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RESEARCH ARTICLE

Health equity considerations in pragmatic trials in Alzheimer's and dementia disease: Results from a methodological review

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Abstract

Introduction: To improve dementia care delivery for persons across all backgrounds, it is imperative that health equity is integrated into pragmatic trials.

Methods: We reviewed 62 pragmatic trials of people with dementia published 2014 to 2019. We assessed health equity in the objectives; design, conduct, analysis; and reporting using PROGRESS-Plus which stands for Place of residence, Race/ethnicity, Occupation, Gender/sex, Religion, Education, Socioeconomic status, Social capital, and other factors such as age and disability.

Results: Two (3.2%) trials incorporated equity considerations into their objectives; nine (14.5%) engaged with communities; 4 (6.5%) described steps to increase enrollment from equity-relevant groups. Almost all trials (59, 95.2%) assessed baseline balance for at least one PROGRESS-Plus characteristic, but only 10 (16.1%) presented subgroup analyses across such characteristics. Differential recruitment, attrition, implementation, adherence, and applicability across PROGRESS-Plus were seldom discussed.

Stuart G Nicholls and Ahmed A Al-Jaishi contributed equally to this study.

Discussion: Ongoing and future pragmatic trials should more rigorously integrate equity considerations in their design, conduct, and reporting.

KEYWORDS
Alzheimer's disease, cluster randomized trials, covariate adjustment, dementia, health equity, pragmatic trials, randomization, subgroup analyses, treatment effect heterogeneity

Highlights

- Few pragmatic trials are explicitly designed to inform equity-relevant objectives.
- Few pragmatic trials take steps to increase enrollment from equity-relevant groups.
- Disaggregated results across equity-relevant groups are seldom reported.
- Adherence to existing tools (e.g., IMPACT Best Practices, CONSORT-Equity) is key.

1 | INTRODUCTION

Alzheimer's disease (AD) and AD-related dementias (AD/ADRD) are major public health concerns with up to 10 million new cases annually worldwide; it is the seventh leading cause of death among adults and death rates are increasing.[1] Furthermore, there are substantial inequalities in the prevalence and management of AD/ADRD across populations.[2–5] In the United States, about two-thirds of people diagnosed with AD/ADRD are women.[6] Older Blacks are twice as likely, and older Hispanic Americans 1.5 times as likely, to have AD/ADRD than older Whites.[7] Lower educational attainment, unemployment, poor quality employment, poor housing conditions and neighborhood deprivation exacerbate the effects of social isolation and lack of mental stimulation and physical activity which are associated with cognitive impairment and dementia.[5] Moreover, the quality of care received by dementia patients shows persistent racial and regional differences.[8] Minority ethno-racial and lower socioeconomic groups have fewer resources and supports to manage the disease.[9] Caregivers are also vulnerable. Dementia care is primarily provided by informal or family caregivers who are most often women.[10]

Despite the known inequalities and inequities in AD/ADRD prevalence, management and outcomes, population groups that experience health disparities continue to be severely underrepresented in randomized controlled trials.[11,12] There is a need for a robust evidence base detailing the effectiveness of AD/ADRD interventions in minority ethno-racial and other socially marginalized populations living with dementia. Consideration must be given to how equity-relevant factors such as race, sex/gender, and socioeconomic status intersect to affect the provision of appropriate dementia care.[13] To inform healthcare policy and practice, we require trials that better reflect the population of people living with dementia, are designed with explicit consideration of health equity, and examine and report effects across subgroups defined by equity-relevant characteristics.

Existing health equity research frameworks that may guide the integration of equity considerations in the design and conduct of pragmatic trials include the National Institutes of Health (NIH) Health Disparities Research Framework,[20] and PROGRESS-Plus – which identifies social stratification factors understood to influence health opportunities and outcomes.[14,15] The PROGRESS-Plus acronym refers to Place of residence, Race/ethnicity/culture/language, Occupation, Gender/sex, Religion, Education, Socioeconomic status, and Social capital and "Plus" factors that indicate other possible determinants of inequity: Plus 1 (age, disability or other personal characteristics attracting discrimination), Plus 2 (feature of relationships that may affect inequity), and Plus 3 (time-dependent relationships that may affect inequity).[14] To best inform health equity-relevant decisions and policies, well-designed and conducted trials must also clearly and transparently report their health equity-relevant details. The 2017 CONSORT (Consolidated Standards of Reporting Trials)-Equity extension was developed with the goal of improving completeness and transparency of health equity-relevant details of trials.[16]

Trials designed to provide evidence that is relevant to clinical or health policy decision-making are described as having a pragmatic (as opposed to explanatory) orientation.[17] To promote pragmatic trials in AD/ADRD, the National Institute on Aging (NIA) funded the **Im**bedded **P**ragmatic **A**lzheimer's disease (AD) and AD-related dementias (AD/ADRD) **C**linical **T**rials (IMPACT) Collaboratory, which has the mission to build the nation's capacity to conduct pragmatic trials of non-pharmacological interventions embedded within healthcare systems for people living with dementia and their care partners.[18] Led by its experts in health equity, IMPACT recently published "Best Practices" to incorporate health equity considerations in all aspects of pragmatic trial design for dementia care across six stages of research[19]: selecting a research question that matters to populations experiencing health inequities; stakeholder engagement; design and analysis; intervention design and implementation; healthcare system and participant selection; and outcome selection.

While there has been renewed interest in designing and conducting trials in AD/ADRD that better reflect the population and care settings,[20] the degree to which health equity considerations have informed the design, conduct, analysis, and reporting of pragmatic trials is unclear. We reviewed pragmatic trials conducted in AD/ADRD to

describe the extent of equity considerations in: (1) the trial focus and objectives; (2) study design, conduct, and analysis; and (3) reporting of results.

RESEARCH IN CONTEXT

1. **Systematic Review**: A previously published MEDLINE filter for trials with pragmatic aims and the Cochrane Dementia and Cognitive Improvement Group's PubMed filter were used to identify primary reports of trials involving people living with dementia, published 2014-2019. We assessed whether equity-relevant characteristics were considered in the study objectives; design, conduct, analysis; and reporting of results.
2. **Interpretation**: Few trials were explicitly designed to generate health equity-relevant evidence. Health equity considerations were mostly limited to assessment of balance at baseline and covariate adjustment in analyses, and most often involved age and sex. However, these practices alone do not facilitate conclusions about treatment-effect heterogeneity across equity-relevant groups. Ideally, disaggregated results and statistical analyses incorporating intervention-by-covariate interactions should be presented across all pre-planned equity-relevant subgroups.
3. **Future Directions**: Adhering to emerging guidelines for design, conduct, and reporting is key. Future studies are needed to evaluate the extent to which recent initiatives may have improved practices.

2 | METHODS

2.1 | Identification of trials included in the review

This study was a secondary analysis of 62 pragmatic trials in AD/ADRD identified in a previously reported review of methodological[21] and ethical characteristics of these trials.[22] Details concerning the search, eligibility, and screening have been published and are summarized in Appendix A. In brief, we used a validated search filter[23] to identify 4337 trials in MEDLINE with pragmatic aims published January 1, 2014, to April 3, 2019. We then applied a separate PubMed search filter from the Cochrane Dementia and Cognitive Improvement Group[24] as well as MeSH terms to these trials to identify the subset that (a) specifically focused on people living with dementia or (b) focused on a broader cohort of older adults (65 years or older) but included people living with dementia as a defined population of interest.

2.2 | Data collection and extraction

Descriptive characteristics of each trial were obtained from our previously published reports[21,22]: country of study conduct; setting (primary care, hospital care, nursing homes, communities); type of experimental interventions; trial design (cluster or individual randomization); number and types of participants randomized (providers, people living with dementia, caregivers); whether and how participants were recruited into the trial (e.g., from clinic patient panels, community outreach efforts); and funding source.

We extracted data on the extent to which each trial considered equity-relevant characteristics in its study objectives; its design, conduct and analysis; and its reporting. In each case, equity-relevance was operationalized using PROGRESS-Plus characteristics. As an example, we extracted the PROGRESS-Plus factors that each trial reported in its baseline descriptive statistics. The data extraction form used to guide extractions is provided in Appendix B. The first domain of data extraction considered the extent that the trial had an equity-relevant focus. We extracted whether the title included equity-relevant terms; whether there was an explicit objective pertaining to equity; whether any results in the abstract were reported across equity-relevant subgroups; and whether the introduction/background of the report discussed anticipated differences in baseline risk, prognostic factors, intervention acceptability, coverage, or effectiveness across subgroups defined by equity-relevant characteristics. Engagement with patients or other key stakeholders (e.g., knowledge users, community groups, decision-makers)[25] has been demonstrated to enhance the relevance of clinical trials[26] and may draw attention to equity-relevant considerations.[27] Therefore, in the first domain we also extracted whether the study reported any patient or other stakeholder engagement. If this was not explicitly reported, we reviewed the acknowledgments and author affiliations to determine whether any such stakeholders were acknowledged or included as co-authors in the manuscript.

The second domain of data extraction examined the extent to which authors incorporated equity-relevant considerations into the study design, conduct, and analysis. Specifically, we extracted: whether eligibility criteria (at the site and individual levels) were defined across equity-relevant characteristics; whether any over-sampling or tailored recruitment designed to reach populations across equity-relevant subgroups was reported as being used; whether randomization was restricted (e.g., stratified) based on equity-relevant factors; whether the analysis adjusted for any equity-relevant characteristics as covariates; and whether any subgroup analyses across equity-relevant characteristics were planned or reported.

The third domain of data extraction concerned the extent to which study results were presented and interpreted along equity-relevant considerations. We extracted whether baseline descriptive statistics were presented across any equity-relevant characteristics; whether differential recruitment, retention, and implementation of and adherence to the intervention were discussed across such characteristics; and whether generalizability/applicability was discussed across such characteristics.

Finally, for the subset of trials reporting subgroup analyses, we extracted details regarding the number of distinct outcomes and

subgroup variables involved as well as statistical methods used. We also extracted whether subgroup analyses were clearly prespecified and justified; whether any of the subgroup variables were restricted in the randomization; whether power or sample size considerations for subgroup analyses were addressed; whether any correction for multiple testing was reported; and whether a forest plot was used to report subgroup results.[28–30]

The data extraction form was pilot tested by seven experienced reviewers (A.A., K.C., L.M., M.T.M., K.D.P., H.N., M.T.) using three randomized trials as a training and calibration exercise. Once completed, reviewers met to review discrepancies and refine the extraction form. Subsequently, the remaining studies were distributed among the first six reviewers, with two extractors per trial. Next, P.N. and L.A. extracted additional details on the subset of trials reporting subgroup analyses. Each pair met to discuss discrepancies; M.T. or V.W. were consulted when discrepancies could not be resolved.

2.3 | Analysis

We summarized results using frequencies and percentages for categorical variables and medians with quartile ranges or mean with standard deviation for continuous variables. We used the Airtable platform (San Francisco)[31] for data extraction/management and SAS 9.4 (Cary, NC) software for our analyses.[32]

3 | RESULTS

Table 1 provides descriptive statistics for the 62 included trials. Trials were conducted mainly in North America and Europe, primarily in nursing homes, and evaluated mainly non-pharmacological interventions targeted at people living with dementia. Nearly two-thirds used cluster randomization; the median number of participants was 267 (Q1-Q3: 140-402). All but three trials actively recruited participants — almost all from patient rosters in an existing clinical or health system as opposed to from community outreach. Funding sources were primarily non-industry.

Table 2 describes the extent that health equity was a focus of the trial. Two trials (3.2%) had explicit health equity objectives: one focused on the impact of an intervention in minority and lower socioeconomic status populations and the other on institutionalized patients with additional comorbidities. Three trials (4.8%) reported results in the abstract across equity-relevant subgroups, and 12 (19.4%) described anticipated differences in baseline risk, prognostic factors, intervention acceptability, coverage, or effectiveness across equity-relevant characteristics in the introduction/background of the trial report. Nine (14.5%) indicated some patient or public engagement in the design or conduct of the trial, while 13 (21.0%) indicated engagement with stakeholders other than patients.

Table 3 describes whether equity-relevant characteristics were considered in the study design, conduct, and analysis. The specific equity-relevant characteristics considered are summarized in Appendix C. Three trials (4.8%) defined eligibility at the site level across equity-relevant criteria (in each case, place of residence), and 24 (38.7%) at the individual level (most commonly race/ethnicity/language/culture and social capital (e.g., requiring a caregiver)). Three trials (4.8%) described special recruitment procedures to increase enrolment of sites that serve minority and socially marginalized groups, and 4 (6.5%) to increase enrolment of individuals from minority and socially marginalized groups. Among 35 trials (56.5%) with some form of restricted randomization, 18 (51.4%) used an equity-relevant characteristic to balance randomization. Among 51 trials (82.3%) reporting covariate-adjusted analyses, 38 (74.5%) adjusted for one or more equity-relevant characteristics. Ten trials (16.1%) reported subgroup analyses; nearly all of these (8, 80%) defined subgroups on one or more equity-relevant characteristics — most commonly the "Plus" characteristic of age/disability followed by sex (Appendix C).

Table 4 describes whether equity-relevant characteristics were considered in the presentation and interpretation of results. The specific equity-relevant characteristics considered are summarized in Appendix C. Seven trials (11.3%) assessed balance at baseline on equity-relevant characteristics at the site or health system level. Although nearly all (58, 93.5%) assessed baseline balance on sex and age/disability, a minority considered other characteristics such as race/ethnicity/language/culture, place of residence, education level, or social capital. Fifteen (24.2%) discussed the presence or absence of differential recruitment across equity-relevant characteristics; 5 (8.1%) differential attrition; 2 (3%) differential implementation/delivery of the intervention; 2 (3.2%) adherence; and 19 (30.6%) generalizability/applicability. (The specific equity-relevant characteristics discussed were not extracted for these items.) Figure 1 compares the percentage of trials reporting equity-relevant characteristics at baseline and in covariate adjustment to the percentage reporting subgroup analyses across these characteristics.

Table 5 presents additional results for the 10 studies reporting subgroup analyses. The statistical method used was a stratified analysis (2 trials), an interaction test (7), and unclear (1). Four trials clearly prespecified all subgroup analyses, 2 provided a rationale for all subgroup analyses, 1 restricted randomization on a subgroup variable, 0 presented sample size calculations, 0 reported a multiplicity adjustment, and 1 reported results using a forest plot.

4 | DISCUSSION

4.1 | Summary of main findings

We provided a descriptive assessment of health equity considerations in 62 pragmatic trials in AD/ADRD. We found that few trials explicitly incorporated equity considerations in their objectives, despite nearly one-fifth indicating in the introduction/background that some equity-relevant differences were anticipated. A minority of trials engaged patients or other stakeholders that represent the study population in the study design or conduct, and few described steps to improve representation through enhanced procedures such as targeted

TABLE 1 Descriptive characteristics of trials included in the review ($N = 62$)

Characteristic	Frequency (%)*
Country of study conduct†	
Canada	2 (3.2%)
United States of America	13 (21.0%)
United Kingdom/ European Union	31 (50.0%)
Australia or New Zealand	5 (8.1%)
Low and Middle-Income Country	4 (6.5%)
Other	9 (14.5%)
Setting	
Primary care	8 (12.9%)
Hospital care	6 (9.7%)
Nursing homes	28 (45.2%)
Communities	15 (24.2%)
Other	5 (8.1%)
Intervention†	
Educational intervention targeting health professionals	19 (30.6%)
Quality improvement targeting organization/healthcare system	17 (27.4%)
Patient non-pharmacological intervention	29 (46.8%)
Patient pharmacological intervention	3 (4.8%)
Any intervention targeting caregivers only	12 (19.4%)
Any intervention targeting the patient-caregiver dyad	8 (12.9%)
Type of design (unit of randomization)	
Individually randomized	24 (38.7%)
Cluster randomized	38 (61.3%)
Number of individuals (or dyads) randomized	
Median (25^{th} to 75^{th} percentiles)	267 (140 to 402)
Types of participants targeted by the intervention†	
Providers or healthcare professionals	10 (16.1%)
Patients living with dementia	60 (96.8%)
Caregivers	23 (37.1%)
Was there recruitment of participants (e.g., patients, caregivers)?	
Yes	59 (95.2%)
No	3 (4.8%)
If yes, how were participants recruited?[a] **($N = 59$)**	
From clinic patient panels in an existing clinical or health system	54 (91.5%)
Community outreach efforts	10 (16.9%)
Other or unclear	2 (3.4%)
Funding source[a]	
Government/international development agencies/universities/institutes	53 (85.5%)
Foundation	15 (24.2%)
Industry	1 (1.61%)
No funding or unclear	3 (4.8%

*Entries are frequency (%) unless otherwise indicated.
[a]A trial can belong to multiple categories; thus, numbers don't add up to 100%.

TABLE 2 Equity-relevant focus and reporting of patient or other stakeholder engagement ($N = 62$)

	Frequency (%)*
Equity relevance identified in the title?	
Yes	1 (1.6%)
No	61 (98.4%)
Does the study provide an explicit objective pertaining to equity?	
Yes*	2 (3.2%)
No	60 (96.8%)
Are any results from subgroup analyses reported in the abstract?	
Yes	3 (4.8%)
No	59 (95.2%)
Any anticipated differences in baseline risk, prognostic factors, intervention acceptability, coverage, or effectiveness across subgroups mentioned or described in introduction?	
Yes	12 (19.4%)
No	50 (80.6%)
Any patient engagement identified?	
Yes	9 (14.5%)
No	52 (83.9%)
Unclear or other	1 (1.6%)
Any engagement with other stakeholders identified?	
Yes	13 (21.0%)
No	48 (77.4%)
Unclear or other	1 (1.7%)

*Appendix C summarizes the specific equity-relevant characteristics considered.

TABLE 3 Equity-relevant considerations in study design, conduct, and analysis ($N = 62$)

	Frequency (%)
Study eligibility criteria at the site or healthcare system level defined across any equity-relevant characteristics?	
Yes*	3 (4.8%)
No	59 (95.2%)
Study eligibility criteria at the individual participant level defined across any equity-relevant characteristics?	
Yes*	24 (38.7%) [c]
No	38 (61.3%)
Any special recruitment procedures described to increase enrolment of sites that serve marginalized groups?	
Yes	3 (4.8%)
No	58 (93.5%)
Unclear or other	1 (1.7%)
Any special recruitment procedures described to increase enrolment of individuals from marginalized groups?	
Yes	4 (6.5%)
No	58 (93.5%)
Does the study consider any form of restricted randomization?	
Yes	35 (56.5%)
No	27 (43.5%)
If yes, is the restricted randomization based on any equity-relevant characteristics? ($N = 35$)	
Yes*	18 (51.4%)
No	17 (49.6%)
Does the study present any covariate-adjusted analyses?	
Yes	51 (82.3%)
No	11 (17.7%)
If Yes, does the analysis adjust for any equity-relevant characteristics? ($N = 51$)	
Yes*	38 (74.5%)
No	13 (25.5%)
Does the report or protocol state that any subgroup analyses were planned or conducted?	
Yes[a]	10 (16.1%)
No	52 (83.9%)
If yes, are equity-relevant characteristics considered in subgroup analyses ($N = 10$)	
Yes*	8 (80.0%)
No	2 (20.0%)

*Appendix C provides details of the equity-relevant characteristics considered.
[a]Appendix D provides details of all subgroup variables examined.

recruitment from population groups that experience health disparities. While the vast majority assessed balance at baseline across equity-relevant characteristics (and thus, had data available for disaggregated presentation of results), far fewer restricted randomization to promote balance on such characteristics and even fewer presented subgroup analyses across such characteristics. Few studies discussed differential recruitment, attrition, implementation, adherence, and applicability across equity-relevant characteristics.

In terms of the specific equity-relevant characteristics considered, sex and the "Plus" characteristic of age and disability were commonly used to assess balance at baseline and for adjustment in analysis; they were also the most common in subgroup analyses. On the other hand, few studies considered education, social capital, socio-economic status, or place of residence in their design or analysis. Participant race/ethnicity/culture/language was reported as part of the baseline demographics in a third of studies, but no study reported disaggregated results or treatment-effect heterogeneity across participant race/ethnicity/culture/language. Although the absolute number of trials presenting subgroup analyses was small, it is notable that when subgroup analyses were presented, adherence to key methodological recommendations for subgroup analyses was poor.

4.2 | Comparison with other studies

Petkovic and colleagues[33] assessed health equity considerations in a random sample of 100 individually randomized and 100 cluster

TABLE 4 Equity relevant presentation and interpretation of results ($N = 62$)

	Frequency (%)
Are any equity-relevant baseline descriptive statistics at the site or healthcare system level reported by trial arm?	
Yes*	7 (11.3%)
No	55 (88.7%)
Are any equity-relevant baseline descriptive statistics at the individual participant level reported by trial arm?	
Yes*	59 (95.2%)
No	3 (4.8%)
Report on differential recruitment between arms across equity-relevant characteristics?	
Yes	15 (24.2%)
Described as present (a limitation)[a]	4 (6.5%)
Described as absent (a strength)[a]	13 (21.0%)
No	47 (75.8%)
Report on differential attrition across equity-relevant characteristics?	
Yes	5 (8.1%)
Described as present (a limitation)[a]	2 (3.2%)
Described as absent (a strength)[a]	4 (6.5%)
No	57 (91.9%)
Report on differential implementation/delivery of the intervention across equity-relevant characteristics?	
Yes	2 (3.2%)
Described as present (a limitation)[a]	2 (3.2%)
Described as absent (a strength)[a]	0 (0%)
No	60 (96.8%)
Report on differential adherence by participants across equity-relevant characteristics?	
Yes	2 (3.2%)
Described as present (a limitation)[a]	1 (1.6%)
Described as absent (a strength)[a]	1 (1.6%)
No	60 (96.8%)
Report on applicability across any equity-relevant characteristics?	
Yes	19 (30.6%)
Described as present (a limitation)[a]	14 (22.6%)
Described as absent (a strength)[a]	6 (9.7%)
No	43 (69.4%)

*Appendix C Table C1 provides details of the equity-relevant characteristics considered.
[a]Not mutually exclusive.

randomized trials published 2013-2015. They specifically sampled trials considered "health equity-relevant," defined as trials that (1) included individuals or populations experiencing social disadvantage within the setting and context of the study or (2) assessed the effects of the intervention on people who experience social disadvantage by either exclusively focusing on such individuals or assessing

TABLE 5 Number and methods of subgroup analyses and adherence to recommendations regarding subgroup analyses ($N = 10$)

	Frequency (%)
Number of distinct outcomes involved in subgroup analyses	
1	3 (30.0%)
2	2 (20.0%)
3+	4 (40.0%)
Unclear	1 (10.0%)
Number of distinct subgroup variables involved in subgroup analyses	
1	3 (30.0%)
2	3 (30.0%)
3+	3 (30.0%)
Unclear	1 (10.0%)
Total number of distinct subgroup analyses reported	
Mean (standard deviation) per trial ($n = 9$)	5.7 (3.7%)
What was the statistical method used to perform subgroup analyses?*	
Stratified analysis across the relevant subgroups	2 (20.0%)
Stratified analysis in a selected subgroup (e.g., analysis of females only)	0 (0.0%)
Interaction test	7 (70.0%)
Unclear	1 (10.0%)
Were all subgroup analyses prespecified?	
Yes	4 (40.0%)
No	4 (40.0%)
Unclear	2 (20.0%)
Was a clear rationale for all subgroup analyses reported?	
Yes	2 (20.0%)
For some but not all	3 (30.0%)
No	5 (50.0%)
Were any of the subgroup variables restricted in the randomization?	
Yes	1 (10.0%)
No	9 (90.0%)
Was a statement about power or sample size included for any subgroup analyses?	
Yes – formal sample size calculation	0 (0.0%)
Yes – mentioned in discussion but not with formal sample size calculation	3 (30.0%)
No	7 (70.0%)
Was any correction for multiple testing reported?	
Yes	0 (0.0%)
No	10 (100.0%)
Was a forest plot used to report the subgroup results?	
Yes	1 (10.0%)
No	9 (90.0%)

*Categories not mutually exclusive.

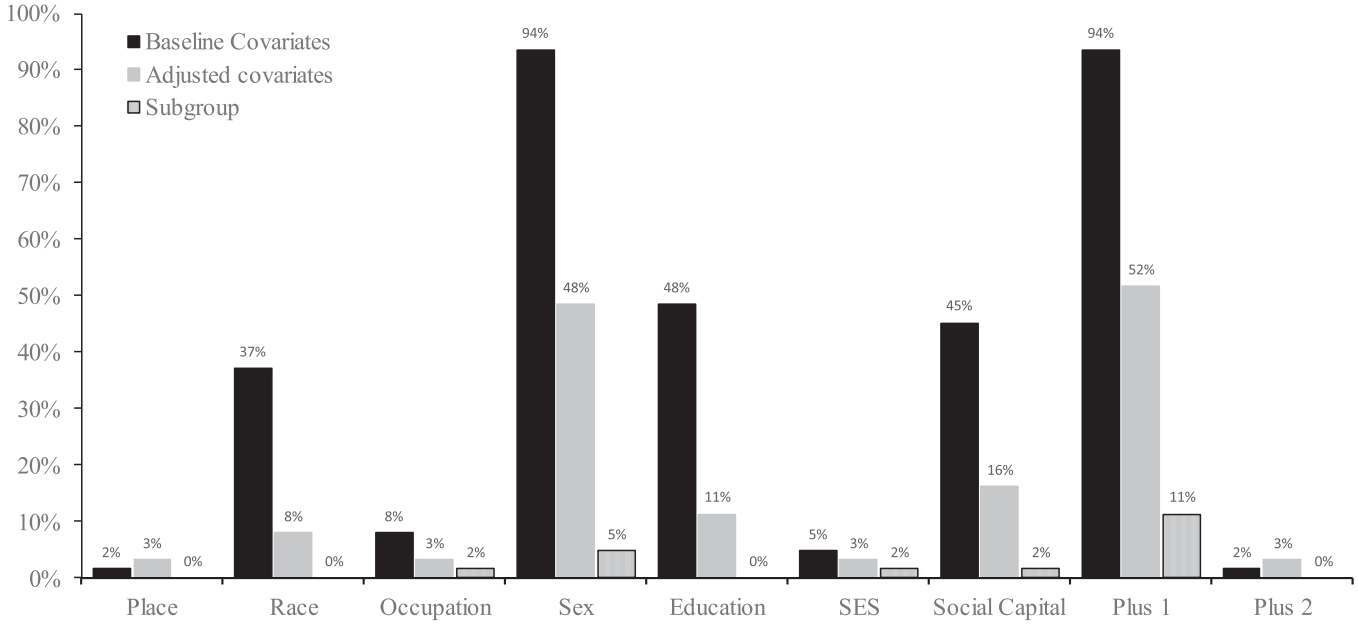

FIGURE 1 Equity-relevant characteristics reported at baseline and in covariate adjustment versus formally evaluated in subgroup analyses. Place, place of residence; Race, race/ethnicity/language/culture; Sex, sex/gender; SES, socioeconomic status; Plus 1, age/disability; Plus 2, features of relationship

differential impacts of the intervention across diverse groups experiencing disadvantage. Our sample, while not limited to health equity-relevant trials, focused on trials with a pragmatic intention which, by definition, ought to emphasize external validity (i.e., applicability) in addition to internal validity. As such, consideration of representativeness of the study population would be relevant. Nevertheless, we found a substantially smaller percentage discussing the applicability of results across equity-relevant characteristics (31% compared to 71% in the review by Petkovic and colleagues) and conducting subgroup analyses across such characteristics (16% compared to 37%).

Our finding that sex and the "Plus" characteristic of age and disability were commonly reported (e.g., in baseline tables and covariate adjustment) is consistent with other studies[33,34] and may point to these data being more readily available (e.g. within health administrative data). The prevalence of studies in our review reporting procedures to increase enrolment of individuals from equity-relevant groups (6%) compares poorly to a recent review of 66 (mostly observational) studies in dementia research which found that 37 (56%) reported on strategies to improve recruitment of racial and ethnic minorities.[27] Finally, the prevalence of trials reporting engagement with patients in our review (15%) is higher than in a previous review of clinical trials more generally[35] as well as in a broader sample of pragmatic trials in which less than 10% of trial reports mentioned patient or public engagement.[36]

4.3 | Strengths and limitations

Our study has several strengths. We used well-trained reviewers and consensus between two reviewers who independently extracted information from each trial to reduce the risk of misclassification. To identify trials for this review, we leveraged a published search filter that has demonstrated good specificity and was considered an efficient way to identify pragmatic trials without relying on authors explicitly labeling their trials as pragmatic.[23] We included trials across a broad range or jurisdictions and settings and used the well-known PROGRESS-Plus framework to operationalize equity-relevance, allowing for a comprehensive analysis.

Our study also has limitations. First, this was a secondary review and analysis of an existing database of pragmatic trials published between 2014 and 2019. Since the protocols for these trials were potentially developed several years before their publication dates, our results may not represent more recent practices. However, our results provide a "baseline" assessment of practices in AD/ADRD trials; future updates may evaluate the degree that recent initiatives have improved practices. Second, although under-representation of populations that commonly experience health inequities has been well-documented and would have been of interest, we were unable to describe the extent that each trial's sampled population was representative of its target populations across equity criteria. Instead, we considered only whether trials reported participant eligibility criteria along equity-relevant characteristics. Third, our review extracted information on reporting of equity-relevant characteristics without specifically considering whether differences in outcomes are inequitable in the context of each trial. As noted by Petkovic and colleagues,[33] reporting results across PROGRESS-Plus characteristics does not necessarily imply that these characteristics are associated with inequities. For example, differences in outcomes across age groups in AD/ADRD do not necessarily constitute an age-related inequity because disease risks increase with age. Fourth, although a substantial proportion of trials in our review

were cluster randomized designs which have unique considerations with respect to equity,[33] we did not differentiate between individually randomized and cluster randomized designs in our analysis. Baseline characteristics at site- or health-system level, for example, might naturally be more often reported in cluster randomized trials to characterize the units of randomization.

4.4 | Recommendations for research and practice

Attention to health equity considerations in the design, conduct, and reporting of pragmatic trials — which, by definition, aim to inform clinical and policy decisions in practice — is essential. A key recommendation is to consider health equity from the planning stages, ideally in collaboration with a statistician. Investigators seem to be aware of the benefits of covariate adjustment in trial analyses: such analyses can increase power and efficiency and can account for potential baseline imbalances between trial arms, as well as differential attrition and adherence. What seems to be less well appreciated is that covariate adjustment does not facilitate conclusions about treatment-effect heterogeneity: such analyses should ideally include the intervention by covariate interaction. Such analyses can be used to identify populations with better or worse outcomes, experiencing potential harms, or having difficulties adhering to treatments.[33] Subgroup analyses must adhere to methodological requirements to avoid increased risks of type I and type II errors: they should ideally be prespecified, based on a limited number of characteristics, and have a clear underlying rationale. Although it may not be possible to ensure that all planned subgroup analyses are adequately powered, steps can be taken to facilitate inclusion of subgroup results in future meta-analyses, or to inform design of future planned trials focused on such subgroups, for example, by stratifying on important subgroup characteristics and presenting results disaggregated across key subgroups. Complete and transparent reporting of subgroup analyses, preferably using forest plots showing point estimates and confidence intervals across relevant subgroups[30] can support policymakers in interpreting the relevance of the findings to groups experiencing social disadvantage.

Subgroup analyses may pose challenges for investigators planning cluster randomized designs due to increased complexity of statistical analysis. A common perception is that larger numbers of clusters are required to conduct subgroup analyses. However, recent methodological results have revealed that detecting treatment-effect heterogeneity in cluster randomized trials may not always require larger sample sizes than detecting the average treatment effect.[37] Methodology for detecting treatment-effect heterogeneity in cluster randomized trials is the topic of ongoing research.[38,39]

Finally, while equity considerations are context dependent, it is insufficient to only consider age and sex. Given the evidence of outcome-related inequities by race/ethnicity, education, socioeconomic status, and social capital, equity-relevant trials should carefully consider PROGRESS-Plus factors in their objectives, design, analysis and reporting, particularly in circumstances where there is disproportionate need or unequal impacts on equity-relevant groups. For example, in an ongoing trial, Juengst et al. are re-evaluating a training intervention to reduce dementia caregiver burden with a special focus on an underserved population.[40] Study materials were culturally adapted to address the needs of Spanish-speaking caregivers. Randomization was stratified by language and gender, and data collection included age, gender, race, ethnicity, education and the nature of the caregiver relationship. Planned subgroup analyses will examine whether intervention effects differ by gender and language.

5 | CONCLUSIONS

Our results indicate missed opportunities for integrating health equity considerations in pragmatic trials in AD/ADRD. The dissemination of the The National Institute on Aging Health Disparities Research Framework[41] and the IMPACT "Best Practice Sheets"[19] have highlighted the importance of fully addressing health equity in study designs reflected in ongoing and recently completed trials.[42,43] Future work should more fully evaluate the period after these frameworks have been disseminated to assess their adoption and impact in reducing health equity gaps in evidence.

AUTHOR CONTRIBUTIONS

M.T., S.L.M., V.W., and A.R.Q. developed the study concept. M.T. and V.W. developed the data extraction form with input from S.G.N., K.C., S.L.M., F.L., C.W., and A.R.Q. A.A.A., K.C., M.T.M., K.D.P., L.M., H.N., P.N., and L.A. extracted data in consultation with M.T. and V.W. A.A.A. managed the database and conducted the statistical analysis. M.T., A.A.A., and S.G.N. prepared the manuscript draft. All authors critically reviewed the manuscript.

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CONFLICT OF INTEREST

C.W. receives consulting income from Cardialen, Eli Lilly & Company, and Research Triangle Institute International. The other authors have no conflicting interests. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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