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Race, Ethnicity, and Sex in Pediatric Eye Disease Investigator Group Clinical Studies

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IMPORTANCE Racial, ethnic, and sex disparities exist in US clinical study enrollment, and the prevalence of these disparities in Pediatric Eye Disease Investigator Group (PEDIG) clinical studies has not been thoroughly assessed.

OBJECTIVE To evaluate racial, ethnic, and sex representation in PEDIG clinical studies compared with the 2010 US Census pediatric population.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional analysis examined PEDIG clinical studies based in the US from December 1, 1997 to September 12, 2022, 41 of which met inclusion criteria of a completed study, a study population younger than 18 years, and 1 or more accompanying publication. Data analysis was performed between November 2023 and February 2024.

EXPOSURE Study participant race, ethnicity, and sex for each clinical study, as collected from peer-reviewed publications, patient-enrollment datasets, and ClinicalTrials.gov.

MAIN OUTCOMES AND MEASURES Median enrollment percentages of female, White, Black, Hispanic, Asian, and other race participants were calculated and compared with the 2010 US Census pediatric population using a 1-sample Wilcoxon rank test. Proportionate enrollment was defined as no difference on a 1-sample Wilcoxon rank test if $P \geq .05$. If $P < .05$, we determined if the median enrollment percentage was greater than or less than 2010 US Census proportion to determine if enrollees were underrepresented or overrepresented. To calculate the magnitude of overrepresentation or underrepresentation, enrollment-census difference (ECD) was defined as the difference between groups' median enrollment percentage and percentage representation in the 2010 US Census. Compound annual growth rate (CAGR) was used to measure temporal trends in enrollment, and logistic regression analysis was used to analyze factors that may have contributed to proportionate representation outcomes.

RESULTS A total of 11 658 study participants in 41 clinical studies were included; mean (SD) participant age was 5.9 (2.8) years and 5918 study participants (50.8%) were female. In clinical studies meeting inclusion criteria, White participants were overrepresented (ECD, 0.19; 95% CI, 0.10-0.28; $P < .001$). Black participants (ECD, −0.07; 95% CI, −0.10 to −0.03; $P < .001$), Asian participants (ECD, −0.03; 95% CI, −0.04 to −0.02; $P < .001$), and Hispanic participants (ECD, −0.09; 95% CI, −0.13 to −0.05; $P < .001$) were underrepresented. Female participants were represented proportionately (ECD, 0.004; 95% CI, −0.036 to 0.045; $P = .21$). White and Asian participants demonstrated a decreasing trend in study enrollment from 1997 to 2022 (White: CAGR, −1.5%; 95% CI, −2.3% to −0.6%; Asian: CAGR, −1.7%; 95% CI, −2.0% to −1.4%), while Hispanic participants demonstrated an increasing enrollment trend (CAGR, 7.2%; 95% CI, 3.7%-10.7%).

CONCLUSIONS AND RELEVANCE In this retrospective cross-sectional study of PEDIG clinical studies from December 1, 1997 to September 12, 2022, Black, Hispanic, and Asian participants were underrepresented, White participants were overrepresented, and female participants were represented proportionally. Trends suggested increasing enrollment of Hispanic participants and decreasing enrollment of White participants over time. This study demonstrates an opportunity to advocate for increased enrollment of underrepresented groups in pediatric ophthalmology clinical studies.

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Invited Commentary
Supplemental content

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Racial, ethnic, and sex disparities are key factors that contribute to nonequitable ophthalmological care delivery and negative vision outcomes in the US population.[1-4] This paradigm extends to the US pediatric population, with higher rates of missed vision screenings and lower rates of access to pediatric ophthalmology care among racial and ethnic minority groups.[5-7] Similarly, female adolescents have been found to be at greater risk for developing visual impairment and have a higher overall prevalence for any visual acuity loss compared with male adolescents.[8,9]

The Pediatric Eye Disease Investigator Group (PEDIG) was founded in 1997 to address clinical knowledge gaps in pediatric ophthalmology through clinical trials and prospective data collection. PEDIG was founded as a multicenter network, in part to facilitate a greater base of representation for the pediatric patients included in its studies.[10,11] Representation remains paramount for the generalizability of study findings in pediatric ophthalmology.

Our study investigated the level of representation of different racial and ethnic groups in PEDIG clinical trials and prospective cohort studies between 1997 and 2022 compared with 2010 US Census data. Additionally, we analyzed the proportional enrollment of male and female participants and sought to identify temporal trends in both the racial, ethnic, and sex makeup of these studies.

Key Points

Question Are participant demographics in Pediatric Eye Disease Investigator Group (PEDIG) clinical studies representative of the US pediatric population?

Findings In this cross-sectional analysis of 11 658 PEDIG study participants in 41 clinical studies from 1997 to 2022, Hispanic, Black, and Asian participants were underrepresented.

Meaning These findings demonstrate racial and ethnic disparities in pediatric ophthalmology clinical study enrollment relative to the US population; changes in PEDIG enrollment practices are associated with a decrease in these disparities and may serve as a model to facilitate more diverse clinical study enrollment.

Methods

The University of Arkansas for Medical Sciences institutional review board exempted this study due to the deidentified nature of the collected data. This retrospective, cross-sectional study, conducted between November 15, 2023, and February 17, 2024, used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and adhered to the principles of the Declaration of Helsinki (2013 version).[12,13]

Study Selection

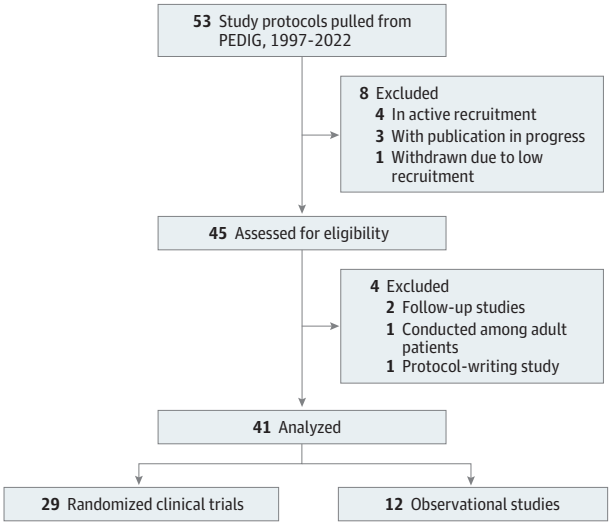
We assessed 53 published study protocols on the PEDIG public website (https://public.jaeb.org/pedig/stdy) for inclusion. Completed studies with at least 1 peer-reviewed publication were eligible for inclusion. Exclusion criteria included studies in active recruitment, studies whose enrollment period had concluded but were still underway, completed studies without published results, and extension studies of previous study protocols (**Figure 1**). Extension studies were excluded as they included the same participants as the originating study and described follow-up outcomes. The study designs analyzed included randomized clinical trials and prospective observational cohort studies.

Data Extraction and Variable Definition

For each study protocol, we collected details on the completed study and its participants through the following sources, in order of priority: study publications, study-specific preenrollment datasets, and published study results on ClinicalTrials.gov. Following the structure of the most commonly reported race and ethnicity categories for each study, we defined the following categories for our analysis: White, Black, Asian, and other races and Hispanic ethnicity. The other races category included participants who self-identified as American Indian or Alaska Native or Native Hawaiian or Other Pacific Islander. Participants self-identifying as more than 1 race, whose race was unreported, or who self-reported as unknown were also included in the other category, per the published approach of Montazeri et al.[14] Of note, all race, ethnicity, and sex data were self-reported by a parent or legally authorized representative for each pediatric participant.

In 5 study publications, Asian participants were reported combined with the other races group, and when checking against each study's preenrollment dataset, data indicated Asian participation. To avoid underestimation of Asian representation, we applied the proportion of Asian enrollment in the preenrollment dataset to the final count in each study publication's other races category to estimate the number of Asian participants. This count was then subtracted from the other races category for these 5 studies to ensure total participant counts remained consistent.

Figure 1. Review of Included and Excluded Clinical Studies for Analysis



PEDIG indicates Pediatric Eye Disease Investigator Group.

Additional variables recorded included total enrollment by sex, study design, study start and end dates, age range of enrollment per study, mean age of enrollment per study, and study topic. We identified 5 study topics, including strabismus, amblyopia, refractive or anterior segment, oculoplastic or eyelid, and other studies. The other studies category included 2 topics—1 retina and the other neuro-ophthalmology.

Statistical Analysis

We compared the demographic data of the included studies with that of the 2010 US Census pediatric population. Pediatric population data were collected from the Annie E. Casey Foundation's Kids Count Data Center.[15] We calculated the proportional enrollment of each group by sex, race, and ethnicity for each study. To meaningfully compare each group with its corresponding census subgroup, we used the published precedent of Brewster et al[16] and determined the enrollment-census difference (ECD), defined as the difference between a group's median enrollment percentage and its percentage of representation in the 2010 US Census. This value was then compared to a value of 0 using a Wilcoxon 1-sample rank sum test.[17,18] Zero was used to represent an ideal point at which there is no difference between trial enrollment and census percentages. Furthermore, given that an ECD value of 0 represents no difference, it also follows that increasingly larger absolute ECD values represent larger magnitudes of overrepresentation, and vice versa.

We also calculated the enrollment-census ratio (ECR), which is the median percentage of enrollment for a particular group divided by its percentage representation in the 2010 US Census pediatric population. ECR values were compared against a value of 1 using a 1-sample Wilcoxon rank test, as a quotient of 1 represents identical ratios between study and census proportions. Given an ECR value of 1 represents identical representation between groups, increasingly larger absolute ECR ratios greater than 1 represent larger magnitudes of overrepresentation. Similarly, increasingly smaller absolute ECR ratios between 0 and 1 represent larger magnitudes of underrepresentation.

Proportionate enrollment was defined as no difference on a 1-sample Wilcoxon rank test if $P \geq .05$. If $P < .05$, we calculated if median enrollment percentage was greater than or less than US census proportions to determine if enrollees were underrepresented or overrepresented. If the enrollment proportion was greater, this group was defined as overrepresented, and if it was lesser, the group was defined as underrepresented. All P value tests were 2-tailed.

While ECD and ECR ratios provided a picture of macrotrends across all 41 studies, we also conducted a secondary analysis for each subgroup in each study using χ^2 analysis comparisons with the 2010 US Census pediatric population. We accounted for multiplicity using Bonferroni corrections, and thus, a more conservative P value < .008 was used to determine if a subgroup within a particular clinical study was overrepresented or underrepresented (eTable 1 in Supplement 1).

A temporal analysis was conducted to assess for cumulative trends in proportional enrollment for each group from 1997 to 2019 using compound annual growth rate (CAGR), with an accompanying Mann-Kendall test to test for significance. The temporal analysis was conducted until 2019 because we used the start dates of included studies as a reference. Lastly, we conducted a multinomial logistic regression analysis to analyze the association between enrollee and study factors that resulted in representation outcomes of proportionate, underrepresented, and overrepresented for a PEDIG study participant (eTable 2 in Supplement 1). We used SPSS version 29.0.1 (IBM) and Python version 3.12.1 (Python Software Foundation) for all statistical analyses.

Table 1. Characteristics of Included Clinical Studies

Characteristic	Total participants (N = 11 658), No. (%)
Total included studies, No.	41
Randomized clinical trials	29
Phase 1	1
Phase 2	1
Phase 3	17
Phase 4	1
Not applicable	9
Observational studies	12
Sex[a]	
Male	5740 (49.2)
Female	5918 (50.8)
Race and ethnicity[a]	
White	7553 (64.8)
Black	1331 (11.4)
Hispanic	1792 (15.4)
Asian	429 (3.7)
Other[b]	553 (4.7)
Participant age, mean (SD), y	5.9 (2.8)
Study topic, No.	
Amblyopia	21
Strabismus	10
Refractive or anterior segment	4
Oculoplastics and eyelid-related conditions	4
Other	2

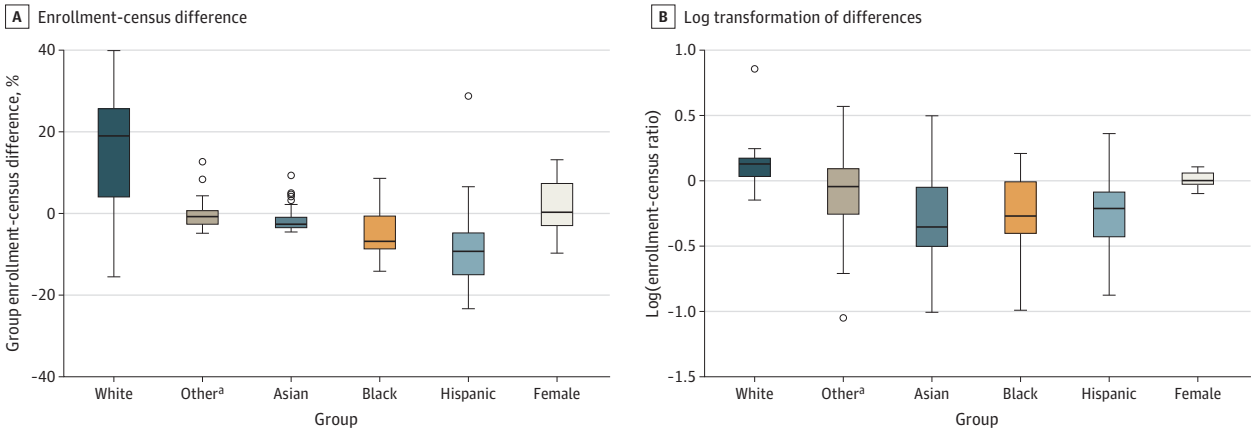
[a] Participant self-reported measures.

[b] The other race category included participants who self-identified as American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or more than one race and participants whose race was unreported or self-reported as unknown.

Results

A total of 53 studies were assessed for eligibility; of these, 41 studies met inclusion criteria, composed of 29 randomized clinical trials and 12 prospective observational cohort studies. Of PEDIG studies, 88.1% reported race and ethnicity data according to the US National Institutes of Health (NIH) and Office of Management and Budget (OMB) classification categories, and nearly all studies (98%) reported any race and ethnicity data.[19] There were 11 658 total participants in the 41 included studies (**Table 1**). The median (IQR) [range] number of participants per study was 186 (116-292) [19-2079], and the

Figure 2. Differences in Trial Enrollment Compared to the 2010 US Pediatric Population



A, Enrollment-census differences (ECD) between clinical study enrollees and 2010 US Census pediatric population. B, Log transformation of enrollment-census ratio comparison between clinical study enrollees and 2010 US Census pediatric population. Horizontal lines inside colored bars indicate the median, colored bars indicate IQR values, whiskers indicate 1.5-fold the IQR values, and circles indicate outliers.

[a]The other race category included participants who self-identified as American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or more than one race and participants whose race was unreported or self-reported as unknown.

mean (SD) number of participants per study was 286 (359). Of the 41 included studies, 31 had enrollment counts less than 286. Female participants comprised a median (IQR) proportion of 49.4% (45.9%-56.7%) of study participants. The most commonly represented racial and ethnic group in studies was White, with a median (IQR) rate of representation of 72.8% (57.6%-72.8%), followed by Hispanic (14.1% [7.9%-18.9%]), Black (7.4% [5.3%-13.7%]), other (4.0% [2.0%-5.7%]), and Asian participants (1.8% [0.9%-3.6%]).

Among the 41 studies, White participants were overrepresented (ECD, 0.19; 95% CI, 0.10-0.28; $P < .001$; ECR, 1.36; 95% CI, 1.20-1.52; $P < .001$) compared with the 2010 US Census pediatric population (**Figure 2**). In contrast, Asian participants (ECD, −0.03; 95% CI, −0.04 to −0.02; $P = .009$; ECR, 0.41; 95% CI, 0.18-0.64; $P = .009$), Black participants (ECD, −0.07; 95% CI, −0.10 to −0.04; $P < .001$; ECR, 0.51; 95% CI, 0.28-0.73; $P < .001$), and Hispanic participants (ECD, −0.09; 95% CI, −0.13 to −0.05; $P < .001$; ECR, 0.61; 95% CI, 0.44-0.78; $P < .001$) were underrepresented. Other race participants were proportionately represented (ECD, −0.007; 95% CI, −0.021 to 0.006; $P = .19$; ECR, 0.84; 95% CI, 0.56-1.13; $P = .19$). Similarly, female participants were proportionately represented (ECD, 0.004; 95% CI, −0.04 to 0.05; $P = .21$; ECR, 1.01; 95% CI, 0.93-1.09; $P = .21$).

Regarding temporal trends in proportional enrollment from 1997 to 2019, we found Asian participants (CAGR, −1.7%; 95% CI, −2.0% to −1.4%; $P = .01$), Black participants (CAGR, −0.7%; 95% CI, −1.1% to −0.3%; $P = .04$), and White participants (CAGR, −1.5%; 95% CI, −2.3% to −0.6%; $P = .002$) demonstrated decreasing proportional enrollment (**Table 2**). Conversely, Hispanic participants demonstrated an increasing trend in proportional enrollment (CAGR, 7.2%; 95% CI, 3.7%-10.7%; $P < .002$) from 1997 to 2019. Running trends in cumulative enrollment can be seen in **Figure 3**.

Table 2. Compound Annual Growth Rates (CAGRs) for PEDIG Clinical Studies From 1997 to 2022

Group	CAGR, % (95% CI)	*P* value[a]
White	−1.5 (−2.3 to −0.6)	.002
Black	−0.7 (−1.1 to −0.3)	.04
Hispanic	7.2 (3.7 to 10.7)	.002
Asian	−1.7 (−2.0 to −1.4)	.01
Other[b]	5.8 (−0.2 to 11.8)	.10
Female	0.6 (−0.1 to 1.2)	.12

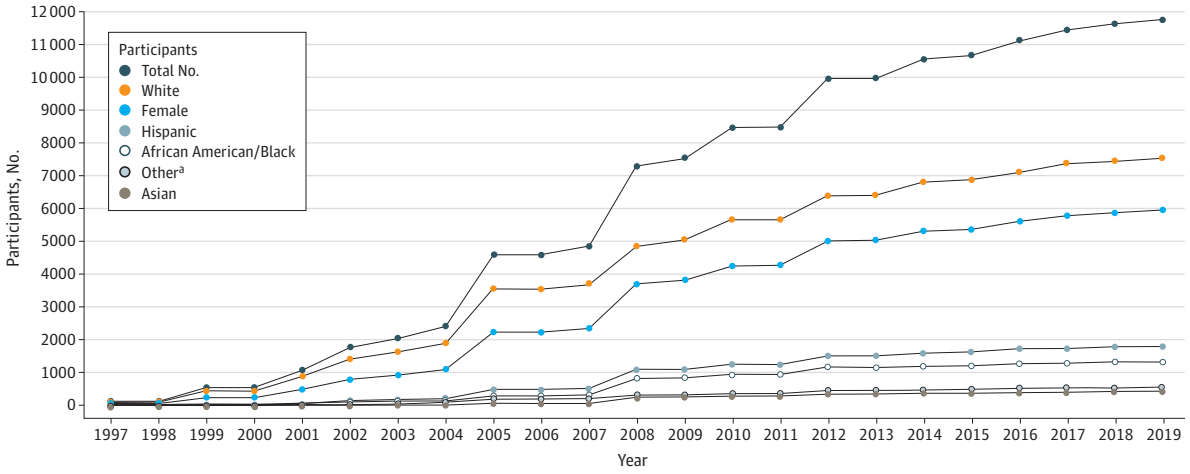
Abbreviation: PEDIG, Pediatric Eye Disease Investigator Group.

[a] Determined by Mann-Kendall test.

[b] The other race category included participants who self-identified as American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or more than one race and participants whose race was unreported or self-reported as unknown.

On multinomial logistic regression modeling, we assessed factors that contributed to representation outcomes of underrepresented and overrepresented compared with proportionate representation outcomes for a PEDIG study participant (eTable 2 in Supplement 1). Hispanic ethnicity was associated with higher odds of being underrepresented (adjusted odds ratio [aOR], 7.61; 95% CI, 1.02-56.62; $P = .05$). Participating in clinical studies with more than 200 participants was associated with higher odds of being disproportionately represented, either underrepresented (aOR, 36.16; 95% CI, 3.49-374.94; $P = .003$) or overrepresented (aOR, 44.74; 95% CI, 3.35-597.89; $P = .004$). Participating in a clinical study on strabismus was associated with higher odds of being disproportionately represented (underrepresented: aOR, 0.09; 95% CI, 0.01-0.60; $P = .01$; overrepresented: aOR, 0.07; 95% CI, 0.01-0.60; $P = .02$).

Figure 3. Running Total of Enrollment for Each Representative Subgroup From 1997 to 2019



The starting year of each study was used.

[a]The other race category included participants who self-identified as American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or more than one race and participants whose race was unreported or self-reported as unknown.

Discussion

To our knowledge, this is the first study to investigate trends in race, ethnicity, and sex in PEDIG clinical studies since PEDIG's inception in 1997. Among these studies, Asian, Black, and Hispanic participants have been the most cumulatively underrepresented. We identified temporal trends that indicated that proportional representation in Hispanic participants is positively increasing year by year. On the whole, female participants were proportionately represented almost uniformly across all included studies, with no appreciable temporal trends.

Recent literature has published varying rates of reporting of race and ethnicity in pediatric and ophthalmology clinical trials, with rates varying from as low as 28.3% to as high as 93.9%.[14,16,20-22] Given PEDIG's standardized approach to reporting race and ethnicity, it was reassuring to find that most studies (88.1%) reported race and ethnicity according to the NIH and OMB classification categories in publications, and nearly all studies (98%) reported any race and ethnicity data.[19] This transparent approach may have positive implications for increasing research generalizability and promoting more equitable treatment outcomes, particularly in underserved populations.[20]

Despite transparent reporting, our findings regarding racial and ethnic representation in PEDIG clinical studies suggest certain groups differed relative to US pediatric population estimates. Asian and Black participants were underrepresented relative to 2010 US Census estimates, and both enrollment groups demonstrated decreasing temporal trends in proportional enrollment over time. This suggested Asian and Black participants' proportional representation in studies is declining relative to the number of PEDIG participants recruited each year.

The dynamics impacting clinical study enrollment are multifactorial and may originate with either the researcher or the patient. Potential contributing factors for underrepresentation in Asian and Black study participants were not directly transparent. However, on regression analysis, larger study sizes were associated with greater odds of being underrepresented for a group. While larger sample sizes may intuitively be associated with greater representation of a population, it is also possible that larger sample sizes may amplify preexisting biases in recruitment practices.[23] Additionally, larger recruitment targets can be more difficult to fill within stipulated recruitment periods, thus resulting in less diversity.[24] Therefore, efforts to identify and improve existing biases in recruiting are warranted. PEDIG founded its equity, diversity, and inclusion committee in 2022 to spearhead this effort.

Another action taken by PEDIG to ensure equitable recruitment has been the recent implementation of enrollment limits based on disease prevalence. For instance, in the MTS1 study on the use of atropine for slowing myopia progression, Asian participants were limited to a certain fixed proportion of enrollees. This was enacted due to the fact that myopia has been reported to affect Asian children at higher rates than other groups.[25,26]

Patient-derived factors may also contribute to overall underrepresentation. Medical mistrust has been identified as a barrier to clinical study enrollment in Asian American and Black communities.[27,28] In light of potential mistrust, incorporating race and ethnicity matching of recruiters and encouraging the development of a trusting relationship with at least 1 health care provider have been suggested as tenable steps to increase enrollment.[28,29]

We found that Hispanic participants were also underrepresented in PEDIG clinical studies. However, they also conversely demonstrated an increasing positive temporal trend. This suggests proportional enrollment of Hispanic patients is increasing annually. Some specific interventions implemented by PEDIG to

improve Hispanic participant recruitment may have played a role, including the availability of Spanish-language informed consent forms. Furthermore, online interpreters are now available for assisting in recruitment of Spanish-speaking families. These interventions, in conjunction with the formation of the equity, diversity, and inclusion committee, suggest that Hispanic participant enrollment in PEDIG studies is improving.

We found that White participants were overrepresented in PEDIG clinical studies and have demonstrated a decreasing temporal enrollment trend. The 2007 passage of the US Food and Drug Administration Amendments Act increased regulations regarding the reporting of race and ethnicity in clinical trials and has been proposed as an impetus for the decreasing temporal trend in enrollment.[30] However, this was found to be nonsignificant on regression analysis. Another explanation for this decreasing temporal trend is that, as the largest proportional group in PEDIG studies, White proportional enrollment may be responsively decreasing as other participant groups collectively achieve more representative enrollment in the total enrollment proportion.

Generally, reports of overall representation in pediatric clinical trials have yielded mixed results. An analysis of 1183 privately and publicly funded pediatric clinical trials from 2007 to 2020 compared with the 2019 US pediatric population reported an overall underrepresentation of Asian (−7%), Black (−6%), and Hispanic participants (−16%) and an overrepresentation of White participants (12%).This was similar to PEDIG studies, which also demonstrated White overrepresentation (19%) and comparable rates of Black underrepresentation (−7%). In contrast, Asian and Hispanic underrepresentation (−3% and −9%, respectively) was improved in PEDIG studies.[16] A more recent analysis of underrepresented racial and ethnic minority participants in 363 NIH-funded pediatric clinical trials from 2017 to 2019 found levels of representation ranged from adequate to overrepresentation in all racial and ethnic minority participant groups relative to the 2021 US Census.[20] Though PEDIG is also funded through the National Eye Institute (a branch of the NIH), PEDIG did not perform as well in terms of proportionate representation for underrepresented minorities overall, though later time periods of recruitment in the pediatric studies may have played a role.

Compared with the equitable recruitment of adults for ophthalmology clinical studies, PEDIG recruitment was on par or better. A recent review of clinical trials in retinal vein occlusion and diabetic macular edema from 2004 to 2020[21] reported an overall underrepresentation of one or more of Asian, Black, and Hispanic participant groups in 68% of included studies compared with the 2010 US Census. By comparison, this measure held true for 21 of 41 PEDIG studies analyzed (51%).

A recent analysis of international pediatric ophthalmology clinical trials[22] compared their proportional representation to all age groups in the 2010 US Census population. This analysis found pediatric ophthalmology clinical trials to be underrepresentative of Hispanic participants (−8%), overrepresentative of White participants (17%), and proportionate for representation of Asian and Black participants. Comparatively, PEDIG did not enroll Asian and Black participants proportionately but performed similarly in Hispanic and White proportionate enrollment.

Alternatively, the Infant Aphakia Treatment Study (IATS) group mirrored the 2000 US Census population in their recruitment process of participants for their multicenter study.[31] Compared with PEDIG, the IATS group was able to demonstrate proportionate representation for each racial and ethnic group included in their study. This outcome was achieved by PEDIG in 10 of 41 included studies (24%) in our analysis. One notable similarity in IATS and PEDIG studies that achieved proportionate representation was study enrollment size. IATS enrolled 114 patients, and all PEDIG studies that achieved proportionate representation enrolled fewer than 200 participants. This echoes our findings that larger studies may face more difficult proportionate recruitment efforts, and closer attention must be paid to enrollment practices, especially as they relate to larger studies.

Limitations

There were several limitations to our study. The comparison group for our study was the 2010 US Census pediatric population. However, this comparison group may have underestimated the level of representation required to achieve adequate generalizability for findings in racial minority groups relative to the prevalence of certain pathologies within these populations. The US Census Bureau also historically reports an undercounting of racial and ethnic minority individuals and infants and children aged 0 to 4.[32] In addition, given that census data were collected for the year 2010, these data may not have accurately reflected the racial and ethnic makeup of the US population near the start and end of our study period. Another possible limitation was that data collected for race, ethnicity, and sex were self-reported, and this may have introduced some biases or inaccuracies at the individual patient survey level. For 5 study publications, Asian participants were included in the other category and thus, assuming equal and maintained proportions for Asian participants from original patient rosters, may have contributed to a slight overestimation or underestimation of Asian enrollment in these studies. Lastly, our study findings took into account the role of different clinical trial factors associated with enrollment, but did not account for individual patient factors, such as willingness to participate or a lack of trust in medical research, which may have impacted enrollment proportions.

Conclusions

In conclusion, racial and ethnic disparities exist in PEDIG clinical study recruitment, which may impact research findings' generalizability to underrepresented groups. Changes implemented in enrollment practices by PEDIG seek to address these disparities and may serve as a model to facilitate more diverse clinical study enrollment. Further efforts and time are still required to fully assess the impact of these changes in reducing or eliminating these disparities.

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