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Reasons for Exclusion from a Smoking Cessation Trial: An Analysis by Race/Ethnicity

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Objective: The exclusion criteria of tobacco cessation randomized clinical trials (RCTs) may have unintended consequences on inclusion and cessation disparities. We examined racial/ethnic differences in: a) exclusion from a group-based cessation RCT; and b) reasons for exclusion.

Design: Quasi-experimental. Inclusion criteria were self-identification as African American/Black, non-Hispanic White, or Hispanic (any race), adults, minimum five cigarettes/day or carbon monoxide reading of ≥ 8 parts per million (ppm), interest in quitting, and spoke/read English. Data were obtained from a parent trial, which is ongoing and will be completed in 2019. Analyses for our present study on participant screening and enrollment were conducted in 2018.

Main Outcome Measures: Study ineligibility, and reasons for exclusion (contraindications for nicotine patch use, serious mental illness [SMI, eg, bipolar disorder or schizophrenia], alcohol dependence or illicit drug use, current tobacco treatment, attendance barriers [eg, transportation], and other concerns [eg, aggressive, intoxicated, disruptive, visibly ill]).

Results: Of 1,206 individuals screened, 36% were ineligible. The most frequent reasons were SMI (28%), alcohol dependence or drug use (10%), and attendance barriers (7%). Ineligibility was greater among African Americans (42%) and Hispanics (37%), compared with Whites (24%; P<.001). Compared with African Americans and Hispanics, Whites were more likely to be excluded for single reasons, including attendance barriers, and medical conditions (P<.05). African Americans were more than twice as likely as Whites to be excluded for 3 or more reasons (12% vs 5% respectively, P<.05).

Conclusions: A notable proportion of smokers were ineligible for this RCT, with SMI as the greatest single cause. Racial/ethnic minorities were more likely to be excluded, with African Americans deemed ineligible for multiple reasons. Findings have implications for RCT generalizability, addressing tobacco disparities and health equity. *Ethn Dis*. 2019;29(1):23-30; doi:10.18865/ed.29.1.23.

Keywords: Randomized Clinical Trials; Tobacco Cessation; Disparities; Racial/Ethnic Differences; Eligibility Criteria; Exclusion Criteria

Introduction

Randomized clinical trials (RCTs) are the gold standard for testing the efficacy of new treatments and ultimately disseminating them into practice and/or community settings. A longstanding concern is the underrepresentation of racial/ethnic minority groups into clinical trials.[1-3] For example, Moon et al[4] concluded that the enrollment fraction in National Cancer Institute-funded cancer clinical trials by race/ethnicity vastly underrepresented US cancer patients. As part of the NIH Revitalization Act of 1993, grant proposals are required to include racial/ethnic minorities as participants, and must indicate their planned distribution of enrollment by race and ethnicity.[5] However, the narrow inclusion/exclusion criteria of RCTs may have the unintended consequence of excluding the most vulnerable participants,[6] such as the medically underserved, those with co-morbidities, or groups who experience disproportionately greater health risks and mortality. As such, findings may have limited generalizability to these subpopulations and have implications for health equity. The present study examined racial/

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ethnic differences in eligibility for enrollment into an RCT designed to address disparities in tobacco cessation.

Racial/ethnic minorities in the United States, compared with Whites, are less likely to quit smoking successfully. Previous research found that the quit rates for African Americans (37.5%) and Hispanics (42.9%) were significantly lower compared with non-Hispanic Whites (50.4%).[7] The prolonged exposure to tobacco products and their harmful constituents contributes to disparities in tobacco-related illnesses, such as cancer and diabetes.[8,9] The most pervasive disparities in tobacco cessation and related illnesses are observed when comparing African Americans and non-Hispanic Whites, yet relatively few studies have focused on African Americans, and even fewer have focused on other racial/ethnic minority groups (eg, Hispanics).[10-12] Thus, as new treatments and interventions are being developed and tested, equitable opportunities to participate in RCTs are important for improving minorities' health and addressing disparities.

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Research literature has examined several factors associated with the underrepresentation of racial/ethnic minorities in clinical trials across health domains. This research has identified health system, provider, and patient-level barriers, including limited access to quality care to racial/ethnic minorities,[2] provider biases and lack of referral to studies,[2] inflexible hours, language requirements (ability to speak English), transportation limitations, medical mistrust,[13] and medical co-morbidities. One way to address these barriers and improve the representation of racial/ethnic minorities in RCTs could be by applying less restricted eligibility criteria, in particular those known to affect participation.

Our present study examined racial/ethnic differences in exclusion from a group-based dual-center tobacco cessation RCT designed to address tobacco cessation disparities. In this RCT, we sought to enroll equal proportions of the three largest racial/ethnic groups in the United States, non-Hispanic Whites, African Americans, and Hispanics. Participants were randomized to a group-based cognitive behavioral therapy (CBT) intervention or an intensity matched general health education (GHE) intervention. Both groups also received nicotine patch therapy. To facilitate inclusion of racial/ethnic minorities and underserved tobacco users, we included light smokers, offset the cost of transportation with nominal reimbursement, and offered the intervention in the morning and evenings. This exploratory study investigated racial/ethnic differences in: a) exclusion from the RCT; and b) reasons for exclusion. Findings from our study contribute to the literature focused on racial/minority representation in clinical trials and has implications for addressing disparities.

Method

RCT Study Design

This study was approved by Institutional Review Boards serving the University of Miami and the Moffitt Cancer Center. The design and methods have been described elsewhere.[14] Briefly, this study tested the efficacy of group CBT for tobacco cessation compared with GHE, using stratified random assignment (by race/ethnicity). Participants in both conditions received 8 group sessions over four weeks, and eight weeks of nicotine patch therapy. Data were obtained from the parent trial,[14] which is ongoing and will be completed in 2019. Analyses for our present study on participant screening and enrollment were conducted in 2018. Our analysis focused on study exclusion criteria, and it is therefore limited to data collected at the initial screening.

Participants

Community-based recruitment occurred in Miami and Tampa, Florida metropolitan areas using multiple approaches, including flyers, advertisements (newspaper, radio, Internet, public transportation), referrals from medical clinics, and social media (eg, Facebook). Inclusion criteria were: 1) self-identification as African American/Black, Hispanic (any race), or non-Hispanic White; 2) smoked five or more cigarettes/day or expired carbon monoxide (CO) of ≥ 8 ppm; 3) aged >18 years; and 4) ability speak/read English at a 6th grade level. Exclusion criteria included: 1) not ready to quit; 2) medical conditions that contraindicated nicotine patch use (eg, pregnancy); 3) self-reported cognitive or serious mental illness that may inhibit group treatment (ie, bipolar disorder, schizophrenia); 4) already receiving smoking cessation treatment; 5) active alcohol dependence or illicit drug use; 6) lack of permanent contact information; 7) barriers to attending intervention sessions (eg, lack of transportation, time of day); and 8) behaviors that were inappropriate for a group intervention (eg, intoxication). The analytic sample consisted of 1,206 screened individuals with a self-identified race/ethnicity (95% of those screened).

Procedures

Screening occurred via telephone or in person. We provided a brief introduction to the study and respondents provided verbal consent for screening. Screening questions were administered by research staff using a structured document with clear decision rules (eg, yes or no questions, with probing questions, as appropriate). Participants deemed eligible were provided with an overview of study procedures, and upon verbal consent, were randomly assigned to a condition (group CBT or group GHE). A primary goal of the parent study was to examine the differential effect of CBT across the three largest racial/ethnic groups in the United States, non-Hispanic Whites, African Americans, and Hispanics. Thus, stratified study site-specific randomization assigned equal numbers of each racial/ethnic group to CBT or GHE. Following screening, eligible participants were scheduled for study orientation/baseline assessment, where they provided written informed consent to participate. Ineligible participants were provided information on local smoking cessation programs and/or referred to the state Quitline, tobacco-free Florida (tobaccofreeflorida.com).

Interventions were conducted on the main campus of Sylvester Comprehensive Cancer Center and at the Moffitt Cancer Center and in a second regional location, with the goal of increasing access for each of the target populations. Each site was accessible via public transportation (ie, bus or train) and adjacent parking was available. Because our interventionists were primarily monolingual English-speakers, we sought to recruit English-speaking tobacco users and advertisements were offered in English only. During the initial study description, we informed participants that they would be compensated up to $190 for completing five assessments, including saliva samples, over 13 months; we also provided compensation ($5) to offset the cost of travel to each session. Group sessions occurred in the mornings or evenings to improve study accessibility.

Assessments

Our report focuses on the screening questions asked prior to study enrollment. We administered a brief screening form that assessed age, sex, cigarettes per day, motivation to quit (yes or no), self-reported diagnosis or current treatment for a serious mental illness (eg, bipolar disorder, schizophrenia; yes or no), current medications, current treatment for tobacco cessation or other substances (yes or no), alcohol use frequency, typical number of drinks per occasion, ability to speak and read English (yes or no), contact information, barriers to attendance (ie, access to transportation by bus or car, availability of childcare during sessions, perceived difficulty attending on-campus sessions), pregnancy/breastfeeding, self-reported diagnosis of a severe heart or breathing condition (yes or no), and self-identified race/ethnicity. We recorded all reasons for ineligibility, and coded single reasons, and all combinations of multiple reasons as "two reasons" or "three or more reasons." Information provided at screening was reviewed for consistency on the baseline measures administered at orientation. A breath carbon monoxide test was administered at the baseline visit.

Statistical Analyses

Descriptive statistics for the overall sample and by racial/ethnic groups summarized variables collected at screening, the overall rate

of study eligibility and ineligibility, and the reasons for ineligibility using frequencies/proportions and means (M) with standard deviations (SD). Where appropriate, screening questions were combined into categories matching the inclusion/exclusion criteria (eg, lack of transportation and difficulty coming to the study site were categorized as "barriers to attendance"). Because minimal data were collected at screening (ie, we did not have significant sociodemographics to include as control variables, such as income or education), we conducted bivariate tests to evaluate racial/ethnic differences. Moreover, such factors would not have affected potential inclusion at screening. We conducted two Chi-squared goodness of fit tests for proportions to analyze racial/ethnic differences in eligibility and reasons for ineligibility. Then, post-hoc chi-squared goodness of fit test was performed to specify racial/ethnic group differences in the reasons for ineligibility. Overall Type-I error (alpha) was set at 5% for statistical hypothesis testing procedures. In each study site, data collection and management were done in FileMaker which is a cross-platform relational database application (FileMaker, Inc. Santa Clara, CA). Data management and statistical analyses were conducted using SPSS version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

Results

The screening sample *(N*= 1,206) was 43% African American/Black, 35% non-Hispanic White, 17% Hispanic, and 5% 'other' race/ethnicity. Screened individuals were 51% female, with a mean age of 48 (SD = 12) and reported smoking an average of 19 cigarettes per day (SD = 11). Hispanics were significantly younger (M = 43.46, SD = 12.52) than African Americans (M = 49.13, SD = 10.77) and non-Hispanic Whites (M = 50.37, SD = 11.93) (P<.05); only one person was excluded due to age (17 years, non-Hispanic White). Overall, 36% of respondents (n=440) were ineligible for the study following screening. There were no significant racial/ethnic differences in sex or smoking intensity. Of those who were excluded, the most common reasons were serious mental illness (27.5%), current diagnosis/treatment of drugs/alcohol dependence (9.5%), and barriers to attendance (7.3%). About 22% were ineligible for two reasons, and 8.8% for three or more reasons (Table 1).

Analysis by race/ethnicity showed significant differences in a) eligibility and b) reasons for ineligibility. First, we found that racial/ethnic minority respondents were less likely to be eligible for participation (χ^2 [3, *N*=1,206]=54.33, P<.001)

Table 1. Reasons for RCT ineligibility by race/ethnicity

	Race/Ethnicity				
	African American/Black, n = 218	**White, n = 104**	**Hispanic, n = 79**	**Other, n = 39**	**Total, n = 440**
	% (n)	**% (n)**	**% (n)**	**% (n)**	**% (n)**
Serious mental illness	28.9 (63)	24 (25)	35.4 (28)	0 (0)a	27.5 (121)
Barriers to attendance	3.7 (8)	16.3 (17)[a]	3.8 (3)	0 (0)	7.3 (32)
Lack of motivation/not interested	1.4 (3)	1 (1)	3.8 (3)	0 (0)	1.6 (7)
Language/inappropriate for group setting	5.5 (12)	1.9 (2)	6.3 (5)	0 (0)	4.3 (19)
Drugs/alcohol dependence	11 (24)	6.7 (7)	12.7 (10)	0 (0)	9.5 (42)
Smoking status	3.2 (7)	2.9 (3)	7.6 (6)	0 (0)	3.9 (17)
Medical condition/NRT contraindications	2.8 (6)	12.5 (13) [a]	0 (0)	0 (0)	4.8 (21)
Race/ethnicity	0 (0)	0 (0)	0 (0)	76.9 (30)[a]	6.8 (30)
Other reason	6.9 (15)	10.6 (11)	3.8 (3)	0 (0)	6.6 (29)
Two reasons	24.8 (54)	19.2 (20)	22.8 (18)	10.3 (4)	21.8 (96)
Three reasons	11.9 (26) [a]	4.8 (5)	3.8 (3)	12.8 (5)[a]	8.8 (39)

a. P<.05 from post-hoc chi-square goodness of fit test.

compared with White respondents. Among African Americans, 42.1% were ineligible, followed by 37.9% of Hispanics and 24.8% of non-Hispanic Whites. Second, we found that reasons for exclusion also differed significantly by race/ethnicity, (χ^2 [30, n=440]=248.21, P<.001). As shown in Table 1, White respondents were significantly more likely to be excluded for single reasons, including barriers to attendance, and medical conditions compared with African Americans and Hispanics (P<.05). African Americans were more than twice as likely as non-Hispanic Whites to be excluded for three or more reasons (12% vs 5% respectively, P<.05), with no difference between Hispanics and Whites.

Discussion

This study examined patterns of ineligibility and reasons for exclusion from participation in a community-based tobacco cessation RCT. The overarching goal of the parent RCT was to test whether a group-based CBT might eliminate racial/ethnic smoking cessation disparities. In planning the study, we sought specifically to recruit equal numbers of participants who self-identified with the three largest racial/ethnic backgrounds in the United States. Thus, an equitable opportunity to participate was essential. Our analysis found that racial/ethnic minority respondents were more likely to be excluded from this trial than non-Hispanic White individuals. We also found racial/ethnic differences in the reasons for exclusion, and that African Americans were more likely to be excluded for a combination of reasons. Findings have wide ranging implications for tobacco cessation research, and to clinical trials more broadly.

Over one-third of individuals screened were ineligible for study participation. This exclusion rate was consistent with or lower than recent tobacco cessation trials across intervention approaches, including intensive behavioral treatments combined with pharmacotherapy.[15,16] Findings highlight a larger point about RCT recruitment and external validity. RCTs tend to have strict criteria for important reasons, such as methodological rigor, increasing internal validity, and reducing the likelihood of adverse events and/or confounding variables. However, narrow inclusion requirements can result in homogenous samples, limited generalizability of findings, and the exclusion of treatment-seekers from opportunities to receive evidence-based and/or cutting-edge care. Statler et al[17] concluded that cancer clinical trials published in high-impact journals may have overly restrictive exclusion criteria and may systematically exclude specific populations. Strict inclusion criteria may also have the unintended consequence of minimizing the impact of the NIH Revitalization Act. Geller et al[6] found that this policy has not increased the inclusion of racial/ethnic minorities in NIH-funded trials. Creative strategies to respond to the greater risk of exclusion will drive meaningful increases in representation and inclusion.

African Americans and Hispanics were more likely to be excluded from the trial compared with non-Hispanic Whites. The greater exclusion of African American smokers is consistent with King et al,[15] who found that African Americans were almost three times more likely to be excluded from an intensive, behavioral (plus pharmacotherapy) RCT compared with non-Hispanic White respondents. They found that African American exclusions occurred at both the initial phone screening and the in-person screening, and that this population was less likely to participate when eligible. In contrast to the present study, King et al did not seek to recruit a sample with equal proportions of specific racial/ethnic groups, and no studies have examined the exclusion of Hispanics from tobacco clinical trials. The greater rates of exclusion among racial/ethnic minorities has implications for equitable inclusion in treatment studies among those who wish to participate, the generalizability of findings to these populations, and tobacco cessation

Our analysis found that racial/ethnic minority respondents were more likely to be excluded from this trial than non-Hispanic White individuals.

disparities. The long-term result will be the persistence of health disparities across tobacco-related conditions (eg, cancer and heart disease).

We carefully considered the eligibility criteria with the goal of maximizing participation in a group-based intervention. The two primary reasons for trial exclusion fall within the category of mental disorders. Self-reported diagnosis of a serious mental illness (ie, bipolar disorder and/or schizophrenia) and substance dependence were the greatest single reasons for ineligibility. There were no differences in these single factors by race/ethnicity. Serious mental illnesses are more prevalent in smokers compared with non-smokers,[18] as is substance dependence,[19] yet many trials exclude participants with these comorbid concerns. In the present study, the interventions were not designed to address the needs of individuals with a serious mental illness (eg, treatment of psychiatric symptoms during nicotine withdrawal) or substance dependence; thus, we provided referrals to appropriate resources. Future options to increase the inclusion of these sub-populations in tobacco treatment RCTs include hiring staff who are trained to manage medication-managed serious mental illnesses and conducting transdiagnostic intervention trials.

We also found racial/ethnic differences in not only the reasons for exclusion from this RCT, but also in the quantity of reasons for exclusion. Non-Hispanic Whites were more likely to be excluded for single reasons, such as contraindications for nicotine replacement therapy and attendance barriers. Compared with non-Hispanic Whites, African Americans were 2.48 times more likely to be excluded for three or more reasons. The top three reasons for exclusion among African Americans were serious mental illness, current substance or alcohol use treatment, or "other" reasons. African Americans were also more likely to be excluded for two reasons, although the difference was not statistically significant. Barriers to clinical trial enrollment, especially among African Americans are multifaceted and include individual-level factors. The current findings suggest that the disparity in eligibility is not a function of any single reason for ineligibility but may result due to compounding reasons. Efforts to improve the underrepresentation of racial/ethnic minorities require multi-level and flexible strategies at the system, study, interpersonal, and individual levels.[20] In the current study, efforts were made to reduce the commonly known barriers to participation in intensive intervention trials, such as transportation and daytime-only scheduling. Despite this, treatment-seeking racial/minorities were less likely to meet the eligibility criteria. This is an important note, since African Americans have a longstanding reputation of underutilization of services, lower help-seeking behavior, being distrustful of research,[21] and being among the "hard-to-reach" populations.[22] In contrast, our findings are consistent with King et al,[15] showing that African Americans were most responsive to our recruitment efforts, yet were most likely to be excluded. We recommend: a) consideration of whether study inclusion and exclusion criteria might place certain populations at a systematic disadvantage; and b) thoughtful consideration of whether automatic implementation of criteria used in previous studies might unexpectedly exclude at-risk populations or limit treatment developers' ability to properly consider efficacy across a host of risk factors. Another recommendation is to conduct pragmatic clinical trials in real-world contexts, when appropriate, to also facilitate inclusion. Future research with a larger sample is needed to conduct more fine-grained analyses to study the combinations of exclusion reasons that result in ineligibility, particularly among racial/ethnic minorities.

Our study makes a substantial contribution to the literature on exclusions from smoking cessation clinical trials and, possibly RCTs more broadly. Strengths of the study include the *a priori* focus on recruiting an equal number of treatment-seekers who self-identified as African American, Hispanic, or non-Hispanic White, which is distinct from most tobacco intervention trials. We implemented a moderately aggressive recruitment plan that included a variety of strategies to attract a diverse sample and were successful in over-representing racial/ethnic minority smokers. The sample size was adequate to detect overall differences in trial exclusion; however, the study was underpowered to fully evaluate racial/ethnic differences in individual reasons for being excluded. Other limitations of the study include the reliance on a brief screening tool, which reduced our ability to con-

firm SMI diagnoses using a structured clinical interview or examine participant characteristics that may also be related to trial exclusion. We did assess current medications, however, which provided some diagnostic confirmation. Our racially/ethnically diverse research staff was trained in the screening protocol and utilized a structured tool, but we cannot rule out the possible role of administrator factors (eg, bias) in trial exclusion. Finally, the ability to read and speak English was an inclusion criterion, which likely affected recruitment and screening of Hispanic smokers, and limits generalizability to non-English speakers.

Conclusion

Our present study has important implications for access to RCTs, the generalizability of clinical trial findings across populations, and tobacco cessation disparities. The underrepresentation of racial/ethnic minorities in clinical trials, including tobacco cessation studies persists. Investigators are encouraged to consider the possibility of conducting pragmatic trials to reduce the exclusion of populations that face an undue burden of morbidity and mortality.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Hooper, Asfar, Unrod, Simmons, Antoni, T. Brandon; Acquisition of data: Hooper, Unrod, Dorsey, Correa, K.Brandon, Antoni, Lee, T. Brandon; Data analysis and interpretation: Hooper, K.Brandon, Antoni, Koru-Sengul, Lee; Manuscript draft: Hooper, Asfar, Correa, K.Brandon, Simmons, Antoni, Koru-Sengul, Lee, T. Brandon; Statistical expertise: Hooper, Koru-Sengul; Acquisition of funding: Hooper, Koru-Sengul,T. Brandon; Administrative: Hooper, Asfar, Unrod, Dorsey, K.Brandon, Simmons, Lee, T. Brandon; Supervision: Hooper, K.Brandon, Antoni, Koru-Sengul, Lee, T. Brandon

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