

T_H17 deficiency there is a local defect of skin development and host defense in the context of immune cell-derived IFN- γ . These findings do not at all rule out the impact of defective T_H17 response in patients with CMC; therefore, we do not propose with our observations that increased IFN- γ signaling in the skin of patients with STAT1 GOF is the sole reason for CMC. However, it could contribute to the severe phenotypes we have observed in patients with STAT1 GOF and could explain why virtually all patients with this mutation will present with mucocutaneous *Candida* problems.^{8,9} Second, this explains that STAT1 GOF mutation skin is normal in the absence of inflammation. However, on inflammation, especially at the feet, hands, and oral cavity, this can result in locally impaired antimicrobial activity. This might also explain that IFN- γ signaling inhibition with the JAK inhibitor ruxolitinib can improve skin lesions without restoring T_H17 responses, because these defects are theoretically already present before fungal infection. Third, it opens up new treatment strategies for STAT1 GOF skin, namely, blocking IFN- γ signaling, which has been successful in several cases.^{8,9} With hematological stem cell transplantation it might be possible to fully restore the CMC phenotype because the immune system might overcome any local defects in the skin. However, conceptually this study underscores that it has to be kept in mind that STAT1 GOF might also have effects in nonimmune cells that would necessarily be restored with hematological stem cell transplantation.

In conclusion, we describe an intrinsic defect of STAT1 GOF patients' skin in the presence of IFN- γ . The defective epithelial structure and the loss of the antimicrobial protein LCE3 with activity against *C. albicans* is likely to contribute to CMC severity in patients with STAT1 GOF mutation. Tissue distribution of LCE3 suggests a possible link of these proteins with the infection predilection sites at the hands, feet, and oral cavity. Moreover, these novel insights put forward another rationale to investigate JAK inhibitors in STAT1 GOF, because it might restore the local skin defects and thus has the potential to lead to clinical benefit.

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Omalizumab effectiveness in asthma-COPD overlap: Post hoc analysis of PROSPERO



To the Editor:

Asthma and chronic obstructive pulmonary disease (COPD) overlap (ACO), defined as the coexistence of clinical features of asthma and COPD, is common.^{1,2} Although ACO is heterogeneous, common subphenotypes of ACO include those with asthma who are older than 40 years with a history of smoking and/or those who have persistent, progressive, and partially reversible airflow limitation.²

Epidemiologic studies suggest that ACO is associated with higher disease burden, lower quality-of-life scores, and higher health care utilization than COPD or asthma alone.^{1,3} Unfortunately, patients with ACO are often excluded from asthma or COPD clinical trials, including trials for recently approved targeted asthma therapies (eg, dupilumab).⁴

Treatment of ACO is directed to treat symptoms and airway inflammation and typically comprises inhaled corticosteroids (ICSs) with add-on bronchodilators (long-acting beta-agonists $\pm$ long-acting muscarinic antagonists) although ACO phenotypes may be less responsive to ICSs than are patients with asthma.³ Omalizumab, a monoclonal anti-IgE antibody approved for patients (≥ 6 years) with moderate-to-severe allergic asthma inadequately controlled with ICSs, is not approved for patients with COPD or ACO. Efficacy of omalizumab in ACO has been

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TABLE I. Baseline demographic and clinical characteristics

Demographic/clinical characteristic	ACO A (n = 56)	Non-ACO A (n = 681)	ACO B (n = 50)	Non-ACO B (n = 663)
Age (y)				
Mean $\pm$ SD	57.6 $\pm$ 10.9	49.8 $\pm$ 14.9	56.8 $\pm$ 12.6	50.0 $\pm$ 14.6
Median (min, max)	59.5 (24, 78)	50.0 (18, 100)	56.0 (23, 86)	50.0 (18, 100)
Sex: female, n (%)	40 (71.4)	447 (65.6)	30 (60.0)	440 (66.4)
Race, n (%)				
White	42 (75.0)	485 (71.2)	43 (86.0)	468 (70.5)
Black/African American	6 (10.7)	103 (15.1)	5 (10.0)	98 (14.8)
Asian	0 (0.0)	33 (4.8)	0 (0.0)	32 (4.8)
American Indian or Alaska Native	0 (0.0)	7 (1.0)	0 (0.0)	7 (1.1)
Native Hawaiian or other Pacific Islander	0 (0.0)	4 (0.6)	0 (0.0)	4 (0.6)
Multiple	2 (3.6)	9 (1.3)	0 (0.0)	11 (1.7)
Other	6 (10.7)	40 (5.9)	2 (4.0)	43 (6.5)
BMI (kg/m ²), median (min, max)	31.4 (17.6, 49.0)	30.2 (17.3, 76.9)	28.9 (19.4, 42.6)	30.4 (17.3, 76.9)
FENO (ppb), median (min, max)	19.0 (5, 151.5)	23.0 (5, 266)	17.0 (5, 142)	23.0 (5, 266)
Blood EOS (cells/ μ L), median (min, max)	200 (40, 800)	220 (0, 2340)	200 (0, 570)	220.0 (0, 2310)
Total IgE (IU/mL), median (min, max)	168.3 (11.2, 7693.0)	176.1 (1.1, 8659.2)	207.8 (5.7, 4846.5)	170.4 (1.1, 8659.2)
Prebronch FEV ₁ (L), mean $\pm$ SD	1.7 $\pm$ 0.7	2.3 $\pm$ 0.8	1.6 $\pm$ 0.6	2.3 $\pm$ 0.8
Prebronch FEV ₁ (%pred), mean $\pm$ SD	62.6 $\pm$ 18.1	75.2 $\pm$ 20.5	53.9 $\pm$ 16.6	75.7 $\pm$ 20.0
Postbronch FEV ₁ (%pred), mean $\pm$ SD	68.5 $\pm$ 19.2	79.8 $\pm$ 19.3	59.0 $\pm$ 16.5	80.4 $\pm$ 18.9
Postbronch FEV ₁ /FVC (%), mean $\pm$ SD	66.7 $\pm$ 11.8	74.9 $\pm$ 11.4	57.7 $\pm$ 9.8	75.5 $\pm$ 10.8
Reversibility (%), mean $\pm$ SD	11.6 $\pm$ 12.6	7.7 $\pm$ 14.5	11.4 $\pm$ 13.0	7.8 $\pm$ 14.5
Exacerbations,* mean $\pm$ SD	3.6 $\pm$ 3.7	3.0 $\pm$ 3.3	3.5 $\pm$ 3.4	3.0 $\pm$ 3.3
ACT baseline, mean $\pm$ SD	12.8 $\pm$ 4.8	13.8 $\pm$ 4.9	11.6 $\pm$ 4.6	13.9 $\pm$ 4.9
Smoking history, n (%)				
Current	12 (21.4)	30 (4.4)	10 (20.0)	31 (4.7)
Former	25 (44.6)	213 (31.3)	40 (80.0)	195 (29.4)
Never smoker	19 (33.9)	436 (64.0)	0 (0.0)	437 (65.9)
Number of packs per year, mean $\pm$ SD†	22.5 $\pm$ 20.5	11.3 $\pm$ 17.2	27.7 $\pm$ 16.7	9.5 $\pm$ 16.8
Years of smoking, mean $\pm$ SD†	28.8 $\pm$ 10.7	14.4 $\pm$ 11.8	28.9 $\pm$ 10.2	13.5 $\pm$ 11.5

BMI, Body mass index; *bronch*, bronchodilator; EOS, eosinophils; FENO, fractional exhaled nitric oxide; FVC, forced vital capacity; %pred, percent predicted.

*During 12-month period before enrollment.

†Former or current smokers.

suggested in case reports,^{5,6} but patients with ACO have also been excluded from omalizumab clinical trials. Therefore, well-conducted, real-life large studies might be good data sources to assess the clinical potential of omalizumab for patients with ACO.

To this end, we performed a *post hoc*, exploratory analysis of clinical outcomes of adult patients with ACO treated with omalizumab in the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) (clinicaltrials.gov identifier: NCT01922037).⁷ PROSPERO, a US, multicenter, single-arm, prospective, 48-week observational study of omalizumab, examined patients 12 years or older with asthma in a real-life setting not excluded for having comorbid COPD or a current or past history of smoking cigarettes.⁷

In PROSPERO, demographic and clinical characteristics, medical history, medication use, and smoking history were documented at baseline. Spirometry was performed at baseline, 6 months, and week 48 according to American Thoracic Society criteria.⁸ The number of exacerbations was recorded at baseline for the period 12 months before study enrollment and monthly during the study period using the same criteria. Exacerbations were defined as worsening of asthma symptoms requiring oral corticosteroids and/or emergency department visit or hospitalization, and were confirmed by medical records. Asthma Control Test (ACT) scores were also recorded at baseline and during the study. The ACT is a 5-item questionnaire that scores each question from 1 (poor control) to 5 (complete control) to yield an

overall ACT score range of 5 to 25. ACT scores of 20 or more reflect well-controlled asthma, scores of 16 to 19 suggest asthma that is not well controlled, and scores of 15 or less indicate asthma that is very poorly controlled. The minimally important difference for the ACT is 3.

Statistical analyses were based on all enrolled adult patients (≥ 18 years) at study enrollment. Descriptive statistics were used to summarize baseline demographic and clinical characteristics at study entry, the number of exacerbations at baseline and at week 48, and the change from baseline to week 48 in FEV₁ measurement and ACT score.

This *post hoc* analysis included 737 of 806 adult patients (91.4%) from PROSPERO who initiated omalizumab. To assess the relative effects of omalizumab in patients with and without ACO, 2 separate mutually exclusive subgroup analyses were performed using 2 different ACO definitions (see Fig E1 in this article's Online Repository at www.jacionline.org). Using data from 737 adult PROSPERO patients, descriptive analyses were performed between the ACO A cohort (n = 56), comprising patients with a medical history of asthma and a COPD diagnosis from medical history or self-report, and the non-ACO cohort (n = 681). Similarly, using data from 713 adult PROSPERO patients who have not missing baseline FEV₁/forced vital capacity ratio value and known smoking status, descriptive analyses were performed between the ACO B cohort (n = 50), comprising patients with a medical history of asthma, a postbronchodilator ratio of FEV₁ over forced vital

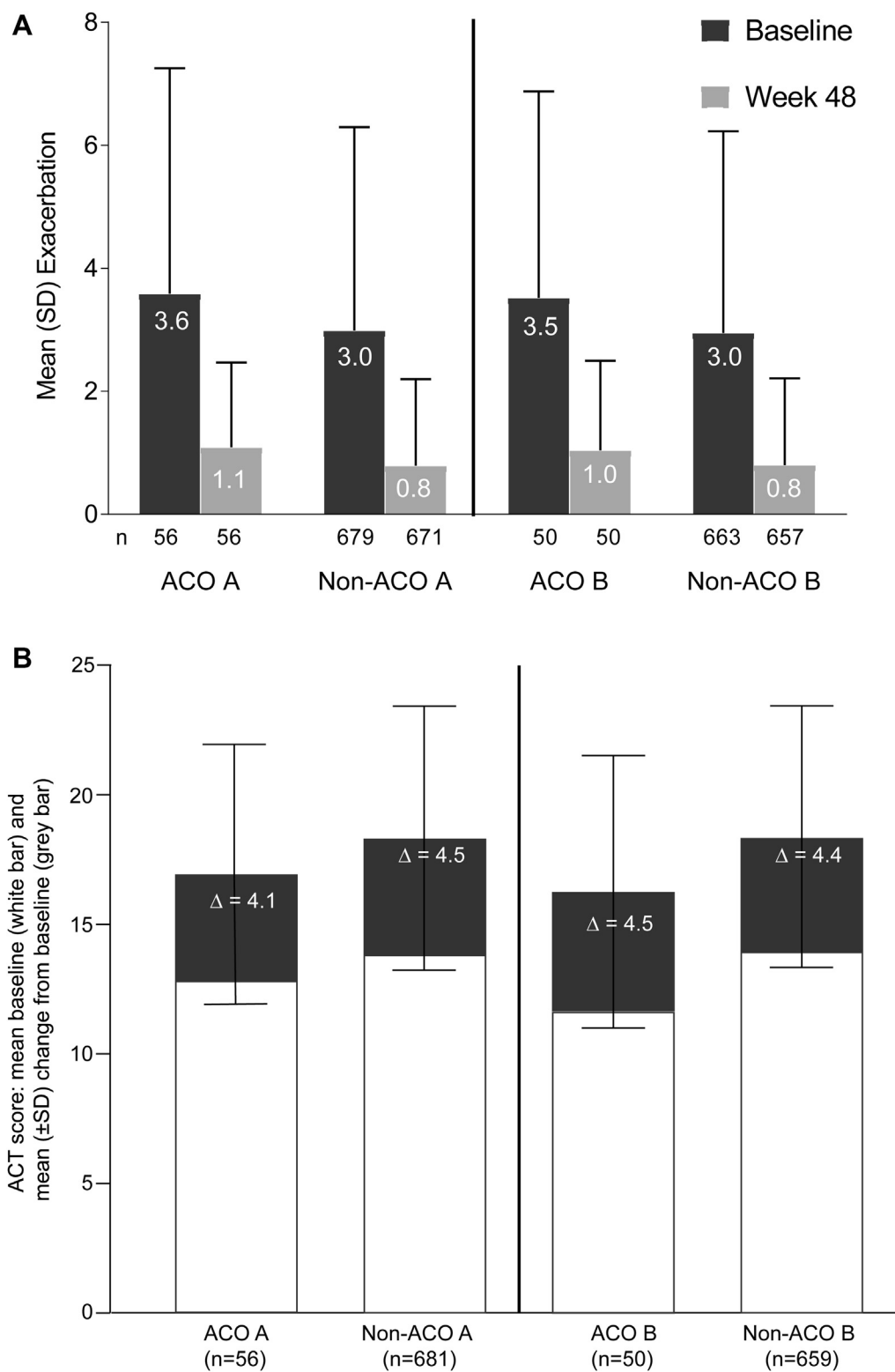


FIG 1. A, Mean exacerbation at baseline and week 48. B, Mean change (gray bar) in ACT score from baseline (white bar) at week 48 of omalizumab treatment in ACO and asthma cohorts.

capacity of less than 0.7, and smoking history of greater than or equal to 10 pack-years, and the non-ACO B cohort ($n = 663$).

Overall, patients in each ACO cohort had a higher mean age compared with their counterparts in the non-ACO cohort (Table I). Median fractional exhaled nitric oxide and blood eosinophil counts were similar in ACO and non-ACO cohorts, whereas total IgE levels at baseline were higher in the ACO B cohort than in the non-ACO B cohort (Table I). As expected, greater numbers of patients were former/current smokers in the each ACO cohort compared with their counterpart non-ACO cohorts (Table I). The mean pack-years in former/current smokers was approximately 2 times greater in the ACO A (22.5 ± 20.5) cohort than in the non-ACO A (11.3 ± 17.2) cohort and approximately 3 times greater in the ACO B (27.7 ± 16.7) cohort than in the non-ACO B (9.5 ± 16.8) cohort. Furthermore, patients in both ACO cohorts who were current/former smokers had done so for longer than patients in their counterpart non-ACO cohort (Table I). Interestingly, mean reversibility was lower in the non-ACO cohorts ($7.6\% \pm 14.5\%$ to $7.8\% \pm 14.5\%$) compared with the ACO cohorts ($11.4\% \pm 13.0\%$ to $11.6\% \pm 12.6\%$; Table I).

In terms of clinical improvement, decreases in mean asthma exacerbation rate compared with their own baseline mean exacerbation rate and clinically significant improvements in ACT scores were similar in ACO A cohort versus the non-ACO A cohort and in the ACO B cohort versus the non-ACO B cohort (Fig 1). The mean percentage (95% CI) of patients achieving or exceeding minimally important difference for ACT during the study was 57.1% (44.2-70.1%) in the ACO A cohort versus 63.5% (59.8-67.2%) in the non-ACO A cohort, and 62.5% (48.8-76.2%) in the ACO B cohort versus 62.9% (59.2-66.5%) in the non-ACO B cohort. Modest mean (95% CI) improvements in postbronchodilator FEV₁ after 48 weeks of treatment, compared with their own baseline values, were observed in both the ACO A and the non-ACO A cohorts. In contrast, a small decrease in postbronchodilator FEV₁ was observed in the ACO B cohort compared with an improvement in the non-ACO B cohort (see Fig E2 in this article's Online Repository at www.jacionline.org). One possible reason for this is the higher proportion of current or former smokers in the ACO B cohort who were also the heaviest smokers in terms of pack-years. Both former and, in particular, current smokers have been observed to have greater declines in FEV₁ than never smokers.⁹ Adverse events and safety results from PROSPERO involved in this analysis have been published previously.⁷

Our analysis of a large-scale, real-world study suggests that patients with ACO treated with omalizumab over 48 weeks experienced improvements in asthma outcomes similar to those in patients without ACO. These findings were present regardless of how patients with ACO were identified and are consistent with results of previously published case series. In 1 case series, 3 patients with ACO treated with omalizumab for more than 1 year showed improvements in ACT scores (from <10 to >20) along with decreases in hospitalizations and exacerbations.⁵ Another case series of 10 patients with ACO similarly found that omalizumab was associated with improvements in ACT score.⁶ Furthermore, patients with COPD typically experience an annual decline in lung function, whereas throughout the 48 weeks of this study, lung function was preserved in the ACO A cohort, suggesting some protection, compared with COPD studies that show

a historical decline in lung function. However, further data are required to confirm if these effects are maintained long-term (>48 weeks).

This analysis of PROSPERO is limited by its *post hoc* nature, as well as the potential for recall bias especially in relation to smoking history, COPD diagnosis, and exacerbations before study entry. The fact that this analysis is based on a study with no placebo control is another limitation. Despite these limitations, this analysis represents one of the largest cohorts to date of patients with ACO treated in a real-world setting. Our analysis suggests that patients with ACO treated with omalizumab had similar clinical outcomes to patients with asthma without ACO in terms of improvements in exacerbation frequency and ACT scores irrespective of how patients with ACO were identified. Furthermore, lung function was preserved throughout the 48 weeks of this study in the ACO cohort identified by a medical history of asthma and a medical history or self-reported diagnosis of COPD.

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Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.html).

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Large-scale, multiethnic genome-wide association study identifies novel loci contributing to asthma susceptibility in adults



To the Editor:

Asthma is a genetically heterogeneous disease. Although many recent genome-wide association studies (GWASs) have implicated multiple loci associated with asthma risk,¹⁻⁴ the impact of genetic variation on asthma susceptibility in large, ethnically diverse human populations has not been fully ascertained. Identifying the genetic variants associated with asthma in well-powered GWASs is crucial for discerning the genetic basis of asthma. Furthermore, it is also necessary to understand how genetic heterogeneity underlying asthma risk may be influenced by ethnic background. The objective of this study was to conduct a large-scale, transethnic GWAS of asthma in individuals in the Kaiser Permanente Northern California Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort.^{5,6}

Demographic information for GERA (68,623 asthma cases and nonasthmatic controls) is provided in Table E1 in this article's Online Repository at www.jacionline.org. GWASs were conducted for 4 racial/ethnic groups within GERA (non-Hispanic white, African American, Asian, and Hispanic), and replicated using data from 2 large consortia, EVE and GABRIEL. Selected single nucleotide polymorphism (SNP) associations with potential functional consequences were profiled using bioinformatic methods. All study procedures were approved by the Institutional Review Board of the Kaiser Foundation Research Institute and Brigham and Women's Hospital. A detailed Methods section is provided in this article's Online Repository at www.jacionline.org.

In non-Hispanic whites, more than 7 million SNPs passed quality control measures and were evaluated by GWASs, of which 646 SNPs met genome-wide significance ($P < 5 \times 10^{-8}$) and were annotated to 2 regions of chromosomes 2 and 6 that include *IL1RL1/IL18R1* and *HLA-DQA1/HLA-DQB1*, respectively; of these, 5 SNPs were also genotyped in GABRIEL and 4 were suggestive in GABRIEL ($P < 1 \times 10^{-5}$) (Fig 1, A; Table I). Eighteen of the genome-wide significant GERA SNPs were also genotyped in EVE; of these, 14 were nominally significant ($P < .05$), and the top 2 SNPs were suggestive ($P < 1 \times 10^{-5}$) (Table I). Thus, a total of 16 GERA SNPs replicated in either EVE or GABRIEL, of which all were annotated to *HLA-DQA1* or *IL1RL1/IL18R1* loci (Fig 1, A; Table I). A survey of 32 published asthma GWASs cited in the National Human Genome Research Institute

(NHGRI) Catalog revealed 113 suggestive associations ($P < 1 \times 10^{-5}$) (see Table E2 in this article's Online Repository at www.jacionline.org). Of these, 87 SNPs (77%) were also genotyped in the GERA non-Hispanic white data set, of which 25 replicated at a Bonferroni-corrected P -value threshold of 4.42×10^{-4} . When the GERA SNP P values were combined with those of the cited NHGRI studies, 44 of 87 (51%) SNPs in 28 unique loci met the Bonferroni-corrected cutoff; of these, 25 SNPs in 16 loci met the traditional genome-wide significance threshold of $P < 5 \times 10^{-8}$ (see Table E2).

In the 3 additional racial/ethnic groups in GERA, 6.4 million to 12.7 million SNPs passed quality control and were evaluated by GWASs. Three SNPs (rs5756210 near FAD-dependent oxidoreductase domain containing 2 [*FOXRED2*], rs10534662 in thioredoxin 2 [*TXN2*], and rs8042955 in *LOC107983974/RP11-739G5.1*) achieved genome-wide significance in Asians, and rs13306275 in collagen type III alpha 1 chain (*COL3A1*) was genome-wide significant in African Americans (Fig 1, A; see Table E3 in this article's Online Repository at www.jacionline.org). No genome-wide significant or suggestive associations replicated for these groups in EVE, GABRIEL, or the NHGRI database. In addition, none of the associations approaching genome-wide significance overlapped with any genome-wide significant/suggestive SNP association across all 4 racial/ethnic groups.

We attempted to discern the potential functional relevance of the most highly significant genome-wide-significant SNPs. The top-ranked SNP in non-Hispanic whites was rs9272513, which is present in an intron of *HLA-DQA1* and is also an eQTL (expression quantitative trait loci) for both *HLA* loci and *IL1RL1/IL18R1* in the lung and circulation (see Table E4 in this article's Online Repository at www.jacionline.org). In addition, rs12712142 was associated with an 11% increased risk of asthma and is an eQTL for *IL1RL1*, reducing transcript expression in the lung (see Fig E1 in this article's Online Repository at www.jacionline.org). Further characterization of rs12712142, which was annotated to the 3'UTR region of *IL1RL1*, showed that it introduces a new binding site for hsa-miR-452-5p, which is also significantly upregulated in airway epithelia samples from those with asthma compared with samples from healthy, nonatopic controls (see Figs E2 and E3 in this article's Online Repository at www.jacionline.org). Because variations across multiple genes within affected pathways could directly impact asthma phenotypes, we analyzed 2143 suggestive ($P < 1 \times 10^{-5}$) associations from non-Hispanic whites in GERA for gene-set and tissue enrichment. Tissue and cell enrichment for relevant gene sets included those related to CD4⁺, CD8⁺, and B- and T-cell growth, morphology, and other activities, whereas 7 tissue enrichment sets included pathways for "T lymphocytes" and "CD4-Positive T lymphocytes" (see Table E5 in this article's Online Repository at www.jacionline.org).

Collectively, these analyses replicated previously reported top asthma GWAS findings as well as increased the significance threshold for many of these associations, in addition to expanding the list of novel SNPs that are strongly associated with asthma risk. Because of differences in GWAS study design, imputation, and available SNP data, most genome-wide significant SNPs from the discovery GWAS were not well represented in EVE or GABRIEL, limiting the total number of SNPs for replication. However, there was a moderate to high level of linkage disequilibrium between the top discovery GWAS SNPs not genotyped in GABRIEL or EVE and the replicated SNPs

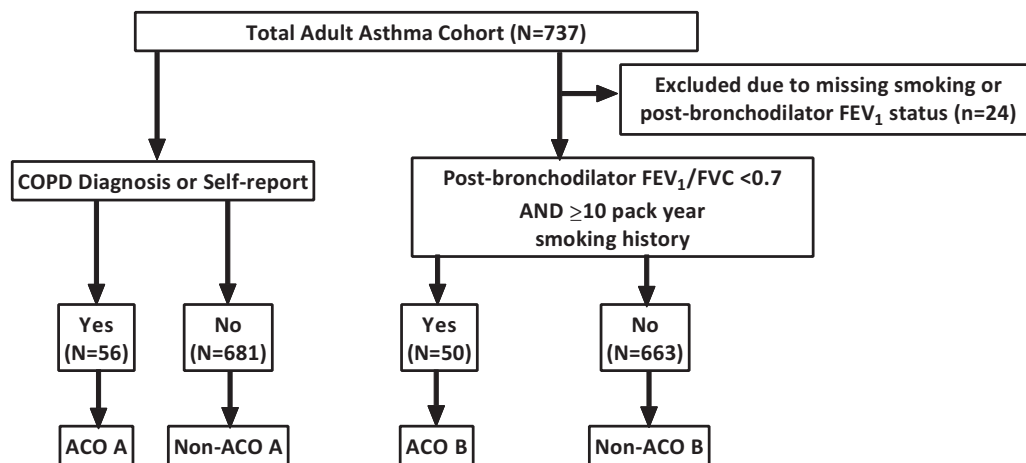


FIG E1. Patient population identification. *FVC*, Forced vital capacity.

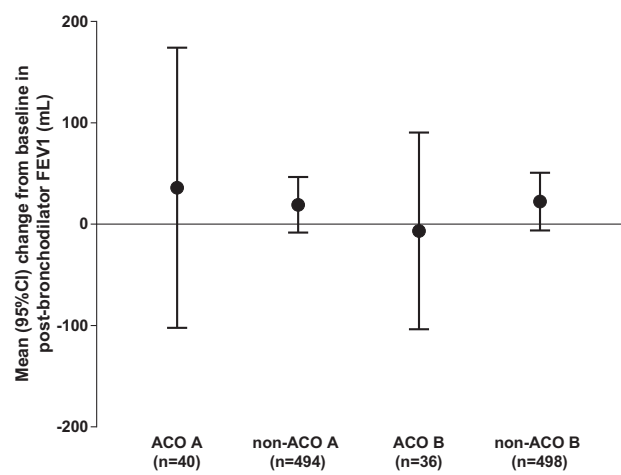


FIG E2. Mean (95% CI) change from baseline in postbronchodilator FEV₁ after 12 months of omalizumab in the ACO and non-ACO cohorts.