

Clinical Communications

Underrepresentation of blacks, smokers, and obese patients in studies of monoclonal antibodies for asthma

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Clinical Implications

- Participants in the randomized control trials for omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab in asthma are more likely to be Caucasian, never smokers, and have lower body mass index in comparison with patients with uncontrolled asthma in the general population.

TO THE EDITOR:

The randomized control trial (RCT) is the highest level of scientific evidence, minimizing systematic bias and increasing the reliability of effect estimates. Strict eligibility and extensive exclusion criteria, however, can limit the generalizability of results.¹ If groups underrepresented in trials are prevalent in everyday practice, there may be differences in efficacy observed in trials compared with effectiveness in real-life practice. Prior studies have shown that children, adults ≥ 65 years, females, Hispanics, and African Americans are often underrepresented in clinical trials.^{2,3}

RCTs have shown the efficacy of multiple biologics in the treatment of severe asthma. Asthma affects over 25 million individuals in the United States and disproportionately affects African Americans and Hispanics.⁴ These minorities, in addition to postpubertal females, obese individuals, and smokers, are more likely to have severe disease and have decreased response to bronchodilators or corticosteroids.⁴⁻⁶ In addition, age could modify therapeutic efficacy as childhood-onset and adult-onset asthma are now recognized as distinct phenotypes.⁷ We compared baseline characteristics of participants enrolled in the RCTs for the biologics currently approved by the Food and Drug Administration (FDA) for severe asthma with participants with uncontrolled asthma from a nationally representative sample.

For each of the biologics, omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab, we identified the seminal placebo-controlled RCTs used in granting FDA approval. We extracted data about trial participants from the medication guides and/or from published results in peer-reviewed journals. For comparison, we used data from the 2005-2012 National Health and Nutrition Examination Survey (NHANES) to generate a nationally representative sample. We identified survey participants aged ≥ 12 years with asthma. Of these, we identified those who were likely to have uncontrolled asthma in 2 ways. NHANES-A were on inhaled corticosteroid (ICS) therapy singly or in combination with a long-acting β -agonist (LABA) and had ≥ 2 exacerbations in the prior year requiring a visit to an emergency department or urgent care center. NHANES-B were also

on ICS and had ≥ 2 exacerbations in the prior year, but in addition had been on 1 or more additional controllers (LABA, long-acting muscarinic antagonists, leukotriene antagonists, and/or methylxanthines) or oral steroids for at least 90 days at the time of interview. Covariates of interest included age, gender, race, body mass index (BMI), and smoking status. Detailed methods are discussed in this article's Online Repository at www.jaci-inpractice.org.

Of 2475 survey participants aged ≥ 12 years with current asthma, we identified 80 and 48 patients in NHANES-A and NHANES-B, respectively. A total of 16 RCTs were identified (see this article's Online Repository at www.jaci-inpractice.org). We used the trial names to identify these studies. Where no trial name is available, we name them based on the relevant biologic, for example, XOLAIR-I is "Trial 1" for omalizumab as listed in the medication guide.

Trial participants were significantly older (range of mean age: 48.6-52.0 years) in comparison with NHANES-A and NHANES-B (42.6 and 43.4 years) in all studies for which mean age and standard deviation were reported (Figure 1, A, and Tables E1-E5, available in this article's Online Repository at www.jaci-inpractice.org). Significantly fewer females were enrolled in the trials (51% to 66%) than in NHANES-A (77% of participants). The direction of effect was similar in comparison with NHANES-B in which 66% of participants were females, but only reached statistical significance in comparison with XOLAIR-II (59%) (Tables E1-E5, available in this article's Online Repository at www.jaci-inpractice.org).

Compared with NHANES-A and -B, 11 of the 15 RCTs that reported proportion of Caucasians had significantly higher proportions of white participants. Compared with NHANES-A and -B, 8 of 9 RCTs reporting percentage of blacks had significantly lower proportion of blacks. Only 5 studies reported Hispanic ethnicity. Three of these 5 had a higher proportion of Hispanics than NHANES-A or -B (Figure 1, B, and Tables E2-E4, available in this article's Online Repository at www.jaci-inpractice.org). In all of the studies where BMI was reported, the mean BMI of the trial participants (27.8-29.6 kg/m²) was significantly lower than in NHANES-A and -B (33.6 and 32.6 kg/m²) (Figure 1, D). The trials included a higher proportion of never smokers (61% to 81%) than NHANES-A or -B (45% and 41%) (Figure 1, D, and Tables E1-E5, available in this article's Online Repository at www.jaci-inpractice.org). The duration of asthma was similar between trial and survey participants in all the studies where reported.

Overall, we found that participants enrolled in trials for the biologics currently approved for the treatment of asthma are older, more likely to be Caucasian and never smokers, and have lower BMI compared with a nationally representative sample of participants with uncontrolled asthma. These findings suggest that study participants may not be representative of the overall population of those with severe uncontrolled asthma. This lack of representativeness may have implications for the estimated treatment effect size of these biologic medicines.

Blacks, obese patients, and smokers are more likely to have severe asthma and demonstrate lower response to bronchodilators, LABA, and/or corticosteroids.^{5,6,8} However, previous work

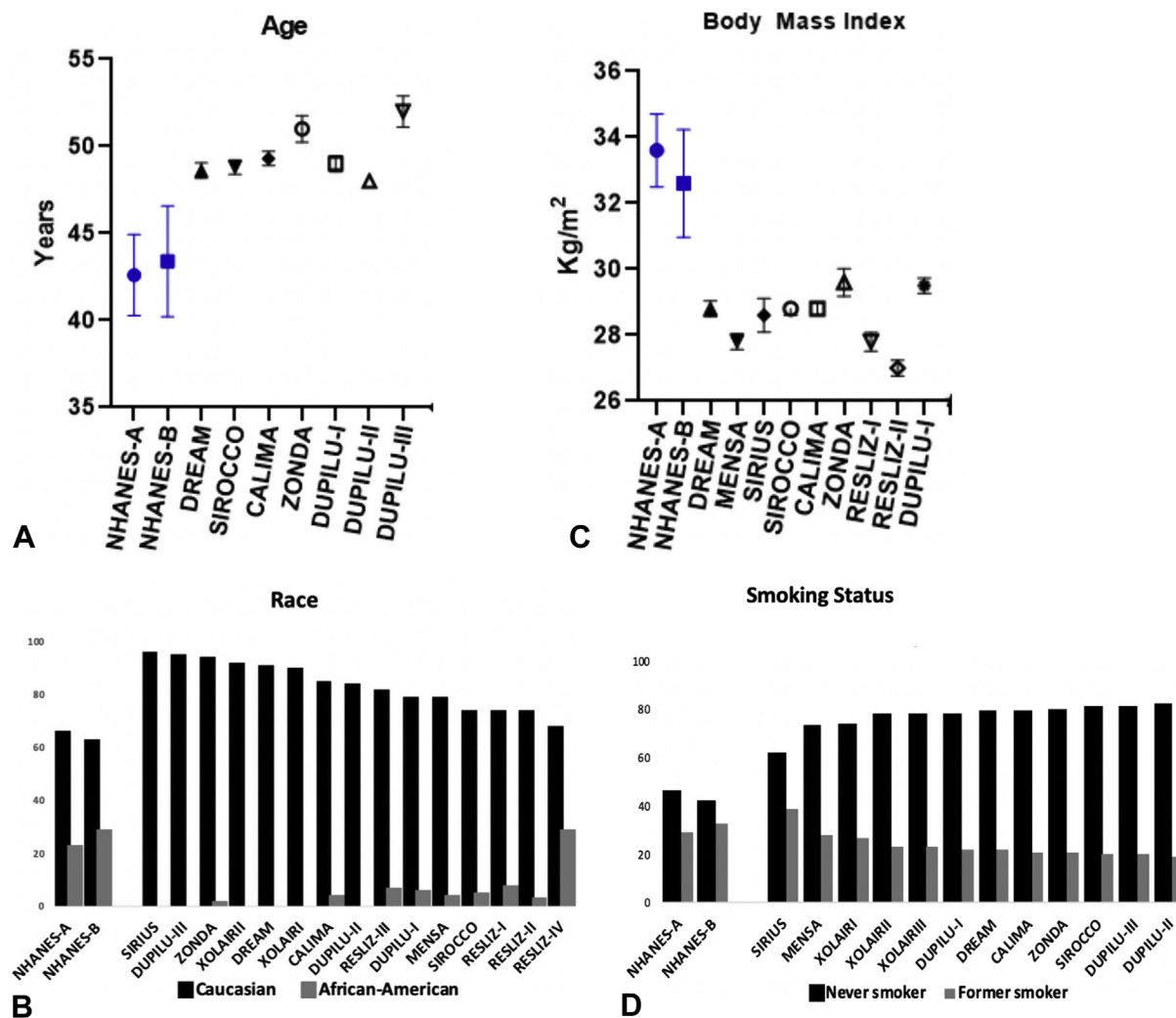


FIGURE 1. A, Mean age in years with error bar; B, proportion of whites and blacks; C, body mass index, in kg/m²; D, proportion of never and former smokers. Proportion of current smokers was 26% in both National Health and Nutrition Examination Survey groups but 0% to 1% in all the studies when reported.

to identify patients likely to respond to biologics have generally focused on asthma severity, IgE levels, and eosinophil counts. Only a few studies have explored the impact of demographic factors on response to these biologics with most of these being retrospective studies or *post hoc* analyses of RCTs. After initial approval, a randomized trial of omalizumab in inner city children, a group with high allergen sensitivity and over 90% being black or Hispanic, showed that omalizumab was very effective in decreasing exacerbations and dose of inhaled glucocorticoid.⁹ In a postmarketing surveillance study using the Australian Xolair Registry, response to omalizumab was found to be similar between obese and nonobese individuals,¹⁰ but a *post hoc* analysis of the DREAM study¹¹ showed greater improvement in exacerbation rates in the cluster of female-predominant obese patients receiving mepolizumab. Similarly, a single-center retrospective study¹² of 42 patients (32 mepolizumab-responders and 10 nonresponders) did not show statistically significant differences between these groups; however, median BMI was 28 kg/m² among the responders, compared with 31 kg/m² among the

nonresponders. In the same study, over half of responders were never smokers compared with 40% of nonresponders. Another study using the Australian Xolair Registry¹³ showed that omalizumab improved asthma control and health-related quality of life in patients with asthma-chronic obstructive pulmonary disease overlap syndrome, but there was no improvement in lung function in this group.

It may be reassuring that these studies have, in general, not shown great differences in the efficacy of these biologics based on demographic subgroups; however, the prevailing knowledge of asthma phenotypes suggests that there is likely to be heterogeneity of treatment effect. For instance, multiple studies have shown that obesity, especially in women, might represent a distinct asthma phenotype and might influence response to biologic therapy.^{11,14} Furthermore, *post hoc* and retrospective analyses may lack adequate power and often suffer from reporting bias.¹⁵ Given the low numbers of smokers, obese individuals, and minorities in these trials of biologics in asthma, *post hoc* analyses are unlikely to have been adequately powered to detect statistically significant

differences when multiplicity is appropriately accounted for. These issues could be limited if adequate numbers of these patient subgroups are enrolled in randomized and prospective trials and if prespecified subgroup analyses are appropriately conducted using the test for interaction rather than reporting different effect sizes in the subgroups. Thus, adequate enrollment of racial minorities, obese patients, and smokers in studies of biologics is necessary for obtaining accurate estimates of efficacy of biologics in these subgroups of patients. Clinical researchers and pharmaceutical companies could consider enrollment methods that will help improve the generalizability of trial results. Finally, given the widespread underrepresentation of minorities in clinical trials in general,¹⁶ regulatory bodies should search for these differences in research designs and help ensure that studies are representative of patient population.

This study has limitations. First, asthma diagnosis for NHANES was by self-report, and uncontrolled asthma as we defined it might reflect health care utilization and not true severity. However, baseline characteristics reported are similar to those of prior asthma epidemiology studies. We also attempted to increase our accuracy by using 2 different definitions, and we found estimates very similar regardless of the group used for comparison. Secondly, although these surveys are large, the number of participants with uncontrolled asthma was small. However, this is more likely to decrease rather than increase the probability of identifying differences, and the differences we have found are mostly at the $P < .001$ level, which is remarkable for such small sample sizes. Furthermore, although we used only 16 studies in these comparisons, there are multiple other studies of these biologics. Some of the studies not considered by the FDA during the approval process, such as the omalizumab in the inner city children study,⁹ may have included a higher proportion of groups underrepresented in these seminal studies. However, these studies were used in granting approval of these biologics. Despite these limitations, we believe that this study highlights the important subject of representativeness of participants in clinical trials of biologics.

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REFERENCES

- Fuller J. Rationality and the generalization of randomized controlled trial evidence. *J Eval Clin Pract* 2013;19:644-7.
- Schmucker DL, Vesell ES. Underrepresentation of women in clinical drug trials. *Clin Pharmacol Ther* 1993;54:11-5.
- Svensson CK. Representation of American blacks in clinical trials of new drugs. *JAMA* 1989;261:263-5.
- Asthma and Allergy Foundation of America and the National Pharmaceutical Council. Ethnic Disparities in the Burden and Treatment of Asthma; 2005. Available from: <https://www.aafa.org/media/1633/ethnic-disparities-burden-treatment-asthma-report.pdf>. Accessed May 16, 2019.
- McGarry ME, Castellanos E, Thakur N, Oh SS, Eng C, Davis A, et al. Obesity and bronchodilator response in black and Hispanic children and adolescents with asthma. *Chest* 2015;147:1591-8.
- Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J* 2013;41:716-26.
- Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. *J Allergy Clin Immunol Pract* 2014;2:489-500.
- Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975-85.
- Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364:1005-15.
- Gibson PG, Reddel H, McDonald VM, Marks G, Jenkins C, Gillman A, et al. Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: the Australian Xolair Registry. *Intern Med J* 2016;46:1054-62.
- Ortega H, Li H, Suruki R, Albers F, Gordon D, Yancey S. Cluster analysis and characterization of response to mepolizumab. A step closer to personalized medicine for patients with severe asthma. *Ann Am Thorac Soc* 2014;11:1011-7.
- Drick N, Seeliger B, Welte T, Fuge J, Suhling H. Anti-IL-5 therapy in patients with severe eosinophilic asthma—clinical efficacy and possible criteria for treatment response. *BMC Pulm Med* 2018;18:119.
- Maltby S, Gibson PG, Powell H, McDonald VM. Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD. *Chest* 2017;151:78-89.
- Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, et al. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. *Am J Respir Crit Care Med* 2013;188:657-63.
- Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189-94.
- Food and Drug Administration (FDA). Minorities in Clinical Trials 2018. Available from: <https://www.fda.gov/consumers/minority-health-and-health-equity/minorities-clinical-trials>. Accessed June 3, 2019.

ONLINE REPOSITORY

METHODS

Data source and study design

Nationally representative sample: NHANES. We analyzed data from 40,790 participants in the 2005-2012 National Health and Nutrition Examination Survey (NHANES). The NHANES, conducted by the National Center for Health Statistics, is a biennial US population-based cross-sectional survey of the noninstitutionalized civilian population. NHANES collects information in 2 phases. The interview phase is conducted in homes, and the medical examination and laboratory evaluation component takes place subsequently in a mobile examination center. Average response rates for the 4-pooled cycles were 76% and 72% for the interview phase and the examination portion, respectively. NHANES uses a complex sampling design such that estimates are representative of the general noninstitutionalized US population. Depending on the survey cycle, some groups are oversampled. These typically include low-income persons, adolescents 12 to 19 years, pregnant persons, persons 60 years of age and above, African Americans, and Hispanics. Sample weights are assigned accordingly to account for the sampling procedure.

Survey participants used for comparison

We considered a subject as having asthma if aged 12 and above and answered the following questions in the affirmative: "Has a doctor or health professional ever told [you/study participant] that [you/s/he had] asthma?" and "Do you still have asthma?"

We defined survey participants who were likely to have had uncontrolled disease out of the group with asthma in 2 ways. We initially identified participants who were on inhaled corticosteroid (ICS) therapy singly or in combination with a long-acting β -agonist (LABA) and who had 2 or more exacerbations in the prior year requiring a visit to an emergency department or urgent care center. For the second group, we identified participants who were on ICSs and on 1 or more additional controllers for at least 90 days at the time of interview and who had 2 or more exacerbations in the prior year requiring a visit to an emergency department or urgent care center. Additional controller included LABA, long-acting muscarinic antagonists, leukotriene antagonists, and theophylline. Participants on oral steroids in addition to ICSs were also included in the cohort.

A participant aged ≥ 20 years was a current smoker if he or she (1) had smoked at least 100 cigarettes in life and (2) reported currently smoking. A nonsmoker had smoked less than 100 cigarettes in life and reported not smoking at the time of the interview. A former smoker had smoked at least 100 cigarettes in

life but was not currently smoking. A participant aged 12 to 19 years was a current smoker if had 1 or more days on which he or she smoked at least a cigarette in the past 30 days as reflected in response to "How many days did you smoke in the past 30 days."

Trial participants used for comparison

For each biologic approved by the Food and Drug Administration (FDA) for the treatment of asthma, omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab, we identified the seminal phase IIb/III trials used in granting FDA approval from each biologic package insert available online or on each biologic's respective company site. Data about trial participants were extracted from these package inserts and/or from the study report published in peer-reviewed journals.

Covariates

We compared baseline demographics: age (continuous or in categories if the study reported categories), gender, race, body mass index, use of oral steroids, smoking status, and blood eosinophil count. We used the data for the intervention arm or the overall population depending on data that were available from the study results available. In some occasions, mostly for race, there were data available on the drug package insert, which were not available in the published article. In such occasions, we used the data from the package insert. When the data were available, we compared proportion of Caucasians and/or African Americans with the data from survey participants. We did not compare Hispanics and Asian/other race to study data in studies where these data were available due to the differences in definitions between NHANES and the studies. For instance, in NHANES, a participant was either Hispanic or non-Hispanic Caucasian, non-Hispanic African American, or non-Hispanic Asian or other, whereas in trial data, race and ethnicity were considered separately such that an individual could be, as an example, a Hispanic African American.

Statistical analysis

We made comparisons with each individual study. For survey data, we report weighted proportions or means. We calculated *P* values for differences in proportions for categorical variables using the 2-sample test of proportions, and the Student *t*-test for continuous variables. Some studies reported only medians and ranges, or means and standard deviations. For those, we were unable to run any statistical tests. For blood eosinophil counts, we used the geometric mean as appropriate and the arithmetic mean when appropriate. All analyses were done as per survey data analyses in STATA (version 15.1; STACorp, College Station, Tex). *P* values of less than .05 were considered statistically significant.

TABLE E1. Comparison of survey participants to trial participants in omalizumab studies

Characteristic	NHANES-A	NHANES-B	XOLAIR-I	P value-A*	P value-B*	XOLAIR-II	P value-A	P value-B	XOLAIR-III	P value-A	P value-B
N	80	48	525			546			246		
Age, y, mean (range)	43 [†] (12-80)	43 [†] (12-80)	39.2 (12-74)	NA	NA	39.5 (12-76)	NA	NA	40.8 (12-75)	NA	NA
Age group, %											
12-17 y	21	22	7.8	<.001	.001	—	NA	NA	—	NA	NA
18-64 y	64	57	89.5	<.001	<.001	—	NA	NA	—	NA	NA
≥65 y	15	21	2.7	<.001	<.001	—	NA	NA	—	NA	NA
Female, %	77	66	59	.002	.34	51	<.001	.05	64	.03	.79
BMI, mean (SD)	33.6 (9.9)	32.6 (11.3)	—			—			—		
Caucasian, %	65	62	89	<.001	<.001	91	<.001	<.001	—		
Asthma duration, y	19.7 (17.6)	21.6 (18.4)	21.6 (NA)	NA	NA	19.7 (NA)	NA	NA	22.5 (15.3)	.17	.72
Never smoked, %	45	41	73	<.001	<.001	77	<.001	<.001	77	<.001	<.001
Former smoker, %	29	33	27	.74	.42	23	.29	.16	23	.32	.18

NHANES-A were patients with asthma who had ≥ 2 exacerbations in the prior year despite ICS or ICS/LABA therapy.

NHANES-B were patients with asthma who had ≥ 2 exacerbations in the prior year despite ICS and ≥ 1 additional controller for 3 months or more.

XOLAIR-I: Busse W, Corren J, Lanier BQ, et al. *J Allergy Clin Immunol* 2001;108:184-90; PMID: 11496232. *XOLAIR-II*: Solèr M, Matz J, Townley R, et al. *Eur Respir J* 2001;18:254-61; PMID: 11529281. *XOLAIR-III*: Holgate ST, Chuchalin AG, Hébert J, et al. *Clin Exp Allergy* 2004;34:632-8; PMID: 15080818.

BMI, Body mass index; *ICS*, inhaled corticosteroid; *LABA*, long-acting β -agonist; *NHANES*, National Health and Nutrition Examination Survey; *SD*, standard deviation.

**P* value-A and *P* value-B comparing trial participants with NHANES group A and B, respectively.

[†]Individuals 80 and over in NHANES are topcoded at 80 years of age.

TABLE E2. Comparison of survey participants to trial participants in mepolizumab studies

Characteristic	NHANES-A	NHANES-B	DREAM	P value-A	P value-B	MENSA	P value-A	P value-B	SIRIUS	P value-A	P value-B
N	80	48	616			576			135		
Age, y, mean (SD)	42.6 (20.8)	43.4 (22.0)	48.6 (11.1)	<.001	.005	50 (12-82)	NA	NA	50 (16-74)	NA	NA
Female, %	77	66	63	.01	.68	57	<.001	.23	55	.001	.18
BMI, mean (SD)	33.6 (9.9)	32.6 (11.3)	28.5 (5.9)	<.001	<.001	27.8 (5.8)	<.001	<.001	28.6 (6.0)	<.001	.002
Caucasian, %	65.0	62.0	90	<.001	<.001	78	.01	.01	95	<.001	<.001
Black, %	22.0	28.0	—	NA	NA	3	<.001	<.001	—	NA	NA
Hispanic ethnicity, %	7	7.0	—	NA	NA	9	.55	.64	4	.33	.40
Asthma duration, y	19.7 (17.6)	21.6 (18.4)	19.1 (14.3)	.73	.25	19.9 (13.8)	.91	.43	18.7 (14.2)	.65	.26
Never smoked, %	45	41.0	78	<.001	<.001	72	<.001	<.001	61	.03	.03
Former smoker, %	29	33.0	22	.21	.11	28	.89	.50	39	.17	.50

DREAM: Pavord ID, Korn S, Howarth P, et al. *Lancet* 2012;380:651-9; PMID: 22901886. *MENSA*: Ortega HG, Liu MC, Pavord ID, et al. *N Engl J Med* 2014;371:1198-207; PMID: 25199059. *SIRIUS*: Bel EH, Wenzel SE, Thompson PJ, et al. *N Engl J Med* 2014;371:1189-97; PMID: 25199060.

BMI, Body mass index; *NHANES*, National Health and Nutrition Examination Survey; *SD*, standard deviation.

TABLE E3. Comparison of survey participants to trial participants in benralizumab studies

Characteristic	NHANES-A	NHANES-B	SIROCCO	P value-A	P value-B	CALIMA	P value-A	P value-B	ZONDA	P value-A	P value-B
N	80	48	1204			1306			220		
Age, y, mean (SD)	42.6 (20.8)	43.4 (22.0)	48.8 (14.3)	<.001	.01	49.3 (14.4)	<.001	.007	51.0 (11.3)	<.001	<.001
Age group, %											
12-17 y	21.0	22	4	<.001	<.001	4	<.001	<.001	0	NA	NA
18-75 y	74.0	72	96	<.001	<.001	96	<.001	<.001	100	NA	NA
Female, %	77	66	66	.04	1.00	62	.007	.57	61	.01	.52
BMI, mean (SD)	33.6 (9.9)	32.6 (11.3)	28.8 (6.8)	<.001	<.001	28.8 (6.6)	<.001	<.001	29.6 (6.2)	<.001	.01
Caucasian, %	65.0	62.0	73	.12	.09	84	<.001	<.001	93	<.001	<.001
Black, %	22.0	28.0	4	<.001	<.001	3	<.001	<.001	1	<.001	<.001
Hispanic ethnicity, %	6.5	6.5	19	.005	.03	23	<.001	.007	—		
Asthma duration, y, median	12	14	15	NA	NA	16	NA	NA	12	NA	NA
Never smoked, %	45	41	80	<.001	<.001	78	<.001	<.001	79	<.001	<.001
Former smoker, %	29	33	20			21	.13	.07	—		

SIROCCO: Bleecker ER, FitzGerald JM, Chanez P, et al. Lancet 2016;388:2115-27; PMID: 27609408. *CALIMA*: FitzGerald JM, Bleecker ER, Nair P, et al. Lancet 2016;388:2128-41; PMID: 27609406. *ZONDA*: Nair P, Wenzel S, Rabe KF, et al. N Engl J Med 2017;376:2448-58; PMID: 28530840.

BMI, Body mass index; *NHANES*, National Health and Nutrition Examination Survey; *SD*, standard deviation.

TABLE E4. Comparison of survey participants to trial participants in reslizumab studies

Characteristic	NHANES-A	NHANES-B	RESLIZ-I	P value-A	P value-B	RESLIZ-II	P value-A	P value-B	RESLIZ-III	P value-A	P value-B	RESLIZ-IV	P value-A	P value-B
N	80	48	489			464			315			496		
Age, y, mean (SD)	42.6 (20.8)	43.4 (22.0)	47 (NA)	NA	NA	47 (NA)	NA	NA	44 (NA)	NA	NA	45 (NA)	NA	NA
Age group, %														
12-17y	21	22	—	NA	NA	—	NA	NA	5	<.001	<.001	—	NA	NA
≥18 y	79	78	—	NA	NA	—	NA	NA	95	<.001	<.001	—	NA	NA
Female, %	77	66	63	.02	.68	63	.02	.68	58	.002	.29	64	.02	.78
BMI, mean (SD)	33.6 (9.9)	32.6 (11.3)	27.8 (6.2)	<.001	<.001	27.0 (5.2)	<.001	<.001	27.6 (NA)			32.2 (NA)	NA	NA
Caucasian, %	65	62	73	.14	.11	73	.14	.11	81	.002	.003	67	.72	.48
Black, %	22	28	7	<.001	<.001	2	<.001	<.001	6	<.001	<.001	28	.26	1.00
Hispanic ethnicity, %	7	7	—	NA	NA	—			27	<.001	.003			
Asthma duration, y	19.7 (17.6)	21.6 (18.4)	19.3 (14.7)	.82	.31	18.5 (13.8)	.49	.15	20.4 (NA)	NA	NA	26.2 (NA)	NA	NA
Never smoked (use appropriate n), %	45	41	—	NA	NA	—	NA	NA	—	NA	NA	—	NA	NA
Former smoker, %	29	33	—	NA	NA	—	NA	NA	—	NA	NA	—	NA	NA

RESLIZ-I and *RESLIZ-II*: Castro M, Zangrilli J, Wechsler ME, et al. *Lancet Respir Med* 2015;3:355-66; PMID: 25736990. *RESLIZ-III*: Bjermer L, Lemiere C, Maspero J, et al. *Chest* 2016;150:789-98; PMID: 27056586. *RESLIZ-IV*: Corren J, Weinstein S, Janka L, et al. *Chest* 2016;150:799-810; PMID: 27018175.

BMI, Body mass index; *NHANES*, National Health and Nutrition Examination Survey; *SD*, standard deviation.

TABLE E5. Comparison of survey participants to trial participants in dupilumab studies

Characteristic	NHANES-A	NHANES-B	DUPILU-I	P value-A	P value-B	DUPILU-II	P value-A	P value-B	DUPILU-III	P value-A	P value-B
N	80	48	776			1902			210		
Age, y, mean (SD)	42.6 (20.8)	43.4 (22.0)	49 (13)	<.001	.006	48 (15)	.002	.04	52 (13)	<.001	<.001
Female, %	77	66	63	.01	.68	63	.01	.67	60	.007	.44
BMI, mean (SD)	33.6 (9.9)	32.6 (11.3)	29.5 (6.3)	<.001	.002	—			—		
Caucasian, %	65	62	78	.009	.01	83	<.001	<.001	94	<.001	<.001
Black, %	22	28	5	<.001	<.001	—	NA	NA	—	NA	NA
Asthma duration, y	20 (18)	22 (18)	22 (15)	.27	1.00	21 (15)	.56	.65	20 (14)	1.00	.39
Never smoked, %	45	41	77	<.001	<.001	81	<.001	<.001	80	<.001	<.001
Former smoker, %	29	33	22	.21	.11	19	.05	.03	20	.13	.07

DUPILU-I: Wenzel S, Castro M, Corren J, et al. Lancet 2016;388:31-44; PMID: 27130691. *DUPILU-II*: Castro M, Corren J, Pavord ID, et al. N Engl J Med 2018;378:2486-96; PMID: 29782217. *DUPILU-III*: Rabe KF, Nair P, Brusselle G, et al. N Engl J Med 2018;378:2475-85; PMID: 29782224.

BMI, Body mass index; *NHANES*, National Health and Nutrition Examination Survey; *SD*, standard deviation.