Journal of Clinical Lipidology (2022) 16, 608–616

Journal of Clinical Lipidology

Under-reporting and under-representation of non-Hispanic Black subjects in lipid-lowering atherosclerotic cardiovascular disease outcomes trials: A systematic review

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KEYWORDS
Non-hispanic black;
Lipid-lowering;
Randomized controlled trials;
Under-reporting;
Under-representation

Abstract:

Background: Non-Hispanic (NH) Black participants have been under-represented in studies of cardiovascular disease.

Objective: We sought to determine the trends of reporting and representation of NH Black subjects in randomized controlled trials (RCTs) of lipid-lowering therapies demonstrating atherosclerotic cardiovascular disease (ASCVD) risk reduction benefit.

Methods: The electronic databases of MEDLINE, EMBASE and ClinicalTrials.gov were searched from 1990-2020. Studies of lipid-lowering therapies (i.e., statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors [PCSK9], and icosapent ethyl) with proven ASCVD benefit, sample sizes of at least 1000 subjects and follow-up of at least 1 year were included (40 RCTs, N=306 747 total participants). We examined articles and supplementary material for participant-level race data. Using United States disease prevalence data, the participation-to-prevalence ratio (PPR) metric was used to estimate the representation of NH Black subjects compared with their reported disease burden (i.e., < 0.8 indicated under-representation; > 1.2, over-representation; and 0.8 to <1.2, adequate representation).

Results: The median (interquartile range) number of participants per trial was 4871 (2434-10077). NH Black enrollees comprised 7.3% (95% CI, 0.9%-15.4%) of the total number of subjects reported.

Abbreviations: RCTs, Randomized controlled trials; NH, Non-Hispanic; LDL-C, Low density lipoprotein-cholesterol; PPR, Participation-to-prevalence ratio; ASCVD, Atherosclerotic cardiovascular disease; ACS, Acute Coronary Syndrome.

The authors confirm no relationship with industry, disclosures, or source of funding for the work presented in this manuscript.
Conflict of interest: None.

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Submitted June 19, 2022. Accepted for publication August 18, 2022.

https://doi.org/10.1016/j.jacl.2022.08.005

During the time intervals 1990-1995, 1996-2000, 2001-2005, 2006-2010, 2011-2015 and 2016-2020, NH Black participation was 0%, 1.1%, 4.4%, 4.8%, 0.2% and 0.7% respectively (P for trend <0.001). For statin trials, the participation of NH Black subjects was reported in 0 studies between 1990-1995 and in 9 of 28 trials from 1996-2020. For ezetimibe and icosapent ethyl, NH Black participants were reported in 0 of 3 and 0 of 1 studies, respectively. For trials of PCSK9 inhibitors, NH Black subjects were reported in 2 of 5 (40%). NH Black participants were under-represented compared with their disease burden in studies evaluating subjects with diabetes, hypercholesterolemia, stable coronary artery disease, and acute coronary syndrome (PPR < 0.8 for all).

Conclusion: NH Black participants are markedly under-represented, and results are under-reported. The inclusion of population and disease specific representation of NH Black persons and their related social determinants of health will help to address the disparity in preventive care for this historically undertreated population.

Introduction

Randomized controlled trials (RCTs) are the most reliable form of scientific evidence and serve as the gold-standard for investigating the safety and efficacy of novel treatments. Despite comprising a significant proportion of the cardiovascular disease population, Non-Hispanic (NH) Black participants have been under-represented and under-reported in these RCTs.[1] Traditionally, in medical studies, race has been represented as a solely biologic construct.[2] However, more recently, race has been recognized as a social construct, and this has resulted in increased attention to the representation of racial minority groups in clinical trials.[3,4] The inclusion and reporting of various racial groups among study participants is necessary to increase generalizability of results to a wider population.

While smaller, short-term, lipid-lowering drug studies suggest similar LDL-C lowering in White and NH Black individuals,[5,6] limited ASCVD outcomes data are available in NH Black subjects. The impact of lipid-lowering drugs on lipid parameters and ASCVD outcomes may differ in accordance with an individual's race, sex, socioeconomic status, education level, drug metabolism, and environmental factors. For example, the SLCO1B1*15 allelic variant occurs at a frequency of 17% in Japanese versus 1% in Black individuals, resulting in reduced function of the organic anion transporter that regulates the hepatic uptake of simvastatin and results in higher serum levels and a higher rate of myopathy in Japanese subjects.[7]

The association between race and health outcomes may be intertwined with ancestry and heritage, as well as socioeconomic, structural, institutional, cultural, demographic, and other factors.[4] While under-reporting and under - representation of non-Hispanic Black participants have been noted in cardiovascular disease trials,[1,8] a systematic review of this issue in large, lipid lowering drug trials has not been previously performed. Based on the recognition that there are differences in both risk and response to treatment in certain racial populations,[5–7,9] the FDA (Food and Drug Association) has recommended that clinical trials should report differences in clinical outcomes in accordance with racial differences.[10] To address this issue, we sought to determine the trends of reporting and representation of NH Black subjects in large RCTs of lipid-lowering therapies demonstrating ASCVD risk reduction benefit.

Methods

This systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[11]

Data sources and searches

Two investigators (J.K.G and M.D) performed the literature search, using databases of MEDLINE/PubMed, EMBASE and ClinicalTrials.gov from January 1990 to December 2020. A broad search strategy was used with relevant search terms, as follows: lipid, statin, ezetimibe, proprotein convertase subtilisin/kexin type 9, icosapent ethyl, and LDL-C (Table 1 in the Supplement). We also searched systematic reviews/meta-analyses conducted on randomized clinical trials (RCTs) of lipid-lowering therapies with ASCVD outcomes for additional information.[12–16] After removing duplicates, 2 of us (J.K.G and M.D) reviewed the records at the title and abstract level, followed by full-text screening based on predetermined study selection criteria.

Study selection

The prespecified inclusion criteria were as follows: (1) RCTs of lipid-lowering therapies with known ASCVD benefit (i.e., statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, and icosapent ethyl); (2) sample size of at least 1000 participants and follow-up duration of at least 1 year; and (3) English language. We selected large RCTs with follow-up periods of at least 1 year because large RCTs with longer follow-up represent the data most often used to formulate Guideline-based treatment recommendations.[13,15] We included RCTs of both primary and

secondary prevention populations. We excluded RCTs performed among patients younger than 18 years, those reporting secondary, interim, open-label RCTs or post hoc analyses. We excluded RCTs of niacin, fibrates, and nonprescription omega 3 fatty acids, given that these drugs have not shown benefit on ASCVD outcomes in the management of dyslipidemia.[9] Studies performed in East Asia (China and Japan) were excluded as the proportion of NH Black persons in the general population was very low.

Data extraction

Two of us (J.K.G and M.D) abstracted the data using prespecified data collection forms, appraised the accuracy of the data, and resolved any discrepancies by consensus after discussion with a third investigator (C.E.O.). The following information was abstracted from RCTs, as follows: title, year of publication, journal, lipid-lowering drug class, setting (i.e., primary vs secondary prevention), target population or indication, total sample size, proportion of NH Black participants, mean or median age, location of study, funding sources, and proportion reporting results based on race. We examined articles and supplementary material for participant-level race/ethnicity data. For missing information, ClinicalTrials.gov was reviewed for additional details.

We categorized a RCT as primary prevention if it identified primary prevention in the methods or if less than 50% of participants had atherosclerotic cardiovascular disease.[16,17] We categorized RCTs according to therapy, setting, target population or indication, location, and funding sources. Consistent with earlier reports[18] and ClinicalTrials.gov designations, funding source was classified as industry; government; non-profit or non-federal organizations, including university or educational institutions; and collaborative trials between non-profit organizations and industries. We divided the locations into exclusively North America (United States and Canada), Europe (Austria, Belgium, Bermuda, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and United Kingdom), Oceania (Australia and New Zealand) and Multiregional including South America and Mexico (Fig. 2).

Outcome measures

We had 3 outcomes of interest. They were: 1) the overall reporting of NH Black participation in RCTs and the reporting of NH Black subjects by lipid-lowering agent used, 2) temporal trends in the participation of NH Black subjects, and 3) the representation of NH Black subjects in RCTs relative to their disease burden in North America.

Statistical analysis

RCTs were separated into 5-year groups based on publication year, with the exception of the 6-year period from 1990-1995. Categorical variables were compared using $\chi 2$ testing and continuous variables were reported as means with standard deviations (SDs) or medians with interquartile ranges (IQRs). A p value of < 0.05 was deemed the level of statistical significance.

A linear trend of proportion for NH Black participants against year of publication was tested with a significance threshold set at 5%. When calculating the proportion of NH Black enrollees per 5- or 6-year interval, if NH Black race was not reported in the manuscript or supplemental material, the assumption was made that these subjects were not enrolled in these studies (Fig. 4). We recognize that in some studies NH Black participants may have been enrolled but not reported. However, the universal designation in baseline characteristics of White race and the frequent designation of those who are not White as "other" precludes the potential to explore outcomes contributed to by racial differences. As such, consistent with multiple societal[10] and major medical journal recommendations[19–21], under-reporting was considered the failure to report NH Black race along with the lack of an explanation within the manuscript or supplemental material for doing so.

To examine the representation of NH Black participants relative to their representation in populations affected by disease, we used the metric of participation-to-prevalence ratio (PPR), which is derived by dividing the percentage of NH Black subjects among trial participants by the percentage of NH Black persons in the disease population.[16,22–24] The denominators were obtained from studies reporting the most recent or epidemiologic population-based data representing disease burden within North America (Table 2 in the Supplement).

In calculating the PPR, the decision was made to include multiregional lipid-lowering trials in comparison with NH Black US disease prevalence, as such trials inform US lipid guideline recommendations. The interpretation of PPR values was based on thresholds used in prior studies [16,22–24]: less than 0.8 indicates under-representation; greater than 1.2, overrepresentation; and close to 1.0, adequate representation. For example, if the prevalence of NH Black persons in the disease population is 50% and RCTs in this disease enrolled 30% NH Black individuals, the PPR would be 30% / 50% = 0.60, indicating under-representation. We selected disease populations of acute coronary syndrome (ACS), stable coronary heart disease (CHD), heart failure (HF), diabetes, and hypercholesteremia. To estimate the prevalence of NH Black participants among the disease population, we divided the prevalence or the incidence of that disease among NH Black participants by the total prevalence or incidence of that disease (Table 2 in the Supplement).[24] All statistical analyses were performed using SPSS (IBM SPSS Statistics for Mac, Version 26.0. Armonk, NY: IBM Corp.).

Results

Of 8051 studies screened after removal of duplicates, 40 RCTs with 306,747 participants were included (Fig. 1). The

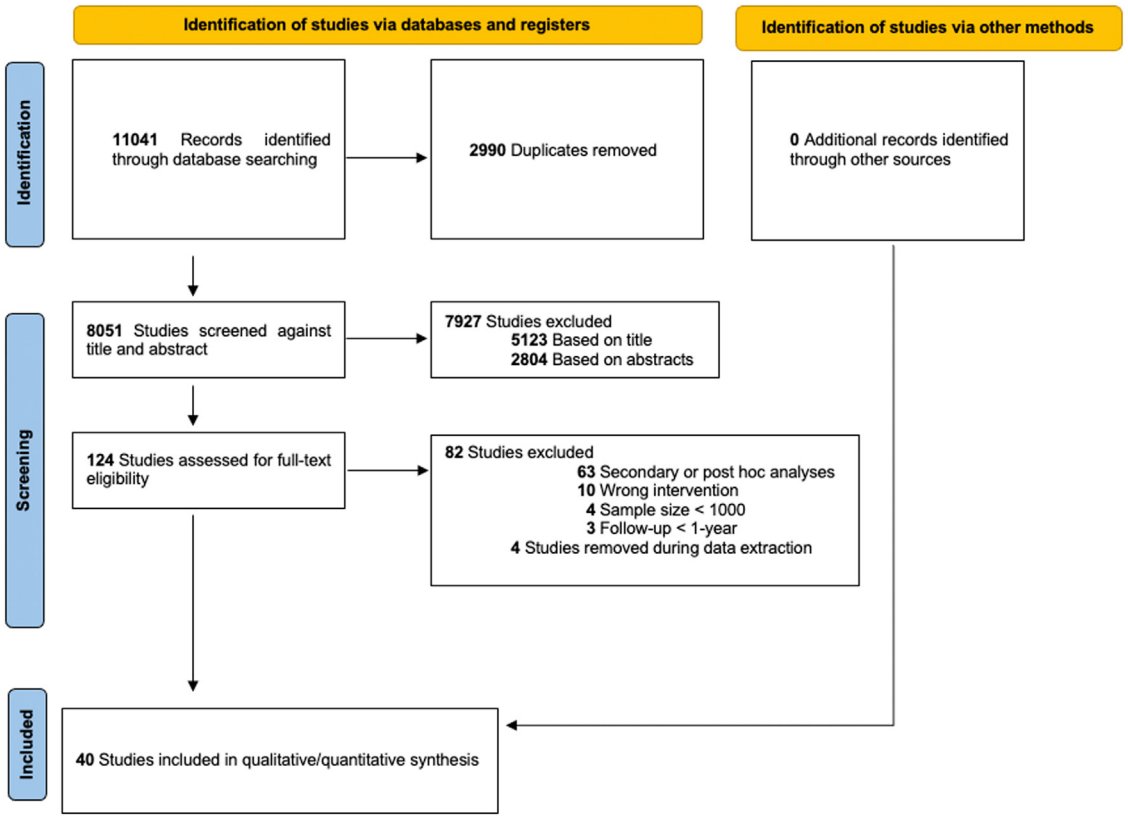
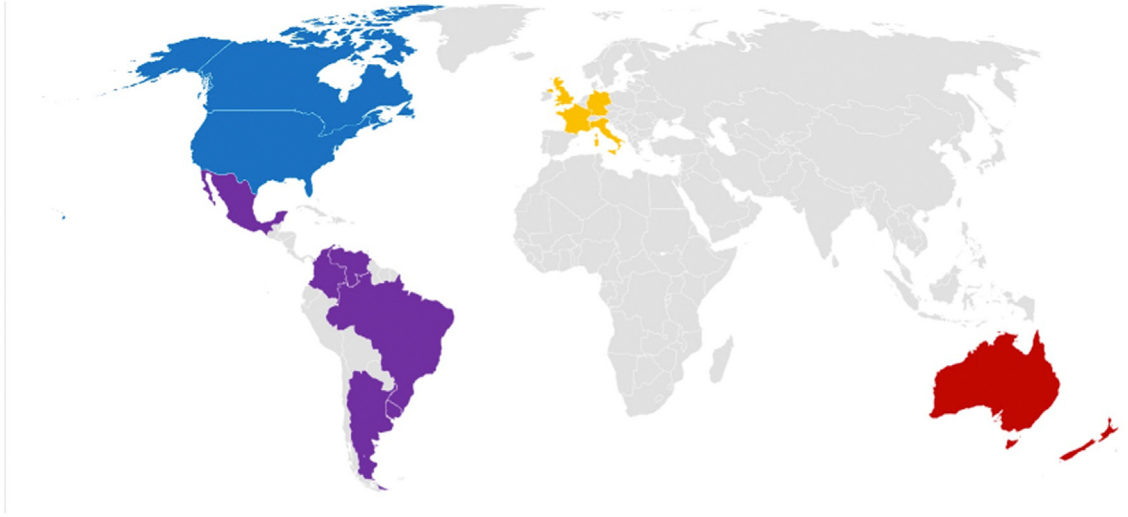


Fig. 1 PRISMA flow diagram of the RCT selection process.



North America	Europe	Oceania	Multiregional
n=26195	n=88427	n=9014	n=183111
Non-Hispanic Black:15.3%	White: 94.6%	Not Reported	Non-Hispanic Black: 2.5%
White: 70.6%			White: 77.1%
Hispanic: 9.3%			Hispanic: 1.8%
Asian: <1%			Asian: 5.3%

Fig. 2 Geographical enrollment of non-Hispanic Black participants enrolled in randomized clinical trials of lipid-lowering therapy in this analysis.

Table 1 Trends in representation of non-Hispanic Black participants in lipid-lowering therapy randomized clinical trials over time.

Characteristic	No. (%) by Publication Year						P Value
	1990-1995	1996-2000	2001-2005	2006-2010	2011-2015	2016-2020	
Trial, No.	3	5	14	8	4	6	NA
Total Participants, No.	14684	22412	86462	51299	34220	97670	NA
Participants per Trial Median (IQR)	6595 (3829-6811)	4159 (1351-6605)	4330 (2187-9723)	4871 (3240-11006)	6868 (3934-11489)	15815 (9311-25310)	
Weighted Age, Mean (SD)	57.0(6.0)	58.7(7.8)	63.2(10.3)	56.9(7.6)	62.5(10.6)	62.4(6.0)	<0.001
Trials Reporting Race	0	4(80)	7(50)	3(37.5)	3(75)	4(66.7)	0.321 (trend)
Trials Reporting the Proportion of NH Black Patients	0	2(40)	2(14.3)	3(37.5)	0	2(33.3)	0.659 (trend)
No. of NH Black Participants	NA	263(1.1)	3769(4.4)	2477(4.8)	74(0.2)	698(0.7)	<0.001 (trend)
Women	1074 (13.3)	3258 (14.5)	24345 (36.9)	13506 (26.3)	10980 (32.1)	29276 (30.0)	0.090
LIPID-LOWERINGTHERAPY							
Statins	3(100)	5(100)	14(100)	7(87.5)	0(0)	2(33.3)	0.015
Ezetimibe	0	0	0	1(12.5)	2(50)	0	
PCSK9 Inhibitors	0	0	0	0	2(50)	3(50)	
Icosapent Ethyl	0	0	0	0(0)	0	1(16.7)	
INDICATIONORBASELINEPOPULATION							
Aortic Stenosis	0	0	0	1(12.5)	0	0	0.382
Chronic Kidney Disease	0	0	2(14.3)	1(12.5)	1(25)	0	
Diabetes	0	0	1(7.1)	1(12.5)	0	0	
Hypercholesterolemia	2(66.7)	1(20)	0	0(0)	0	0	
Hypercholesterolemia with Risk Factors for ASCVD	1(33.3)	1(20)	3(21.4)	2(25)	2(50)	2(33.3)	
Risk Factors for ASCVD without Hypercholesterolemia	0	0	1(7.1)	2(25)	0	2(33.3)	
Acute Coronary Syndrome	0	3(60)	5(35.7)	1(12.5)	1(25)	2(33.3)	
Stable Coronary Heart Disease	0	0	2(14.3)	2(25)	0	0	
Heart Failure	0	0	0	2(25)	0	0	
SETTING							
Primary Prevention	2(66.7)	1(20)	6(42.9)	5(62.5)	2(50)	1(16.7)	0.273
Secondary Prevention	1(33.3)	4(80)	8(57.1)	3(37.5)	2(50)	5(83.3)	
LOCATION							
North America	0	4(80)	2(14.3)	0	0	0	<0.001
Europe	2(66.7)	0	7(50)	4(40)	0	0	
Oceania	0	1(20)	0	0	0	0	
Multiregional	1(33.3)	0	5(35.7)	4(40)	4(100)	6(100)	
FUNDING							
Industry	2(66.7)	4(80)	10(71.4)	7(87.5)	2(50)	3(50)	0.454
Government	0	0	0	0	0	0	
University/Organization	1	0	1(7.2)	0	0	0	
Other/ Combined	0(33.3)	1(20)	3(21.4)	1(12.5)	2(50)	3(50)	

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; NA, not applicable; PCSK9, proprotein convertase subtilisin/kexin type 9.

list of included RCTs is provided in Table 3 of the Supplement Material. The median (IQR) number of participants per RCT was 4871 (2434-10077). A total of 31 trials (77.5%) of statins with 188,549 participants, 3 (7.5%) of ezetimibe with 29,287 participants, 5 (12.5%) of PCSK9 inhibitors with 80,732 participants and 1 (2.5%) of icosapent ethyl with 8179 participants were analyzed (Table 3 in the Supplemental Material). A total of 23 studies (57.5%) with 203 893 participants were of secondary prevention, and 17 (42.5%) with 102 854 participants were of primary prevention. Participants with hypercholesterolemia were the most commonly studied population (12 studies [30%] with 113 947 patients), followed by ACS (12 [30%] with 104 313 patients, risk factors for ASCVD without hypercholesterolemia (5 [12.5%] with 43 877 patients), chronic kidney disease (3 [7.5%] with 15 403 patients), stable coronary heart disease (2 [5%] with 12 433 patients), diabetes (2 [5%] with 5 249 patients), heart failure (2 [5%] with 9642 patients) and aortic stenosis (1 [2.5%] with 1873 patients).

Overall, 13 trials (32.5%) with 88,427 participants were conducted in Europe, 20 (50%) with 183,111 participants were multiregional, 6 (15%) with 26,195 participants were

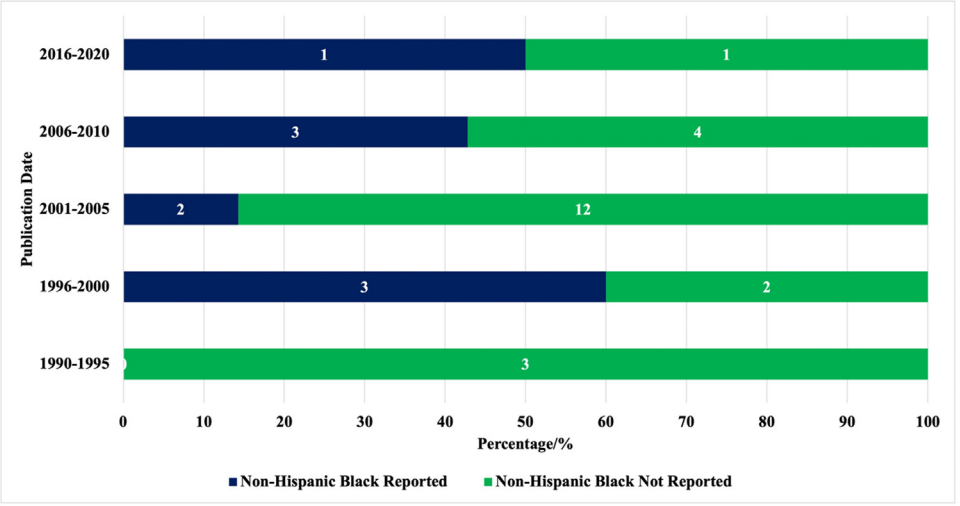


Fig. 3 Proportion of randomized controlled trials of statin monotherapy reporting non-hispanic black race.

conducted in North America, and 1 (2.5%) with 9014 participants was conducted in the Oceanic region. More than two-thirds of the studies (28 [70.0%] with 200,250 participants) were industry funded, 2 (5.0%) with 16,950 participants were funded by universities, and 10 (25.0%) with 89,547 participants were funded by other nonfederal and nonprofit organizations.

The reporting of non-Hispanic Black subjects in lipid lowering trials

Race was reported in 21 of 40 (52.5%) of the included trials between 1990 and 2020. Additionally, the inclusion of NH Black participants was reported in 11 of the 40 (27.5%) lipid lowering trials. For statin trials, the participation of NH Black enrollees was not reported in those done between 1990-1995. During the periods 1996-2020 NH Black subjects were reported in 9 of 28 trials, representing 6734 NH Black among 79,462 participants in which NH Black enrollees were reported (Fig. 3). For ezetimibe or icosapent ethyl, NH Black participants were reported in 0 of 3 and 0 of 1 studies, respectively. For trials of PCSK9 inhibitors, NH Black subjects were reported in 2 of 5 (40%) during 2011-2020, representing 547 NH Black enrollees among 31,629 of 80,732 participants in which NH Black enrollees were reported.

Temporal trends of non-hispanic black subjects in lipid lowering trials

NH Black subjects comprised 7.3% (95% CI, 0.9%-15.4%) of the total number of participants reported. NH Black participation was not reported from the period 1990 to 1995 (0%), increased during the period 2001 to 2005 (4.4%) and 2006-2010 (4.8%), and was lower during the periods 2011-2015 (0.2%) and 2016-2020 (0.7%) (P for trend <0.001), see Fig. 4.

The representation of non-Hispanic Black in rcts compared with their disease burden in North America

NH Black participants were markedly under-represented compared with their disease burden in studies evaluating subjects with diabetes (PPR, 0.18), hypercholesterolemia (PPR, 0.33), stable coronary artery disease (PPR, 0.20) and acute coronary syndrome (PPR, 0.08), see Fig. 5.

Discussion

Major medical journals have recently advocated a call to action to address racial disparities in clinical decision-making.[19–21] In this systematic review of ASCVD outcomes trials of lipid-lowering therapies, we found that: 1) there was consistent under-reporting of NH Black subjects in both statin and non-statin lipid lowering trials, 2) the overall participation of NH Black subjects was low and remained so over time, as compared to their reported disease burden, and 3) NH Black participants were under-represented in trials evaluating subjects with diabetes mellitus, hypercholesterolemia, stable coronary artery disease and acute coronary syndromes. These findings are of particular importance as NH Black persons represent 12.4% of the US population and carry a disproportionately higher burden of ASCVD morbidity and mortality when compared to White individuals.[25,26]

Racial differences may impact both risk and clinical manifestations of ASCVD.[9] As compared to NH Whites or Mexican Americans, NH Black populations have higher concentrations of HDL-C and lipoprotein (a) and lower levels of triglycerides and LDL cholesterol.[9] In addition, they have a higher prevalence of type 2 diabetes mellitus and hypertension.[25] While the impact on ASCVD risk of non-lipid related risk factors in NH Blacks is generally considered to be greater than of lipid abnormalities, our study highlights the need for more data examining the benefits and risks of the

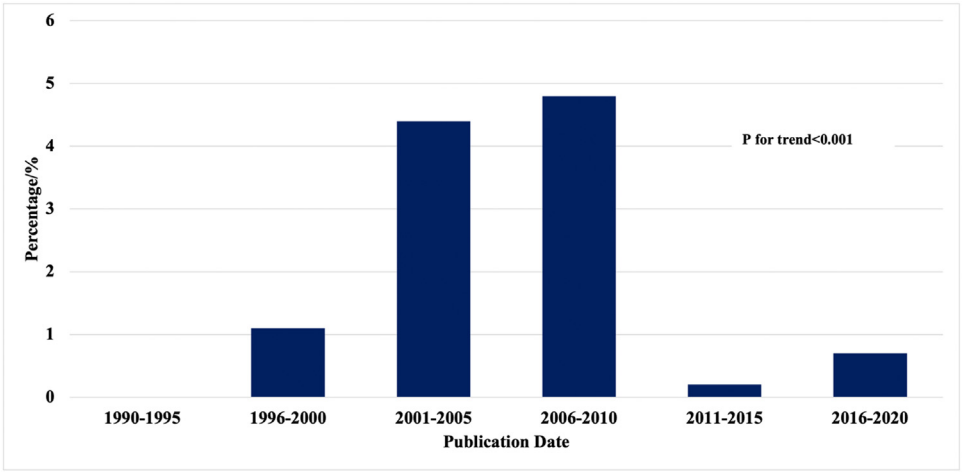


Fig. 4 Proportion of non-hispanic black participants enrolled in randomized controlled trials of lipid-lowering therapy for the period 1990 to 2020.

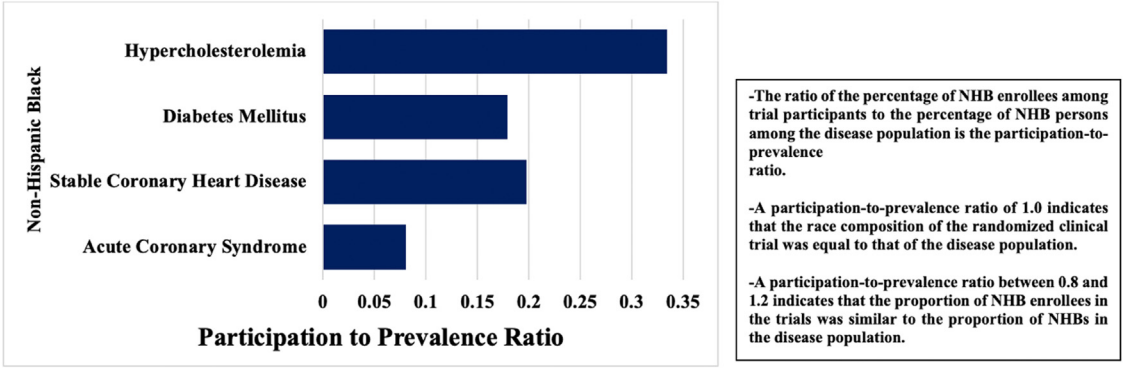


Fig. 5 Participation-to-prevalence ratio of non-hispanic black participants in lipid-lowering therapy randomized clinical trials, prevalence-corrected estimate.

use of lipid-lowering therapies with proven ASCVD benefit in the NH Black population.

ASCVD risk prediction in NH Black patients has improved since the introduction of the Pooled Cohort Equations (PCE). The 2018 Blood Cholesterol Treatment Guideline identifies South Asian ethnicity as a risk enhancing factor, but no comment is made about differential treatment based on NH Black race.[9] In fact, with regard to NH Black patients the Guideline states, "no sensitivity to statin dosage is seen, as compared to NH White individuals". Available studies report similar LDL-C lowering efficacy of ezetimibe,[27] alirocumab[28] and evolocumab[29] regardless of race. However, even in these studies there is under-representation of NH Black participants for ezetimibe (279 NH Black subjects of 3030 total participants), alirocumab (154 of 2136) and evolocumab (245 of 6182). While the publication of the only icosapent ethyl study included in this review dichotomized racial participation by White versus non-White, data from a sub-group analysis that was limited to participants from the United States showed that 3.4% of those receiving icosapent ethyl were NH Black subjects.[30] Thus, inadequate NH Black participation in lipid-lowering trials and underpowered ASCVD outcomes data in such individuals limit the generalizability of recommendations for lipid therapy in such individuals.

In our systematic review, not only did the reporting of NH Black persons in statin trials remain low over time, but NH Black participation was not reported in trials of ezetimibe and icosapent ethyl, and in less than half of five contemporary PCSK9 inhibitor trials. Similar to our findings, one recent study reviewed 71 RCTs cited in the 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood Cholesterol and found that race was only reported in 59.1% and NH Black subjects in 32.4% of trials.[31] On the other hand, by using the PPR metric and evaluating the participation and reporting trends of NH Black enrollment over time, our analysis builds upon the findings of the aforementioned study. Despite the higher prevalence of ASCVD in NH Black compared to White persons, NH Black patients are prescribed lipid-lowering therapy less frequently than White individuals and are less likely to achieve guideline-recommended lipoprotein goals, despite their increased risk.[7] For this reason, increased NH Black enrollment and reporting must be encouraged to lessen race-based differences in cardiovascular outcomes.

Our study also pointed out that NH Black participants are under-represented in lipid-lowering trials compared to their disease burden. Why are they under-represented? Some possible explanations include: 1) under-enrollment due to language barriers, disparities in socioeconomic position, and unique cultural practices[32]; 2) lack of patient willingness to participate in clinical trials as a result of longstanding structural racism and associated mistrust in clinical research studies[33]; 3) reduced trial access to both NH Black patients and community clinicians, as most US trials occur at large academic centers or research institutes[34]; and 4) limited screening of NH Black persons for enrollment either because of possible implicit biases or other socioeconomic factors or medical reasons that make their participation more difficult.

A clinician's ability to extrapolate trial results to any specific patient depends upon, among other factors, an appreciation of race and social determinants of health.[10] These differences will not be adequately addressed until there is sufficient racial representation of clinical trialists and other team members, engagement of trusted community clinicians in clinical research, and the development of participation sites for clinical trials in underserved communities. Trusted clinician-patient relationships promote transparency and open dialogue, and shared decision-making about the benefits and risks of trial participation.[35]

Limitations

Our study has certain limitations. This is an RCT-level systematic review, and we did not have access to individual participant data. We selected large RCTs with at least 1 year follow-up, since studies with extended follow-ups are most often used to inform guideline-based treatment recommendations. However, a degree of selection bias by ignoring small trials is inevitable. The assumption inherent in our statistical calculations that the absence of comment on NH Black participation reflects the absence of NH Black subjects, may result in some underestimation of NH Black enrollment. However, our rationale for taking this approach was previously described. We did not review the effectiveness of treatments based on demographic subgroups because of limited NH Black enrollment, demographic heterogeneity, and insufficient powering of results to draw definitive conclusions.

Conclusions

In this systematic review of RCTs of lipid-lowering therapies, we demonstrated that there is inadequate enrollment of NH Black participants, results are under-reported, and NH Black individuals are under-represented compared to their disease burden. The inclusion of population and disease specific representation of NH Black persons and their related social determinants of health will help to address the disparity in preventive care for this historically undertreated population. An informed clinician-patient discussion should include acknowledgement of these limitations in shared decision-making.

Acknowledgements

We would like to thank Dr. Karol Watson and Dr. Roger Blumenthal, who took time to review, critically appraise and provide insightful suggestions to improve the content of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2022.08.005.

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