Journal of the Neurological Sciences 394 (2018) 107–111

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical short communication

Representation of ethnic groups in dementia trials: systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Dementia
Race
Ethnicity
Clinical trial
Meta-analysis

ABSTRACT

Background: Despite the projected increase in dementia cases affecting various ethnic groups worldwide, representation of these ethnic groups in randomized controlled trials (RCTs) of treatments to improve cognitive function in persons with dementia or mild cognitive impairment (MCI) is unclear. We aimed to quantify the inclusion of various ethnicities in dementia treatment RCTs.

Methods: RCTs published between January 1, 2000 and August 1, 2017 (inclusive) were included. Participants were community-dwelling adults with a diagnosis of either dementia or MCI randomized to receive either pharmacological or non-pharmacological interventions to improve cognitive function. Analyses were performed to determine study-level characteristics associated with recruitment of various ethnic groups. Random effects meta-analyses were conducted to determine the pooled prevalence for each ethnicity.

Results: A total of 96 RCTs consisting of 37,278 participants (57.2% female) were included in the final analysis. Only 39 (39.4%) trials reported the ethnicity of included participants. The pooled proportion of non-Caucasian trial participants was 11.4% (95% CI, 7.5 to 15.9%). Meta-regression results showed that there has been a slow increase in representation of non-Caucasian ethnic groups over time (0.6% per year, *P value* = 0.041).

Conclusions: There is an underreporting of the ethnicity of trial participants and underrepresentation of non-Caucasian ethnic groups in RCTs designed to improve cognitive function in persons with dementia or MCI.

1. Introduction

The total number of people living with dementia worldwide is expected to triple by 2050 from the current 50 million living world-wide [1]. Much of the expected burden from increasing numbers of people living with dementia will be felt in developing countries, thus affecting various ethnicities [2,3]. Differences in overall survival of patients with Alzheimer's disease (AD) based on race or ethnicity have been described [4]. Furthermore, studying the effects of medications on various populations is not only important to improve the generalizability of results, but can also lead to insights into biological differences e.g., association of HLA-B*1502 in Asians and a higher risk of Steven-Johnson syndrome with carbamazepine or the reduced effectiveness of inhibition of angiotensin converting enzyme for lowering blood pressure in African/black individuals with hypertension [5,6].

Poor representation of ethnic groups in randomized controlled trials (RCTs) has been previously described for both neurological and non-neurological disorders [7–9]. Despite the increase in dementia-related research over the past decades, inclusion of patients with varying ethnicities in dementia treatment RCTs remains low [10–12]. We conducted a systematic review and meta-analysis (adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines) to examine the inclusion of ethnic groups in dementia treatment trials [13].

2. Methods

We searched MEDLINE, EMBASE, and *clinicaltrials.gov* for articles published in English from January 1, 2000 to August 1, 2017 (inclusive) [Appendix e-1]. We screened references from included studies to identify additional eligible RCTs.

We included published full-text phase 3 or 4 RCTs that met the following criteria: (1) participants were community-dwelling with a diagnosis of dementia (Alzheimer's disease (AD), mixed, or vascular) or

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https://doi.org/10.1016/j.jns.2018.09.012
Received 27 May 2018; Received in revised form 10 September 2018; Accepted 11 September 2018
Available online 12 September 2018
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mild cognitive impairment (MCI), (2) there was both an intervention (pharmacological or non-pharmacological therapy) and a comparison group receiving placebo or another intervention, and (3) focused on improving cognitive function, measured change in cognition as either a primary or secondary outcome [using Alzheimer's disease Assessment Scale-Cog (ADAS-Cog), Mini-mental status exam (MMSE) or Montreal Cognitive Assessment (MoCA)]. We excluded completed RCTs that were not published as full-text articles because they did not report patient characteristics such as ethnicity of the participants – our primary outcome of interest.

Two reviewers (MVV and PKR) independently screened all titles and abstracts and completed full-text review of all eligible studies. We abstracted the following information from each study: trial data (year of publication, single or multicenter, country, funding source, journal name); demographics (total number of participants, average age, percent female); intervention data (drug vs. therapy, duration of follow-up); trial results (primary outcome, statistically significant or not); and outcomes of interest for this study (percentage and type of ethnicity, language of administration of cognitive assessment). Proportion of a particular ethnic group in an RCT was only included if it was explicitly mentioned in their manuscript or methods i.e., an RCT conducted in one of the Asian countries was not by default said to have included 100% Asians, unless it was explicitly mentioned.

We tested the impact of a priori determined RCT-level factors on reporting of ethnicity in RCTs using *t*-tests for continuous variables and χ^2 tests for categorical variables. We pre-specified study-level variables such as mean age, mean follow-up time (in weeks), proportion of female participants and sample size as continuous variables. We dichotomized categorical variables as listed in Table 1. For variables such as impact factor, we used median value as a cut off to convert them into binary variables. Using random effects meta-analyses, we calculated the pooled estimate and 95% confidence interval for the proportion of each ethnic group. Our primary outcome was non-Caucasian ethnicity – a composite of Asian, Caribbean/African black, Hispanic/Latino, and other ethnicities. We used the "*metaprop*" routine in STATA, which was specifically designed for meta-analyses of binomial data or proportions [14]. We used the exact binomial method to compute 95% confidence intervals, with the Freeman-Tukey double arcsine transformation of proportions and inverse-variance weights to develop random effects models. Details of this procedure are listed elsewhere. [15] We used a two-tailed alpha of 0.05 to determine statistically significant result. All data analysis was performed using StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP and SAS V.9.4 (Carey, NC).

Table 1
Differences in trial characteristics between those studies that did and those that did not report ethnicity of the trial participants.

Characteristics	Ethnicity reported	Ethnicity not reported	*P* value
	N = 39	*N* = 60	
Average proportion of females (Q1-Q3)	59.9 (54.7–66.7)	53.2 (50.0–62.5)	< **0.001**
weighted mean Age (years), mean (SD)	73.1 (0.6)	74.0 (0.4)	0.17
Follow-up in weeks, mean (SD)	44.3 (30.3)	41.5 (37.0)	0.67
Sample size, mean (SD)	567 (66.1)	252 (31.5)	< **0.001**
Severe dementia, MMSE ≤10 (vs. mild/moderate), n(%)	17 (44.7)	19 (35.2)	0.39
Alzheimer's disease (vs. other), n(%)	36 (92.3)	42 (70.0)	**0.01**
Multicenter (vs. single), n(%)	37 (94.9)	43 (71.7)	**0.007**
Results statistically significant (vs. not), n(%)	13 (34.2)	29 (49.1)	0.20
Multinational (vs. single country), n(%)	15 (38.5)	13 (21.7)	0.11
Industry (vs. public/mixed), n (%)	33 (84.6)	23 (45.1)	< **0.001**
Drug (vs. other), n(%)	35 (89.7)	38 (63.3)	**0.005**
High impact factor journal (IF > 8.4), n(%)	11 (28.2)	13 (21.7)	0.48
English language exclusion (yes vs. no), n(%)	3 (7.7)	2 (3.3)	0.38

IF impact factor, SD standard deviation, MMSE mini-mental status exam, n is the number of studies, Q1-Q3 refer to 25th and 75th percentile.
P values in bold represent statistically significant result at a two-tailed alpha of 0.05.

2.1. Sensitivity analyses

We used univariable meta-regression analyses for continuous variables and subgroup analyses for categorical variables to assess if the high heterogeneity in the pooled estimate could be addressed by the study-level factors, without adjusting for multiple testing. We reported *P* values for the interaction term in the subgroup analyses (values over 0.05 suggested no heterogeneity between groups). We made an ad hoc decision to exclude 2 out of 39 studies (Moreno et al. and Baum et al.) in the meta-regression model to allow for normal distribution of proportion of non-Caucasian ethnicity (primary outcome) in order to satisfy the normality assumptions of meta-regression. These studies were conducted in Mexico and Hong Kong and led to skewed distribution of our primary outcome: proportion of non-Caucasian ethnicity.

3. Results

After removing duplicate studies, a total of 10,554 records were screened. 195 eligible studies underwent full text-review and 96 RCTs, amounting to 99 study populations, were included in the final review [Appendix e-2].

A total of 37,278 individuals (57.2% females) of which 29,686 (79.3%) had AD, 2371 (6.4%) had vascular dementia, 4595 (12.3%) had MCI, and 626 (1.7%) had either AD or MCI (authors did not specify). The weighted mean age of our study population was 73.4 years [standard deviation (SD) 3.26] and the mean length of follow-up was 42.6 weeks (SD 34.2). Only 36 (37.5%) RCTs (39 trial populations) reported information on the ethnicity of included participants [Appendix e-3]. Trial characteristics that were associated with reporting ethnicity of trial participants in the published manuscript are listed in Table 1. None of the 39 trials reported the results of the intervention by ethnicity (in subgroup or sensitivity analysis).

The pooled proportion of non-Caucasian ethnicity was 11.4% (95% confidence interval, 7.5 to 15.9%) among 39 trial populations. Pooled estimates for Asian, African/Caribbean black, Hispanic/Latino, and other ethnicities were 13.2% (number (n) =14 studies), 2.4% (*n* = 18), 19.1% (*n* = 6) and 2.4% (n = 18), respectively (Fig. 1). The primary outcome estimate did not vary across the subgroups (Fig. 1). Meta-regression results suggested that the percentage of non-Caucasian ethnicity representation has increased over time (Fig. 2). In addition, larger sample size was associated with greater reporting of ethnicity (0.8% increase for every 100 participants in a trial, *P* = 0.025) [Appendix e-4].

4. Discussion

We found that the ethnicity of participants is not well reported in RCTs, and that non-Caucasian ethnic groups were not well-represented in dementia treatment RCTs to date. However, similar to the National Institute of Neurological Disorders and Stroke (NINDS) funded trials between 1985 and 2008 that saw an increase in the enrolment of ethnic groups, our study too observed a slow shift toward the inclusion of different ethnic groups [16]. In addition, we identified trial characteristics associated with reporting of the ethnicity of trial participants: multinational trials, trials with higher numbers of female participants, larger sample sizes, drug therapy trials, or Alzheimer's disease as the

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