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Race reporting and disparities in clinical trials on Alzheimer's disease: A systematic review

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ABSTRACT

Introduction: Race is an important health determinant and should adequately be considered in research and drug development protocols targeting Alzheimer's disease (AD).
Methods: A systematic review of available randomized controlled trials (RCTs) on the currently marketed treatments for AD was conducted with the aim of 1) documenting the reporting of race, and 2) exploring the impact of race on the efficacy and safety/tolerability of the considered medications.
Results: Overall, 59.2% of the 49 retained RCTs reported information concerning the race of participants. Only a striking minority of enrolled patients was constituted of blacks and Hispanics. None on the retained studies reported results on the efficacy and safety/tolerability of the tested treatment separately for racial groups nor performed sensitivity analyses accounting for the race of participants.
Discussion: Race has insufficiently been reported in previous interventional studies on AD. Its potential association with the effectiveness and safety/tolerability of the tested medications has completely been neglected.

1. Introduction

Race is an important health determinant. Substantial differences across racial groups for various medical conditions (e.g., cancer (Eley et al., 1994),cardiovascular diseases (Gillum et al., 2011) and risk factors (Frank et al., 2014), HIV/AIDS (Chapin-Bardales et al., 2017)) in terms of incidence, pathophysiology, phenotypic expression, and outcomes have been documented. Such disparities assume special relevance nowadays due to the increasing racial diversity of our populations and the promises of "precision medicine" approaches (Collins and Varmus, 2015). Nevertheless, minority groups are generally underrepresented in randomized controlled trials (RCTs) (Sardar et al., 2014). Furthermore, a poor reporting of information on the race of research participants has repeatedly been documented (Berger et al., 2009; Corbie-Smith et al., 2003; Ma et al., 2007).

In line with other chronic diseases, Alzheimer's disease (AD) and related dementias are significantly influenced by racial determinants at different levels. Cohort studies (mostly conducted in the US) have repeatedly reported major racial inequalities in dementia incidence (Mayeda et al., 2016). Accordingly, cross-sectional studies have frequently shown a higher prevalence of dementia among blacks and Hispanics compared to whites and Asians (Alzheimer's Association, 2016; Mehta and Yeo, 2017). These discrepancies have mostly been attributed to differences in socioeconomic factors (e.g., educational level) and, to a lesser extent, in other genetic or clinical variables (e.g., apolipoprotein E genotype, depression, cerebrovascular diseases, smoking) (Rodriguez et al., 2018; Yaffe et al., 2013). Race has also been found to affect the phenotypic manifestation of AD in terms of disease severity and presentation, with black patients commonly exhibiting an earlier onset of cognitive disturbances, a greater severity of cognitive and functional symptoms, and a more evident impairment of specific cognitive domains (e.g., visual naming and constructional praxis) compared to white individuals (Shadlen et al., 1999; Welsh et al., 1995). Similarly, AD symptoms may appear earlier among Hispanics than in non-Hispanic whites (Clark et al., 2005). Relevant differences across racial groups have been observed for other clinical aspects and outcomes such as neuropsychiatric symptoms (Sink et al., 2004), mortality rate (Mehta et al., 2008), likelihood of receiving diagnosis and

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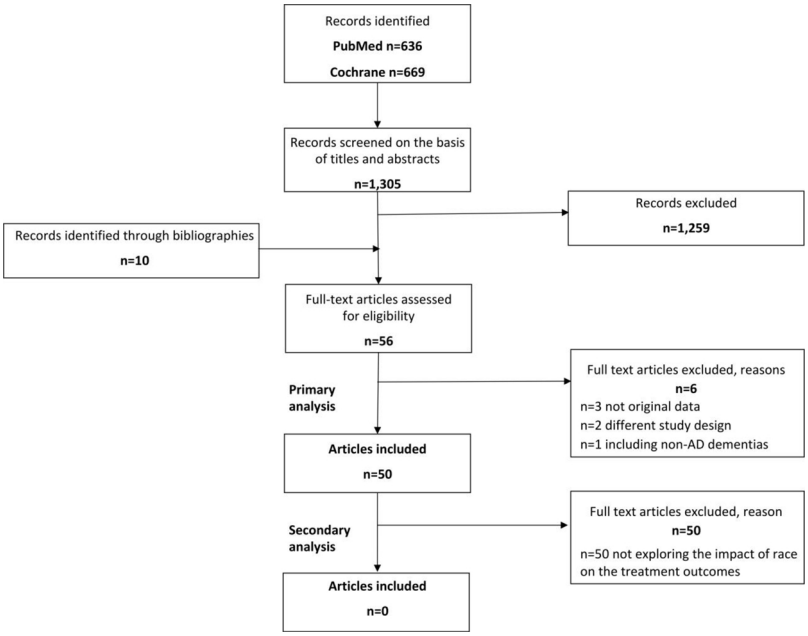

Fig. 1. Flowchart of articles selection.

anti-dementia treatments (Mehta et al., 2005), and use of long-term services and support (Cooper et al., 2010). Finally, recent post-mortem studies have revealed that African American and Caucasian patients with dementia differ in neuropathological changes, suggesting a varying magnitude of the underlying pathophysiological processes (mostly attributable to differences in genetic susceptibility) (Graff-Radford et al., 2016).

All these considerations represent compelling reasons for considering race in research and drug development protocols targeting AD. Nevertheless, most of the available knowledge in the field almost exclusively comes from research studies of Caucasians, and non-white groups are still marginally included in dementia trials (Shin and Doraiswamy, 2016). However, it might be expected the race of research participants to be at least adequately reported (if not even considered for dedicated analyses) in order to enhance the generalizability of the emerging evidence. To test this hypothesis, we conducted a systematic review of available RCTs on the currently marketed treatments for AD (i.e., cholinesterase inhibitors [ChEIs] and memantine) with the aim of 1) documenting and quantifying the reporting of race, and 2) exploring the impact of such determinant on the efficacy and safety/tolerability of the considered medications.

2. Methods

The present review was conducted and reported according to the PRISMA statement for systematic reviews (http://www.prisma-statement.org).

2.1. Search strategy and selection criteria

A structured literature search was conducted on PubMed and the Cochrane databases to identify all relevant studies on humans published in English between 1996 (year of publication of the first RCT on donepezil in AD (Rogers and Friedhoff, 1996)) and March 2018. A combination of the following search terms was used: ("donepezil" OR "galantamine" OR "rivastigmine" OR "memantine" OR "cholinesterase inhibitor*") AND ("Alzheimer" OR "alzheimer's" OR "alzheimers"). The bibliographies of the retrieved studies were also examined to identify further potentially eligible publications.

Two authors (M.Ca. and V.Z.) independently screened the records identified by the search strategy, based on their title and abstract. The full-texts of studies pertinent to the topic of the review were then collected and examined. The following set of predefined inclusion criteria was adopted:

1) reporting results from randomized, placebo-controlled trials;
2) recruiting participants with a diagnosis of "probable AD" formulated according to the National Institute of Neurological and Communicative Disorders and Stroke -Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984) or to the Diagnostic and Statistical Manual of mental disorders - fourth edition (DSM-IV) criteria (American Psychiatric Association, 2000);
3) exploring the efficacy of one ChEI (i.e., donepezil, rivastigmine, galantamine) or memantine in monotherapy or in combination with a ChEI on cognitive and/or functional and/or behavioral outcomes.

Studies reporting head-to-head comparisons between two or more drugs or between different doses of the same pharmacological compound, or investigating non-clinical outcomes (e.g., biomarker-based surrogate endpoints) were not considered.

The impact of race on the efficacy and safety/tolerability of the four medications was secondarily explored in those studies 1) reporting results separately for racial groups, and/or 2) performing *ad hoc*, secondary, or *post hoc* analyses accounting for variables pertaining to the race of participants.

Disagreements in the above-described selection process were solved by consensus, or involving a third reviewer (F.R.). The flow diagram depicted in Fig. 1 shows the selection of the articles of interest for the present review.

2.2. Data extraction and analysis

Two independent reviewers (M.Ca. and V.Z.) extracted the following data from the retained studies: number of participants, mean age, sex distribution, tested pharmacological intervention, country/countries where the RCT was carried out, and year of publication. For each clinical trial, data on whether the race of participants was reported (in the tables or the Results section) and how race was classified were collected. The following races were considered: white (or Caucasian or

Non-Hispanic white); Black (or African American); Asian (or Oriental or Asian/Pacific); and Native American. We also collected data on Hispanics (or Latino) because the Hispanic origin of participants is still commonly intended as a race category in research reports (Berger et al., 2009), despite being more frequently indicated as an ethnicity by US federal policies (United States Census Bureau, 2017).

Finally, we examined whether any efficacy and/or safety tolerability analysis was conducted by race (as mentioned in the Methods, Results, or Discussion sections). Changes in reporting race over time were assessed with Chi-Square test for trend.

3. Results

3.1. Search results

The bibliographic searches identified a total of 1305 articles, with 45 records considered as potentially relevant after the screening based on titles and abstracts. Ten articles were additionally selected by manually examining the bibliographies of the retrieved studies. Six articles were subsequently excluded because they did not meet the predefined inclusion criteria. Thus, 50 publications, reporting the findings of 49 unique RCTs (two articles provided complementary information on the same research protocol) were ultimately selected (Fig. 1). A high inter-rater agreement (> 90%) was reported by the two reviewers performing the study selection process. The detailed characteristics of the retained studies are reported in Table A1. Their geographical location is depicted in Fig. 2.

3.2. Reporting of race

Overall, 59.2% of RCTs reported information concerning the race of participants (Table 1). The reporting rate was higher for the trials testing the efficacy of memantine (75.0%), donepezil (66.7%) and galantamine (55.6%), whereas it was lower in those on rivastigmine (30.0%). The reporting of race was found to not significantly change over time considering four consecutive time periods (i.e., 61.5% in 1996–2000, 33.3% in 2001–2004, 71.4% in 2005–2008 and 70.0% in 2009–2017; $p = 0.42$). Moreover, no differences in race reporting were detected between RCTs including or not including US sites ($p = 0.25$).

Among the 29 studies with available data on race, two were restricted to patients of white race, five to only Asian participants, whereas 22 enrolled multiracial populations. Half of these latter studies specified only the most frequent racial group. Only three reports provided information on how race was assessed. Specifically, race was defined by assignment from the investigator in two studies (Howard et al., 2007, 2012) and by self-identification of participating subjects in the remaining one (Winblad et al., 2007).

Overall, 78.4% of patients with AD recruited in the considered RCTs were whites, 13.0% were of Asian race, while only a striking minority was constituted of blacks and Hispanics (4.4% cumulatively)(Table 1 and Fig. 3). In particular, the median percentage of whites included in the multiracial studies was 92.5% (interquartile range: 90.5%–96.8%).

3.3. Exploring the impact of race on treatment outcomes

None on the retained studies reported results on the efficacy and safety/tolerability of the tested treatment separately for racial groups nor performed *ad hoc*, secondary, or *post hoc* analyses accounting for the race of participants. Specifically, no study examined the possible association between race and treatment outcomes, adopted data on race in subgroup analysis or as adjustment covariates in the statistical models.

4. Discussion

To our knowledge, this study constitutes the first attempt to systematically collect and discuss the available evidence concerning the reporting of race in RCTs on AD, and to explore if and to what extent such health determinant is taken into account when investigating the efficacy of novel, targeted pharmacological compounds and their safety/tolerability profiles.

Encouragingly, the majority of RCTs provided information regarding the racial composition of the sampled populations, with a rate of reporting that, though far to be considered as optimal, is higher in comparison to that registered in other medical fields (Berger et al., 2009; Hoel et al., 2009; Mitchell et al., 2009) and for other baseline characteristics of AD patients (Canevelli et al., 2018a,b). Nevertheless, the description of the race of participants was mostly insufficient and incomplete. In particular, the majority of reports did not specify how race was assessed, as instead required by available guidelines (Kaplan and Bennett, 2003; "Uniform requirements for manuscripts submitted to biomedical journals", 2010). In fact, the agreement between different assignment methods is high in white and black populations, while is lower for other racial groups (Lee et al., 2003). Moreover, in most of the studies, the reporting was restricted only to the principal racial group despite recruiting variegate populations. Indeed, providing a more complete and detailed description of such determinant should greatly enhance the external validity (i.e., generalizability) of the study findings and their clinical implementation in “real world” contexts that are increasingly characterized by racial and ethnic pluralisms and inequalities.

It seems even more worrisome that the potential impact of race on

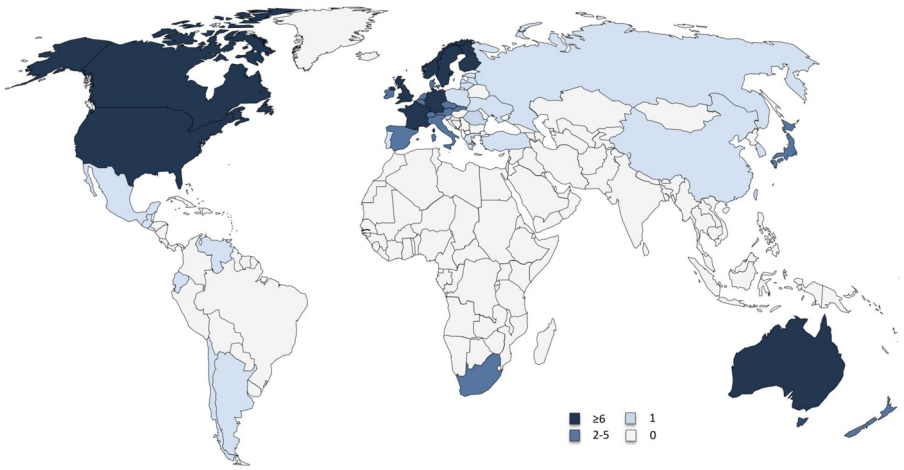

Fig. 2. Geographical location of the clinical sites involved in the 49 included studies.

Table 1
Main characteristics of the 49 included studies.

	Donepezil	Rivastigmine	Galantamine	Memantine	Total
Studies (n)	18	10	9	12	49
Participants (n)	5,504	4,908	6,493	4,089	21,000
Age (weighted mean ± SD)	75.8 ± 5.1	73.2 ± 2.4	75.1 ± 3.3	76.2 ± 4.3	74.8 ± 4.4
Sex (F,%)	64.5	63.3	64.4	63.9	64.1
Studies reporting race (n)	12	3	5	9	29
Race of participants*					
White (%)	76.4	57.6	92.6	78.2	78.4
Black (%)	1.9	0.4	0.7	0.6	1.0
Hispanic (%)	0.8	0	0.3	14.3	3.4
Asian (%)	19.6	35.0	3.3	0	13.0
Native American (%)	0.02	0	0	0	≈0
Missing/unspecified (%)	1.3	7.0	3.1	6.9	4.2
Impact of race on treatment outcomes (n)	–	–	–	–	–

* White or Caucasian or Non-Hispanic white; Black or African American; Asian or Oriental or Asian/Pacific; the "Missing" category includes missing information, and unspecified races.

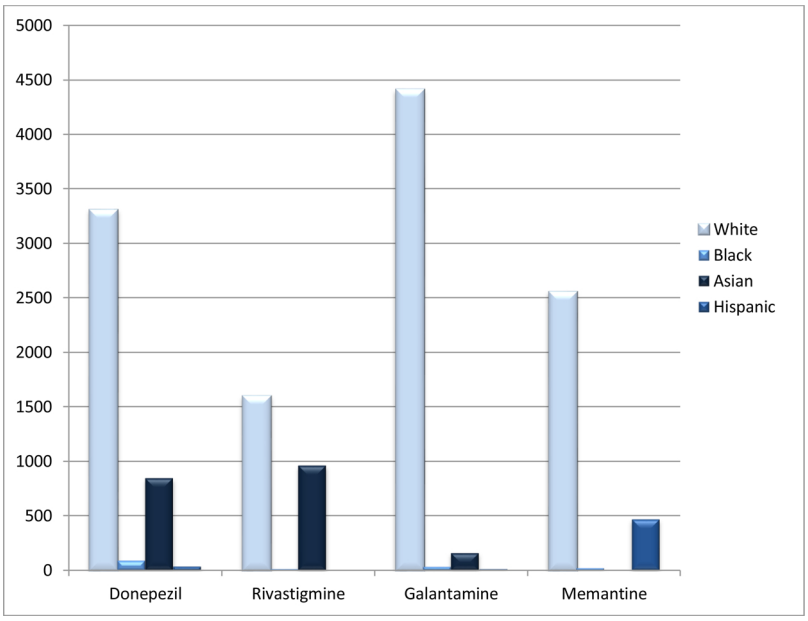

Fig. 3. Race representation in the considered randomized controlled trials. Data are expressed as number of participants. White or Caucasian or Non-Hispanic white; Black or African American; Asian or Oriental or Asian/Pacific.

the efficacy and safety profiles of novel pharmacological treatments has totally been overlooked in RCTs targeting AD. In fact, none of the retrieved studies reported outcome data tabulated by race groups, as now recommended by the Food and Drug Administration(FDA)(Food and Drug Administration, 2016). Moreover, no study performed dedicated analyses to explore the possible association between race and outcomes. In other words, to date, no evidence exists concerning differences across racial groups in the response to the currently marketed pharmacological treatments for AD. Nevertheless, race may account for substantial differences in both pharmacodynamics and pharmacokinetics of drugs (Yasuda et al., 2008). Differences in the effectiveness of medical products (e.g., beta-blockers, angiotensin converting enzyme inhibitors, antidepressants) have already been observed in racially distinct subgroups (Food and Drug Administration, 2016; Murphy et al., 2013; Yasuda et al., 2008). Accordingly, there is evidence for racial disparities in adverse drug events associated with various pharmacological classes (e.g., antiepileptic drugs, anticoagulants, cardiovascular therapies) (Food and Drug Administration, 2016; Baehr et al., 2015; McDowell et al., 2006). More specifically, since AD is increasingly recognized as an area of health disparities, addressing its biological and phenotypic variability will be crucial for the development of precise and effective therapeutics (Ferretti et al., 2018). Therefore, a proper attention should be dedicated to the main sources of heterogeneity (e.g., sex and gender, race, socioeconomic status, comorbidities) when designing and conducting drug development protocols. Encouragingly, a relevant amount of data on these determinants has already been collected by previous RCTs and may be readily available for dedicated analyses within a cost-effective open-data approach (Krumholz and Peterson, 2014).

The present findings are also confirmatory of previous reports concerning the representation of racial groups in AD research. To date, most of existing evidence on the efficacy and safety of the currently adopted medications for AD has been produced in white populations (as easily understood from the geographic location of the studies), whereas only few data have been obtained in other groups (i.e., African Americans and Hispanics). This trend does not reflect the profound demographic modifications that are transforming (and will further transform) our societies worldwide. In the US, more than half of all Americans are projected to belong to a minority group by 2044 (Bureau, 2019). Along the same lines, by 2050, the proportion of racial minorities with AD will increase from 20% to 42% (Alzheimer's Association, 2010). Thus, there is the risk that most of our knowledge on the disease may hardly be transferable to a large part of the global populations of AD patients.

Several hypotheses can be posited to explain our findings. The poor

description of race in RCTs should be framed in a wider tendency to underreport the main sociodemographic attributes of research participants (particularly when represented by older people) (van Deudekom et al., 2017). More specifically, diverse factors might limit the reporting of race such as the reticence of subjects to disclose race/ethnicity, the lack of confidence in methods of ascertaining these attributes, or publication bias (Burke et al., 2011; Corbie-Smith et al., 2003). Language barriers, concerns on documentation status, the lack of accurate knowledge about ongoing protocols, the poor understanding and trust of informed consent procedures, the geographic distribution of enrollment sites can hinder the participation of minority groups in research (Murthy et al., 2004; Swanson and Ward, 1995). Moreover, controversies about "data dredging" and subgroup analysis (frequently not planned in advance and, thus, underpowered to detect statistical differences) could have made the investigators less prone to report and analyze their data by race (Corbie-Smith et al., 2003; Altman, 1998; Schwartz, 2001).

Some limitations of the present review are worth to be mentioned and discussed. Given the main aim of the study (i.e., describing and evaluating the reporting of race in RCTS on AD), we did not perform a quality assessment of the retained articles. In fact, providing information concerning other methodological aspects and risk of biases would not have added further relevance to the observed findings. We had instead decided to restrict the quality ascertainment only to studies investigating the impact of race on treatment outcomes (secondary objective of the review). Nevertheless, no study met the predefined eligibility criteria to be included in this analysis. We limited our review to AD dementia and to the pharmacological therapies currently available in the market. It is possible that race has been (and is being) differently considered by studies targeting other dementias and/or testing novel compounds and/or adopting different methodological designs (e.g., head-to-head randomized trials and studies exploring non-clinical surrogate endpoints). In this latter regard, we only focused on placebo-controlled RCTs investigating clinical outcomes as they are the most commonly used standards for evaluating efficacy and safety/tolerability in clinical research and guiding physicians toward evidence-based decision-making (especially in the field of AD (Cummings et al., 2018)). Finally, we did not focus on those sociocultural determinants (e.g., nationality, language, religion) defining the ethnicity of participants.

In conclusion, race has insufficiently been reported in previous interventional studies on AD. Its potential association with the effectiveness and safety/tolerability of the tested medications has completely been neglected. According to available guidelines and recommendations (Food and Drug Administration, 2016; "Uniform requirements for manuscripts submitted to biomedical journals", 2010), a greater effort should be made to improve the collection and reporting of data on the race (and ethnicity) of research participants, including those with AD. Moreover, this attribute should always be taken into account when performing efficacy and safety analysis. In this regard, the FDA requires sponsors to present a summary of safety and effectiveness data by demographic subgroups (including racial subgroups), as well as an analysis of whether modifications of dose or dosage intervals are needed for specific subsamples (Food and Drug Administration, 2016). Overall, these measures may likely enhance the external validity of RCTs findings, improve the discrimination between responders and non-responders (thus resulting in a better definition of efficacy and safety profiles for novel medications), and pave the way for the identification of precision medicine approaches.

Conflicts of interest

Marco Canevelli is supported by a research grant of the Italian Ministry of Health (GR-2016-02364975) for the project "Dementia in immigrants and ethnic minorities living in Italy: clinical-epidemiological aspects and public health perspectives" (ImmiDem).

Matteo Cesari has received honoraria for presentations at scientific meetings and/or research funding from Nestlé and Pfizer. He is involved in the coordination of an Innovative Medicines Initiative-funded project (including partners from the European Federation Pharmaceutical Industries and Associates [Sanofi, Novartis, Servier, GSK, Lilly]). The other Authors have no conflict of interest to disclose.

Role of the funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A

Table A1

Table A1
Characteristics of the 49 studies included in the primary and secondary analyses. Data are expressed as % or mean ± standard deviation.

Reference	Country	n =	Mean age	Sex (F)	Race #					
					White	Black	Asian	Hispanic	Nat. Am.	Missing
Donepezil										
Rogers 1996	US	161	71.8 ± 1.1*	60.2	96.3	3.1	0	0	0	0.6
Rogers 1998a	US	468	73.7	63.5	95.7	2.8	0	0	0	1.5
Rogers 1998b	US	473	73.4 ± 1.1*	61.9	94.9	3.0	0	0	0	2.1
Burns 1999	AU, BE, CA, DE, FR, IE, NZ, UK, ZA	818	71.7 ± 0.6*	57.5	99.4	0	0	0	0	0.6
Greenberg 2000	US	60	75.0 ± 9.5	50.0	–	–	–	–	–	–
Homma 2000	JP	228	69.8 ± 0.5*	67.1	0	0	100	0	0	0
Feldman 2001	AU, CA, FR	290	73.6 ± 0.5*	61.0	–	–	–	–	–	–
Mohs 2001	US	431	75.3 ± 0.1*	62.9	92.1	2.8	0	0	0	5.1
Winblad 2001	DK, FI, NL, NO, SE	286	72.5 ± 0.6*	64.3	100	0	0	0	0	0
Courtney 2004	UK	565	–	59.2	–	–	–	–	–	–
Holmes 2004	UK	96	78.7 ± 0.1*	61.5	–	–	–	–	–	–
Seltzer 2004	US	153	74.0 ± 1.3*	53.6	–	–	–	–	–	–
Winblad 2006	SE	248	84.9 ± 0.6*	76.6	99.6	0	0	0	0	0.4
Black 2007	AU, CA, FR, UK, US	343	78.0 ± 8.1	70.3	76.1	11.7	1.2	10.5	0.3	0.2

(*continued on next page*)

Table A1 (*continued*)

Reference	Country	n=	Mean age	Sex (F)	Race #					
					White	Black	Asian	Hispanic	Nat. Am.	Missing
Howard 2007	UK	259	84.6 ± 0.3*	84.5	97.3	1.9	0	0	0	0.8
Winstein 2007	US	10	86.1 ± 8.1	70.0	–	–	–	–	–	–
Homma 2008	JP	302	78.2 ± 1.4*	81.1	0	0	100	0	0	0
Jia 2017	CN	313	70.8 ± 1.1*	64.9	0	0	100	0	0	0
Rivastigmine										
Agid 1998	AT, BE, CH, CZ-SK, DE, DK, FI, FR, IE, NO, SE, UK	402	69.4 ± 8.4	56.2	–	–	–	–	–	–
Corey-Bloom 1998	US	699	74.5	60.9	–	–	–	–	–	–
Forette 1999	BE, CA, FR, NO, UK	70	71.2 ± 7.5	–	–	–	–	–	–	–
Rosler 1999	AT, CH, DE, FR, US	725	72.0	59.0	97.0	0	0	0	0	3.0
Potkin 2001	US	27	75.9 ± 6.9	–	–	–	–	–	–	–
Lopez-Pousa 2004	ES	218	77.6	77.1	–	–	–	–	–	–
Karaman 2005	TR	44	73.7 ± 0.5*	54.5	–	–	–	–	–	–
Feldman 2007	AU, CA, IE, IT, UK, ZA	678	71.4 ± 0.4*	59.0	–	–	–	–	–	–
Winblad 2007a-b	CL, CZ, DE, DK, FI, GT, IL, IT, KR, MX, NO, PE, PL, PT, RU, SE, SK, TW, US, UY, VE	1190	73.6 ± 0.6*	66.5	75.0	0.9	9.1	0	0	15.0
Nakamura 2011	JP	855	74.6 ± 7.2	68.3	0	0	100	0	0	0
Galantamine										
Raskind 2000	US	636	75.4 ± 0.5*	61.9	91.4	0	0	0	0	8.6
Tariot 2000	US	978	76.9 ± 0.8*	63.9	92.8	0	0	0	0	7.2
Wilcock 2000	CA, DE, FI, FR, NO, SE, NL, UK	653	72.2 ± 0.4*	62.6	–	–	–	–	–	–
Rockwood 2001	AU, CA, NZ, UK, US, ZA	386	75.0 ± 0.4*	55.7	–	–	–	–	–	–
Wilkinson 2001	UK	285	73.7 ± 1.3*	57.5	–	–	–	–	–	–
Brodaty 2005	AU, CA, NZ, ZA, US	965	76.5 ± 7.8	64.0	91.1	3.4	2.2	1.4	0	1.9
Suh 2008	KR	138	75.5 ± 8.5	75.4	0	0	100	0	0	0
Burns 2009	BE, CH, ES, FI, FR, IT, NL, NO, SE, UK	407	83.6 ± 0.1*	81.0	–	–	–	–	–	–
Hager (2014)	CZ, DE, EE, FR, GR, IT, LV, LT, RO, RU, SI, SK, UA	2045	73.0 ± 8.8	64.8	99.9	0	0	0	0	0.1
Memantine										
Reisberg 2003	US	252	76.1 ± 8.1	67.5	90.1	4.4	0	0	0	5.5
Tariot 2004	US	404	75.5 ± 0.0*	64.8	91.1	0	0	0	0	8.9
Peskind 2006	US	403	77.5 ± 0.7*	58.8	91.3	0	0	0	0	8.7
van Dyck 2007	US	350	78.2 ± 0.1*	71.4	80.9	0	0	0	0	19.1
Bakchine 2008	AT, BE, DK, ES, FI, FR, GR, LT, NL, PL, SE, UK	470	74	63.0	100	0	0	0	0	0
Porsteinsson 2008	US	433	75.4 ± 0.8*	52.2	–	–	–	–	–	–
Fox 2012	UK	149	84.6 ± 0.3*	73.8	98.0	0	0	0	0	2.0
Saxton 2012	AU, NZ, ZA	265	74.9 ± 0.2*	58.1	90.6	0	0	0	0	9.4
Howard 2012	UK	295	77.1 ± 8.4	65.0	95.0	3.0	0	0	0	2.0
Grossberg 2013	AR, CL, MX, US	677	76.5 ± 0.4*	72.0	25.0	0	0	68.9	0	6.1
Herrmann 2013	CA	369	74.9 ± 0.3*	58.3	–	–	–	–	–	–
Wang 2013	CN	22	65.2 ± 0.7*	63.6	–	–	–	–	–	–

AR: Argentina; AT: Austria; AU: Australia; BE: Belgium; CA: Canada; CH: Switzerland; CL: Chile; CN: China; CZ: Czech Republic; DE: Germany; DK: Denmark; EE: Estonia; ES: Spain; FI: Finland; FR: France; GR: Greece; GT: Guatemala; IE: Ireland; IL: Israel; IT: Italy; JP: Japan; KR: Korea; LV: Latvia; LT: Lithuania; MX: Mexico; NL: Netherlands; NZ: New Zealand; NO: Norway; PE: Peru; PL: Poland; PT: Portugal; RO: Romania; RU: Russia; SE: Sweden; SK: Slovakia; SI: Slovenia; TR: Turkey; TW: Taiwan; UA: Ukraine; UK: United Kingdom; US: United States; VE: Venezuela; ZA: South Africa.
*Weighted mean values. #White or Caucasian or Non-Hispanic white; Black of African American; Asian or Oriental or Asian/Pacific; the "Missing" category includes missing information, and unspecified races. Nat. Am. = Native American. - Data not available.

References

Altman, D.G., 1998. Within trial variation—a false trail? J. Clin. Epidemiol. 51, 301–303. https://doi.org/10.1016/S0895-4356(98)00005-5.

Alzheimer's Association, 2010. 2010 Alzheimer's disease facts and figures. Alzheimers Dement. 6, 158–194. https://doi.org/10.1016/j.jalz.2010.01.009.

Alzheimer's Association, 2016. 2016 Alzheimer's disease facts and figures. Alzheimers Dement. 12, 459–509.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders (IV-TR), 4th edn—text revised. Washington, DC.

Baehr, A., Peña, J.C., Hu, D.J., 2015. Racial and ethnic disparities in adverse drug events: a systematic review of the literature. J. Racial Ethn. Health Disparities 2, 527–536. https://doi.org/10.1007/s40615-015-0101-3.

Berger, J.S., Melloni, C., Wang, T.Y., Dolor, R.J., Frazier, C.G., Samad, Z., Peterson, E.D., Mark, D.B., Newby, L.K., 2009. Reporting and representation of race/ethnicity in published randomized trials. Am. Heart J. 158, 742–747. https://doi.org/10.1016/j.ahj.2009.08.018.

Bureau, U.C., 2019. Projections of the Size and Composition of the U.S: 2014-2060 [WWW Document]. n.d.. (Accessed 7.19.18). https://www.census.gov/library/publications/2015/demo/p25-1143.html.

Burke, J.F., Brown, D.L., Lisabeth, L.D., Sanchez, B.N., Morgenstern, L.B., 2011. Enrollment of women and minorities in NINDS trials. Neurology 76, 354–360. https://doi.org/10.1212/WNL.0b013e3182088260.

Canevelli, M., Bruno, G., Vanacore, N., de Lena, C., Cesari, M., 2018a. Are we really tackling the "evidence-based medicine issue" in Alzheimer's disease? Eur. J. Intern. Med. 35, e29–e30.

Canevelli, M., Bruno, G., Vico, C., Zaccaria, V., Lacorte, E., Iavicoli, I., Vanacore, N., Cesari, M., 2018b. Socioeconomic disparities in clinical trials on Alzheimer's disease: a systematic review. Eur. J. Neurol. 52, e32–e34. https://doi.org/10.1111/ene.13587.

Chapin-Bardales, J., Rosenberg, E.S., Sullivan, P.S., 2017. Trends in racial/ethnic disparities of new AIDS diagnoses in the United States, 1984-2013. Ann. Epidemiol. 27, 329–334. https://doi.org/10.1016/j.annepidem.2017.04.002. e2.

Clark, C.M., DeCarli, C., Mungas, D., Chui, H.I., Higdon, R., Nuñez, J., Fernandez, H., Negrón, M., Manly, J., Ferris, S., Perez, A., Torres, M., Ewbank, D., Glosser, G., van Belle, G., 2005. Earlier onset of Alzheimer disease symptoms in Latino individuals compared with Anglo individuals. Arch. Neurol. 62, 774–778. https://doi.org/10.1001/archneur.62.5.774.

Collins, F.S., Varmus, H., 2015. A new initiative on precision medicine. N. Engl. J. Med. 372, 793–795. https://doi.org/10.1056/NEJMp1500523.

Cooper, C., Tandy, A.R., Balamurali, T.B.S., Livingston, G., 2010. A systematic review and meta-analysis of ethnic differences in use of dementia treatment, care, and research. Am. J. Geriatr. Psychiatry 18, 193–203. https://doi.org/10.1097/JGP.0b013e3181bf9caf.

Corbie-Smith, G., St George, D.M.M., Moody-Ayers, S., Ransohoff, D.F., 2003. Adequacy of reporting race/ethnicity in clinical trials in areas of health disparities. J. Clin. Epidemiol. 56, 416–420.

Cummings, J., Lee, G., Ritter, A., Zhong, K., 2018. Alzheimer's disease drug development pipeline: 2018. Alzheimers Dement. 4, 195–214. https://doi.org/10.1016/j.trci.2018.03.009.

Eley, J.W., Hill, H.A., Chen, V.W., Austin, D.F., Wesley, M.N., Muss, H.B., Greenberg, R.S., Coates, R.J., Correa, P., Redmond, C.K., 1994. Racial differences in survival from breast cancer. Results of the National Cancer Institute Black/White Cancer Survival

Study. JAMA 272, 947–954.
Ferretti, M.T., Iulita, M.F., Cavedo, E., Chiesa, P.A., Schumacher Dimech, A., Santuccione Chadha, A., Baracchi, F., Girouard, H., Misoch, S., Giacobini, E., Depypere, H., Hampel, H., Women's Brain Project and the Alzheimer Precision Medicine Initiative, 2018. Sex differences in Alzheimer disease - the gateway to precision medicine. Nat. Rev. Neurol. https://doi.org/10.1038/s41582-018-0032-9.
Food and Drug Administration, 2016. Collection of Race and Ethnicity Data in Clinical Trials. Guidance for Industry and Food and Drug Administration Staff.
Frank, A.T.H., Zhao, B., Jose, P.O., Azar, K.M.J., Fortmann, S.P., Palaniappan, L.P., 2014. Racial/ethnic differences in dyslipidemia patterns. Circulation 129, 570–579. https://doi.org/10.1161/CIRCULATIONAHA.113.005757.
Gillum, R.F., Kwagyan, J., Obisesan, T.O., 2011. Ethnic and geographic variation in stroke mortality trends. Stroke 42, 3294–3296. https://doi.org/10.1161/STROKEAHA.111.625343.
Graff-Radford, N.R., Besser, L.M., Crook, J.E., Kukull, W.A., Dickson, D.W., 2016. Neuropathologic differences by race from the national Alzheimer's coordinating center. Alzheimers Dement. 12, 669–677. https://doi.org/10.1016/j.jalz.2016.03.004.
Hoel, A.W., Kayssi, A., Brahmanandam, S., Belkin, M., Conte, M.S., Nguyen, L.L., 2009. Under-representation of women and ethnic minorities in vascular surgery randomized controlled trials. J. Vasc. Surg. 50, 349–354. https://doi.org/10.1016/j.jvs.2009.01.012.
Howard, R.J., Juszczak, E., Ballard, C.G., Bentham, P., Brown, R.G., Bullock, R., Burns, A.S., Holmes, C., Jacoby, R., Johnson, T., Knapp, M., Lindesay, J., O'Brien, J.T., Wilcock, G., Katona, C., Jones, R.W., DeCesare, J., Rodger, M., CALM-AD Trial Group, 2007. Donepezil for the treatment of agitation in Alzheimer's disease. N. Engl. J. Med. 357, 1382–1392. https://doi.org/10.1056/NEJMoa066583.
Howard, R., McShane, R., Lindesay, J., Ritchie, C., Baldwin, A., Barber, R., Burns, A., Dening, T., Findlay, D., Holmes, C., Hughes, A., Jacoby, R., Jones, Rob, Jones, Roy, McKeith, I., Macharouthu, A., O'Brien, J., Passmore, P., Sheehan, B., Juszczak, E., Katona, C., Hills, R., Knapp, M., Ballard, C., Brown, R., Banerjee, S., Onions, C., Griffin, M., Adams, J., Gray, R., Johnson, T., Bentham, P., Phillips, P., 2012. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N. Engl. J. Med. 366, 893–903. https://doi.org/10.1056/NEJMoa1106668.
Kaplan, J.B., Bennett, T., 2003. Use of race and ethnicity in biomedical publication. JAMA 289, 2709–2716. https://doi.org/10.1001/jama.289.20.2709.
Krumholz, H.M., Peterson, E.D., 2014. Open access to clinical trials data. JAMA 312, 1002–1003. https://doi.org/10.1001/jama.2014.9647.
Lee, L.M., Lehman, J.S., Bindman, A.B., Fleming, P.L., 2003. Validation of race/ethnicity and transmission mode in the US HIV/AIDS reporting system. Am. J. Public Health 93, 914–917.
Ma, I.W.Y., Khan, N.A., Kang, A., Zalunardo, N., Palepu, A., 2007. Systematic review identified suboptimal reporting and use of race/ethnicity in general medical journals. J. Clin. Epidemiol. 60, 572–578. https://doi.org/10.1016/j.jclinepi.2006.11.009.
Mayeda, E.R., Glymour, M.M., Quesenberry, C.P., Whitmer, R.A., 2016. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. Alzheimers Dement. 12, 216–224. https://doi.org/10.1016/j.jalz.2015.12.007.
McDowell, S.E., Coleman, J.J., Ferner, R.E., 2006. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ 332, 1177–1181. https://doi.org/10.1136/bmj.38803.528113.55.
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34, 939–944.
Mehta, K.M., Yeo, G.W., 2017. Systematic review of dementia prevalence and incidence in United States race/ethnic populations. Alzheimers Dement. 13, 72–83. https://doi.org/10.1016/j.jalz.2016.06.2360.
Mehta, K.M., Yin, M., Resendez, C., Yaffe, K., 2005. Ethnic differences in acetylcholinesterase inhibitor use for Alzheimer disease. Neurology 65, 159–162. https://doi.org/10.1212/01.wnl.0000167545.38161.48.
Mehta, K.M., Yaffe, K., Pérez-Stable, E.J., Stewart, A., Barnes, D., Kurland, B.F., Miller, B.L., 2008. Race/ethnic differences in AD survival in US Alzheimer's disease centers. Neurology 70, 1163–1170. https://doi.org/10.1212/01.wnl.0000285287.99923.3c.
Mitchell, K.W., Carey, L.A., Peppercorn, J., 2009. Reporting of race and ethnicity in breast cancer research: room for improvement. Breast Cancer Res. Treat. 118, 511–517. https://doi.org/10.1007/s10549-009-0411-4.
Murphy, E., Hou, L., Maher, B.S., Woldehawariat, G., Kassem, L., Akula, N., Laje, G., McMahon, F.J., 2013. Race, genetic ancestry and response to antidepressant treatment for major depression. Neuropsychopharmacology 38, 2598–2606. https://doi.org/10.1038/npp.2013.166.
Murthy, V.H., Krumholz, H.M., Gross, C.P., 2004. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA 291, 2720–2726. https://doi.org/10.1001/jama.291.22.2720.
Rodriguez, F.S., Aranda, M.P., Lloyd, D.A., Vega, W.A., 2018. Racial and ethnic disparities in dementia risk among individuals with low education. Am. J. Geriatr. Psychiatry 26, 966–976. https://doi.org/10.1016/j.jagp.2018.05.011.
Rogers, S.L., Friedhoff, L.T., 1996. The Efficacy and Safety of Donepezil in Patients with Alzheimer's Disease: Results of a US Multicentre, Randomized, Double-blind, Placebo-controlled Trial. The Donepezil Study Group, Dement. Basel Switz. 7, pp. 293–303.
Sardar, M.R., Badri, M., Prince, C.T., Seltzer, J., Kowey, P.R., 2014. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. JAMA Intern. Med. 174, 1868–1870. https://doi.org/10.1001/jamainternmed.2014.4758.
Schwartz, R.S., 2001. Racial profiling in medical research. N. Engl. J. Med. 344, 1392–1393. https://doi.org/10.1056/NEJM200105033441810.
Shadlen, M.F., Larson, E.B., Gibbons, L., McCormick, W.C., Teri, L., 1999. Alzheimer's disease symptom severity in blacks and whites. J. Am. Geriatr. Soc. 47, 482–486.
Shin, J., Doraiswamy, P.M., 2016. Underrepresentation of african-Americans in Alzheimer's trials: a call for affirmative action. Front. Aging Neurosci. 8, 123. https://doi.org/10.3389/fnagi.2016.00123.
Sink, K.M., Covinsky, K.E., Newcomer, R., Yaffe, K., 2004. Ethnic differences in the prevalence and pattern of dementia-related behaviors. J. Am. Geriatr. Soc. 52, 1277–1283. https://doi.org/10.1111/j.1532-5415.2004.52356.x.
Swanson, G.M., Ward, A.J., 1995. Recruiting minorities into clinical trials: toward a participant-friendly system. J. Natl. Cancer Inst. 87, 1747–1759.
Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication, 2010. J. Pharmacol. Pharmacother. 1, 42–58.
United States Census Bureau, 2017. Race and Ethnicity.
van Deudekom, F.J., Postmus, I., van der Ham, D.J., Pothof, A.B., Broekhuizen, K., Blauw, G.J., Mooijaart, S.P., 2017. External validity of randomized controlled trials in older adults, a systematic review. PLoS One 12, e0174053. https://doi.org/10.1371/journal.pone.0174053.
Welsh, K.A., Fillenbaum, G., Wilkinson, W., Heyman, A., Mohs, R.C., Stern, Y., Harrell, L., Edland, S.D., Beekly, D., 1995. Neuropsychological test performance in African-American and white patients with Alzheimer's disease. Neurology 45, 2207–2211.
Winblad, B., Cummings, J., Andreasen, N., Grossberg, G., Onofrj, M., Sadowsky, C., Zechner, S., Nagel, J., Lane, R., 2007. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease–rivastigmine patch versus capsule. Int. J. Geriatr. Psychiatry 22, 456–467. https://doi.org/10.1002/gps.1788.
Yaffe, K., Falvey, C., Harris, T.B., Newman, A., Satterfield, S., Koster, A., Ayonayon, H., Simonsick, E., 2013. Effect of socioeconomic disparities on incidence of dementia among biracial older adults: prospective study. BMJ 347, f7051. https://doi.org/10.1136/bmj.f7051.
Yasuda, S.U., Zhang, L., Huang, S.-M., 2008. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. Clin. Pharmacol. Ther. 84, 417–423. https://doi.org/10.1038/clpt.2008.141.