Underrepresentation of Non-White Children in Trials of Statins in Children with Heterozygous Familial Hypercholesterolemia

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Background: The elimination of disparities in cardiovascular health is a major focus of the Healthy People 2010 national public health agenda. However, identifying and addressing such disparities within the realm of pediatrics in general, and preventive cardiology in particular, has not received recent attention. In published pediatric clinical trials of statins in heterozygous familial hypercholesterolemia that report race, minority children are underrepresented.

Objectives: The purpose of this analysis was 3-fold: 1) to obtain and report on the racial composition of statin trials in children with heterozygous familial hypercholesterolemia; 2) to explore the hypothesis that founder effects among populations of White children may have facilitated or favored their inclusion in statin trials; and 3) to determine whether the selective lipid screening guidelines based on family history may inadvertently identify fewer minority children who would otherwise qualify for investigative trials.

Design: We conducted a Medline search to identify all pediatric familial hypercholesterolemia statin trials. We contacted the corresponding authors to obtain race/ethnicity data and to obtain information about the presence of founder effects in the populations studied. We conducted a second literature search for evidence that selective, family medical history–based screening of children for hypercholesterolemia, as proposed by the National Cholesterol Education Program, might fail to identify minority children who would otherwise qualify for inclusion in these studies.

Results: Ninety-two percent of the 885 children enrolled in statin trials were White. A predominance of White children was found even in studies from countries with a sizable population of non-White children and where founder effects have not been described. Strong but indirect evidence from both the adult literature and the pediatric literature suggests that the family history–based selective screening engenders healthcare disparities for minority and disadvantaged children.

Conclusions: Non-White children are underrepresented in international clinical trials of statins. Both ethical and pharmacogenomic arguments exist to justify efforts to correct this. Our findings suggest that intensive efforts will be required to arrive at a fair representation of minority children in studies of pediatric heterozygous familial hypercholesterolemia. (*Ethn Dis.* 2009;19:166–171)

Key Words: Minority Groups, Health Services Accessibility, Guidelines, HMG-CoA Reductase Inhibitors, Statins, Familial Hypercholesterolemia, Cholesterol

Introduction

Minority children are underrepresented in clinical trials of heterozygous familial hypercholesterolemia (HeFH) treated with 3′-hydroxy-3′-methylglutaryl coenzyme A reductase inhibitors (HMG CoA reductase inhibitors, or statins). Of 313 children enrolled in 3 studies, 90% were White, 3% were Black, 1% were Asian, and 6% were classified as other.[1–3] In view of the goals and directives of both the NIH[4] and Healthy People 2010[5] that call for decreasing healthcare disparities in minority and under-served populations and the recognition that inclusion of minorities in clinical research is critical to the process of addressing the health needs of minority communities,[6] we undertook a study to understand why so few minority children were enrolled in statin studies.

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Although a large body of literature exists about racial disparities in the diagnosis and treatment of adult clinical trials of coronary disease[7,8] such information is scarce in pediatrics.[9–11] Children included in many clinical trials of statins have HeFH, a genetically determined form of pediatric hypercholesterolemia that has a prevalence of 1 in 500 people worldwide.[12] However, localized areas of increased prevalence of HeFH among White children exist in North America, South Africa, and Europe.[13] This phenomenon—known as a founder effect—is defined as the effect that a single founding ancestor with a disease-producing allelic mutation has on increasing the prevalence of a condition in a culturally or geographically isolated community or close-knit population.

We hypothesized that founder effects may have predisposed researchers to selectively include White children in statin studies conducted in these countries. To our knowledge, the hypothesis that founder effects influence the composition of these studies has not been explored. Second, we hypothesized that applying selective testing guidelines on the basis of a family history of hypercholesterolemia or early cardiovascular disease may cause minority and underserved children to inherit their parents' and grandparents' healthcare disparities. Specifically, severely hypercholesterolemic minority children who would qualify for these studies may not have been identified because the pediatric National Cholesterol Education Program (NCEP) guidelines[14] recommend selective screening (lipid testing) of children with either a parental history of hypercholesterolemia or a parental or grandparental history of premature coronary artery disease.

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The NCEP recommendations could, in turn, be less sensitive for identifying high-risk minority and under-served children because the parents and grandparents of these children may experience 1 or more of the following:[15]

- diminished access to care and to testing
- inequity in the application of the adult NCEP guidelines, which call for universal testing
- health literacy problems that render the accurate self-reporting of an elevated total cholesterol or premature coronary disease in a parent or grandparent less likely
- incomplete family medical histories due to immigration from areas of the world with underdeveloped health care systems
- greater likelihood of an incomplete family history because of separation among disadvantaged families.

We conducted a review of the literature to test these hypotheses.

METHODS

To assess the racial composition of pediatric statin trials, we used the Medline database to search the English-language literature for existing efficacy trials of statin use in children aged ≤18 years with HeFH. Our search terms were "children" or "pediatric," "statin" or "HMG CoA Reductase inhibitor," "heterozygous familial hypercholesterolemia," "minority," "African," "African American," "Hispanic," "Asian," "Asian American," and "Australian Aboriginal." Case reports were excluded. Trials including adult patients and pediatric patients in whom separate data for the children with HeFH could not be extracted were excluded. We searched the references of eligible papers and added any newly identified studies. We attempted to contact the principal investigator of each study, with a sequence of emails, telephone calls, and facsimiles, to inquire about the racial composition of each study and to ask whether founder effects were present in the patient population under study.

We did not ask the corresponding authors about our second hypothesis: that the sensitivity of the NCEP guidelines was diminished by a decreased access to care among minority parents and that this, in turn, diminished the identification of their offspring with HeFH who would be study candidates. To assess this hypothesis, we searched the English literature in Medline concerning cholesterol-screening guidelines and healthcare disparities in under-served populations. We searched both the pediatric and the adult literature because selective screening and subsequent identification of high-risk minority and under-served children is linked to the availability of parental and grandparental lipid levels and to their cardiovascular disease history, which is, in turn, is linked to parental and grandparental healthcare access and quality. We reviewed these articles for evidence that the pediatric NCEP selective testing scheme might engender a healthcare disparity for minority children. We used the search terms "health services accessibility," "ethnic minorities," "African Americans," "Asian Americans," "Hispanic Americans," "cholesterol," "practice guidelines," "disparity," and "adult treatment panel."

RESULTS

We retrieved 226 articles; of these, 17 trials involving 1281 children fulfilled the inclusion criteria. Of these, 8 were randomized controlled clinical trials,[1–3,16–20] 6 were prospective cohort studies,[21–26] 1 was a time-series comparison with 4 randomized arms after a placebo run-in,[27] 1 was a nonrandomized matched series,[28] and 1 was a randomized cross-over study.[29]

Three of the 17 studies provided detailed race/ethnicity information in the original article.[1–3] Of the 14 remaining studies that did not include details on ethnicity, communication with the corresponding authors enabled us to define the racial composition of an additional 7 studies.[16,17,20,22–24,26] Overall, race/ethnicity data were available for 10 of the 17 studies and 855 of 1261 children (68%). Of these 855 children, 9 were Black (1.1%), 11 were Asian (1.3%), 38 were unspecified non-White (4.4%), 788 were White (92.2%), and none were Hispanic (Table 1). Authors of the remaining studies for which ethnicity details were not reported could not be reached for any further information.[18,19,21,25,27–29]

Table 2 presents a summary of the studies for which the racial/ethnic composition could be determined. In 1 study, children were classified as either White or non-White.[3] Accordingly, we used the category "unspecified non-White." Similarly, the corresponding author of another study[17] disclosed that >90% of patients were White (Dr Evan Stein personal communication); therefore, we used a conservative estimate of 90% White and 10% unspecified non-White." Other corresponding authors disclosed that their study samples were entirely White.[16,22–24,26]

In 2 of the studies,[16,26] corresponding authors confirmed the presence of a founder effect, whereas in 10 other trials[1,2,17–20,23,25,27,29] we suspected a founder effect on the basis of personal communications or the literature. In 5 trials, the presence of a founder effect was highly unlikely or unknown.[3,21,22,24,28]

We found 28 articles that related to mechanisms by which the pediatric NCEP guidelines might underidentify high-risk, non-White children. Because selective testing of children in the pediatric NCEP guidelines is driven by a family history of either hypercholesterolemia or the premature onset of cardiovascular disease, articles that addressed disparities in testing and in the provision of a complete and accurate family medical history among adults

Table 1. Ethnic composition of statin studies in children with HeFH*

	Black	Asian	Hispanic	Unspecified, Non-White	White
Total (*N*=855)	9	11	0	38	788
Percent	1.1	1.3	0	4.4	92

The racial composition of pediatric statin studies worldwide is shown for 855/1261 (68%) children for whom data was available. Several studies and personal communications dichotomized ethnicity data as white and non-white; this information was captured using the categories listed above.

* HeFH – heterozygous familial hypercholesterolemia.

were relevant to our concerns. After removing those articles that pertained to racial disparities in attaining NCEP treatment goals for adult patients, 3 articles remained regarding screening adults for hypercholesterolemia.[30–32] One study that used the third National Health and Nutrition Examination Survey found that 66% of Whites, compared with 50% of African Americans and 37% of Mexican Americans, had undergone cholesterol screening.[30] A study that used the Medical Expenditure Panel Survey found among a sample of 14,226 adults that Mexican Americans and Asians/Pacific Islanders, but not African Americans or other Hispanics, were less likely than were Whites to report having had their cholesterol checked.[31] Data from 149,692 participants in the 1999 Behavioral Risk Factor Surveillance System also showed that both Asians and Hispanics were less likely to have been screened than were Whites.[32] Socioeconomic and demographic factors such as younger age, lower levels of income and education, and reduced access to health care all predicted lower rates of cholesterol screening in adults.[31,32]

In the literature on the utility of the pediatric NCEP guidelines, we found 4 pediatric studies that addressed the sensitivity of the guidelines for minority or disadvantaged children.[9–11,33] We found no studies that performed a head-to-head comparison of the sensitivity of the pediatric NCEP guidelines for children of different races/ethnicities. Nonetheless, several papers made observations directly relevant to this issue. Using data derived from a biracial community in Bogalusa, Louisiana, paternal history of vascular disease was found to be unobtainable from 19% of Black children versus 10% of White children.[9] Even after the removal of children with incomplete family medical histories, the analyses demonstrated that the sensitivity and specificity of family history among 4- to 17-year-olds to identify those with either an elevated low-density lipoprotein cholesterol or total cholesterol value above the 95th percentile was consistently higher for White children. In a socioeconomically disadvantaged high-risk population of predominantly African American children, a complete family history of coronary heart disease was available for only 24% of the sample of 300 children.[10] Despite this, the prevalence of a positive family history of premature coronary heart disease in their sample was 29%, a prevalence that was comparable to what the NCEP predicted, based on data derived from a predominantly White sample of children from families enrolled in the Lipid Research Clinics studies. Finally, a large school-based study of the sensitivity and positive predictive value of the NCEP guidelines found that more parents of children who reported having had a cholesterol measurement were White than were non-White—76% vs. 68%.[33] Furthermore, Whites made up 84% of the group that could report a value for their cholesterol level but only 62% of the group that did not know this information.

DISCUSSION

We conducted a secondary analysis of the ethnic composition of pediatric statin trials and found that 92% of the study participants were White. The results confirm our original observation

Table 2. Ethnic composition of statin trials in children with heterozygous familial hypercholesterolemia and probability of a founder effect

	No. of Patients							
Country	**Total**	**Black**	**Asian**	**Hispanic**	**Unspecified Non-White**	**White**	**Founder Effect**	**Reference**
Canada*	63	0	0	0	0	63	Confirmed	16
Greece*	16	0	0	0	0	16	Confirmed	23
Netherlands, South Africa*	84	0	1	0	18	65	Confirmed	26
Netherlands	72	5	1	0	0	66	Likely	1
Finland, United States*	132	0	0	0	0	123	Likely	17
Canada, Norway, South Africa, United States	187	3	3	0	9	172	Likely	2
Netherlands*	214	1	6	0	0	207	Likely	20
Austria	13	0	0	0	0	13	Unknown/unlikely	22
Austria*	20	0	0	0	0	20	Unknown/unlikely	24
United States	54	0	0	0	11	43	Unknown/unlikely	3

* Ethnic composition determined through personal communication with corresponding author; other studies reported ethic composition in the published article.

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that, despite a literature that is drawn from many different countries, non-White children are underrepresented in these studies of severely hypercholesterolemic children. We hypothesized that founder effects skewed the composition of study samples toward White children and that the recommendations of the pediatric NCEP guidelines may have also contributed by inadvertently underidentifying minority children who might have otherwise qualified for these studies. Eleven of the studies we reviewed were conducted in European countries with predominantly White populations. Nonetheless, even in locales with sizable non-White populations in these countries, we found that minority children were underrepresented. Of interest, no studies published in English were conducted in Central or South America, the Caribbean, Asia, or Africa outside of South Africa.

Founder Effects and Underrepresentation

In our communications, 2 authors directly confirmed that founder effects were operative in their study samples. We found indirect evidence, in some cases strong evidence, that founder effects favoring the identification and inclusion of White children were likely to be operative in several studies; this effect likely determined, at least in part, the underrepresentation of minority children in these studies as a whole. There may be several reasons for this possibility, not least of which is that many researchers and research centers may be drawn to areas where the prevalence of lipid disorders is high. Centers that have experience in HeFH may also receive a lot of referrals from populations with increased prevalence.

The argument could be made that in some of the cited studies, the local population would not be expected to have a substantial number of ethnic minorities. However, with recent trends in immigration in the 1980s and 1990s, some of these countries have sizeable populations of ethnic minorities. For example, a 1999 estimate of the population of the Netherlands indicated that up to 8% (≈17% in 2008) of the ≈16.5 million population were non-Western and non-White immigrants.[34] Similarly, we found that studies conducted in the United States and South Africa did not include an ethnic mixture that represented the population as a whole.

Selective Screening Guidelines and Bias

We found supporting evidence for our second hypothesis in both the pediatric and adult literature. Our second hypothesis is critically linked to our first in that it is through targeted testing that new pediatric cases of HeFH may be identified. Targeted testing, although in itself an insensitive measure, is a primary way that children with HeFH are identified for inclusion in studies.[35] Previously published literature has documented that the pediatric NCEP guidelines are less sensitive for ethnic minority and socioeconomically disadvantaged children.[9–11] Our review of the existing adult literature documenting disparities in the testing of minority adults helps explain why this is the case. Without testing minority adults, family history of hypercholesterolemia for minority children cannot be known. The ongoing controversy regarding the utility of the pediatric guidelines[36–38] may have diverted attention from the recognition that the selective screening approach has the potential to engender a healthcare disparity for minority children.

While we have documented a serious underrepresentation of minority children in these trials and we believe that geography, founder effects, and a decreased case-finding effect promulgated by the NCEP guidelines may be in effect, other factors are likely to be at work and may be more relevant than those we have focused on. Minority groups may be underrepresented in clinical trials because of decreased access to care, language barriers, less flexible transportation and employment arrangements, and skepticism regarding the benefits of participation in research. Concerns that minority groups are being used for experimentation may also exist and deter participation.[6]

Limitations

Our investigation has several limitations. We relied entirely on a review of the English-language literature. We were not able to verify the reports of the influence of founder effects with DNA tests. We relied on the authors' report or a literature review alone. We were not able to obtain information about the racial/ethnic composition of some of the published studies. Nonetheless, given the locations of these studies, their inclusion would not be likely to substantially alter our primary findings. Finally, our methods did not permit us to assess the relative contribution of founder effects, population composition, and potential disparities in the identification of non-White children engendered by selective testing.

Future Research

Our findings suggest that intensive efforts will be required to arrive at a fair representation of minority children in studies of pediatric familial hypercholesterolemia. Both ethical and pharmacogenomic arguments[39] justify targeted efforts to identify and address the unique barriers to inclusion in clinical

trials that minority children at high risk of early atherosclerosis face. Any newly issued screening guidelines should be crafted to eliminate any disparities in sensitivity for identifying minority children. In particular, as much as eliminating disparities in cardiovascular health is a major focus of the Healthy People 2010 national public health agenda, we believe that the focus on adult disparities should be matched with a commensurate effort in children.

The most specific strategy to identify pediatric HeFH may be to form a linkage of pediatric lipid specialists to young adult survivors of myocardial infarctions through the adult cardiology services. Young survivors of myocardial infarction would be offered screening for their progeny. As such, a strategy that identifies survivors of coronary heart disease and, subsequently, their progeny may be more aggressive and likely to capture minority patients and children, in particular. This may achieve the dual goals of reducing disparities in these groups and increasing enrollment of minorities in research.

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