

Title Page

Title:

Racial and Ethnic Backgrounds of U.S. Randomized Controlled Trials in Obstetrics and Gynecology and Comparison to U.S. General Population: A Retrospective Review

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Abstract

Objective: To determine if the racial and ethnic compositions of the participants in Obstetrics and Gynecology randomized controlled trials (RCTs) conducted in the U.S. match that of the general U.S. population.

Design: Retrospective analysis of U.S. RCTs.

Setting: United States.

Population: Women enrolled in U.S. RCTs.

Methods: Racial and ethnic composition of RCT participants published in two premier US journals, *Obstetrics and Gynecology* and *American Journal of Obstetrics and Gynecology*, from January 2010 to April 2020 were collected and analyzed.

Main outcome measures: Comparison of the racial and ethnic composition of the U.S. RCTs to U.S. General population.

Results: Chi-square analysis showed significant deviations from the U.S. general population in both Obstetrics ($p < 0.001$) and Gynecology ($p < 0.05$). We observed an overrepresentation of Black race and an underrepresentation of White and Asian races overall Obstetrics and in most subcategories. We observed an overrepresentation of Black race and an underrepresentation of Asian race in Gynecology overall and in most subcategories. White race representation was similar to the general population on average, but with wide variation across studies especially among the subcategories. Hispanic ethnicity was overall underrepresented.

Conclusions: RCTs in the field of Obstetrics and Gynecology conducted in the U.S. deviate from the general population with regard to racial and ethnic distributions.

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Keywords: U.S. Randomized Controlled Trials, Racial and Ethnic Backgrounds, Obstetrics and Gynecology

Tweetable Abstract: Racial and ethnic composition in U.S. RCTs' participants showed deviation from that of the US general population, and notable for overrepresentation of Black race.

Introduction

Evidence based medicine (EBM), a term first articulated in the early 1990's, defined as the use of sound scientific data from clinical trials to formulate clinical guidelines, has been one of the central concepts in clinical medicine with significant and diverse effects. It is used to determine which treatment or intervention ought to be adopted from a public health standpoint and affects how research is funded through its influence on policy makers. Perhaps most significantly, EBM is also an essential component in formulating clinical practice guidelines by dictating the everyday practice of clinicians, whose medical decision making is judged against these standards. In turn, EBM also sets the legal standard of care.^{1,2}

Randomized controlled trials (RCTs) are considered the highest level of evidence (Level 1) in the hierarchical system used to classify the vast number of research publications available.³ As such, evidence derived from RCTs is given particular importance in EBM, and consequently in clinical guidelines. Despite this, RCTs can lack external validity due to the narrow clinical settings in which they are conducted.^{4 5} The United States is unique in terms of the diversity of its population. Therefore, RCTs conducted in U.S. include participants from different races and ethnicity. Since races and ethnicity are associated with prevalence and outcome of diseases^{6,7}, racial and ethnic composition of patients included in RCTs can alter their results and thus the generalizability of the conclusions of the studies to the wider population.

The primary aim of this study was to determine if the racial and ethnic background of RCT study populations reflects that of the U.S. general population. If the racial and ethnic compositions were not representative of US demographics, we sought to characterize those deviations.

Methods

Study selection and classification: A query was conducted through the Ovid Medline Online Database using “Randomized Controlled Trial” as the key word to search and identify all RCTs published in two U.S. leading journals, *Obstetrics and Gynecology* and the *American Journal of Obstetrics and Gynecology*.

Inclusion criteria were randomized controlled trials conducted in US, with data available on racial and ethnic distributions of the study participants, published in either journal between January 2010 and April 2020. Studies were excluded if they were conducted in part or wholly outside of the United States, had incomplete data with regards to racial and ethnic distributions, were secondary or follow up analyses to avoid counting the same study population multiple times, and when the study subjects are not the patients in Obstetrics and Gynecology.

Included studies were classified as either Obstetrics or Gynecology studies as appropriate. After the selection of the articles, subcategories were created based on the study topics and if ten or more papers fell within a specific category. If the requisite minimum of ten studies could not be reached, the remaining articles were classified as “Other.” Obstetrics articles were subcategorized as follows: “Cesarean Section”, “Medical Complications”, “Antepartum and Postpartum Care”, “Labor and Delivery”, and “Preterm Births”. Gynecology articles were subcategorized as follows: “Family Planning (including contraception and abortion)”, “Female Pelvic Medicine and Reconstructive Surgery”, and “Other GYN”.

Since this study is a retrospective analysis of the published articles, it is exempted from IRB review.

The racial/ethnic classification and controls: The racial and ethnic groups of interest in this analysis were “Non-Hispanic White”, “Non-Hispanic Black”, “Asian”, “Hispanic”, and “Others,” which encompassed participants identifying as being of more than one race, Native American, or Pacific Islander origin. This classification was chosen because it was used most often in the papers of our interest.

We used CDC Wonder database to obtain the racial and ethnic distributions of women who gave birth during the period between 2016 and 2018, and this served as a control for Obstetrics papers.⁸(Table 1) The control for the Gynecology articles was obtained from the Kaiser Family Foundation and United States Census Bureau website estimates in 2018.⁹ (Table 2). Compared to US census 2010, the 2018 racial and ethnic composition was relatively stable. (2010 data was as follows: non-Hispanic White population at 63.7%, non-Hispanic Black population at 12.2%, non-Hispanic Asian population at 4.7% and Hispanic population at 16.3%)¹⁰ The CDC birth data had lower White and higher Black, Asian and Hispanic populations than the U.S. general population data. We considered this to be more appropriate control because we were analyzing pregnant populations.

Statistical analysis: Chi-squared Goodness-of-Fit analysis was used to evaluate if the racial and ethnic distribution of RCT participants in U.S. deviates from that of U.S. general population. The Shapiro-Wilson test determined normality of the distribution. To assess if each race and ethnic group deviates from the general population, the Single-Sample T-test was applied when the distribution was non-normal, and the One-Sample Wilcoxon Signed Rank Test was utilized when the distribution was normal. All data analyses were performed using R Studio (Version 1.2.5001, 2019). with an alpha value of 0.05, and a p-value of less than or equal to 0.05 considered statistically significant.

Results

576 articles were originally identified, of which 317 were excluded: 162 because they were conducted partially or completely outside of the United States, 76 for incomplete data on racial distribution, and 63 for being either secondary analysis or meta-analysis studies, or not RCT's. Finally, 16 studies with a focus on residency education were excluded for having a study population consisting of primarily resident physicians. (Figure S1)

The remaining 259 articles were included for analysis. 104 articles were Obstetrics and 155 were Gynecology. The racial and ethnic compositions were extracted from each article and expressed as percentages. Chi- squared analysis showed deviations in racial and ethnic composition from the general population in Obstetrics studies($p<0.001$). Subsequently, Obstetrics articles were divided into subcategories as follows: 33 “Cesarean Section” articles, 10 “Medical Complications” articles, 22 “Antepartum and Postpartum Care” articles, 23 “Labor and Delivery” articles, and 16 “Preterm Birth” Articles. Chi-squared analysis showed significant deviations in all the subcategories. (Table 1).

To determine which groups are either overrepresented or underrepresented, further analyses were carried out. The results were summarized as box plots in Figure 1. In summary, White race was underrepresented in “Total Obstetrics” articles ($p<0.001$), “Cesarean Sections” ($p<0.01$), “Medical Complications” ($p<0.001$), “Labor and Delivery” ($p<0.001$), “Antepartum and Postpartum Care” ($p<0.01$), but in “Preterm Birth” subcategory their representation was close to general population. Black race was overrepresented in “Total Obstetrics “ ($p<0.001$)

“Cesarean Section” ($p < 0.001$), “Labor and Delivery” ($p < 0.01$), “Antepartum and Postpartum Care” ($p < 0.001$), “Preterm Birth” ($p < 0.01$), but underrepresented in “Medical Complications” ($p < 0.05$). Asian race was underrepresented in “Total Obstetrics” ($p < 0.001$) and all the subcategories. Hispanic ethnicity representation was comparable to general population in “Total Obstetrics” articles and most of the subcategories, except for overrepresentation in “Medical Complications” ($p < 0.01$), and underrepresentation in “Preterm Birth” ($p < 0.05$). Patients whose race/ethnicity was classified as “Others” were shown to be have similar representation to general population in “Total Obstetrics” and all subcategories in Obstetrics articles. (Figure 1)

Chi-squared analysis of the Gynecology studies also showed deviation from the general US population ($p < 0.05$). (Table 2) Since the ages of the subjects in the Gynecology articles vary widely compared to Obstetrics, we looked to see if there is a correlation between the race/ethnic group and age. A positive correlation between the age of the study participants and the percentage of White subjects was identified, ($R = 0.59$), and conversely, a negative correlation was revealed between participant age and percentage of non-White subjects ($R = 0.64$). (Figure S2)

The Gynecology articles were subclassified as follows: 54 “Family Planning”, 41 “Female Pelvic Medicine and Reconstructive Surgery”, and 60 articles classified as “Other GYN”. The articles classified as “Other GYN” within the Gynecology subcategories included studies pertaining to gynecologic surgery, assisted reproductive technology, vaginitis, and HPV vaccines, with none of these subcategories surpassing an article count greater than 10. Chi-squared analysis again showed deviation from the US general population in “Total Gynecology” and all 3 subcategories. (Table 2)

Analysis per each race and ethnic group in Gynecology studies are presented as box plots in Figure 2. White race representations in “Total Gynecology” and “Other GYN” articles were comparable to general population, but they were underrepresented in “Family Planning” ($p<0.001$), overrepresented in “Female Pelvic Medicine and Reconstructive Surgery” ($p<0.001$). Black race was overrepresented in “Total Gynecology” ($p<0.001$), “Family Planning” ($p<0.001$) and “Other GYN” ($p<0.001$) but underrepresented in “Female Pelvic Medicine and Reconstructive Surgery” ($p<0.01$). Asian race was underrepresented in “Total Gynecology” ($p<0.001$) and all 3 subcategories. Hispanic population’s representation was comparable to general population in “Family Planning” but underrepresented in “Total Gynecology” and 2 other subcategories ($p<0.001$). “Other” population was overrepresented in “Family Planning” ($p<0.001$) and showed similar representation to general population in “Female Pelvic Medicine and Reconstructive Surgery” and “Other GYN”.

Additionally, as shown in Figures 1 and 2, large interquartile ranges were noted both total and all across the subcategories indicating the wide variation of the data.

Discussion

Main Findings: Our analysis showed that racial and ethnic compositions in RCTs on average deviated from the general U.S. population, most consistently showing overrepresentation of Black race and underrepresentation of Asian race. Underrepresentation of White race was also observed in Obstetrics. In the Obstetrics studies, an overrepresentation of Black race was seen in all categories except “Medical Complications.” For a subcategory such as “Preterm Birth”, overrepresentation of the Black population is expected because of the known high preterm birth rate in this group.¹¹ However, Black race’s overrepresentation observed in other categories, such as “Labor and Delivery” or “Antepartum and Postpartum Care”, cannot be explained as there should not be any differences among different racial and ethnic groups.

An overrepresentation of Hispanic ethnicity and underrepresentation of Black and Asian races were seen in the “Medical Complications” category (mostly gestational diabetes and hypertensive disorder). The reason for this finding is unclear, as Black race is known to be at increased risk for hypertension.¹² Moreover, the races at increased risk for gestational diabetes include Hispanic, Black, Asian, Pacific American, and Native American populations¹³, making the sole overrepresentations of Hispanic participants puzzling.^{12, 13}

Asian race was underrepresented in both Obstetrics and Gynecology, and all their subcategories. The Asian population is a minority in the United States, and fewer enrollments are therefore expected in the RCTs. However, despite this allowance, our results reveal an underrepresentation of Asian people in RCT’s. A recent article reported that Asian population is less likely, and Black population is more likely, to consent to RCTs compared to White population.¹⁴ This may be another factor for the racial distribution pattern we observed.

We also noted a wide variation in the racial distribution among studies. For example, in Gynecology studies, the percentage of White participants varied from 1.52% to 98.0%, an extremely wide range, indicating the heterogeneity of the study participants' pool among the studies.

Strengths and limitations: To our knowledge, this is the first study to look at the racial and ethnic composition of U.S. RCT participants in Obstetrics and Gynecology. While each study may not necessarily follow the national distribution, the deviation we observed in the RCTs as a whole might raise the question regarding the applicability of their findings to the general U.S. population.

The main limitation of the study is that this is a retrospective analysis of the data extracted from previously published articles in two U.S. journals. However, these are the premier U.S. journals in general Obstetrics and Gynecology, and we were able to review a significant number of articles from this search. We limited our analysis to the last 10 years to characterize the relatively current studies because of the recent increasing awareness of the differences among races and ethnicity in health care. Very few studies in gynecologic oncology or reproductive endocrinology were identified, likely because the RCTs in these fields are published elsewhere. Further studies will be needed to better define the racial distribution in these subspecialties.

Interpretation: One of the most striking findings of this analysis was the consistent overrepresentation of Black race among the U.S. RCTs. This was contrary to the concerns expressed by many experts that minority groups were underrepresented in biomedical research (Black and Hispanic populations).^{15, 16} While overrepresentation of Black race appears to be a welcoming finding in terms of minority representation, this deviation may affect the outcomes of select RCTs, and therefore the generalizability of their findings. Through the cultural difference

and socioeconomic disparities, race and ethnicity can greatly influence disease burden, response to treatment, and more.

In obstetrics, higher preterm birth (PTB) rates have been observed among Black Americans than other racial groups¹⁷. One of the interventions to reduce the rate of PTB was 17-alpha hydroxyprogesterone (17-P) administration. The efficacy of 17-P was validated by at least 2 RCTs conducted in the US.^{18, 19} However, this treatment was recently questioned because of the findings described in the PROLONG trial, which demonstrated no benefit of 17-P administration, thus prompting an FDA panel recommendation to withdraw its approval.²⁰ The PROLONG trial was conducted in multiple international centers, of which more than half were outside the US, with a study population that was predominantly Caucasian (89%) and only 6-7% was Black race. One possibility is that this difference in study populations may have contributed to the conflicting results. This may underscore the limitation of RCTs as their results may not be applicable to the population outside of the study group.

When we divided Gynecology studies into 3 groups, “Female Pelvic Medicine and Reconstructive Surgery” and “Family Planning” accounted for more than 60% of the studies, and interestingly exhibited entirely opposite racial distributions, with an overrepresentation of White subjects in the former, and an underrepresentation of the same group in the latter. In the “Total Gynecology”, White population’s representation was similar to general population. However, it is likely because these groups cancelled each other out. This also explains the positive and negative correlation seen between age and the percentage of White and non-White participants among the Gynecology study participants, respectively, as the papers in “Female Pelvic Medicine and Reconstructive Surgery” group focused on older patients while the “Family Planning” category is focused on younger population.

An underrepresentation of White race was observed in the Obstetrics papers overall, and, in all but one (Preterm Birth) of the obstetric subcategories. This, together with an overrepresentation of Black race, was similar to that observed in the “Family Planning” subcategory of the Gynecology papers. One possible reason for this may lie in the recruitment methods of these women. Many, if not most, of the RCTs were conducted at large academic medical centers. These hospitals often serve lower income populations and tend to have higher rates of Black patients compared to other hospital types. Given that the subjects of these studies are women of reproductive age, it is plausible that studies performed on this population of women were primarily done in these medical centers’ clinics, resulting in the overrepresentation of Black race we have observed. In other words, inclusion of Black population is a reflection of the racial composition of the patients’ population of the clinics, and it may not be the results of active efforts to include the minority group. Conversely, the overrepresentation of White population in the “Female Pelvic Medicine and Reconstructive Surgery” category may simply be because this field has more White patients than other racial and ethnic groups, resulting in a skewed racial composition, not due to the exclusion of the minority groups.

Conclusions: We found that the U.S. RCTs published in two prominent U.S. Obstetrics and Gynecology journals do not accurately represent the racial and ethnic distribution of our overall population. Our study is not questioning the validity of an individual RCT, nor claiming that each study’s participants must mirror U.S. population. However, as the racial and ethnic compositions of studies can strongly influence their results, it is important that physicians be mindful of these characteristics when interpreting study conclusions, especially because they are often incorporated into practice guidelines geared towards the general population.^{5, 21-23} It may

also indicate the possible difficulty in generating such general guidelines in a country like U.S. which consists of diverse population.

Disclosure of interests: None declared.

Contribution of authorship: YA had the original idea of the study. NC, YW, CP, JG, SL performed data collection and statistical analyses. All the authors gave input at various stages of the study, contributed to the interpretation of the data and participated in the preparation of the manuscript.

Details of ethical approval: The study was exempt from IRB review because of it is a retrospective analysis of published data.

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