjusted for age and sex of the healthy control (C), asthma (A), obesity (O), and asthma and obesity (AO) groups by the following formula: $\text{mean}_{AO}/((\text{mean}_A - \text{mean}_C) + (\text{mean}_O - \text{mean}_C))$.

proteins elevated in the AO group but that were also elevated in the asthma only and/or the obesity only group (Table S1). Synergy between the effect of asthma and obesity on protein concentrations was most marked for CCL8, followed by IL-33, IL-17C, and FGF-23, whereas the effect of asthma and obesity on CLEC7A seemed to be additive (Figure 2). The inclusion of specific IgE in the ANCOVA models reduced the estimated differences in the AO vs C comparisons for IL-33 to 88%, FGF-23 to 89%, IL-17C to 90%, and CCL8 to 96% of the estimated differences without IgE in the model, whereas the inclusion of specific IgE increased the estimated differences in the AO vs C comparison for CLEC7A to 107%. With specific IgE included in the models, FGF-23, IL-17C, and IL-33 were no longer significantly different between the AO and C groups but statistical trends remained (Figure 3).

4 | DISCUSSION

We were able to identify five proteins, CCL8, CLEC7A, FGF-23, IL-17C, and IL-33, as biomarkers associated specifically with the combination of asthma and obesity in children and adolescents. To our knowledge, CCL8, CLEC7A, FGF-23, and IL-17C have not previously been studied in the context of pediatric asthma and obesity. The protein biomarkers that were most clearly elevated in the combination of asthma and obesity were CCL8, FGF-23, IL-17C, and IL-33.

IL-17C is a cytokine expressed primarily in epithelium, including respiratory epithelium, as opposed to the rest of the IL-17 family that are mainly expressed in hematopoietic cells.[18] The receptor for IL-17C, IL-17RE, is expressed by Th17 cells and IL-17C activates Th17 cells to increase IL-17A production and has been shown to recruit neutrophils to the lung.[19,20] Studies of IL-17C in the asthma context are scarce, although recently it was found that knockout of the IL-17RE in mice led to milder virus-induced asthma exacerbations.[21] Whether IL-17C is associated with lung function, airway hyperresponsiveness, asthma control or exacerbation rate is not known.

CLEC7A and IL-33 have previously been shown to play a role in the differentiation and/or activation of Th17 cells. The C-lectin family member CLEC7A is a pattern recognition receptor, and signaling through CLEC7A activation in dendritic cells was shown to promote Th17 differentiation.[22] IL-33 is an alarmin produced by non-hematopoietic cells at tissue barriers, and it is released in response to tissue damage including in conjunction with viral infections.[23] IL-33 induces type 2 inflammation through the activation of both innate lymphoid cells type 2 and Th2 cells and is a well-known player in the chronic inflammation and airway hyperresponsiveness of allergic asthma.[23,24] In addition, it has been shown that IL-33, through an effect on dendritic cells, can promote Th17 cell differentiation.[25] Interestingly, blood leukocyte expression

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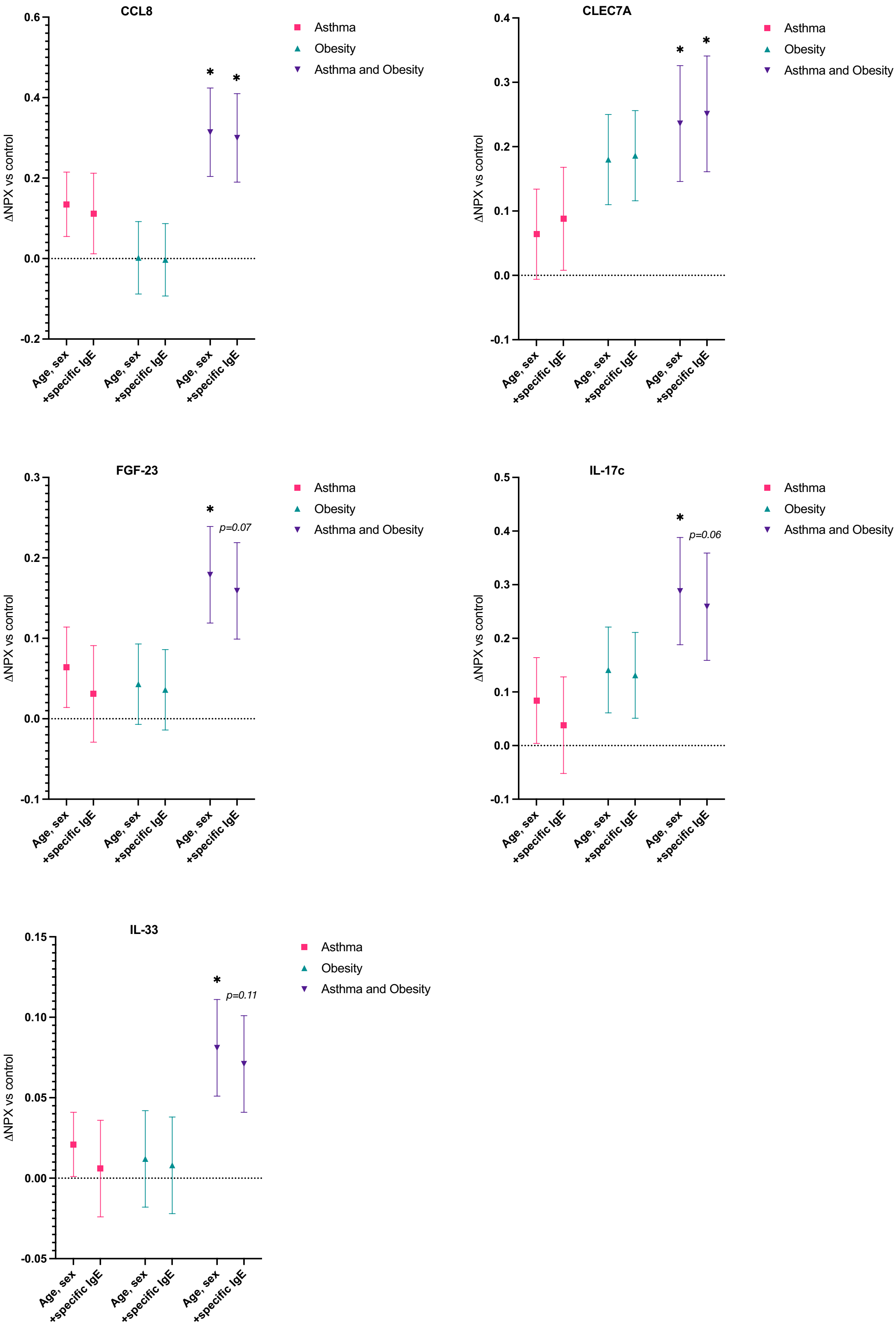

FIGURE 3 Estimated difference of the obesity, asthma, and asthma and obesity groups vs healthy controls for indicated protein biomarkers adjusted for the indicated covariates (age and sex or age, sex, and specific IgE). *$p < .05$ vs healthy controls in ANCOVA with Tukey's post hoc test.

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of IL-17A and the Th17 transcription factor Retinoid-related orphan receptor C are both increased in obesity-related asthma in children and adolescents.[8] Taken together, this points to the importance of Th17 cells in the context of obesity-related asthma in childhood and adolescence. Whether targeting the IL-17 family cytokines or Th17 cells in this specific patient group would be a successful treatment regimen is not known, and may be an interesting prospect for future research.

CCL8 (also known as monocyte chemoattractant protein-2) is a chemokine that can drive type 2 inflammation, and it has been shown that CCL8 is higher in moderate-to-severe allergic asthma than in mild allergic asthma.[26] It has previously been shown that rhinovirus can induce CCL8 secretion from blood monocytes and airway macrophages,[27] and this chemokine is greatly upregulated in acute respiratory illness.[28] Furthermore, CCL8 gene expression in respiratory epithelial cells correlated strongly with viral load in asymptomatic viral infections,[29] and subclinical rhinovirus infections were associated with systemic eosinophil activation in individuals with asthma.[30] To our knowledge, CCL8 has not previously been studied in the context of asthma and obesity in children and adolescents. Taken together, previous studies and our present findings of the involvement of IL-17C, IL-33, and CCL8 points to viral defense at mucosal barriers as an important mechanism in obesity-related asthma in children and adolescents. Importantly, this is in line with adult data both on gene expression in $CD4^+$ T cells and extracellular vesicle micro-RNA of individuals with asthma and obesity which pointed to the importance of upregulation of interferon signaling and viral infection pathways.[31,32] The role of adipose tissue-derived extracellular vesicles in obesity-related lung disease has recently gained attention and would be an interesting topic for future studies in pediatric obesity-related asthma.[33]

FGF-23 is a fibroblast growth factor in the endocrine FGF-19 family that regulates phosphate balance through klotho-dependent FGFR1c signaling in the kidney.[34] FGF-23 is to the best of our knowledge not studied in asthma but is elevated in plasma in mild chronic obstructive pulmonary disease, and has a proinflammatory effect in airway epithelium.[35] Whether FGF-23 is associated with lung function, airway hyperresponsiveness and/or asthma symptoms would be interesting research questions for future study.

We included allergen-specific IgE in the ANCOVA models as a marker of adaptive type 2 inflammation, as these mechanisms could confound the study of innate inflammatory mechanisms induced in the combination of asthma and obesity. However, the magnitude of the estimated differences between the AO and C group only changed slightly when adjusting for the sum of IgE-antibody concentrations, even though the comparisons of the AO versus the C group were no longer statistically significant for FGF-23, IL-17C, and IL-33. Thus, a minor part of the effect of asthma and obesity on these protein biomarkers might be through adaptive type 2 mechanisms.

Given the exploratory nature of the present study, all findings will need to be confirmed in targeted analyses also providing absolute plasma concentrations of the proteins of interest. The lack of data on lung function and asthma control are obvious limitations to the present study, and these data should be included in future studies. Furthermore, the use of BMI as the only measure of adiposity is a limitation, and it would be of interest to include more detailed information on adipose tissue distribution in the future study of these biomarkers. The difference in time the samples were stored in the freezer could affect results but we believe that by removing proteins that differed between cohorts within the control group we should have removed any proteins with large effects of freezer storage time since the biggest difference in storage time was between cohorts. The approach with pre-selected protein panels limited our flexibility to study some important aspects of the association between asthma and obesity, for instance, the contribution of adipokines such as adiponectin and leptin.[14,36] Some protein biomarkers were for many individuals below the limit of detection but were still included in this exploratory study. However, there are some caveats to this approach and the precision of the estimated effect sizes can be low for proteins with a high percentage of samples below limit of detection. Furthermore, since protein biomarkers below limit of detection are concentrated to a very narrow range of the standard curve the ability to detect statistically significant differences will be impaired for these proteins, and, thus, negative findings among these proteins should be interpreted with caution. Future studies should utilize analytical systems with higher sensitivity.

In conclusion, we found five candidate protein biomarkers specific for the combination of asthma and obesity in children and adolescents. We suggest that, among these, the most interesting for future studies are CCL8, FGF-23, IL-17C, and IL-33, which have previously shown to play important roles in mucosal host defense against viral infections, and in the differentiation and/or activation of Th17 cells.

AUTHOR CONTRIBUTIONS

Hannes Manell: Writing – original draft; conceptualization; methodology; formal analysis; visualization; investigation. **Nikolaos Tsolakis:** Writing – review and editing; investigation; conceptualization; methodology. **Christer Janson:** Funding acquisition; conceptualization; investigation; writing – review and editing. **Andrei Malinovschi:** Conceptualization; investigation; funding acquisition; writing – review and editing. **Kjell Alving:** Funding acquisition; conceptualization; methodology; supervision; resources; investigation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in relation to the present study.

PEER REVIEW

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