

Reporting, Representation, and Subgroup Analysis of Race and Ethnicity in Published Clinical Trials of Atopic Dermatitis in the United States Between 2000 and 2009

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Abstract: To review the literature on atopic dermatitis (AD) clinical trials published in the United States between 2000 and 2009 to examine the representation of racial and ethnic minorities in those trials and determine the extent to which investigators reported on demographic variables and performed a subanalysis. A PubMed search was performed including all clinical trials for management of AD published between 2000 and 2009. Three reviewers analyzed articles matching the search criteria. Data recorded included incorporation of demographic data at baseline and in the analysis and result interpretations. Of 645 PubMed search results, only 78 articles originated in the United States and fit the search criteria; 59.5% of these included reports of race or ethnicity. Of the studies reporting race or ethnicity, the subject population mainly included 62.1% white, 18.0% black, 6.9% Asian, and 2.0% Hispanic. Despite increasing awareness in the United States of the importance of reporting demographic data in clinical trials, there has been no significant improvement in reporting in AD clinical trials over the past 10 years. When reporting occurs, the categorization of ethnicities, methods of reporting data, and incorporation of the data into the results are lacking or flawed. In addition, aside from blacks, U.S. minorities appear to be under-represented in AD clinical trials.

Birth and immigration trends predict that, as an aggregate, ethnic minority groups, including African Americans, Asians, Native Americans, Alaskans, and Hispanics, will encompass up to 50% of the U.S. population by 2050 and that Hispanics and Asians will double their representation by that time (1). Currently there is a paucity of clinical, basic, and epidemiologic research

addressing the structural, functional, and clinical differences in cutaneous disorders between ethnic and minority populations.

Clinical trials play a significant role in the advancement of medical knowledge and improvement of patient care. Results from clinical trials address relevant existing questions regarding the treatment and management

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of disease, but they also guide future research directions and priorities. African Americans, Asian Pacific Islanders, and Hispanics and Latinos represented fewer than 10% of individuals participating in clinical trials testing cancer drugs between 1995 and 1999 (1). There have been several initiatives created to correct these disparities in clinical trial participation. The National Institutes of Health (NIH) Revitalization Act of 1993 (2) requires that applicants for federal research funding provide a strategy for the inclusion of women, children, and racial and ethnic groups into clinical trials. The Food and Drug Administration (FDA) Modernization Act of 1997 provides guidance on the standardization of data collection regarding minority groups (1), although it does not mandate their inclusion.

The objectives of this study were to use the literature on atopic dermatitis (AD) clinical trials published between 2000 and 2009 to examine the representation of ethnic minorities in those trials and to perform a sub-analysis of the extent to which investigators reported on demographic variables.

METHODS

A PubMed search was performed during November 2009 to identify all clinical trials for prevention, treatment, or management of AD published between 2000 and 2009. The investigators repeated the search for accuracy with updates in January 2010 and trained library staff at Eastern Virginia Medical School verified the search in October 2010. The investigators then reviewed titles consistent with defined search parameters in the full text. The inclusion criterion was limited to human subject studies, but was not limited by randomization, blinding, or methods of control in the studies. All articles matching the search criteria were then analyzed and included in the results, with three separate reviewers performing and recording data collection. Data were recorded for each article for the country of origin, year of publication, study design, treatment or management type (e.g., topical, systemic, behavioral), subject number and age range, and sponsorship. Data on the reporting of race and ethnicity, socioeconomic status (SES), sex, and incorporation of demographic data in the analysis and results interpretations were collected.

DATA ANALYSIS AND STATISTICAL METHODS

Three independent reviewers compiled raw data, and statistical analysis was performed at the Eastern Virginia Medical School Epidemiology-Biostatistics Research Support Center. Continuous data were described using

means and standard deviations, and categorical data were described using proportions. Fisher's exact test was used to test the association between the demographic variables (race and ethnicity, SES, sex, and use of the demographic subgroups when interpreting the data), the study's year of publication and sponsorship, and the size of the study. The data were separated into two groups based on the country of origin: U.S. or non-U.S. $p < 0.05$ was considered significant. All the analyses were performed in SAS 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Of 645 PubMed search results, 402 articles were reviewed in full text. Of these, 363 fit the search criteria and 78 of these originated in the United States and were included in the analysis. The average number of subjects per study was 203.8 ± 257.3 . The majority of the studies (89.9%) involved topical or systemic treatments or both. The remaining studies involved behavior modification, education, or observation. This review comprised 24.1% adult-only studies (age ≥ 18), 50.6% children-only studies (age < 18), and 21.5% with adults and children. Most of the studies were industry sponsored (65.8%), 6.4% were federally funded, 58.2% were randomized, 44.3% were double blind, 10.1% were single blind, 54.4% were placebo controlled, 19.0% had active controls, and 30.4% were open label.

Race and Ethnicity

Of the 78 articles included, 46 (59.0%) included reports of race and ethnicity ($p = 0.11$) (Fig. 1), and 2 of these 46 studies (2.6%) documented the method by which race or ethnicity was assigned (self-reporting or investigator classification), 8 (10.3%) used their recorded demographics in their results interpretation, and none discussed possible implications for clinical practice. Thirty-six (46.2%) of the 46 studies reporting race or ethnicity simply reported baseline information on race and ethnicity but did not refer to these data when analyzing or interpreting the results. Three (3.8%) of the studies reported "no difference in baseline demographics," but did not state which demographics were recorded. No association was found between the year of publication and the likelihood of reporting race or ethnicity. All studies except one that reported race or ethnicity used broad classification groups without providing more-specific information on definitions of the classification terms, ancestry, and culture. Examples of these broad classification groups include white, Caucasian, non-

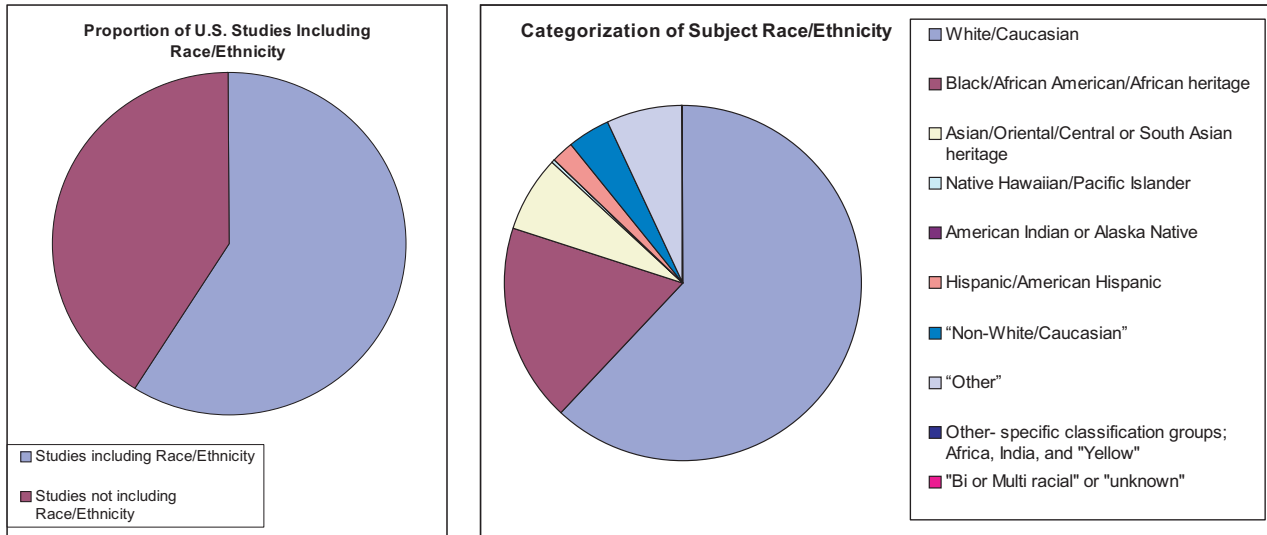


Figure 1. Left, proportion of U.S. AD clinical trials performed between 2000 and 2009 reporting subject race and ethnicity. Right depicts the detailed categorization of race and ethnicity in studies reporting on this data.

white/non-Caucasian, black, African American, Asian, Oriental, "yellow," Hispanic, and "other." Six of the 78 (7.7%) studies simply stated race and ethnicity as "all" white or Caucasian or "mostly" white or Caucasian. The only significant correlation with reporting of race and ethnicity was with the number of subjects in the study. The more study subjects, the greater the likelihood that race and ethnicity ($p < 0.001$) was reported. Reporting race and ethnicity was not significantly associated with the other variables, including sponsorship (federal or pharmaceutical), year of publication (Fig. 2), study design, treatment or management type, and subject age.

Of the 46 articles reporting race and ethnicity, 22,202 subjects participated. As discussed above, the studies generally reported race and ethnicity in broad terms, al-

though one article published in 2006 attempted to assign more-specific categories based upon "heritage." Some of the categories included in this study were Arabic and north African, east and southeast African, central and south Asian heritage, and African heritage. Two studies (published in 2008 and 2009) provided categories for "more than one race" or "bi- or multiracial." When the subjects from these studies were combined into one large group ($n = 22,202$) and synonymous classification groups were combined (e.g., combining "black" and "African American"), the population breakdown included 13,679 (62.1%) white or Caucasian; 3,954 (18.0%) black, African American, or African heritage; 1,523 (6.9%) Asian, Oriental, or central or south Asian heritage; 7 (0.03%) "yellow;" 57 (0.3%) Native Hawaiian

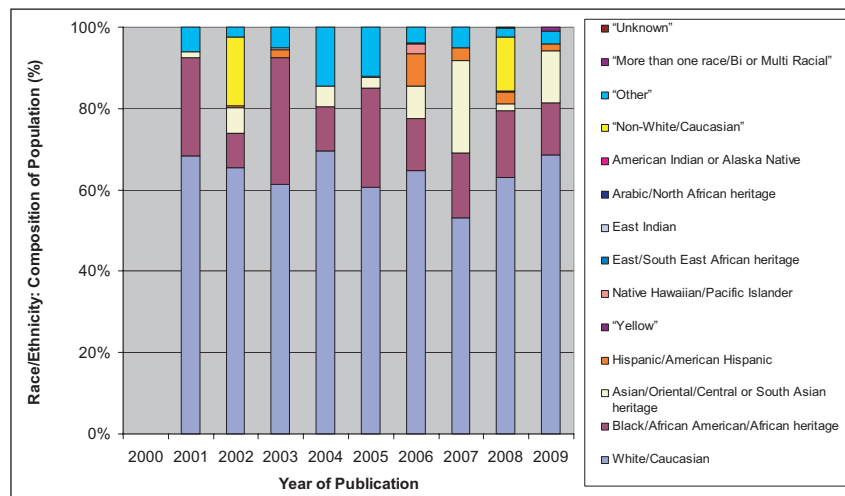


Figure 2. Composition of subjects included in U.S. atopic dermatitis clinical trials according to year of publication. Data were taken from the 46 U.S. studies that included this information in their publication.

or Pacific Islander; 3 (0.01%) east or southeast African heritage; 1 (0.005%) Arabic or North African heritage; 4 (0.02%) American Indian or Alaskan Native; and 441 (2.0%) Hispanic. Additionally, 829 (3.8%) were classified as “non-white or -Caucasian,” 1,506 (6.8%) were classified as “other,” 12 (0.05%) were classified as “more than one race” or “bi- or multiracial,” and 5 (0.02%) were classified as “unknown” (Fig. 1).

Other Demographic Variables

Sex was reported in 81.0% of studies, but no study discussed sex when analyzing the results. SES was rarely reported (1.3%) and was not discussed in any of the studies when analyzing the results.

DISCUSSION

Investigators have demonstrated variations in the prevalence and clinical presentation of AD between different racial and ethnic groups (3). In the United States, black and Asian or Pacific Islander children are seen more frequently for AD than other racial groups (4,5). London-born black Caribbean children were more often diagnosed with AD than their white counterparts (6). In this London study, when subjects were classified according to race or ethnicity, the prevalence of AD was white 8.7%, black Caribbean 16.3%, mixed 14.9%, black other 22%, and black African 4.7% (6). Another study from London demonstrated that black children with AD were six times as likely to have severe AD as white children (7). These authors suggest that physicians are underestimating the severity of AD in black children because erythema scores can be misleading in darker skin types. A study involving 5,912 patients visiting a U.S. suburban pediatric practice found that the prevalence of AD varied significantly according to ethnicity: 8.5% Filipino, 5.6% other Asian origin, 3.7% black, 3.2% mixed race, 2.8% white (not of Hispanic origin), and 2.0% Hispanic (8).

Analysis of the 2003 National Survey of Children's Health data (9) demonstrated that 10.7% of children had had a diagnosis of eczema in the previous 12 months and that significant risk factors included metropolitan living and education level in the household greater than high school. It was concluded that social and environmental factors may strongly influence disease expression (9). Cultural and behavioral factors that affect the skin barrier function also have a significant role, and there is a link between higher hygiene score and subsequent risk of eczema (10), illustrating SES as a critical determinant of health (11).

This review of AD clinical trials demonstrates that there has been no significant increase between 2000 and

2009 in reporting of demographic data (Fig. 2), despite mandates by the U.S. federal government and recommendations by the FDA. Only 59% of AD clinical trials reported race and ethnicity as a baseline demographic characteristic; there was no significant correlation with the year of publication. Furthermore, only 10.3% of the studies reporting race or ethnicity at baseline commented on race or ethnicity in the interpretation of their results (e.g., significant differences in results or findings in African American and white participants). None of the studies discussed possible implications for clinical practice. All of the trials that reported race or ethnicity used broad and nonspecific classification groups, such as white, black, and Asian, and 7.7% of the U.S. studies reported that their populations were “all” or “mostly” white or Caucasian. Only 2.6% of the studies reported how race was assigned (self-reporting or investigator observation), all of which were self-reported. Inclusion of other variables was rare, with only 1.3% of the studies reporting SES. SES variables (education, household income, poverty) are often excluded from demographic data, despite the evidence demonstrating a strong environmental and sociocultural link to the development of eczema. Eighty-one percent of the studies reported sex. This is not surprising, considering that sex is a noncontroversial categorical variable. As we will discuss below, race and ethnicity are far more complex and controversial.

Given the observational evidence suggesting an association between AD and demographic variables such as race, ethnicity, SES, and environmental factors, it is surprising that, in the United States, these variables are underreported and rarely used in the analysis of data and outcomes. Omission and insufficient descriptive data of race and ethnicity represents a missed opportunity to potentially identify leads about disease etiology, identify at-risk groups, and determine whether the biology of a particular disease varies between ethnic and racial groups. A prerequisite to understanding whether racial or ethnic differences exist in AD is to collect sufficient data according to race and ethnicity. The major challenges that researchers, clinicians, and policymakers encounter in reporting on race and ethnicity are described below; they include underrepresentation of minority groups in clinical trials and the controversies surrounding definitions and the categorization of racial and ethnic groups (12).

Underrepresentation of Minority Groups in Clinical Trials

To study differences in outcomes between racial and ethnic populations, there needs to be adequate representation of these groups in clinical trials. A report from

2004 demonstrated that racial and ethnic minorities are less likely to enroll in U.S. cancer trials than their white counterparts. Difficulty in recruiting African Americans in clinical trials is well documented, but there is no consensus as to why this occurs. A study performed in 2008 showed greater distrust of medical research among African American parents (13). Nevertheless, the struggle to recruit minorities is worthwhile. One promising report showed that, although overall participation of racial and ethnic groups is small, African American representation closely approximates their representation in the U.S. population (14). We found an alarmingly disproportionate underrepresentation of Hispanics, who constitute 16.3% of the U.S. population but only 0.3% of the subjects included in this review (14). Our findings are consistent with those of prior studies. Other underrepresented groups include Native Hawaiian or Pacific Islanders, American Indians or Alaskans, and Asians (15).

Controversies Surrounding Race and Ethnicity

There is often no distinction between race and ethnicity, with the terms often used interchangeably. Although these terms are commonly used in the medical literature, their definitions are often not specified and are unclear and imprecise (16,17). “Race” is defined as grouping based upon a combination of physical and phenotypic characteristics, including skin color, hair texture, and facial structural characteristics (17). “Ethnicity” at its root means nation, but it has become a complex entity that refers to the group one belongs to or perceives to belong to (17). This can include geographical or ancestral origin, cultural tradition, language, and other shared characteristics. Therefore the term ethnicity is a dynamic term that is not easily measured (17). Ethnicity is more than race, nationality, or religion, but can include these variables. Because of their overlapping elements, race and ethnicity are often used interchangeably, leading to the hybrid term “race or ethnicity.”

Directive 15 from the Office of Management and Budget stipulates that federal agencies collect data on at least four racial groups: white, black, American Indian or Alaskan Native, and Asian or Pacific Islander. Another ethnic group should also be included—Hispanic (18)—but Directive 15 does not define race or ethnicity and confesses that the classification is not “scientific or anthropological in nature (18).”

Categorization of Race and Ethnicity

In the United States (19,20) and other countries (21) there has been much debate not only about the meaning

of the words “race” and “ethnicity,” but also about terms used to categorize them. The concern is that terms such as white, black, and Asian are used to encompass a heterogeneous population that has different cultures, environments, and geographic origins. Efforts have been made to better separate these heterogeneous populations and the 2010 U.S. Census identified 10 subcategories of Asians and Pacific Islanders. Nevertheless, the largest racial grouping in the United States, white, has received little scrutiny or attention. According to the 2010 U.S. Census, more than 72% of the population was classified as white, but with no further subcategories (15). “White” is erroneously used as a category for everyone excluded from other racial and ethnic groups (20). The U.S. Office of Management and Budget’s Directive 15 defines a white person as a person having origins in Europe, North Africa, or the Middle East (18). Until recently, individuals from India were considered white on the U.S. Census, and Middle Eastern people still are (20). Replacing white with another well accepted term, Caucasian, is also flawed. The term Caucasian is an ill-defined historical term referring to people from the Caucasus region of Central Europe (17). Therefore most populations with origins in India, Pakistan, and Bangladesh are Caucasian. A similar problem is also found with the groups lumped under “black, African American, or Negro,” which now make up 12.6% of the U.S. population (15). This group includes African Americans, Kenyans, Nigerians, and Haitians (15). This is flawed because the nature of an association can change or disappear when data from several groups are combined to form a single group.

Assignment of Race or Ethnicity

Self-reporting of race or ethnicity is recommended as the criterion standard method of assignment of race or ethnicity (22), but the actual method of assigning race, self-reporting or investigator interpretation, is rarely described in publications of clinical trials. This distinction is particularly important in racial groups other than white and black, because there is a low rate of agreement between subjects and observers (23,24). Self-reporting of race can also be problematic; in the 2000 U.S. Census, 800,000 people responded that they were black and white (25). In our study we found that only 2 of the 78 articles (2.6%) reported how race was assigned.

Generalizing Results of Clinical Trials

Generalizability addresses whether the results from a clinical trial are applicable outside of a controlled trial setting (26). Clinical trials usually collect baseline

data from the participants to document the baseline comparability of the treatment groups, perform a subgroup analysis to determine whether there are differences in subject outcome between subject groups, and perform covariate-adjusted analyses to account for variables that are related to patient outcome, especially if these variables are disproportionate between treatment groups (27). The purpose of subgroup analysis is to examine the consistency of treatment effects across demographic or disease subgroups. Small trial size (most studies have only enough power to detect overall main effects, and subgroups may be too small to reach any significant conclusions) and imprecise terminology of race and ethnicity are challenges to performing subgroup analyses and may deter investigators from reporting and analyzing these characteristics (27). We found that in AD clinical trials, even when baseline demographic characteristics (e.g., race, ethnicity, SES) are recorded, the data are not interpreted using statistical subgroup analysis, leaving clinicians unable to determine whether differences in patient outcome are consistent across groups or dependent on a particular patient characteristic (27).

Limitations

This study has several limitations. Given that it focused exclusively on clinical trials of AD, the results are limited to this specific disease entity. To combine data from a diverse set of trials using different terminologies and study designs, we merged large categories together that are generally perceived as synonymous (e.g., white and Caucasian). Because our data date back only to 2000, we are unable to compare reporting differences before and after the NIH Revitalization Act or the FDA Modernization Act of 1997. Lastly, we cannot address the reasons for low enrollments of minority participants because we do not have data on subjects who screen failed (i.e., did not qualify for the clinical trial and were not enrolled), on subjects in nonpublished clinical trials, or on methods of recruitment.

CONCLUSIONS

There are numerous studies that suggest differences in disease prevalence and the clinical spectrum of AD in populations defined according to race and ethnicity. It is crucial to understand the etiology of these differences to optimize management and treatment. There are no published guidelines for reporting race, ethnicity, or other demographic data in the mainstream peer-reviewed dermatology journals. When demographic characteristics are reported, the investigators and authors determine the terminology and categorization, which are not based on

journal or publication standards. A framework of standard categories is needed so that data across multiple studies can be compared. Transparent reporting of data on race and ethnicity and subgroup analysis, when appropriate, is essential for translating and generalizing the results from clinical trials into clinical practice. This study clearly demonstrates a need for greater representation of ethnic minorities, better reporting, and a priori subgroup analyses in clinical trials of AD.

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