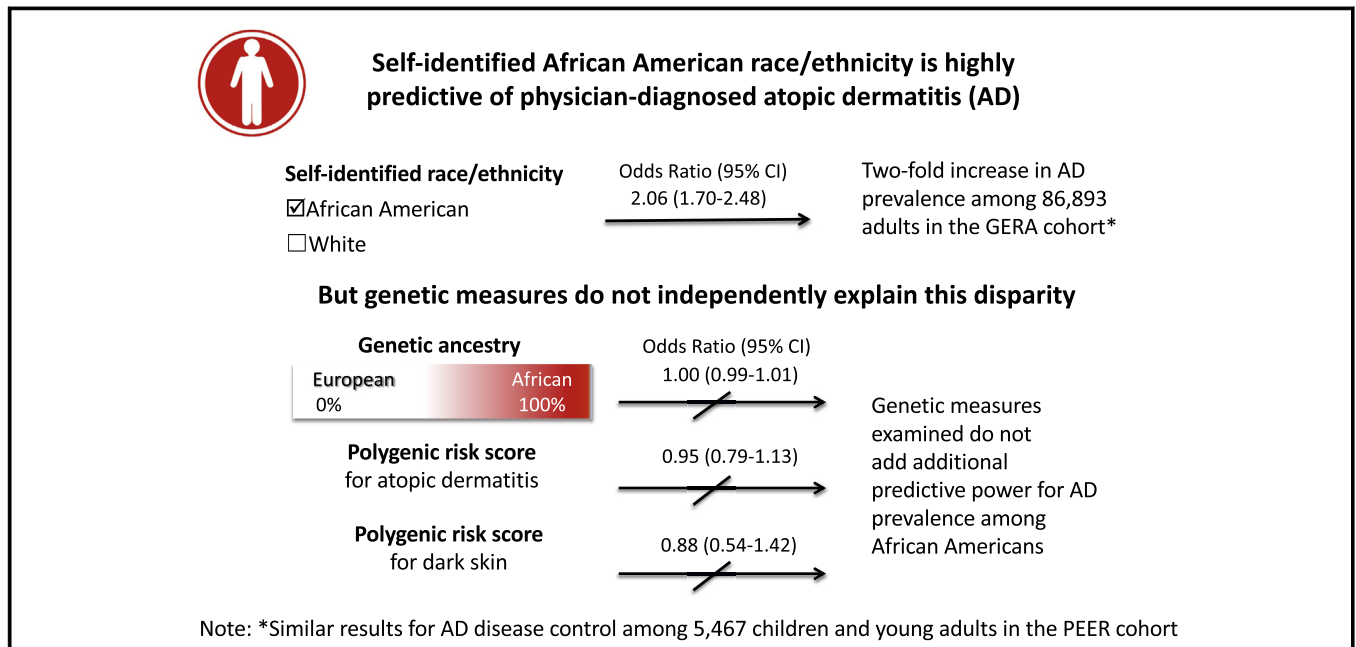


# Genetic ancestry does not explain increased atopic dermatitis susceptibility or worse disease control among African American subjects in 2 large US cohorts



Katrina Abuabara, MD, MA, MSCE,<sup>a</sup> Yue You, PhD,<sup>b</sup> David J. Margolis, MD, PhD,<sup>c</sup> Thomas J. Hoffmann, PhD,<sup>d</sup> Neil Risch, PhD,<sup>d,e</sup> and Eric Jorgenson, PhD<sup>e</sup> *San Francisco, Berkeley, and Oakland, Calif, and Philadelphia, Pa*

## GRAPHICAL ABSTRACT



**Background:** Atopic dermatitis (AD) is more common among African American children. Whether there are racial/ethnic difference among adults with AD and the causes for those disparities are unclear.

**Objective:** We sought to examine the relationship between self-reported race/ethnicity and AD and determine whether African genetic ancestry is predictive of these outcomes among African American subjects.

**Methods:** We analyzed data from 2 independent multiethnic longitudinal studies: 86,893 subjects aged 18 to 100 years from the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort and 5467 subjects aged 2 to 26 years from the national Pediatric Eczema Elective Registry (PEER) cohort. The primary outcomes were physician-diagnosed AD in GERA and repeated measures of self-reported disease control among patients with

From <sup>a</sup>the Program for Clinical Research, Department of Dermatology, University of California, San Francisco; <sup>b</sup>the Division of Biostatistics and Epidemiology, University of California, Berkeley; <sup>c</sup>the Department of Dermatology and Center for Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia; <sup>d</sup>the Institute for Human Genetics and Department of Epidemiology and Biostatistics, University of California, San Francisco; and <sup>e</sup>the Division of Research, Kaiser Permanente, Oakland.

K.A. is supported by grants from the Robert Wood Johnson Foundation and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS; K23 AR073915). E.J. is supported by grants from the National Eye Institute (R01 EY027004) and the National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK116738). Support for participant enrollment, survey completion, and biospecimen collection for the GERA was provided by the Robert Wood Johnson Foundation, the Wayne and Gladys Valley Foundation, the Ellison Medical Foundation, and Kaiser Permanente National and Regional Community Benefit programs. Genotyping of the GERA cohort was funded by a grant from the National Institute on Aging, the National Institute of Mental Health, and the National Institute of Health Common Fund (RC2 AG036607 to Cathy Schaefer and N.R.).

Disclosure of potential conflict of interest: K. Abuabara receives research funding for atopic dermatitis from the National Institutes of Health (NIH) and the Robert Wood Johnson Foundation and is a consultant to TARGETPharma, a company developing a prospective atopic dermatitis registry. D. J. Margolis receives funding for research on atopic dermatitis from the NIH and Valeant and is a consultant for Sanofi and GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 31, 2018; revised June 19, 2019; accepted for publication June 26, 2019.

Available online July 29, 2019.

Corresponding author: Katrina Abuabara, MD, MA, MSCE, Department of Dermatology, University of California San Francisco (UCSF), 2340 Sutter St, N421, San Francisco, CA 94115. E-mail: [Katrina.abuabara@ucsf.edu](mailto:Katrina.abuabara@ucsf.edu).

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2019.06.044>

physician-diagnosed AD at 6-month intervals in PEER. We examined whether self-identified African American race/ethnicity was predictive of these outcomes and then tested whether a continuous measure of African genetic ancestry was associated with outcomes within the African American group. **Results:** AD was more common among self-identified African American subjects than non-Hispanic white subjects in GERA (4.4% vs 2.1%; odds ratio, 2.06; 95% CI, 1.70-2.48) and less well-controlled in PEER subjects (odds of 1-level worse control, 1.91; 95% CI, 1.64-2.22). However, African genetic ancestry was not associated with AD risk or control among self-identified African American subjects in either cohort, nor did an AD polygenic risk score or genetic skin pigment score explain the AD disparities in patients with AD.

**Conclusion:** Ancestry-related genetic effects do not explain increased AD prevalence or poorer disease control among African American subjects. (J Allergy Clin Immunol 2020;145:192-8.)

**Key words:** Atopic dermatitis, eczema, genetic ancestry, disease control, racial/ethnic disparities

Data from cross-sectional studies suggest that atopic dermatitis (AD; synonymous with atopic eczema)<sup>1</sup> is more common and more severe among African and African American children than non-Hispanic white children, but there are conflicting reports about whether AD remains more common among African American subjects as they age and little data about why racial/ethnic disparities might exist in patients with AD.<sup>2-7</sup> Data on physician-diagnosed disease are sparse, and existing estimates might be biased by self-report and are limited to a single time point.<sup>8</sup> Using a longitudinal registry of children and young adults with physician-diagnosed mild-to-moderate AD, we previously found that African American race/ethnicity was one of the strongest predictors of a pattern of persistently active (vs resolving) AD during adolescence and early adulthood.<sup>9</sup> Because AD often waxes and wanes in severity, with extended periods of apparent disease remission in some patients, additional studies are needed to understand the nature of racial/ethnic disparities in both children and adults.

Investigations into the nature and causes of disparities in AD might elucidate mechanisms of disease susceptibility and persistence and can inform targeted intervention strategies. AD is known to have strong genetic, environmental, and sociocultural influences,<sup>10</sup> but there are limited data on the extent to which these factors might affect racial/ethnic disparities. To date, most genetic research has been performed in European and Asian populations; however, 1 recent genome-wide association study found a novel locus for AD in African American subjects.<sup>11</sup> Additionally, some studies suggest that filaggrin-null mutations (the strongest known genetic risk factor for AD) are less common in populations of African descent, although other studies suggest these findings might be due to technical genotyping limitations.<sup>12-16</sup> Therefore additional research is needed to understand whether the increased burden of AD in African American subjects is caused by other genetic or nongenetic factors.

Race and ethnicity are complex constructs that incorporate a range of social, cultural, and genetic factors. For ancestrally admixed populations, measures of individual genetic ancestry can be calculated that represent differentially distributed genetic

#### Abbreviations used

AD: Atopic dermatitis  
GERA: Genetic Epidemiology Research on Adult Health and Aging  
ICD-9: International Classification of Diseases, ninth edition  
PEER: Pediatric Eczema Elective Registry  
PRS: Polygenic risk score

factors that vary according to historical geographic separations. African American subjects typically have a mix of genetic ancestry from European and African populations and a score ranging from 0% to 100% that represents the ancestry proportions from those 2 populations can be calculated for each subject.<sup>17</sup>

A subject's proportion of a particular genetic ancestry, which is continuous, might offer a more nuanced method for understanding disparities in outcomes beyond simple dichotomous self-identified racial and ethnic categories, and genetic ancestry analyses are increasingly being used to understand the genetic contribution to disease traits in admixed populations.<sup>18-20</sup> For example, African genetic ancestry has been shown to predict lung function and asthma exacerbations among African American subjects better than self-reported race/ethnicity alone.<sup>19,21</sup> To our knowledge, no studies have yet examined the role of genetic ancestry in patients with AD.

The objectives of this study were to determine (1) whether there are differences in AD prevalence and control between self-identified US African American and white subjects and (2) whether African genetic ancestry and/or polygenic risk scores (PRSs) underlying AD and skin pigment are predictive of these outcomes among African American subjects in 2 large US cohorts. The rationale for a 2-stage approach is to understand whether genetic factors provide additional explanatory evidence regarding AD disparities beyond self-identified race/ethnicity alone.

## METHODS

### Cohorts

The Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort, which is described in detail elsewhere, is health system based and includes adults aged 18 years and older.<sup>22</sup> It was created to enable studies of genetic and environmental influences on health. Briefly, adult members of Kaiser Permanente Northern California, an integrated health delivery system with a membership of about 4.1 million representative of the general population in northern California, were asked to complete a written survey, completed a broad written consent form, and provided a saliva sample for extraction of DNA to be linked to their electronic health record. The mean length of electronic health record follow-up is 23.5 years. Broad written consent was obtained, and the study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

The Pediatric Eczema Elective Registry (PEER) is an ongoing prospective observational registry of patients aged 2 to 26 years with physician-diagnosed mild-to-moderate AD from across the United States. The study was designed to investigate whether pimecrolimus, a topical calcineurin inhibitor, is associated with cancer, and an inclusion criterion was pimecrolimus use for at least 6 weeks before enrollment.<sup>23</sup> The diagnosis of AD was confirmed with the UK Working Party criteria.<sup>24</sup> Patients are followed with mailed surveys every 6 months for up to 10 years, and follow-up is independent of office visits and treatment decisions. After enrollment into the cohort, participants were asked to provide additional consent and saliva samples through mail for DNA extraction. The study was approved by the University of Pennsylvania

Institutional Review Board. We included data from participants with at least 1 follow-up survey in the registry between 2004 and 2016; the mean duration of follow-up was 6.2 years.

In both cohorts participants were asked in a baseline questionnaire to select 1 or more race/ethnicity/nationality categories that best described themselves. For this study, we only included subjects who self-identified as African American and/or non-Hispanic white. In the GERA cohort 93.8% of participants endorsed a single race/ethnicity/nationality group and 6.2% endorsed 2 or more, and in the PEER cohort 93.1% of participants endorsed a single race/ethnicity group and 6.9% endorsed 2 or more. Subjects who endorsed more than 1 race/ethnicity group were included with the African American group for the primary analyses provided that African American/black ethnicity was at least 1 of the categories endorsed. In a sensitivity analysis we repeated main analyses excluding these subjects.

DNA samples were available by design for all of the GERA participants and for 755 (13%) subjects enrolled in the PEER cohort. For the latter, those who provided samples were more likely to self-identify as white and have a history of atopy, younger age at onset, higher family income at baseline, and longer duration of follow-up in the cohort (see [Table E1](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

## Genetic ancestry estimation

In GERA a principal components analysis was performed with the smartpca program, which is part of the EIGENSOFT 4.2 software package, on data genotyped with Affymetrix Axiom arrays.<sup>25</sup> Individual ancestral admixture proportions were then estimated by using the full maximum-likelihood software package frappe to calculate the probability of a set of genome-wide genotypes in a subject as a weighted average of allele frequencies of putative ancestors, where the weights represent the admixture proportions.<sup>17,26,27</sup>

In PEER a panel of 186 previously validated ancestry informative markers<sup>28,29</sup> genotyped with Illumina's GoldenGate technology (Illumina, San Diego, Calif) was used to estimate genetic ancestry. Ancestry estimates were calculated assuming 3 ancestral populations by using a model-based clustering approach with the program STRUCTURE.<sup>30</sup>

## AD PRS

A genome-wide genetic ancestry estimate might not accurately reflect the specific genetic variants that underlie the risk for AD. Therefore, using the most recently published genome-wide association study of AD,<sup>31</sup> we constructed a PRS for AD risk using 27 single nucleotide polymorphisms and weights based on the regression coefficients in that study.

## Skin pigment PRS

We also tested the hypothesis that differences in skin pigment between European and African American subjects could underlie the difference in risk of AD between the 2 racial/ethnic groups. To test this hypothesis, we created a dark versus light skin pigment PRS based on 39 single nucleotide polymorphisms from a recent study of skin color.<sup>32</sup>

## Primary outcomes

The primary outcome in GERA was a physician's diagnosis of AD defined on the basis of 2 or more International Classification of Diseases, ninth edition (ICD-9), codes for AD (691.8) on separate dates. In sensitivity analyses we tested the effect of varying the number of codes required to meet the definition from 1 to 3.

In PEER all of the participants had physician-diagnosed AD, and the primary outcome was a repeating measure of disease control. Patients were asked the following: "During the last 6 months would you say your (or your child's) skin has shown complete disease control, good disease control, limited disease control, or uncontrolled disease?" They were also asked whether they had used any prescription treatments for their AD. Inactive disease was defined as self-reported complete control without treatment. The disease

control question was chosen because it is easily interpreted and comprehensive and has been shown to have good overlap with validated measures of AD severity recommended for use in clinical trials.<sup>33-35</sup>

Multivariable adjusted models included sociodemographic factors and atopic comorbidities previously shown to be related to AD: sex, history of atopy (yes/no), age at assessment (continuous), age at enrollment into the cohort (continuous), self-reported income at enrollment (3-level categorical variable), education (3-level categorical variable, GERA only), duration of follow-up (continuous, PEER only), and age at disease onset (continuous, PEER only). In GERA atopic history was based on the presence of 2 or more ICD-9 codes for allergic rhinitis, asthma, or both. Asthma was defined by using ICD-9 codes 493, 493.01, 493.1, 493.11, 493.82, 493.9, 493.91, and 493.92. Allergic rhinitis was defined by using ICD-9 codes 477, 477.1, 477.2, 477.8, and 477.9. In PEER atopic history was based on a self-reported history of physician-diagnosed asthma or seasonal allergies.

## Statistical analyses

Associations with self-reported race/ethnicity were examined by using logistic regression models to estimate the odds of AD (yes/no) in African American subjects compared with non-Hispanic white subjects in GERA, and ordinal multilevel mixed-effects models were used to estimate the subject-specific odds of a 6-month period of worse disease control in PEER. These models were then repeated among only self-identified African American subjects to test for an association between a continuous measure of African genetic ancestry and AD prevalence (GERA) or control (PEER). The rationale for this approach was to test the additional predictive value of genetic ancestry beyond self-identified race/ethnicity and has been used in similar analyses for asthma and lung function.<sup>21,36</sup>

In *post hoc* analyses we replicated our models including information on genetic ancestry for all participants (including self-identified white subjects). In addition, we repeated the models with 2 new PRSs (described above) to further test whether genetic factors are related to disparities in AD risk. First, we tested the AD PRS for association with AD among the European and African American subjects using regression analysis and also whether its inclusion in the regression model attenuated the association of self-reported race/ethnicity with AD in the GERA cohort. Second, we included a skin phenotype PRS as a covariate in a regression analysis, including both the white and African American subjects in GERA, to determine whether the effect of self-reported race/ethnicity was attenuated and also in an analysis of the African American subjects alone to see whether the pigment PRS was predictive of AD risk within that population. Additional methodological details are included in the supplemental material for this article. Statistical analyses were performed with Stata 15 and R software,<sup>37,38</sup> and all tests were 2-sided.

## RESULTS

### Participants' characteristics

This study included 86,893 subjects who self-identified as non-Hispanic white and/or African American in GERA and 5,467 subjects who self-identified as non-Hispanic white and/or African American in PEER. Participants from GERA were older, had higher incomes, and had lower overall rates of atopy than participants in PEER ([Table I](#)). The distribution of demographic characteristics varied by self-reported race/ethnicity: in the GERA cohort, compared with white subjects, African American subjects had lower incomes, had lower levels of education, were younger at enrollment, and had greater rates of allergies and asthma. In the PEER cohort, compared with white subjects, African American subjects were more likely to be female, have lower family incomes, have less atopic history, and enroll at an older age (although they had similar reported age at AD onset).

When we compared subjects with and without AD in the GERA cohort, we found that cases were more likely to be female

**TABLE I.** Participants' characteristics

| GERA cohort                             | Total (n = 86,893) | African American* (n = 3,380) | White (n = 83,513) | P value† |
|-----------------------------------------|--------------------|-------------------------------|--------------------|----------|
| Female sex, no. (%)                     | 50,225 (57.8)      | 1,950 (57.7)                  | 48,275 (57.8%)     | .896     |
| Annual income in US dollars, no. (%)    |                    |                               |                    |          |
| <\$20,000                               | 3,890 (4.5%)       | 231 (6.8%)                    | 3,659 (4.4%)       | <.001    |
| \$20,000-\$60,000                       | 24,113 (27.8%)     | 1,116 (33.0%)                 | 22,997 (27.5%)     |          |
| >\$60,000                               | 51,719 (59.5%)     | 1,781 (52.7%)                 | 49,938 (59.8%)     |          |
| Missing                                 | 7,171 (8.3%)       | 252 (7.5%)                    | 6,819 (8.3%)       |          |
| Education, no. (%)                      |                    |                               |                    |          |
| Less than high school                   | 1,545 (1.8%)       | 110 (3.3%)                    | 1,435 (1.7%)       | <.001    |
| High school or equivalent               | 31,957 (36.8%)     | 1,419 (42.0%)                 | 30,538 (36.6%)     |          |
| College or graduate school              | 48,363 (55.7%)     | 1,579 (46.7%)                 | 46,784 (56.0%)     |          |
| Missing                                 | 5,028 (5.8%)       | 272 (8.0%)                    | 4,756 (5.7%)       |          |
| History of atopy, no. (%)               | 29,254 (33.7%)     | 1,346 (39.8%)                 | 27,908 (33.4%)     | <.001    |
| Age at cohort enrollment (y), mean (SD) | 63.6 (14.3)        | 60.5 (14.3)                   | 63.8 (14.3)        | <.001    |
| PEER cohort                             | Total (n = 5,467)  | African American* (n = 3,251) | White (n = 2,216)  | P value† |
| Female sex, no. (%)                     | 2,914 (53.3%)      | 1,844 (56.7%)                 | 1,070 (48.3%)      | <.001    |
| Annual income in US dollars, no. (%)    |                    |                               |                    |          |
| <\$25,000                               | 2,222 (40.6%)      | 1,911 (58.8%)                 | 311 (14.0%)        | <.001    |
| \$25,000-\$50,000                       | 810 (14.8%)        | 445 (13.7%)                   | 365 (16.5%)        |          |
| >\$50,000                               | 1,009 (18.5%)      | 218 (6.7%)                    | 791 (35.7%)        |          |
| Missing                                 | 1,426 (26.1%)      | 677 (20.8%)                   | 749 (33.8%)        |          |
| History of atopy, no. (%)               | 4,033 (73.8%)      | 2,291 (70.5%)                 | 1,742 (78.6%)      | <.001    |
| Age at cohort enrollment (y), mean (SD) | 7.21 (4.12)        | 7.31 (4.15)                   | 7.06 (4.07)        | .027     |

Values significant at the  $P < .05$  level are shown in boldface.

\*Includes 516 subjects in the GERA cohort and 184 subjects in the PEER cohort who self-reported both African American and another race.

†P values are from  $\chi^2$  tests for categorical variables and  $t$  tests for continuous variables.

and have a history of other atopic comorbidities, and these effects were consistent in each race/ethnicity group. Among African American subjects, cases were also more likely to enroll in the cohort at a younger age, and among white subjects, cases were more likely to have lower incomes. There were no significant differences in educational attainment (see Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Self-reported race/ethnicity and AD

AD was more common and under worse control among African American than white subjects. The primary outcomes of a physician's diagnosis in the GERA cohort and disease control in the PEER cohort are shown by race/ethnicity in Fig 1 and Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). In the GERA cohort 4.4% of African American subjects versus 2.1% of white subjects ( $P < .001$ ) met the definition of AD. In the PEER cohort, compared with white subjects, African American subjects reported worse disease control at all ages, and the mean proportion of surveys in which respondents reported active disease during the prior 6 months was greater among African American subjects (94.5% vs 84.4%,  $P < .001$ ).

In multivariable models we found African American subjects had an approximately 2-fold increase in both the odds of AD (odds ratio, 2.06; 95% CI, 1.70-2.48) in the GERA cohort and the odds of 1-level worse control (odds ratio, 2.02; 95% CI, 1.71-2.37) in the PEER cohort (Table II).

### African genetic ancestry and AD

The distribution of African genetic ancestry among self-identified African American subjects (including 516 subjects in the GERA cohort and 184 subjects in the PEER cohort who

self-reported African American plus at least 1 other racial/ethnic group) ranged from 0% to 100% and was similar in both cohorts (mean, 74% [SD, 17%] in the GERA cohort and 76% [SD, 17%] in the PEER cohort; see Fig E1 and Table E3 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

African genetic ancestry showed no association with AD outcomes among African American subjects in either cohort (Table II). Genetic ancestry was modeled as a continuous variable ranging from 0% to 100%, and the primary results reflect the odds of a 1% increase in genetic ancestry. To make the magnitude of association clearer, we also calculated the odds on a larger scale. In the GERA cohort the odds of AD for each quartile increase in African ancestry were 1.07 (95% CI 0.83-1.36), and in the PEER cohort the odds of poorer disease control for each quartile increase in ancestry were 1.05 (95% CI, 0.72-1.53).

As described in the Methods section, for the principal analysis, we modeled the effect of African genetic ancestry only among African American subjects. When we included all participants (self-identified African American and white subjects) in the African genetic ancestry models, we again found no significant association between genetic ancestry and AD (see Table E4 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

Similarly, we found that predicted skin color was not independently associated with AD beyond self-identified race/ethnicity alone in an analysis that included both white and African American subjects, nor was it associated with AD within only the African American group (see Table E5 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Finally, we found that although a PRS was highly predictive of AD overall, it was not correlated with genetic ancestry, it did not attenuate the association of self-reported race/ethnicity in the regression model of AD risk in the entire sample, and it was not predictive of AD

TABLE II. Multivariate model results

| GERA cohort                                      | Model 1: Odds of AD among full cohort<br>(n = 76,060), odds ratio (95% CI)                              | Model 2: Odds of AD among African<br>American subjects<br>(n = 3,161), odds ratio (95% CI)                          |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
|                                                  |                                                                                                         |                                                                                                                     |
| Percentage African ancestry (by 1-unit increase) | NA                                                                                                      | 1.00 (0.99-1.01)                                                                                                    |
| Self-identified race (African American vs white) | <b>2.06 (1.70-2.48)</b>                                                                                 | NA                                                                                                                  |
| Sex (female vs male)                             | <b>1.25 (1.13-1.39)</b>                                                                                 | <b>1.70 (1.11-2.59)</b>                                                                                             |
| Income                                           |                                                                                                         |                                                                                                                     |
| <\$20,000                                        | Reference                                                                                               | Reference                                                                                                           |
| \$20,000-\$60,000                                | 0.86 (0.69-1.08)                                                                                        | 0.80 (0.36-1.77)                                                                                                    |
| >\$60,000                                        | <b>0.77 (0.62-0.96)</b>                                                                                 | 1.09 (0.50-2.36)                                                                                                    |
| Education                                        |                                                                                                         |                                                                                                                     |
| Less than high school                            | Reference                                                                                               | Reference                                                                                                           |
| High school or equivalent                        | 0.95 (0.66-1.39)                                                                                        | 3.02 (0.40-22.7)                                                                                                    |
| College or graduate school                       | 1.06 (0.73-1.54)                                                                                        | 2.69 (0.36-20.4)                                                                                                    |
| History of atopy                                 | <b>2.19 (1.99-2.42)</b>                                                                                 | <b>1.92 (1.31-2.81)</b>                                                                                             |
| Age (each additional year)                       | <b>1.00 (1.00-1.00)</b>                                                                                 | <b>1.00 (0.98-1.01)</b>                                                                                             |
| PEER cohort                                      | Model 1: Odds of 1-level worse disease<br>control among full cohort<br>(n = 2,041), Odds ratio (95% CI) | Model 2: Odds of 1-level worse disease<br>control among African American subjects<br>(n = 257), odds ratio (95% CI) |
|                                                  |                                                                                                         |                                                                                                                     |
| Percentage African ancestry (by 1-unit increase) | NA                                                                                                      | 1.00 (0.99-1.02)                                                                                                    |
| Self-identified race (African American vs white) | <b>2.02 (1.71-2.37)</b>                                                                                 | NA                                                                                                                  |
| Sex (female vs male)                             | <b>1.20 (1.06-1.37)</b>                                                                                 | <b>1.83 (1.09-3.07)</b>                                                                                             |
| Income                                           |                                                                                                         |                                                                                                                     |
| <\$25,000                                        | Reference                                                                                               | Reference                                                                                                           |
| \$25,000-\$50,000                                | 0.94 (0.79-1.12)                                                                                        | 0.93 (0.48-1.81)                                                                                                    |
| >\$50,000                                        | <b>0.73 (0.61-0.88)</b>                                                                                 | <b>0.66 (0.32-1.39)</b>                                                                                             |
| History of atopy                                 | <b>1.20 (1.04-1.39)</b>                                                                                 | <b>1.46 (0.78-2.70)</b>                                                                                             |
| Age (each additional year)                       |                                                                                                         |                                                                                                                     |
| Age at cohort enrollment                         | <b>1.23 (1.21-1.25)</b>                                                                                 | <b>1.16 (1.07-1.25)</b>                                                                                             |
| Age at survey                                    | <b>0.82 (0.81-0.83)</b>                                                                                 | <b>0.88 (0.84-0.92)</b>                                                                                             |

Values significant at the  $P < .05$  level are shown in boldface.

NA, Not applicable.

among self-identified African American subjects in contrast to its strong association with AD risk in white subjects (see Table E6 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Sensitivity analyses

We repeated our analyses in the GERA cohort, varying the number of ICD-9 code diagnoses required to meet the definition of AD, and found that the strength of association between self-reported race/ethnicity and AD increased with more codes. However, there continued to be no association between African genetic ancestry and AD outcomes among self-identified African American subjects (see Table E7 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). We also repeated the analyses excluding 25 subjects from PEER who had self-identified as both African American and white and again found similar results (see Table E8 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### DISCUSSION

We found that AD was more common among adults and under worse control among children who self-identified as African American compared with those who self-identified as non-Hispanic white in 2 large US cohorts. However, these racial/ethnic differences were not associated with a continuous measure of genetic ancestry, nor were they associated with specific genetic factors underlying AD risk or skin pigment. Our results suggest that genetic factors that vary according to

historical geographic separations are unlikely to explain the observed differences and that social and environmental factors that vary by race/ethnicity warrant additional research.

It is important to note that self-identified race/ethnicity and genetic ancestry are 2 distinct but correlated constructs. As shown in Fig E1, there was a great deal of variation in genetic ancestry among African American subjects, and the rationale for examining this more nuanced measure was to test whether genetic data offered additional predictive power beyond self-identified race/ethnicity alone.

To our knowledge, this is the first study to examine the relationship between genetic ancestry and AD. Although we did not find evidence for an association between global genetic ancestry and AD in African American subjects, we cannot rule out the possibility that there might be genetic differences by race/ethnicity not fully captured by ancestry estimates. We found that an AD PRS was highly predictive of AD in white but not African American subjects similar to a recent genome-wide association study of AD in African American subjects that was not able to replicate known AD and allergy genetic loci in an African American population.<sup>11</sup> These results suggest that the genetic architecture of risk in African American subjects might be quite distinct from that in white subjects, and this underscores the need for additional genetic studies of AD in African American subjects, in whom the prevalence is greatest. Of note, the lack of any strong specific gene association findings in that study<sup>11</sup> also suggests that location-specific, as opposed to genome-wide

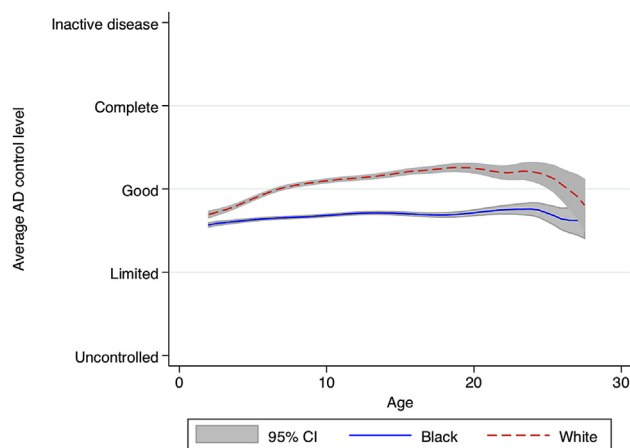


**FIG 1.** Association between self-reported race/ethnicity and AD control in the PEER cohort. The graph is a local polynomial smoothed plot with gray shading for the 95% CIs generated from cross-sectional calculations of average AD control level at each age.

genetic, ancestry is unlikely to explain the higher rate of AD in African American subjects. Additionally, there might be racial/ethnic differences in gene transcription. A recent study that sought to characterize the global molecular profile of patients with AD found significant variation in cellular infiltrates, as well as expression of immune and barrier genes between African American and white subjects.<sup>39</sup> The extent to which such changes are due to environmental and behavioral factors should be explored in future work.

The fact that the skin pigment PRS did not correlate with AD risk in the GERA cohort provides evidence that AD is likely independent of skin pigment *per se* and that the pigment difference between African American and white subjects does not explain the AD prevalence difference. New research showing that darker skin pigmentation results in better barrier function and greater inflammatory thresholds might help explain this finding.<sup>40</sup>

Our results suggest that social and environmental factors are likely to play an important role in AD disparities and warrant additional research. In both cohorts in our study, lower income was associated with AD outcomes independent of self-reported race/ethnicity. Our findings contrast with those from a systematic review and meta-analysis that found AD was associated with greater socioeconomic position.<sup>41</sup> Of note, the majority of studies included in the review came from European populations with less racial/ethnic diversity, and there was a great deal of heterogeneity between estimates. US studies on income and AD are mixed, likely because of differences in the way AD is defined (by self-report vs a physician's diagnosis) and whether studies adequately controlled for differential access to health care. Two US studies found income had no effect on childhood AD after controlling for race/ethnicity and insurance status,<sup>2,4</sup> one found greater household income was associated with adult AD,<sup>6</sup> and another found the opposite in a large population-based sample of individuals aged 0 to 100 years.<sup>5</sup> Additional work needs to be done to understand the effect of socioenvironmental factors, including whether differential exposure to microbes, pollutants, stress, differences in health care access, and treatment explain disparities.

We chose to use the GERA and PEER cohorts because they have complementary strengths and limitations. Patients enrolled

in the PEER cohort met the widely accepted and validated UK Working Party diagnostic criteria<sup>24,42</sup> and had detailed measures of disease control over time. AD is an episodic condition, meaning that symptoms wax and wane and patients might experience periods without any clinical signs or symptoms. Therefore repeated measures of disease activity and control are important to understanding the course and burden of the disease.

By contrast, diagnoses were limited to ICD codes in the GERA cohort, which might have induced misclassification bias. When we performed stratified analyses by number of diagnostic codes, we found that effect sizes increased with the number of diagnostic codes (which might reflect both the validity and severity of the diagnosis) in our primary analyses of self-reported race/ethnicity, but even with increasing numbers of diagnostic codes, there remained no association between genetic ancestry and AD among African American subjects.

Ancestry was estimated by using genome-wide data in the GERA cohort; however, the PEER cohort had less robust measures based on a limited number of ancestry informative markers. Nonetheless, the distribution of genetic ancestry was similar in both cohorts. Genetic data were only available for a subset of the PEER cohort. Although we cannot rule out the possibility of selection bias, the probability that the contribution of a biospecimen was differentially correlated with degree of African genetic ancestry is small.

Finally, although participants in the PEER cohort might have had differential access to health care, participants in the GERA cohort were all members of the Kaiser Permanente Health provider system. An overall strength of our study is use of 2 large longitudinal cohorts with physician-diagnosed AD, and the consistency of results across both populations is reassuring.

Our results are important in the context of the treatment revolution currently underway in patients with AD.<sup>43</sup> African American subjects are historically underrepresented in clinical research, and as new agents enter clinical testing, it is important to consider the extent to which trial populations are representative of the actual population of affected subjects. Our results imply that subanalyses to detect heterogeneous treatment responses should be based on social, environmental, and demographic factors in addition to biomarkers or genetic polymorphisms.

We thank the Kaiser Permanente Northern California members who have generously agreed to participate in the Kaiser Permanente Research Program on Genes, Environment, and Health.

**Clinical implications: Self-report of race/ethnicity can help to identify patients at higher risk of AD and poor AD control.**

## REFERENCES

1. Silverberg JI, Thyssen JP, Paller AS, Drucker AM, Wollenberg A, Lee KH, et al. What's in a name? Atopic dermatitis or atopic eczema, but not eczema alone. *Allergy* 2017;72:2026-30.
2. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011;131:67-73.
3. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009;124:1251-8.e23.
4. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis* 2014;25:107-14.
5. Hanifin JM, Reed ML, Eczema P, Impact Working G. A population-based survey of eczema prevalence in the United States. *Dermatitis* 2007;18:82-91.

6. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol* 2013;132:1132-8.
7. Mahdavinia M, Fox SR, Smith BM, James C, Palmisano EL, Mohammed A, et al. Racial differences in food allergy phenotype and health care utilization among US children. *J Allergy Clin Immunol Pract* 2017;5:352-7.e1.
8. Kramer U, Schafer T, Behrendt H, Ring J. The influence of cultural and educational factors on the validity of symptom and diagnosis questions for atopic eczema. *Br J Dermatol* 1998;139:1040-6.
9. Abuabara K, Hoffstad O, Troxel AB, Gelfand JM, McCulloch CE, Margolis DJ. Patterns and predictors of atopic dermatitis disease control past childhood: an observational cohort study. *J Allergy Clin Immunol* 2018;141:778-80.e6.
10. Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016;387:1109-22.
11. Almogueria B, Vazquez L, Mentch F, March ME, Connolly JJ, Peissig PL, et al. Novel locus for atopic dermatitis in African Americans and replication in European Americans. *J Allergy Clin Immunol* 2019;143:1229-31.
12. Winge MC, Bilcha KD, Lieden A, Shibeshi D, Sandilands A, Wahlgren CF, et al. Novel filaggrin mutation but no other loss-of-function variants found in Ethiopian patients with atopic dermatitis. *Br J Dermatol* 2011;165:1074-80.
13. Polcari I, Becker L, Stein SL, Smith MS, Paller AS. Filaggrin gene mutations in African Americans with both ichthyosis vulgaris and atopic dermatitis. *Pediatr Dermatol* 2014;31:489-92.
14. Margolis DJ, Gupta J, Apter AJ, Hoffstad O, Papadopoulos M, Rebbeck TR, et al. Exome sequencing of filaggrin and related genes in African-American children with atopic dermatitis. *J Invest Dermatol* 2014;134:2272-4.
15. Easwarkanthan M, Xu D, Flanagan C, Rzhetskaya M, Hayes MG, Blekhan R, et al. Atopic dermatitis susceptibility variants in filaggrin hitchhike hornerin selective sweep. *Genome Biol Evol* 2016;8:3240-55.
16. Margolis DJ, Mitra N, Gochmayer H, Wubbenhorst B, D'Andrea K, Kraya A, et al. Uncommon filaggrin variants are associated with persistent atopic dermatitis in African Americans. *J Invest Dermatol* 2018;138:1501-6.
17. Banda Y, Kvale MN, Hoffmann TJ, Hesselson SE, Ranatunga D, Tang H, et al. Characterizing race/ethnicity and genetic ancestry for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. *Genetics* 2015;200:1285-95.
18. Gupta J, Johansson E, Bernstein JA, Chakraborty R, Khurana Hershey GK, Rothenberg ME, et al. Resolving the etiology of atopic disorders by using genetic analysis of racial ancestry. *J Allergy Clin Immunol* 2016;138:676-99.
19. Hernandez-Pacheco N, Flores C, Oh SS, Burchard EG, Pino-Yanes M. What ancestry can tell us about the genetic origins of inter-ethnic differences in asthma expression. *Curr Allergy Asthma Rep* 2016;16:53.
20. Mountain JL, Risch N. Assessing genetic contributions to phenotypic differences among 'racial' and 'ethnic' groups. *Nat Genet* 2004;36(suppl):S48-53.
21. Kumar R, Seibold MA, Aldrich MC, Williams LK, Reiner AP, Colangelo L, et al. Genetic ancestry in lung-function predictions. *N Engl J Med* 2010;363:321-30.
22. Kvale MN, Hesselson S, Hoffmann TJ, Cao Y, Chan D, Connell S, et al. Genotyping informatics and quality control for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. *Genetics* 2015;200:1051-60.
23. Kapoor R, Hoffstad O, Bilker W, Margolis DJ. The frequency and intensity of topical pimecrolimus treatment in children with physician-confirmed mild to moderate atopic dermatitis. *Pediatr Dermatol* 2009;26:682-7.
24. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131:383-96.
25. Patterson N, Price AL, Reich D. Population structure and eigenanalysis. *PLoS Genet* 2006;2:e190.
26. Tang H, Peng J, Wang P, Risch NJ. Estimation of individual admixture: analytical and study design considerations. *Genet Epidemiol* 2005;28:289-301.
27. Choquet H, Paylakhi S, Kneeland SC, Thai KK, Hoffmann TJ, Yin J, et al. A multiethnic genome-wide association study of primary open-angle glaucoma identifies novel risk loci. *Nat Commun* 2018;9:2278.
28. Reiner AP, Carlson CS, Ziv E, Iribarren C, Jaquish CE, Nickerson DA. Genetic ancestry, population sub-structure, and cardiovascular disease-related traits among African-American participants in the CARDIA Study. *Hum Genet* 2007;121:565-75.
29. Stefflova K, Dulik MC, Barnholtz-Sloan JS, Pai AA, Walker AH, Rebbeck TR. Dissecting the within-Africa ancestry of populations of African descent in the Americas. *PLoS One* 2011;6:e14495.
30. Pritchard JK, Stephens M, Rosenberg NA, Donnelly P. Association mapping in structured populations. *Am J Hum Genet* 2000;67:170-81.
31. Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet* 2015;47:1449-56.
32. Chaitanya L, Breslin K, Zuniga S, Wirken L, Pospiech E, Kukla-Bartoszek M, et al. The HlrisPlex-S system for eye, hair and skin colour prediction from DNA: introduction and forensic developmental validation. *Forensic Sci Int Genet* 2018;35:123-35.
33. Chang J, Bilker WB, Hoffstad O, Margolis DJ. Cross-sectional comparisons of patient-reported disease control, disease severity, and symptom frequency in children with atopic dermatitis. *Br J Dermatol* 2017;177:e114-5.
34. Eichenfield LF, Lucky AW, Boguniewicz M, Langley RG, Cherill R, Marshall K, et al. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. *J Am Acad Dermatol* 2002;46:495-504.
35. Kapp A, Papp K, Bingham A, Folster-Holst R, Ortonne JP, Potter PC, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol* 2002;110:277-84.
36. Pino-Yanes M, Thakur N, Gignoux CR, Galanter JM, Roth LA, Eng C, et al. Genetic ancestry influences asthma susceptibility and lung function among Latinos. *J Allergy Clin Immunol* 2015;135:228-35.
37. StataCorp. Stata statistical software: release 15. College Station (TX): StataCorp LLC; 2017.
38. Team RC. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2013.
39. Sanyal RD, Pavel AB, Glickman J, Chan TC, Zheng X, Zhang N, et al. Atopic dermatitis in African American patients is TH2/TH22-skewed with TH1/TH17 attenuation. *Ann Allergy Asthma Immunol* 2019;122:99-110.e6.
40. Lin TK, Man MQ, Abuabara K, Wakefield J, Sheu H, Tsai J, et al. By protecting against cutaneous inflammation, deep epidermal pigmentation provided additional advantages for ancestral humans. *J Invest Dermatol* 2019;139(suppl):S137.
41. Uphoff E, Cabieses B, Pinart M, Valdes M, Anto JM, Wright J. A systematic review of socioeconomic position in relation to asthma and allergic diseases. *Eur Respir J* 2015;46:364-74.
42. Vakharia PP, Chopra R, Silverberg JI. Systematic review of diagnostic criteria used in atopic dermatitis randomized controlled trials. *Am J Clin Dermatol* 2018;19:15-22.
43. Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought? *J Allergy Clin Immunol* 2017;140:633-43.

## REFERENCES

- E1. Chaitanya L, Breslin K, Zuniga S, Wirken L, Pospiech E, Kukla-Bartoszek M, et al. The HirisPlex-S system for eye, hair and skin colour prediction from DNA: introduction and forensic developmental validation. *Forensic Sci Int Genet* 2018;35:123-35.
- E2. Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet* 2015;47:1449-56.
- E3. Hoffmann TJ, Choquet H, Yin J, Banda Y, Kvale MN, Glymour M, et al. A large multiethnic genome-wide association study of adult body mass index identifies novel loci. *Genetics* 2018;210:499-515.
- E4. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. *Nat Methods* 2011;9:179-81.
- E5. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet* 2012;44:955-9.
- E6. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* 2009;5:e1000529.
- E7. Marchini J, Howie B. Genotype imputation for genome-wide association studies. *Nat Rev Genet* 2010;11:499-511.

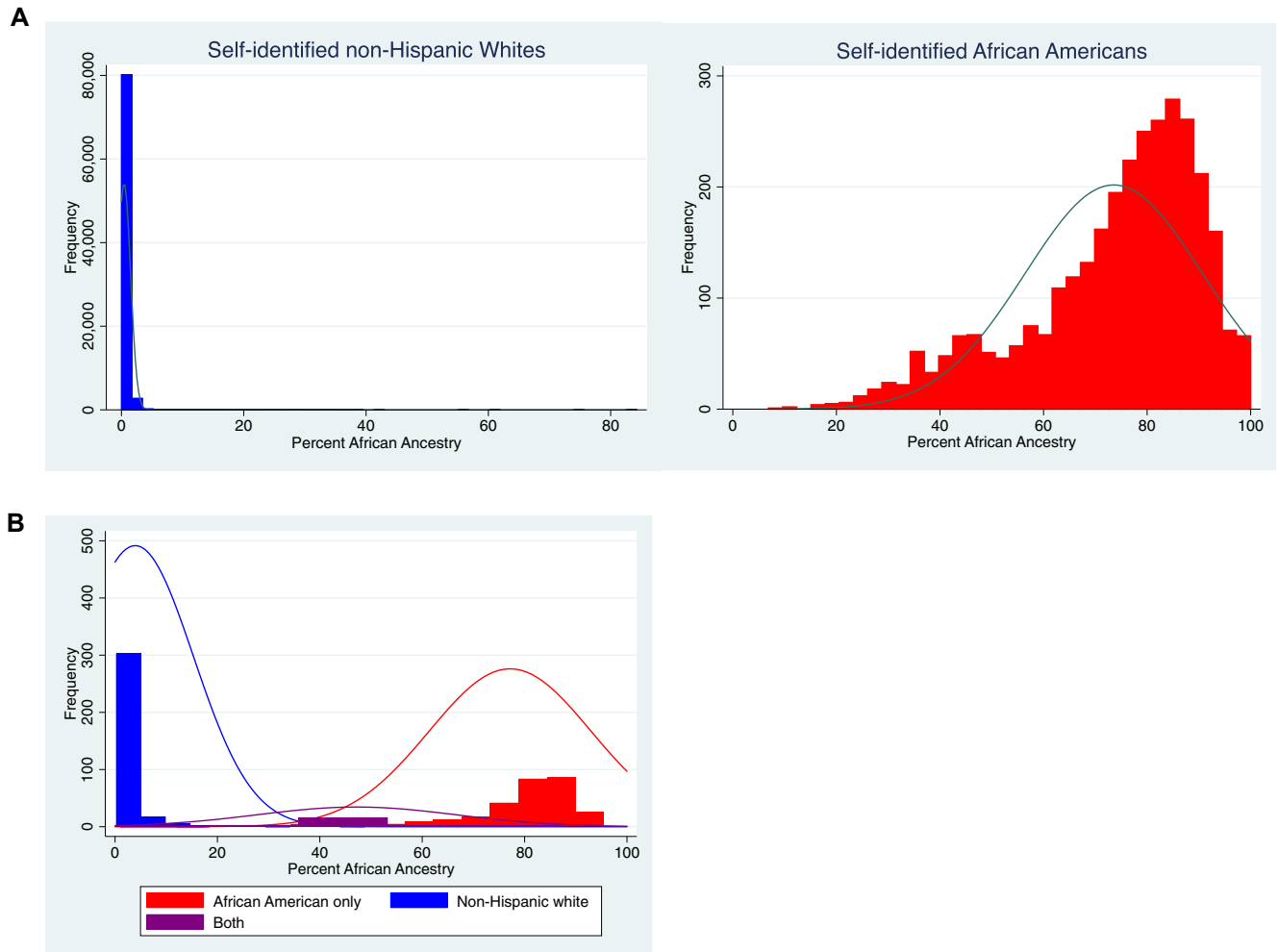


**FIG E1.** Percentage of African ancestry, as estimated by means of genetic markers in the GERA and PEER cohorts, among those who identified as African American is shown in **A** and **B**, respectively. Note that 2 graphs are shown separately in Fig E1, A, because of the difference in numbers of participants (note that the *y-axis* differs for each graph).

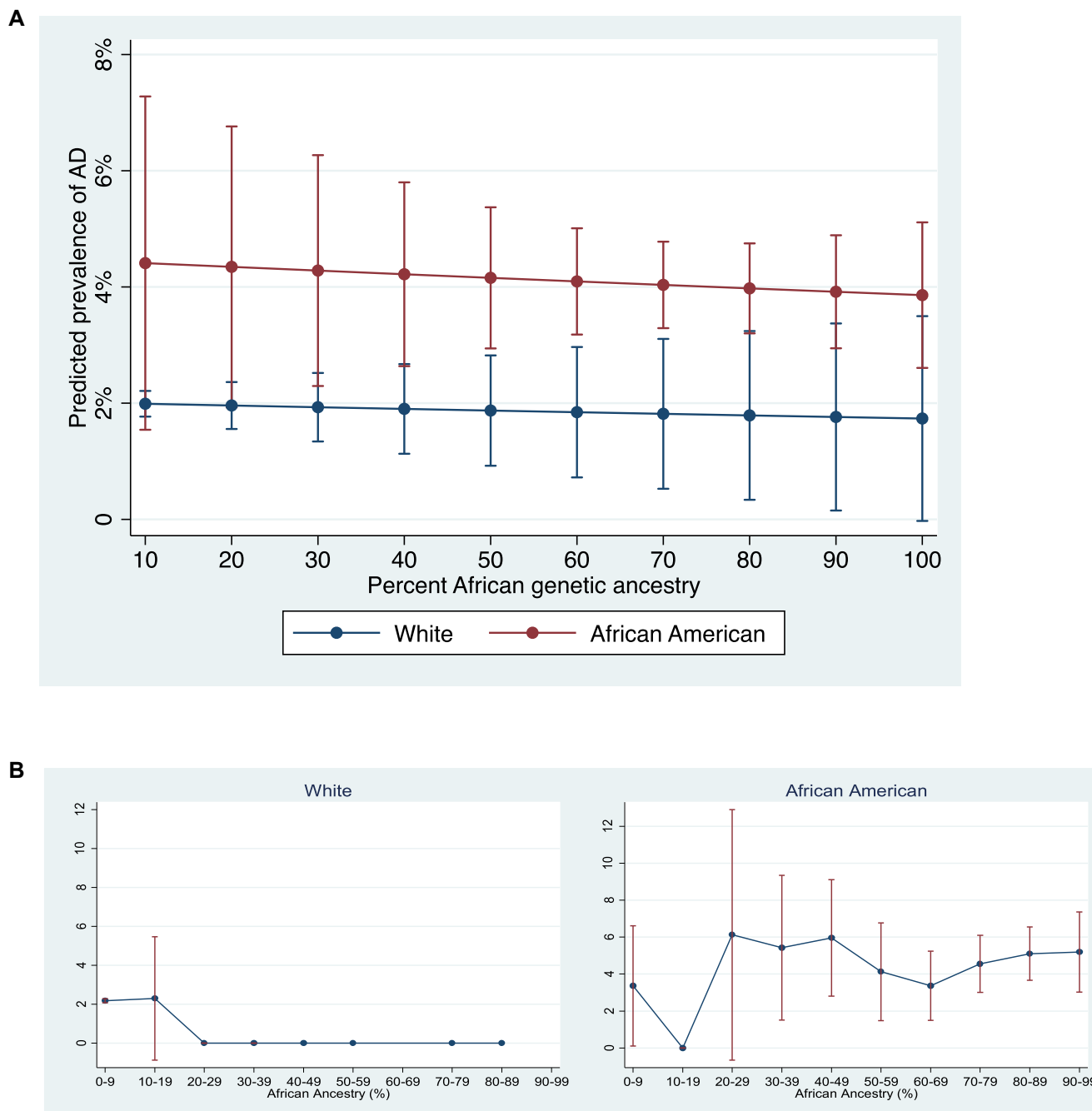


**FIG E2. A,** Predicted prevalences and 95% CIs for AD among self-identified white and African American subjects calculated from the adjusted regression model using the GERA cohort is similar across the range of African genetic ancestry. **B,** Actual prevalence of AD for each decile band of African ancestry in the GERA cohort among self-identified white and African American subjects.

**TABLE E1.** Comparison of patients' characteristics by whether genetic information was available in the PEER cohort

| PEER cohort                                                | No DNA available (n = 5,515) | Provided DNA (n = 755) | P value*        |
|------------------------------------------------------------|------------------------------|------------------------|-----------------|
| Female sex, no. (%)                                        | 2,942 (53.3)                 | 391 (51.8)             | .440            |
| Self-reported race, no. (%)                                |                              |                        |                 |
| African American/black†                                    | 2,939 (53.3)                 | 322 (42.6)             | <b>&lt;.001</b> |
| White                                                      | 2,135 (38.7)                 | 379 (50.2)             |                 |
| Other                                                      | 441 (8.0)                    | 54 (7.2)               |                 |
| Income, no. (%)                                            |                              |                        |                 |
| <\$25,000                                                  | 2,289 (41.5)                 | 218 (29.0)             | <b>&lt;.001</b> |
| \$25,000-\$50,000                                          | 816 (14.8)                   | 138 (18.3)             |                 |
| >\$50,000                                                  | 921 (16.7)                   | 257 (34.1)             |                 |
| Missing                                                    | 1,485 (26.9)                 | 140 (18.6)             |                 |
| Personal or family history of atopy, no. (%)               | 4085 (74.1)                  | 597 (79.1)             | <b>.004</b>     |
| Age at onset (y), mean (SD)                                | 2.30 (3.08)                  | 1.94 (2.75)            | <b>&lt;.001</b> |
| Age at enrollment (y), mean (SD)                           | 7.20 (4.15)                  | 7.02 (3.77)            | .210            |
| No. of surveys, mean (SD)                                  | 9.7 (6.1)                    | 15.3 (5.2)             | <b>&lt;.001</b> |
| Level of disease control at baseline, mean (SD)            | 1.49 (0.74)                  | 1.40 (0.72)            | <b>&lt;.001</b> |
| Mean level of disease control across all visits, mean (SD) | 1.80 (0.69)                  | 1.80 (0.66)            | .860            |

Values significant at the  $P < .05$  level are shown in boldface.

\*P value from  $\chi^2$  test for categorical variables and  $t$  test for continuous variables.

†Includes 184 subjects who self-reported both African American and white race.

**TABLE E2.** Self-reported race/ethnicity, AD, and covariates in the GERA cohort

| GERA cohort                             | African American*  |                          |                 | White                |                           |                 |
|-----------------------------------------|--------------------|--------------------------|-----------------|----------------------|---------------------------|-----------------|
|                                         | AD, n = 147 (4.4%) | No AD, n = 3,233 (95.7%) | P value†        | AD, n = 1,710 (2.1%) | No AD, n = 81,803 (98.0%) | P value†        |
| Female sex                              | 103 (70.1%)        | 1,847 (57.1%)            | <b>.002</b>     | 1,076 (62.9)         | 47,199 (57.7)             | <b>&lt;.001</b> |
| Annual income in US dollars             |                    |                          |                 |                      |                           |                 |
| <\$20,000                               | 10 (6.8%)          | 221 (6.8%)               | .464            | 92 (5.4%)            | 3,567 (4.4%)              | <b>.008</b>     |
| \$20,000-\$60,000                       | 42 (28.6%)         | 1,074 (33.2%)            |                 | 515 (30.1%)          | 22,483 (27.5%)            |                 |
| >\$60,000                               | 80 (54.4%)         | 1,701 (52.6%)            |                 | 962 (56.3%)          | 48,976 (59.9%)            |                 |
| Missing                                 | 15 (10.2%)         | 237 (7.3%)               |                 | 141 (8.3%)           | 6,778 (8.3%)              |                 |
| Education                               |                    |                          |                 |                      |                           |                 |
| Less than high school                   | 2 (1.4%)           | 108 (3.3%)               | .389            | 35 (2.1%)            | 1,400 (1.7%)              | .534            |
| High school or equivalent               | 61 (41.5%)         | 1,358 (42.0%)            |                 | 615 (36.0%)          | 29,923 (36.6%)            |                 |
| College or graduate school              | 75 (51.0%)         | 1,504 (46.5%)            |                 | 971 (56.8%)          | 45,813 (56.0%)            |                 |
| Missing                                 | 9 (6.1%)           | 263 (8.1%)               |                 |                      |                           |                 |
| History of atopy                        | 84 (57.1%)         | 1,262 (39%)              | <b>&lt;.001</b> | 893 (52.2)           | 24,912 (32.5)             | <b>&lt;.001</b> |
| Age at cohort enrollment (y), mean (SD) | 58.0 (14.7)        | 60.6 (14.3)              | <b>.032</b>     | 63.5 (15.8)          | 63.7 (14.3)               | .476            |

Values significant at the  $P < .05$  level are shown in boldface.

\*Includes 516 subjects who self-reported both African American and another race/ethnicity.

† $P$  value from  $\chi^2$  test for categorical variables and  $t$  test for continuous variables.

**TABLE E3.** Distribution of African genetic ancestry by self-identified race/ethnicity

| Self-identified race/ethnicity | No.    | Median % African ancestry | Interquartile range | Mean % African ancestry | SD    |
|--------------------------------|--------|---------------------------|---------------------|-------------------------|-------|
| GERA cohort                    |        |                           |                     |                         |       |
| Non-Hispanic white             | 83,414 | 0.43%                     | 0.0% to 0.7%        | 0.4%                    | 1.1%  |
| African American               | 3,156  | 77.9%                     | 65.0% to 86.1%      | 73.6%                   | 17.1% |
| PEER cohort                    |        |                           |                     |                         |       |
| Non-Hispanic white             | 342    | 1.1%                      | 0.6% to 2.4%        | 3.9%                    | 11.2% |
| African American               | 321    | 81.7%                     | 72.9% to 86.2%      | 75.5%                   | 17.3% |
| Both                           | 15     | 41.0%                     | 38.2% to 44.8%      | 38.4%                   | 11.0% |
| African American only          | 306    | 82.0%                     | 74.9% to 86.4%      | 77.3%                   | 15.4% |

**TABLE E4.** Multivariate model results, including both self-identified African American and white subjects

| GERA cohort                                                                                                      |                         |
|------------------------------------------------------------------------------------------------------------------|-------------------------|
| Model 2: Odds of AD among the full cohort, including both genetic ancestry and self-identified race (n = 70,984) |                         |
| Percentage African ancestry (by 1-unit increase)                                                                 | 1.00 (0.99-1.01)        |
| Self-identified race (African American vs white)                                                                 | <b>2.23 (1.04-4.95)</b> |
| Sex (female vs male)                                                                                             | <b>1.25 (1.12-1.38)</b> |
| Income                                                                                                           |                         |
| <\$20,000                                                                                                        | Reference               |
| \$20,000-\$60,000                                                                                                | 0.85 (0.68-1.07)        |
| \$60,000                                                                                                         | 0.76 (0.61-0.95)        |
| Education                                                                                                        |                         |
| Less than high school                                                                                            | Reference               |
| High School or equivalent                                                                                        | 0.95 (0.65-1.37)        |
| College or graduate school                                                                                       | 1.05 (0.72-1.52)        |
| History of atopy                                                                                                 | <b>2.19 (1.99-2.42)</b> |
| Age (each additional year)                                                                                       | 1 (1.00-1.00)           |
| PEER cohort                                                                                                      |                         |
| Model 2: Odds of AD among the full cohort, including both genetic ancestry and self-identified race (n = 541)    |                         |
| Percentage African ancestry (by 1-unit increase)                                                                 | 1.00 (0.99-1.02)        |
| Self-identified race (African American vs white)                                                                 | 1.77 (0.63-4.91)        |
| Sex (female vs male)                                                                                             | <b>1.72 (1.20-2.46)</b> |
| Income                                                                                                           |                         |
| <\$25,000                                                                                                        | Reference               |
| \$25,000-\$50,000                                                                                                | 0.88 (0.53-1.48)        |
| >\$50,000                                                                                                        | <b>0.43 (0.26-0.71)</b> |
| History of atopy                                                                                                 | 1.62 (1.06-2.47)        |
| Age (each additional year)                                                                                       |                         |
| Age at cohort enrollment                                                                                         | <b>1.24 (1.16-1.31)</b> |
| Age at survey                                                                                                    | <b>0.81 (0.79-0.84)</b> |

Values significant at the  $P < .05$  level are shown in boldface.

**TABLE E5.** Regression models for AD, including predicted skin color in the GERA cohort

| GERA cohort                                                                                                                   |                         |
|-------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Distribution of skin color prediction*                                                                                        | Mean (SD)               |
| Overall probability of dark-to-black skin (n = 86,893)                                                                        | 0.04 (0.16)             |
| Probability of dark-to-black skin among self-identified white subjects (n = 83,513)                                           | 0.01 (0.05)             |
| Probability of dark-to-black skin among self-identified African American subjects (n = 3,380)                                 | 0.71 (0.37)             |
| Odds of AD†                                                                                                                   | Odds ratio (95% CI)     |
| For each unit increase in the probability of dark-to-black skin in full cohort                                                | <b>2.05 (1.62-2.59)</b> |
| For each unit increase in the probability of dark-to-black skin in the full cohort, also controlling for self-identified race | 0.90 (0.58-1.41)        |
| Probability of dark-to-black skin among self-identified African American subjects                                             | 0.88 (0.54-1.42)        |

Values significant at the  $P < .05$  level are shown in boldface.

\*Skin color was predicted by using HRisPlex-S software (<https://hirisplex.erasmusmc.nl/>).<sup>E1</sup> Skin color was predicted by using 39 variants (the rare rs312262906 and rs201326893 variants were not imputed in our cohort; for additional details on genotype imputation in the cohort, see notes of Table E6). Outputs are a prediction probability for 5 categories that sum up to 1: very pale, pale, intermediate, dark, and dark-to-black.

†All models also controlled for sex, income, education, history of atopy, and age.

**TABLE E6.** Regression models for AD, including PRSs, in the GERA cohort

| GERA cohort                                                 |             |                  |
|-------------------------------------------------------------|-------------|------------------|
| Distribution of PRS*                                        | Mean        | SD               |
| Overall (n = 86,893)                                        | −0.01       | 1.00             |
| Among self-identified white subjects (n = 83,513)           | −0.03       | 1.00             |
| Among self-identified African American subjects (n = 3,380) | 0.64        | 0.93             |
| Odds of AD†                                                 |             |                  |
|                                                             | Odds ratio  | 95% CI           |
| PRS among full cohort                                       | <b>1.13</b> | <b>1.07-1.18</b> |
| PRS among self-identified white subjects                    | <b>1.18</b> | <b>1.10-1.21</b> |
| PRS among self-identified African American subjects         | 0.95        | 0.79-1.13        |
| PRS among full cohort also adjusted for genetic ancestry‡   | <b>1.13</b> | <b>1.08-1.19</b> |

Values significant at the  $P < .05$  level are shown in boldface.

\*Standardized PRS based on 27 variants from the most recent AD genome-wide association study meta-analysis.<sup>E2</sup> The PRS was created by summing up the additive coding of each risk variant weighted by the log odds ratio of the variant and then standardized for interpretability by subtracting the mean and dividing by the SD (ie,  $z$  score). Of note, for a sensitivity analysis, a second PRS was created, assuming that all risk variants have the same effect and results were similar (data not shown). Genotype imputation of variants used in the risk score has been described previously.<sup>E3</sup> Briefly, subjects were prephased with Shape-it v2.1.727<sup>E4</sup> and imputed from the 1000 Genomes Project (<http://1000genomes.org>) cosmopolitan reference panel with Impute2 v2.3.0.<sup>E5,E6</sup> After excluding variants with  $r^2$  values of less than 0.3<sup>E7</sup> and a minor allele count of less than 20, we retained 24,149,855 and 21,485,958 single nucleotide polymorphisms in non-Hispanic white and African American subjects, respectively.

†Models additionally adjusted for sex, income, education, history of atopy, and age.

‡The model also adjusted for continuous measures of genetic ancestry. Note that the Pearson correlation coefficient between PRS and genetic ancestry in the entire cohort was 0.133.

**TABLE E7.** Regression models with alternative definitions of AD in the GERA cohort

| Definition of AD                                     | Adjusted odds ratio (95% CI)     |                                  |                                |
|------------------------------------------------------|----------------------------------|----------------------------------|--------------------------------|
|                                                      | 1+ ICD-9 codes, n = 7,032 (8.1%) | 2+ ICD-9 codes, n = 1,857 (2.1%) | 3+ ICD-9 codes, n = 788 (0.9%) |
| Model 1: Odds of AD among full cohort                |                                  |                                  |                                |
| African American self-reported race/ethnicity        | <b>1.42 (1.26-1.60)</b>          | <b>2.06 (1.70-2.48)</b>          | <b>2.55 (1.96-3.31)</b>        |
| Model 2: Odds of AD among African American subjects* |                                  |                                  |                                |
| Per 1% increase in African ancestry                  | 1.00 (1.00-1.00)                 | 1.00 (0.99-1.01)                 | 1.00 (0.99-1.02)               |
| Per 25% increase in African ancestry                 | 1.03 (0.86-1.22)                 | 1.02 (0.78-1.35)                 | 1.09 (0.75-1.60)               |

Values significant at the  $P < .05$  level are shown in boldface.

\*Modeled as a continuous variable; results from a single model are displayed in 2 formats for interpretability.

**TABLE E8.** Multivariable regression results, excluding those who self-identified as both African American and white

|                                                  | PEER cohort                                                                                       |                                                                                                               |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
|                                                  | Model 1: Odds of 1-level worse disease control among full cohort (n = 3,960), odds ratio (95% CI) | Model 2: Odds of 1-level worse disease control among African American subjects (n = 243), odds ratio (95% CI) |
| Percentage African Ancestry (by 1-unit increase) | NA                                                                                                | 1.00 (0.98-1.01)                                                                                              |
| Self-identified race (African American vs white) | <b>2.03 (1.73-2.40)</b>                                                                           | NA                                                                                                            |
| Sex (female vs male)                             | 1.21 (1.06-1.38)                                                                                  | <b>1.79 (1.05-3.06)</b>                                                                                       |
| Income                                           |                                                                                                   |                                                                                                               |
| <\$25,000                                        | Reference                                                                                         | Reference                                                                                                     |
| \$25,000-\$50,000                                | 0.95 (0.80-1.14)                                                                                  | 0.96 (0.48-1.90)                                                                                              |
| >\$50,000                                        | 0.72 (0.60-0.88)                                                                                  | 0.54 (0.25-1.18)                                                                                              |
| History of atopy                                 | <b>1.23 (1.06-1.42)</b>                                                                           | 1.66 (0.87-3.17)                                                                                              |
| Age (each additional year)                       |                                                                                                   |                                                                                                               |
| Age at cohort enrollment                         | <b>1.23 (1.20-1.25)</b>                                                                           | <b>1.14 (1.05-1.23)</b>                                                                                       |
| Age at survey                                    | <b>0.82 (0.81-0.83)</b>                                                                           | <b>0.88 (0.85-0.92)</b>                                                                                       |

Values significant at the  $P < .05$  level are shown in boldface.

NA, Not applicable.