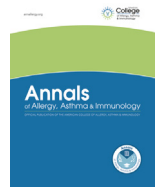




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Immunoglobulin G and immunoglobulin G subclass concentrations differ according to sex and race

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ABSTRACT

Background: Serum immunoglobulin G (IgG) concentrations are integral to the workup of immune deficiencies and IgG4-related disease (IgG4-RD). Demographic differences in IgG concentrations are poorly described but can influence test interpretation, contribute to racial disparities in primary immunodeficiency diagnosis, and explain demographic differences in IgG concentrations in IgG4-RD.

Objective: To assess differences in IgG and IgG subclass concentrations according to sex and race.

Methods: We identified patients with IgG and IgG subclass concentrations measured in a large health care system. Multivariate-adjusted differences in IgG and IgG subclass concentrations and the proportion of subjects with results outside of reference ranges according to sex and race were estimated.

Results: Of the 12,851 patients, the mean age was 54.7 years and 7917 (62%) were female. Of these, 11,673 (91%) were white, 611 (5%) were black, and 302 (2%) were Asian. Compared with the mean concentrations of white patients, Asian and black patients had higher mean concentrations of IgG (1340.0 and 1504.4 vs 988.1 mg/dL, $P < .001$), IgG1 (782.0 and 938.4 vs 592.4 mg/dL, $P < .001$), IgG2 (493.5 and 384.2 vs 305 mg/dL, $P < .001$), IgG3 (76.6 and 91.9 vs 55.9 mg/dL, $P < .001$), and IgG4 (140.4 and 53.6 vs 41.6 mg/dL, $P < .001$). Immunoglobulin G subclass 4 concentrations were higher in males than those in females (56.3 vs 37.4 mg/dL, $P < .001$). Similar observations were made when comparing the proportions of patients with results outside of reference ranges and after stratifying by diagnosis.

Conclusion: Immunoglobulin G and IgG subclass concentrations differ according to sex and race. These findings may have implications for the interpretation of these test results but require confirmation in diverse, healthy populations.

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Introduction

Serum immunoglobulin G (IgG) and IgG subclass concentrations are used in the evaluation of patients with immune deficiencies (eg,

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primary immunodeficiency^{1,2} and common variable immunodeficiency^{3,4}) and some autoimmune diseases^{5,6} (eg, IgG4-related disease [IgG4-RD]^{7–10} and Sjögren's syndrome¹¹). Although the interpretations of some laboratory tests are made in the context of patient demographics, such as the glomerular filtration rate and creatinine kinase,^{12–14} sex and race are not considered when interpreting IgG and IgG subclass concentration results.

Although some data have suggested IgG and IgG subclass concentrations may vary by demographics, studies were small or restricted to particular conditions.^{15–19} For instance, black patients with periodontal disease have higher IgG subclass concentrations

Table 1
Cohort Characteristics

	Sex		Race			Overall (N = 12,851)
	Female (N = 7917)	Male (N = 4934)	Asian (N = 302)	Black (N = 611)	White (N = 11,673)	
Male (N, %)	–	4934 (100%)	143 (47.4%)	222 (36.3%)	4470 (38.3%)	4934 (38.4%)
Race (N, %)						
White	7203 (91.0%)	4470 (90.6%)	–	–	11673	11,673 (90.8%)
Black	389 (4.9%)	222 (4.5%)	–	611	–	611 (4.8%)
Asian	159 (2.0%)	143 (2.9%)	302	–	–	302 (2.4%)
Other	166 (2.1%)	99 (2.0%)	–	–	–	265 (2.1%)
Age (years) at first test (mean, SD)	54.9 (17.9)	54.3 (18.9)	51.6 (18.2)	52.8 (16.5)	55.0 (18.3)	54.7 (18.2)
No of tests per subject (median, IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)

Abbreviation: IQR, interquartile range.

than nonblack patients,^{15–17} and Asian and male patients with IgG4-RD have higher IgG4 concentrations than non-Asian and female patients, respectively.^{18,19} Small studies have also found differences in other immunoglobulin concentrations (ie, IgA, IgE, and IgM) according to sex and race.^{20–24} In addition, studies have described unexplained racial disparities in the diagnosis of immunodeficiency.^{25,26}

Comprehensively measuring and characterizing these differences may shed light on the observed demographic differences in the manifestation and prevalence of certain conditions and would affect the interpretation of immunoglobulin testing across clinical settings. To address these knowledge gaps, we investigated demographic differences in IgG and IgG subclass concentrations in a large, racially diverse cohort of patients who underwent testing for a variety of indications.

Methods

Cohort Description

The Partners Research Patient Data Registry (RPDR) was queried to identify patients who had at least 1 IgG subclass concentration measured between January 1, 1989, and March 15, 2018, within the Partners HealthCare network. The RPDR is a centralized clinical data warehouse that contains electronic health information (eg, demographics, diagnoses) for more than 6.5 million patients. Approximately half of the population in the greater Boston, Massachusetts, area receives care within the Partners HealthCare network. Because of known variations in IgG concentrations in the pediatric population, only patients 18 years old and above were

included.^{27,28} This study was approved by the institutional review board of Partners HealthCare.

Immunoglobulin Concentrations

All IgG, IgG subclass, IgA, IgE, and IgM laboratory results, their associated reference ranges, and the date of each test were extracted from the RPDR.

Covariates

Date of birth, sex, self-reported race, home address, and diagnostic (International Classification of Diseases [ICD]-9 or ICD-10) billing codes were extracted from the RPDR. Patients with unknown race were excluded from the analysis after confirming that their inclusions did not impact our findings. Median household income was assigned according to the subject's billing address zip code and was used to estimate socioeconomic status.²⁹ The medical condition for which the test was ordered was determined using the primary diagnostic billing code closest to the date of the test result. Clinical Classifications Software grouped diagnostic codes into mutually exclusive categories that included immune deficiencies, autoimmune diseases, infectious conditions, gastrointestinal disorders, and pulmonary diseases (Appendix Material).³⁰

Statistical Analysis

Continuous variables are presented as mean (SD) or median (interquartile range), as appropriate. Categorical variables are presented as N (%). In the primary analysis, we analyzed each subject's first test result. Immunoglobulin G and IgG subclass concentrations were compared across sex and race categories using *t*

Table 2
Distribution of Patients (N, %) With IgG or IgG Subclass Concentrations Above or Below Reference Ranges According to Sex and Race

IgG subclass	Sex		Race			Overall (N = 12,851)
	Female (N = 7917)	Male (N = 4934)	Asian (N = 302)	Black (N = 611)	White (N = 11,673)	
IgG						
> ULN (N, %)	747 (9.4%)	490 (9.9%)	68 (22.5%)	209 (34.2%)	907 (7.8%) ^a	1237 (9.6%)
< LLN (N, %)	1142 (14.4%)	847 (17.2%) ^a	16 (5.3%)	25 (4.1%)	1922 (16.5%) ^a	1989 (15.5%)
IgG1						
> ULN (N, %)	673 (8.5%)	463 (9.4%)	61 (20.2%)	198 (32.4%)	822 (7.0%) ^a	1136 (8.8%)
< LLN (N, %)	1428 (18.0%)	1012 (20.5%) ^a	24 (8.0%)	31 (5.1%)	2356 (20.2%) ^a	2440 (19.0%)
IgG2						
> ULN (N, %)	271 (3.4%)	200 (4.1%)	52 (17.2%)	48 (7.9%)	355 (3.0%) ^a	471 (3.7%)
< LLN (N, %)	1883 (23.8%)	1181 (23.9%)	24 (8.0%)	104 (17.0%)	2891 (24.8%) ^a	3064 (23.8%)
IgG3						
> ULN (N, %)	394 (5.0%)	297 (6.0%) ^a	34 (11.3%)	84 (13.8%)	551 (4.7%) ^a	691 (5.4%)
< LLN (N, %)	949 (12.0%)	653 (13.2%) ^a	30 (10.0%)	28 (4.6%)	1520 (13.0%) ^a	1602 (12.5%)
IgG4						
> ULN (N, %)	483 (6.1%)	517 (10.5%) ^a	75 (24.8%)	73 (12.0%)	819 (7.0%) ^a	1000 (7.8%)
< LLN (N, %)	744 (9.4%)	425 (8.6%)	10 (3.3%)	37 (6.1%)	1106 (9.5%) ^a	1169 (9.9%)

Abbreviations: IgG, immunoglobulin G; LLN, lower limit of normal; ULN, upper limit of normal.

^a*P* < .05

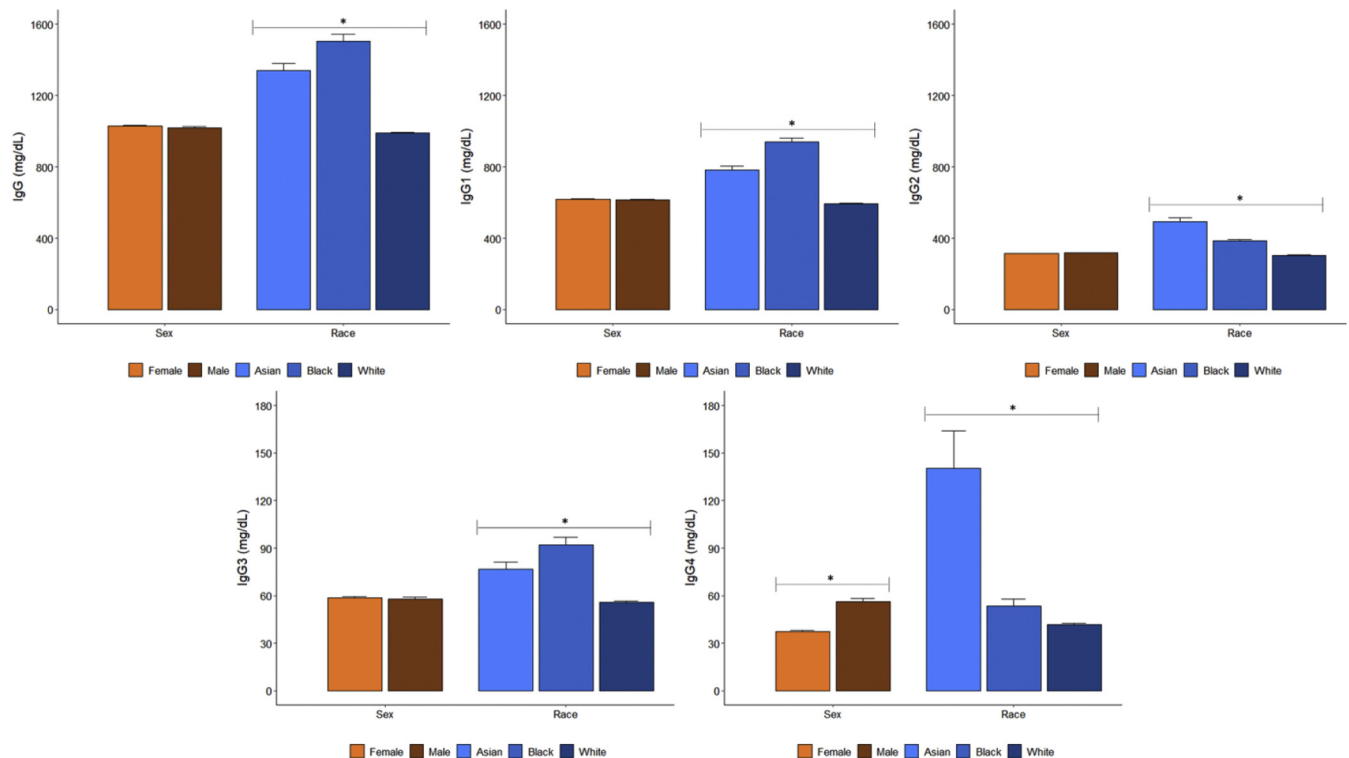


Figure 1. IgG and IgG subclass concentrations (mean and SE) according to sex and race (*indicates $P < .05$ for comparison across groups). IgG, immunoglobulin G.

tests and analyses of variance, respectively. The proportion of patients in each demographic group with a result above the upper limit of normal (ULN) and below the lower limit of normal (LLN) was determined and differences in the distribution of these proportions across demographic groups were compared using χ^2 tests. Multivariate linear regression was used to estimate differences in IgG and IgG subclass concentrations across sex and race subgroups after adjustments for age, sex, and/or race. We used logistic regression to compare the proportion of patients across demographic groups with results above or below the assay's reference range after adjustments for age, sex, and/or race.

We performed multiple sensitivity analyses. First, we compared sex and race differences in IgG and IgG subclass concentrations among patients with specific conditions using linear regression. Second, we repeated the primary analysis (ie, univariate and multivariate linear regression) using each subject's highest test result and the first test result standardized to the associated reference range ULN. Third, we used generalized estimation

equation linear regression models to compare IgG and IgG subclass concentration measurements using all available results for each subject. Fourth, we repeated the primary analysis after excluding patients with an associated diagnosis code commonly used for immunodeficiency (ICD9: 279.x or ICD10: D80, D81, D82, D83, D84) and after excluding patients with an IgG or IgG subclass concentration below the LLN.

To evaluate potential explanations for observed sex and race in IgG and IgG subclass concentrations, we performed 2 secondary analyses. First, we assessed whether similar differences were observed when comparing IgA, IgE, and IgM concentrations across demographic groups using the same methods as in the primary analysis. Second, we evaluated whether our observed associations concerning sex and race differences in IgG and IgG subclass concentrations persisted after adjustment for household income using multivariate linear regression.

All P values were 2-sided with a significance threshold less than .05. Statistical analyses were performed using SAS version 9.4 (SAS

Table 3
Multivariate-Adjusted IgG Concentration Differences (mg/dL) According to Sex and Race (β , 95% CI)^a

IgG subclass (mg/dL)	Sex		Race		
	Female	Male	Asian	Black	White
IgG	+10.7 (−7.4, +29.9)	0.0 (Reference)	+356.3 (+295.9, +416.7) ^b	+517.6 (+475.3, +559.9) ^b	0.0 (Reference)
IgG1	+5.8 (−6.3, +17.9)	0.0 (Reference)	+189.7 (+150.7, +228.7) ^b	+345.6 (+317.6, +373.6) ^b	0.0 (Reference)
IgG2	−1.7 (−8.2, +4.8)	0.0 (Reference)	+189.7 (+168.8, +210.7) ^b	+80.1 (+65.1, +95.2) ^b	0.0 (Reference)
IgG3	+0.7 (−2.1, +3.4)	0.0 (Reference)	+21.1 (+12.2, +29.9) ^b	+36.1 (+29.5, +42.5) ^b	0.0 (Reference)
IgG4	−18.2 (−22.0, −14.3) ^a	0.0 (Reference)	+97.9 (+85.5, +110.2) ^b	+12.8 (+3.9, +21.6) ^b	0.0 (Reference)

Abbreviation: IgG, immunoglobulin G.

^aAdjusted for age but data not presented.

^b $P < .05$

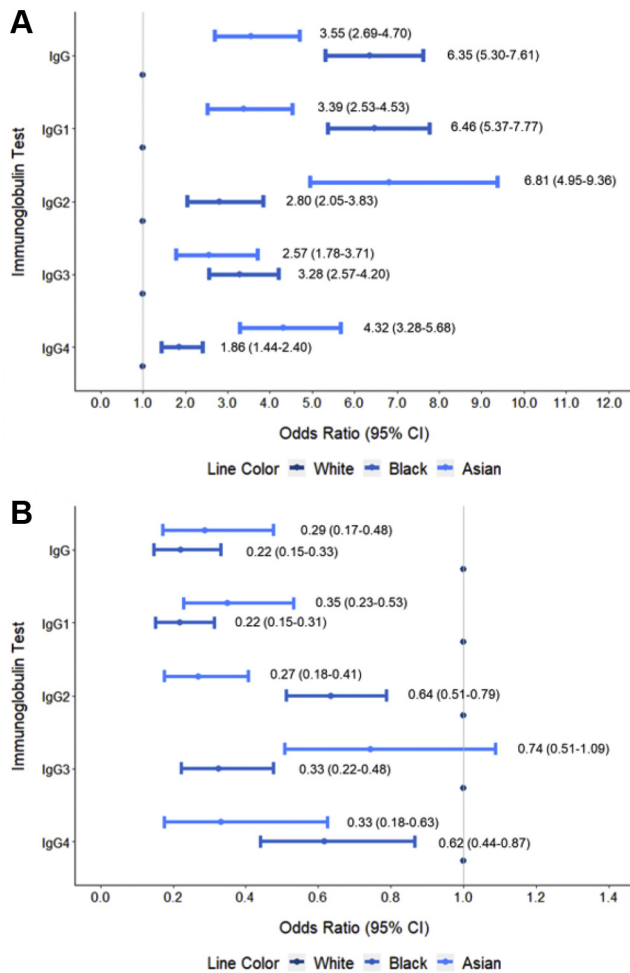


Figure 2. Multivariate-adjusted odds ratio (95% CI) of having an IgG or IgG subclass concentration above (A) or below (B) the reference range according to race. IgG, immunoglobulin G.

Institute, Cary, North Carolina) and R version 3.5.0 (R Core Team, Vienna, Austria).

Results

Cohort Description

Of the 12,851 cases, 4934 (38.4%) were male and the mean (SD) age was 54.7 (± 18.3) years. Of the total number of patients, 11,673 (90.8%) were white, 611 (4.8%) were black, and 302 (2.4%) were Asian (Table 1). The median (interquartile range) IgG subclass measurements per subject during the study period was 2.^{1,3} The mean (SD) serum IgG, IgG1, IgG2, IgG3, and IgG4 concentrations were 1024.6 (± 500.2) mg/dL, 616.7 (± 347.4) mg/dL, 314.6 (± 184.6) mg/dL, 58.4 (± 77.5) mg/dL, and 44.6 (± 109.7) mg/dL, respectively. The IgG, IgG1, IgG2, IgG3, and IgG4 concentrations were above the ULN in 9.6%, 8.8%, 3.7%, 5.4%, and 7.8% of patients, respectively, and below the LLN in 15.5%, 19.0%, 23.8%, 12.5%, and 9.1% of patients, respectively (Table 2).

Differences According to Sex

Female patients had lower IgG4 concentrations (37.4 [± 75.2] mg/dL vs 56.3 [± 148.5] mg/dL, $P < .001$) and less often had IgG3 (5.0% vs 6.0%, $P = .01$) and IgG4 (6.1% vs 10.5%, $P < .001$) concentrations above the ULN than those in male patients in crude analyses (Fig 1, Table 2). In adjusted analyses (Table 3), only differences in IgG4 concentrations persisted such that female patients had lower serum IgG4 concentrations ($\beta = -18.2$ mg/dL, 95% CI: -22.0 to -14.3 , $P < .001$) and female patients were less likely to have an IgG4 concentration above the ULN (adjusted odds ratio [OR] 0.56, 95% CI: 0.49-0.64).

Differences According to Race

In unadjusted analyses, Asian and black patients had higher IgG (1340.0 and 1504.4 vs 988.1 mg/dL, $P < .001$), IgG1 (782.0 and 938.4 vs 592.4 mg/dL, $P < .001$), IgG2 (493.5 and 384.1 vs 305.0 mg/dL, $P < .001$), IgG3 (76.6 and 91.9 vs 55.9 mg/dL, $P < .001$), and IgG4 (140.4 and 53.6 vs 41.6 mg/dL, $P < .001$) subclass concentrations than those in

Table 4
Multivariate-Adjusted IgG Concentration Differences (mg/dL) According to Sex and Race Stratified by Selected Indication for Testing (Asian vs White Patients and Black vs White Patients) (β , 95% CI)^a

	Allergy/Immunology			Autoimmune Disease		
	Asian	Black	White	Asian	Black	White
No. of Patients (N, %)	35 (2.6%)	18 (1.3%)	1317 (96.1%)	20 (4.0%)	36 (7.3%)	440 (88.7%)
IgG	+375.1 (+207.3, +543.0) ^b	+191.8 (−32.3, +415.9)	Ref	+508.3 (+206.0, +810.7) ^b	+342.8 (+128.0, +557.6) ^b	Ref
IgG1	+162.2 (+61.1, +263.3) ^b	+163.3 (+25.5, +301.2) ^b	Ref	+324.9 (+121.3, +528.4) ^b	+215.8 (+64.4, +367.1) ^b	Ref
IgG2	+233.7 (+175.4, +292) ^b	+57.2 (−19.2, +133.6)	Ref	+323.0 (+224.0, +422.0) ^b	+55.0 (−13.1, +123)	Ref
IgG3	+10.5 (−2.4, +23.5)	+20.8 (+3.0, +38.6) ^b	Ref	+36.5 (+3.5, +69.5) ^b	+25.2 (+0.5, +50.0) ^b	Ref
IgG4	+201.7 (+155.0, +248.4) ^b	+2.5 (−49.3, +54.2)	Ref	+280.4 (+202.4, +358.3) ^b	+4.1 (−37.7, +46.0)	Ref
	GI Disorder			Infection		
	Asian	Black	White	Asian	Black	White
No. of Patients (N, %)	29 (3.7%)	60 (7.7%)	694 (88.6%)	36 (2.3%)	80 (5.1%)	1449 (92.6%)
IgG	+136.8 (−49.6, +323.3)	+445.2 (+313.4, +577.0) ^b	Ref	+222.0 (+62.2, +381.7) ^b	+598.1 (+491.6, +704.6) ^b	Ref
IgG1	+108.6 (−25.6, +242.8)	+322.8 (+223.8, +421.9) ^b	Ref	+124.4 (+16.4, +232.4) ^b	+475.9 (+394.1, +557.7) ^b	Ref
IgG2	+130.8 (+67, +194.6) ^b	+101.8 (+58.1, +145.5) ^b	Ref	+130.9 (+78.4, +183.5) ^b	+65.0 (+28.6, +101.3) ^b	Ref
IgG3	+15.2 (−13.2, +43.7)	+16.5 (−3.3, +36.4)	Ref	+16.7 (−3.3, +36.7)	+69.8 (+49.6, +90.0) ^b	Ref
IgG4	+19.6 (+1.9, +37.3) ^b	+14.9 (+2.1, +27.7) ^b	Ref	+10.8 (−4.2, +25.8)	+15.4 (+5.0, +25.7) ^b	Ref

Abbreviations: GI, gastrointestinal; IgG, immunoglobulin G.

^aAdjusted for age and sex but data not presented.

^b $P < .05$

white patients (Fig 1). Because of these differences, Asian and black patients more often had IgG (22.5% and 34.2% vs 7.8%, $P < .001$), IgG1 (20.2% and 32.4% vs 7.0%, $P < .001$), IgG2 (17.2% and 7.9% vs 3.0%, $P < .001$), IgG3 (11.3% and 13.8% vs 4.7%, $P < .001$), and IgG4 (24.8% and 12.0% vs 7.0%, $P < .001$) concentrations above the ULN. In contrast, white patients more often had IgG (16.5% vs 5.3% and 4.1%, $P < .001$), IgG1 (20.2% vs 8.0% and 5.1%, $P < .001$), IgG2 (24.8% vs 8.0% and 17.0%, $P < .001$), IgG3 (13.0% vs 10.0% and 4.6%, $P < .001$), and IgG4 (9.5% vs 3.3% and 6.1%, $P < .001$) concentrations below the LLN compared with that of Asian and black patients, respectively (Table 2).

These differences persisted in adjusted analyses (Table 3, Fig 2A–B). For example, compared with the IgG concentrations in white patients, black patients were less likely to have an IgG concentration below the LLN (adjusted OR: 0.22, 95% CI: 0.15–0.33) and Asian patients were more likely to have an IgG4 concentration greater than the ULN (adjusted OR: 4.32, 95% CI: 3.28–5.68).

Sensitivity Analyses

We found similar differences in IgG and IgG subclass concentrations across demographic groups when adjusted analyses were restricted to patients with similar diagnoses (Table 4), when concentrations were standardized to each assay reference range's ULN (eTable 1), when the highest concentrations for each subject were used (eTable 2), when all available IgG and IgG subclass concentration measurements for each subject were used (eTable 3), and when all subjects with a diagnosis of immune deficiency were excluded (eTable 4). In addition, we performed an analysis in which we excluded subjects with an IgG or IgG subclass concentration below the LLN and our results remained unchanged.

Secondary Analyses

Immunoglobulin A and IgE concentrations also differed according to sex and race. Females had lower IgA ($\beta = -18.3$ mg/dL, 95% CI: -25.3 to -11.3 , $P < .001$) and IgE ($\beta = -122.0$ mg/dL, 95% CI: -178.4 to -65.6 , $P < .001$) and higher IgM ($\beta = +19.3$ mg/dL, 95% CI: 11.6 – 27.0 , $P < .001$) than those in male patients (eTable 5). Compared with the IgA and IgE concentrations in white patients, Asian and black patients had higher IgA ($\beta = +62.1$ mg/dL, 95% CI: 40.3 – 83.9 , $P < .001$ and $\beta = +103.4$ mg/dL, 95% CI: 86.9 – 119.8 , $P < .001$, respectively) and IgE ($\beta = +172.8$ mg/dL, 95% CI: -11.0 to 356.6 , $P = .07$ and $\beta = +488.9$ mg/dL, 95% CI: 338.6 – 639.3 , $P < .001$, respectively) concentrations (eTable 5). Immunoglobulin M concentrations did not differ across race subgroups.

In analyses adjusted for household income, differences in IgG and IgG subclass concentrations among Asian, black, and white patients were attenuated but persisted (eTable 6).

Discussion

We found significant differences in IgG and IgG subclass concentrations across demographic groups. Our observations persisted regardless of the clinical indication for testing. In particular, Asian and black patients have significantly higher IgG and IgG subclass concentrations than those in white patients, and male patients have higher IgG4 concentrations than those in female patients. These variations in IgG and IgG subclass concentration measurements led to significant demographic differences in the proportion of patients with results outside of normal reference ranges. These provocative observations require confirmation in an external data source that includes a diverse, healthy population.

Our findings suggest that demographic differences in IgG and IgG subclass concentrations may lead to certain demographic groups being more or less likely to be classified as having abnormal test results and affect the likelihood that certain diagnoses are made. For instance, Asian patients are more likely to have elevated serum IgG4 concentrations and may, therefore, be more likely to be

labeled as having IgG4-RD than a white patient with a similar clinical history. Similarly, because of differences in the proportion of patients with IgG and IgG subclass concentration results below the LLN among white patients when compared with those in black or Asian patients, the likelihood of a diagnosis of immunodeficiency may be more often rendered among white patients. The use of race in the interpretation of test results has been controversial,³¹ but, in contrast to other tests, not accounting for racial differences in immunoglobulin concentrations may contribute to disparities in the diagnosis of certain conditions (such as immunodeficiencies) among minority groups.^{25,26} Population-based studies in diverse cohorts are necessary to determine whether the prevalence of immunodeficiencies differs across racial subgroups when conventional reference ranges are used.

To our knowledge, this is the first study to comprehensively assess differences in IgG and IgG subclass concentrations between adult Asian, black, and white patients, as well as male and female patients, in a large cohort with diverse indications for testing. We expanded upon previous observations concerning differences in IgA and IgE concentrations across racial groups by including Asian patients. Black patients with asthma were previously found to have higher IgE concentrations than those in white patients, and healthy black patients have been found to have higher IgA concentrations than those in white patients.^{20,21,24,32}

Previous studies evaluated the impact of socioeconomic status and smoking on these observations, but no associations were observed.^{21,33} In contrast, we found some attenuation of the associations between racial groups and differences in immunoglobulin concentrations after adjusting for socioeconomic status. These conflicting findings may have something to do with how socioeconomic status was estimated, requiring further study. Because of a lack of data on smoking status, we were unable to assess its effect on our observations. Given that black and Asian patients had higher levels of all immunoglobulins, our observations may reflect generalized, nonspecific activation of immunoglobulin-producing B cells because of environmental factors, genetic predisposition, or chronic infection. For instance, mechanistic and clinical evidence suggests an association between higher IgE concentrations and chronic viral infections.^{34,35}

Our study has certain limitations. First, although our cohort was large, the majority of patients were white. Despite this, we had sufficient power to detect significant differences across racial groups. We relied on self-reported race, which is a complex concept but one that is commonly used in epidemiologic analyses. Second, the number of patients in each diagnostic condition group was relatively small, which limited our ability to detect significant differences in some groups. However, we were able to detect similar trends across subgroups with these conditions as in our primary analysis. Third, we conducted this study using patients for whom testing was performed because of a clinical indication; future studies are necessary to confirm these observations in healthy patients. However, our findings are similar to those made in other studies in which healthy patients were taken from the general population.^{20–22} In addition, our observations persisted after excluding patients in whom testing was performed for immunodeficiency as the indication. Fourth, although we were unable to determine the method used for tests (eg, nephelometry), we confirmed our observations after standardizing measurements to the ULN for each assay. Moreover, it is unlikely that the method of immunoglobulin assessment would confound observations concerning comparisons across demographic groups (ie, any differences would not be differential by sex or race).

We found that IgG and IgG subclass concentrations vary according to sex and race. These provocative observations have the potential to affect the interpretation of these diagnostic tests in the

clinical setting and research. The observed variations may contribute to differences in the manifestation (eg, IgG4 concentration elevations in IgG4-RD) and prevalence of various diagnoses (eg, disparities in immunodeficiency diagnoses) across racial groups. Before implementing any changes in practice, additional studies are necessary to confirm these observations in diverse, healthy populations to further examine explanatory factors and assess the effect of these differences on the likelihood of being diagnosed with certain conditions.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2020.03.018>.

References

- Parker AR, Skold M, Ramsden DB, Ocej-Vinyals JG, Lopez-Hoyos M, Harding S. The clinical utility of measuring IgG subclass immunoglobulins during immunological investigation for suspected primary antibody deficiencies. *Lab Med*. 2017;48(4):314–325.
- Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol*. 2015; 136(5):1186–1205.e2078.
- Oksenhendler E, Gerard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. *Clin Infect Dis*. 2008;46(10):1547–1554.
- Filion CA, Taylor-Black S, Maglione PJ, Radigan L, Cunningham-Rundles C. Differentiation of common variable immunodeficiency from IgG deficiency. *J Allergy Clin Immunol Pract*. 2019;7(4):1277–1284.
- Poplawska-Kita A, Kosciuszko-Zdrodowska M, Siewko K, et al. High serum IgG4 concentrations in patients with Hashimoto's thyroiditis. *Int J Endocrinol*. 2015; 2015:706843.
- Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis*. 2015;74(1):14–18.
- Xia CS, Fan CH, Liu YY. Diagnostic performances of serum IgG4 concentration and IgG4/IgG ratio in IgG4-related disease. *Clin Rheumatol*. 2017;36(12): 2769–2774.
- Culver EL, Sadler R, Simpson D, et al. Elevated serum IgG4 levels in diagnosis, treatment response, organ involvement, and relapse in a prospective IgG4-related disease UK cohort. *Am J Gastroenterol*. 2016;111(5): 733–743.
- Yamada K, Yamamoto M, Saeki T, et al. New clues to the nature of immunoglobulin G4-related disease: a retrospective Japanese multicenter study of baseline clinical features of 334 cases. *Arthritis Res Ther*. 2017;19(1):262.
- Kawa S, Skold M, Ramsden DB, Parker A, Harding SJ. Serum IgG4 concentration in IgG4-related disease. *Clin Lab*. 2017;63(9):1323–1337.
- Liu Y, Li J. Preferentially Immunoglobulin (IgG) subclasses production in primary Sjogren's syndrome patients. *Clin Chem Lab Med*. 2011;50(2): 345–349.
- Pottel H, Hoste L, Delanaye P, Cavalier E, Martens F. Demystifying ethnic/sex differences in kidney function: is the difference in (estimating) glomerular filtration rate or in serum creatinine concentration? *Clin Chim Acta*. 2012; 413(19–20):1612–1617.
- Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant*. 2016;31(5): 798–806.
- Grams ME, Matsushita K, Sang Y, et al. Explaining the racial difference in AKI incidence. *J Am Soc Nephrol*. 2014;25(8):1834–1841.
- Haralambieva IH, Salk HM, Lambert ND, et al. Associations between race, sex and immune response variations to rubella vaccination in two independent cohorts. *Vaccine*. 2014;32(17):1946–1953.
- Gunsolley JC, Pandey JP, Quinn SM, Tew JG, Schenkein HA. The effect of race, smoking and immunoglobulin allotypes on IgG subclass concentrations. *J Periodont Res*. 1997;32(4):381–387.
- Quinn SM, Zhang JB, Gunsolley JC, Schenkein JG, Schenkein HA, Tew JG. Influence of smoking and race on immunoglobulin G subclass concentrations in early-onset periodontitis patients. *Infect Immun*. 1996;64(7): 2500–2505.
- Qi R, Chen LYC, Park S, et al. Utility of serum IgG4 levels in a multiethnic population. *Am J Med Sci*. 2018;355(1):61–66.
- Wallace ZS, Zhang Y, Perugino CA, et al. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis*. 2019;78(3):406–412.
- Maddison SE, Stewart CC, Farshy CE, Reimer CB. The relationship of race, sex, and age to concentrations of serum immunoglobulins expressed in international units in healthy adults in the USA. *Bull World Health Organ*. 1975;52(2):179–185.
- Tollerud DJ, Brown LM, Blattner WA, et al. Racial differences in serum immunoglobulin levels: relationship to cigarette smoking, T-cell subsets, and soluble interleukin-2 receptors. *J Clin Lab Anal*. 1995;9(1): 37–41.
- Gonzalez-Quintela A, Alende R, Gude F, et al. Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. *Clin Exp Immunol*. 2008;151(1):42–50.
- Gergen PJ, Arbes Jr SJ, Calatroni A, Mitchell HE, Zeldin DC. Total IgE levels and asthma prevalence in the U.S. population: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol*. 2009;124(3): 447–453.
- Joseph CL, Ownby DR, Peterson EL, Johnson CC. Racial differences in physiologic parameters related to asthma among middle-class children. *Chest*. 2000; 117(5):1336–1344.
- Kobrynski L, Powell RW, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001–2007. *J Clin Immunol*. 2014; 34(8):954–961.
- Cunningham-Rundles C, Sidi P, Estrella L, Doucette J. Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. *J Allergy Clin Immunol*. 2004;113(4):747–755.
- Herrod HG. Clinical significance of IgG subclasses. *Curr Opin Pediatr*. 1993;5(6): 696–699.
- Hanson LA, Soderstrom R, Avanzini A, Bengtsson U, Bjorkander J, Soderstrom T. Immunoglobulin subclass deficiency. *Pediatr Infect Dis J*. 1988;7(5 Suppl): S17–S21.
- Berkowitz SA, Traore CY, Singer DE, Atlas SJ. Evaluating area-based socioeconomic status indicators for monitoring disparities within health care systems: results from a primary care network. *Health Serv Res*. 2015; 50(2):398–417.
- Healthcare Cost and Utilization Project (HCUP) Clinical Classification Software (CCS) Fact Sheet. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.hcup-us.ahrq.gov/toolssoftware/ccs/ccsfactsheet.jsp. Accessed 7 Oct 2019; 2012.
- Eneanya ND, Yang W, Reese PP. Reconsidering the consequences of using race to estimate kidney function. *JAMA*. 2019;322(2):113–114.
- Nyenhuis SM, Krishnan JA, Berry A, et al. Race is associated with differences in airway inflammation in patients with asthma. *J Allergy Clin Immunol*. 2017; 140(1):257–265.e11.
- McMillan SA, Douglas JP, Archbold GPR, McCrum EE, Evans AE. Effect of low to moderate levels of smoking and alcohol consumption on serum immunoglobulin concentrations. *J Clin Pathol*. 1997;50(10):819–822.
- Welliver RC, Ogra PL. The role of IgE in pathogenesis of mucosal viral infections. *Ann N Y Acad Sci*. 1983;409:321–332.
- Zambrano JC, Carper HT, Rakes GP, et al. Experimental rhinovirus challenges in adults with mild asthma: response to infection in relation to IgE. *J Allergy Clin Immunol*. 2003;111(5):1008–1016.

Supplementary Data

eTable 1Multivariate-Adjusted Differences in IgG and IgG Subclass Concentrations Standardized to the Upper Limit of Normal According to Sex and Race (β , 95% CI)

IgG subclass (mg/dL)	Sex		Race		
	Female	Male	Asian	Black	White
IgG	+0.003 (−0.01, +0.02)	0.0 (Reference)	+0.3 (+0.2, +0.3) ^a	+0.4 (+0.3, +0.4) ^a	0.0 (Reference)
IgG1	+0.004 (−0.01, +0.02)	0.0 (Reference)	+0.2 (+0.2, +0.3) ^a	+0.4 (+0.3, +0.4) ^a	0.0 (Reference)
IgG2	−0.004 (−0.01, +0.01)	0.0 (Reference)	+0.3 (+0.3, +0.3) ^a	+0.1 (+0.1, +0.1) ^a	0.0 (Reference)
IgG3	+0.004 (−0.02, +0.03)	0.0 (Reference)	+0.2 (+0.1, +0.2) ^a	+0.2 (+0.2, +0.3) ^a	0.0 (Reference)
IgG4	−0.2 (−0.2, −0.1) ^a	0.0 (Reference)	+0.9 (+0.8, +1.1) ^a	+0.2 (+0.1, +0.2) ^a	0.0 (Reference)

Abbreviation: IgG, immunoglobulin G.

^aP < .05**eTable 2**Multivariate-Adjusted Differences (mg/dL) in IgG and IgG Subclass Concentrations According to Sex and Race Using Each Subject's Highest Concentration (β , 95% CI)

IgG subclass (mg/dL)	Sex		Race		
	Female	Male	Asian	Black	White
IgG	−47.4 (−70.8, −24.1) ^a	0.0 (Reference)	+415.4 (+340.1, +490.7) ^a	+587.3 (+534.4, +640.3) ^a	0.0 (Reference)
IgG1	+1.2 (−11.2, +13.5)	0.0 (Reference)	+197.2 (+157.8, +236.6) ^a	+344.9 (+316.6, +373.1) ^a	0.0 (Reference)
IgG2	−4.0 (−10.7, +2.8)	0.0 (Reference)	+199.3 (+117.9, +220.8) ^a	+77.6 (−62.1, +93.0) ^a	0.0 (Reference)
IgG3	−0.0 (−2.9, +2.8)	0.0 (Reference)	+23.2 (+14.2, +32.3) ^a	+36.2 (+29.7, +42.7) ^a	0.0 (Reference)
IgG4	−20.9 (−25.2, −16.6) ^a	0.0 (Reference)	+100.8 (+87.0, +114.6) ^a	+13.4 (+3.6, +23.2) ^a	0.0 (Reference)

Abbreviation: IgG, immunoglobulin G.

^aP < .05**eTable 3**Multivariate-Adjusted Differences (mg/dL) in IgG and IgG Subclass Concentrations According to Sex and Race Using all Available IgG and IgG Subclass Concentrations for Each Subject (β , 95% CI)

IgG subclass (mg/dL)	Sex		Race		
	Female	Male	Asian	Black	White
IgG	+17.3 (−48.0, +82.7)	0.0 (Reference)	+565.0 (+354.6, +775.5) ^a	+624.0 (+437.0, +811.0) ^a	0.0 (Reference)
IgG1	−7.0 (−25.7, +11.7)	0.0 (Reference)	+216.8 (+150.5, +283.1) ^a	+361.6 (+292.1, +431.2) ^a	0.0 (Reference)
IgG2	−19.2 (−32.6, −5.8) ^a	0.0 (Reference)	+243.1 (+152.6, +333.5) ^a	+93.3 (−47.5, +139.1) ^a	0.0 (Reference)
IgG3	−2.3 (−6.0, +1.4)	0.0 (Reference)	+28.6 (+10.8, +46.4) ^a	+49.5 (+26.1, +73.0) ^a	0.0 (Reference)
IgG4	−51.5 (−74.3, −28.8) ^a	0.0 (Reference)	+148.0 (+44.3, +251.8) ^a	+25.7 (−14.0, +65.4)	0.0 (Reference)

Abbreviations: IgG, immunoglobulin G.

^aP < .05**eTable 4**Multivariate-Adjusted IgG Concentration Differences (mg/dL) Excluding Patients Diagnosed With Immune Deficiency According to Sex and Race (β , 95% CI)

IgG subclass (mg/dL)	Race		
	Asian	Black	White
IgG	+367.8 (+303.2, +432.4) ^a	+513.9 (+469.7, +558.0) ^a	0.0 (Reference)
IgG1	+200.5 (+159.2, +241.7) ^a	+347.2 (+318.1, +376.3) ^a	0.0 (Reference)
IgG2	+191.4 (+169.3, +213.5) ^a	+75.6 (+60.0, +91.2) ^a	0.0 (Reference)
IgG3	+20.9 (+11.2, +30.7) ^a	+35.8 (+28.9, +42.7) ^a	0.0 (Reference)
IgG4	+104.1 (+90.4, +117.9) ^a	+10.8 (+1.2, +20.4) ^a	0.0 (Reference)

Abbreviation: IgG, immunoglobulin G.

^aP < .05

eTable 5Multivariate-Adjusted Differences in IgA, IgE, and IgM Concentrations According to Sex and Race (β , 95% CI)^a

Ig Class	Sex		Race		
	Female	Male	Asian	Black	White
IgA (mg/dL)	−18.3 (−25.3, −11.3) ^b	0.0 (Reference)	+62.1 (+40.3, +83.9) ^b	+103.4 (+86.9, +119.8) ^b	0.0 (Reference)
IgE (mg/dL)	−122.0 (−178.4, −65.6) ^b	0.0 (Reference)	+172.8 (−11.0, +356.6)	+488.9 (+338.6, +639.3) ^b	0.0 (Reference)
IgM (IU/mL)	+19.3 (+11.6, +27.0) ^b	0.0 (Reference)	−0.0 (−24.2, +24.1)	−2.5 (−20.8, +15.8)	0.0 (Reference)

Abbreviation: IgG, immunoglobulin G.

^aAdjusted for age but data not presented.^b $P < .05$ **eTable 6**Age-, Sex-, Race-, and Socioeconomic Status—Adjusted Differences in IgG and IgG Subclass Concentrations (β , 95% CI)^a

IgG subclass (mg/dL)	Sex		Race		
	Female	Male	Asian	Black	White
IgG	+11.0 (−7.3, +29.3)	0.0 (Reference)	+360.8 (+300.1, +421.5) ^b	+520.6 (+477.5, +563.6) ^b	0.0 (Reference)
IgG1	+5.6 (−6.6, +17.7)	0.0 (Reference)	+193.7 (+154.5, +232.9) ^b	+344.0 (+315.5, +372.6) ^b	0.0 (Reference)
IgG2	−1.8 (−8.3, +4.8)	0.0 (Reference)	+189.3 (+168.3, +210.3) ^b	+82.7 (+67.4, +98.0) ^b	0.0 (Reference)
IgG3	+0.5 (−2.3, +3.3)	0.0 (Reference)	+21.3 (+12.4, +30.3) ^b	+35.2 (+28.6, +41.7) ^b	0.0 (Reference)
IgG4	−18.3 (−22.2, −14.4) ^b	0.0 (Reference)	+99.3 (+86.7, +111.8) ^b	+12.2 (+3.2, +21.2) ^b	0.0 (Reference)

Abbreviation: IgG, immunoglobulin G.

^aAdjusted for age but data not presented.^b $P < .05$