Received: 12 August 2024 | Revised: 17 October 2024 | Accepted: 18 October 2024

DOI: 10.1002/trc2.70016

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Designing and implementing the IDEAL Study: A randomized clinical trial of *APOE* genotype disclosure for late-onset Alzheimer's disease in an urban Latino population

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Funding information
National Institutes of Health (NIH), National Center for Advancing Translational Sciences, Grant/Award Number: UL1TR001873; National Human Genome Research Institute, Grant/Award Number: T32HG010030; National Institute on Aging, Grant/Award Number: R01AG062528

Abstract

INTRODUCTION: The *Información de la Enfermedad de Alzheimer para Latinos* (IDEAL) Study is a randomized clinical trial investigating the psychosocial, behavioral, and cognitive impacts of apolipoprotein E (*APOE*) genotype disclosure for late-onset Alzheimer's disease (AD) among Latinos.

METHODS: We used address-based sampling to recruit English- and Spanish-speaking Latinos aged 40–64 living in northern Manhattan for a community-based Baseline Survey about their knowledge and opinions about AD. Participants eligible for the clinical trial were invited to complete an Introductory Session, including AD and genetics education and informed consent, before undergoing genotyping for *APOE*. Participants were then randomized to learn their risk of AD by age 85 (range: 21%–55%) based

on either Latino ethnicity and family history alone, or the same factors and their *APOE* genotype. Risk information is provided in a semi-structured genetic counseling session. Psychological impacts, health-related behavioral changes, and cognitive performance are evaluated 6 weeks, 9 months, and 15 months later via surveys and qualitative interviews. To promote cultural competence, study materials were developed by a multidisciplinary team including bilingual and bicultural staff, Latinx content experts, and genetic counselors.

RESULTS: We sent invitations to 91,433 households; 5542 (6.1%) responded, 2120 completed the Baseline Survey (78.5% online; 21.5% via computer-assisted telephone interview), and 2087 were deemed eligible, yielding a response rate of 2.3%. Many participants expressed appreciation for the opportunity to contribute to AD research. We randomized 374 participants for the clinical trial.

DISCUSSION: We describe the study design, recruitment and retention strategies, and interventions employed in the IDEAL Study. Our design provides a framework for future studies using rigorous mixed methods. Our findings may facilitate the development of culturally-sensitive educational materials about AD and genetic testing, as well as genetic counseling protocols, to improve coping and adjustment in response to receiving risk information.

KEYWORDS

APOE genotype disclosure, behavioral, clinical trial, Latino: Hispanic, memory test, mixed methods, psychosocial, randomized, social implications

Highlights

- The *Información de la Enfermedad de Alzheimer para Latinos* (IDEAL) Study investigates apolipoprotein E (*APOE*) genotype disclosure among Latinos using mixed methods.
- We recruited adults 40–64 years of age without Alzheimer's disease (AD) for a community-based survey and randomized trial.
- Trial participants receives AD risk estimates with or without *APOE* genotypes.
- Psychosocial, behavioral, and cognitive impacts are assessed over 15 months.
- Findings may inform AD educational materials and genetic counseling protocols.

1 | BACKGROUND

Apolipoprotein E (*APOE*) remains the strongest genetic predictor for late-onset Alzheimer's disease (AD). Demand for pre-symptomatic *APOE* testing will likely increase given the growing interest in genetic testing among relatives of persons with AD and the general population,[1–5] the availability of direct-to-consumer genetic testing,[6] the major prevention trials targeting persons at high genetic risk (including *APOE* ε4 homozygotes),[7–9] and the recent approval of amyloid beta (Aβ)–reduction therapies.[10,11] Improved understanding of the impacts of testing, sources of response variability, and inclusion of diverse samples are critical for providing safe and effective disclosure of AD genetic risk information.

Previous research found little significant distress in response to *APOE* genetic testing, even among persons who learned they had elevated risk.[12–15] However, most studies, including the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study,[14,16] primarily enrolled well-educated non-Hispanic Whites with a family history of AD. Furthermore, most previous studies assessed impact through standardized measures of depression and anxiety, which may not capture the kinds of distress experienced[17] or the coping strategies used.[18] Qualitative research shows that receiving genetic information has important psychosocial effects that are not well captured through standardized measures.[19–21] In addition, in one study, *APOE* ε4 heterozygotes who were informed about their genetic status had worse subjective and objective memory test performance than heterozygotes who were not informed,[22] suggesting that attention to cognitive outcomes is needed.

Previous studies have not adequately represented Latinos, the second largest U.S. ethnic group, comprising 18% of the population.[23]

Although AD incidence rates vary among Latino subgroups,[24] data from the Washington Heights-Inwood Columbia Aging Project (WHICAP), a longitudinal, community-based study in northern Manhattan, indicate that AD incidence is about twice as high among Caribbean Latinos (primarily Dominicans) as among persons of European ancestry.[25–28] Yet, no previous study has investigated the impacts of receiving AD genetic risk information among Latinos.

The *Información de la Enfermedad de Alzheimer para Latinos* (IDEAL) Study addresses the limitations of previous research through a longitudinal, community-based study of Latinos with and without a family history of AD, using a mixed-methods design. To assess the impacts of receiving *APOE* genetic information, participants from the same communities included in WHICAP were randomized to learn their risk of developing AD by age 85 based on either ethnicity and family history alone, or the same factors and their *APOE* genotype. Impacts are evaluated at 6 weeks, 9 months, and 15 months after risk disclosure (Figure 1). The primary objective of the IDEAL Study is to determine whether psychosocial, behavioral, and cognitive outcomes differ between persons who do and do not learn their *APOE* genotype. Table 1 summarizes the aims of the quantitative and qualitative study components.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (e.g., PubMed) and meeting abstracts and presentations. Previous research found little significant distress in response to apolipoprotein E (*APOE*) genetic testing, even among persons who learned they had elevated risk. However, most studies enrolled well-educated non-Hispanic Whites with a family history of Alzheimer's disease (AD) and utilized only standardized measurements of depression and anxiety. These relevant studies are appropriately cited.
2. **Interpretation**: The *Información de la Enfermedad de Alzheimer para Latinos* (IDEAL) Study addresses the limitations of previous research through a longitudinal, community-based study of Latinos with and without a family history of AD, using a mixed-methods design.
3. **Future directions**: Our design provides a framework for future studies using rigorous mixed methods. Our findings may facilitate the development of culturally-sensitive educational materials about AD and genetic testing, as well as genetic counseling protocols, to improve coping and adjustment in response to receiving risk information.

2 | METHODS

Study materials (Table 2) were developed in both Spanish and English by a multidisciplinary team with good representation of bilingual Latinx professionals. Surveys include both validated and novel scales, including some used in the REVEAL Study.[14,16] Because the IDEAL Study began shortly after the coronavirus 2019 (COVID-19) pandemic began, data collection was conducted remotely.

2.1 | Baseline survey

First, we conducted a community-based Baseline Survey within zip codes 10026–10027, 10029, 10030–10035, 10037, and 10039–10040 (New York City community districts 9 [Hamilton Heights and Manhattanville], 10 [Central Harlem], 11 [East Harlem], and 12 [Washington Heights and Inwood]). Residents of these areas were eligible if they were 40–64 years of age, self-identified as Hispanic or Latino, spoke Spanish or English, and did not report a prior AD diagnosis.

For the survey, administered by Abt Global Inc. (Abt), households in the targeted areas were identified using address-based sampling of lists from the U.S. Postal Service (USPS) Computerized Delivery Sequence file. When possible, telephone numbers were matched to the address from other data sources (e.g., credit bureau, LexisNexis). Abt mailed a letter describing the survey to each household with a $2.00 pre-incentive and an information sheet (Appendix A) containing the elements of informed consent without requiring a signature.

Participants completed the survey either online or via computer-assisted telephone interview (CATI). Three postcards were sent to non-responders at 2-week intervals following the initial letter. Two weeks after the last postcard, bilingual interviewers called non-responding households with an appended phone number up to six times to complete the survey by CATI, selecting the household resident 40–64 years of age who was at home and had the most recent birthday. To improve participation, Abt sent another letter and three postcards to a subset of non-responding households ($N = 16{,}500$) ≈1 year after the initial mailing, and up to five text messages to those with appended telephone numbers, excluding anyone on the national Do Not Call list.

Baseline Survey participants were excluded from the remainder of the study if they reported previous AD-related genetic testing, a family history consistent with early onset, likely autosomal dominant AD, or suicidality (response other than "not at all" to the Patient Health Questionnaire-9 [PHQ-9][29] item, "Thoughts that you would be better off dead or of hurting yourself in some way"). To assess consistency with likely autosomal dominant AD, board-certified genetic counselors collected and evaluated the complete family history for participants who reported one or more relatives with dementia onset at age 60 or younger. In addition, participants were excluded if they reached the maximum number of contact attempts for any study step before randomization, reported illnesses that raised safety concerns (e.g., serious mental illness), or had a relative who was participating in the IDEAL Study. Participants received $30.00 for completing the Baseline Survey and each subsequent survey.

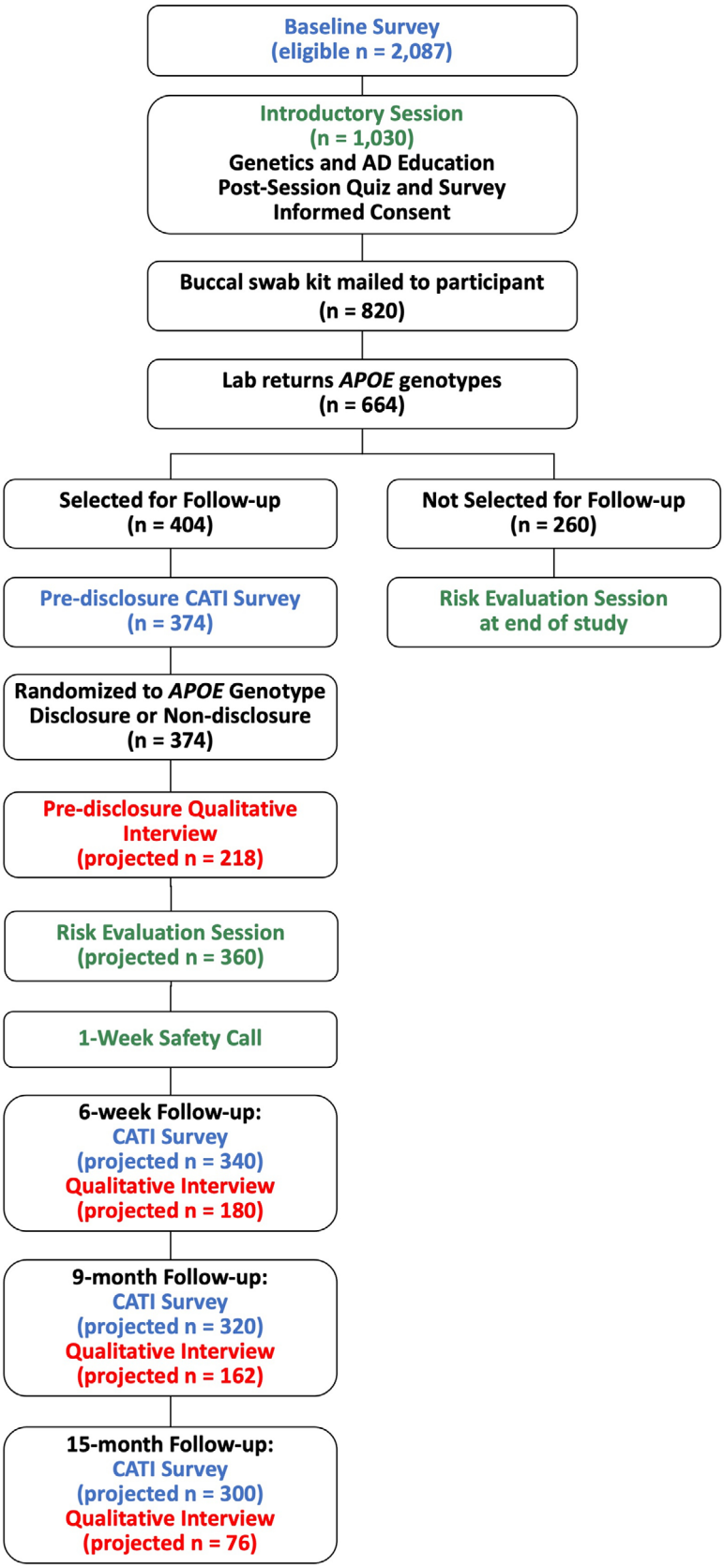

FIGURE 1 Study flow diagram. The study flow diagram illustrates the study steps in chronological order, beginning with the Baseline Survey. Quantitative study components are shown in blue; education or genetic counseling study components are shown in green; and qualitative study components are shown in red. CATI, computer-assisted telephone interview.

TABLE 1 Primary aims of the *Información de la Enfermedad de Alzheimer para Latinos* (IDEAL) Study.

Quantitative Surveys	Qualitative Interviews
To assess the impacts of receiving *APOE* genotype information on psychosocial outcomes, memory test performance, and health-related behaviors, including: A. Comparison of outcomes, at each time point, between participants randomized to receive or not receive *APOE* genotypes, overall and within strata defined by *APOE* genotypes B. Identification of factors that underlie variability in response to the receipt of genetic information C. Exploration of the patterns of longitudinal response to receipt of risk information	To investigate, using a stress and coping theoretical framework, the lived experience and impacts of receiving *APOE* genotype information, including: A. Examination, at each time point, of the ways in which participants understand and appraise AD risk information, how this is influenced by their lay belief systems, and what coping strategies they enact to contend with their risk for AD B. Investigation of how coping strategies may change over time C. Assessment of the ways in which different coping strategies may enhance or impede adjustment to AD risk information

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E.

2.2 | Introductory session

Participants who completed the Baseline Survey and were eligible for the clinical trial were sent a study brochure (Appendix B) inviting them to the "Introductory Session." This session, implemented in Qualtrics (Qualtrics, Provo, UT), included a 15-min narrated and animated presentation (Appendix C) about AD and genetics, the risks and benefits of genetic testing, and the expectations of enrolled participants. Alternatively, participants could complete the session via telephone with a genetic counselor, using the same materials mailed to them beforehand.

After the presentation, participants completed a 14-item quiz that assessed understanding of information needed for informed consent (e.g., procedures, risks/benefits). Those who scored <67% on the quiz could watch the presentation again and retake the quiz up to two additional times. Following the quiz, participants completed a survey (Table 2). Those who passed the quiz were presented with the consent form (Appendix D), which they could sign electronically or, for those completing the session via telephone, through a mailed consent form. The consent form requested that participants indicate their willingness to be contacted for ancillary studies, have their risk disclosure session video-recorded, and designate a proxy for receiving their genetic results. We contacted participants weekly for up to 13 weeks after sending the brochure using calls, texts, and emails. Participants received $75.00 for completing this session.

2.3 | Biospecimen collection

Buccal swab deoxyribonucleic acid (DNA) collection kits for *APOE* testing were mailed to participants who signed the consent form. After mailing the kit, we sent participants texts and emails including a link to a 2-min video demonstrating how to collect the sample and mail it to the laboratory (Molecular Testing Labs, Vancouver, WA). We contacted participants weekly for up to 10 weeks through calls, texts, and emails. Participants received $25.00 for completing the kit. Biological samples were retained for 90 days after collection. Participants who reported having had outside *APOE* genetic testing before randomization were removed from the study.

2.4 | Selection for follow-up and Pre-disclosure Survey

After receiving their *APOE* results, we selected participants for the clinical trial. Because outcomes might differ depending on *APOE* genotype, we included everyone with an ε4 allele and an equal number of those without an ε4 allele. The sample of those selected without an ε4 allele was frequency-matched to those with an ε4 allele by age group (40–49, 50–59, 60–64); gender (man, woman); and first-degree AD family history (present, absent). Participants not selected will receive their *APOE* genotype and AD risk estimate at the end of the study by videoconference with a genetic counselor. Abt contacted selected participants for a Pre-disclosure Survey (Table 2) by CATI.

2.5 | Randomization

Participants who completed the Pre-disclosure Survey were randomized to disclosure or nondisclosure with an allocation ratio of 1:1 using permuted block randomization with a mixed block size of four and six for a parallel group superiority trial. Randomization was stratified by number of ε4 alleles, resulting in 50% with an ε4 allele in each group. To balance potential confounders, randomization was also stratified by age group, gender, and first-degree AD family history.

Participants in the disclosure arm are given their risk of developing AD by age 85 based on their Latino ethnicity; number of ε4 alleles (0, 1); and AD family history (0, ≥1 affected parent or sibling). Those in the nondisclosure arm are given an estimate of their risk of developing AD by age 85 based on the same factors excluding their *APOE* genotype. We created Excel files containing permuted blocks for each stratification group and implemented a program that sorted participants into the next row of the Excel file that matches their characteristics. The allocation sequence was hidden from all participant-facing study staff until assigned. Given ethical concerns about withholding potentially

TABLE 2 Schedule of quantitative survey instruments and qualitative interview topics.

Quantitative instrument[a]	Baseline Survey	Introductory Session	Pre-disclosure Survey	Safety Call	Post-disclosure Survey[c]		
					6-week	9-month	15-month
Demographics (age, ethnicity, education, etc.)	x						
AD family history and caregiving experiences	x						
[b]AD knowledge	x						x
[b]AD concerns, risk factor, and treatment beliefs	x						
Genetics knowledge	x						
[b]Interest in genetic testing for AD	x						
[b]Previous experience with genetic testing for AD and other diseases	x						
Estimated personal and community-average AD risk	x						
[b]*Perceived threat of AD*	x				x	x	x
Depressive symptoms: PHQ-9	x				x	x	x
Anxiety symptoms: GAD-7	x				x	x	x
Psychological Acculturation Scale: PAS		x					
Familism		x					
Fatalism: PFI		x					
Pandemic Emotional Impact Scale		x					
Current perceived stress: PSS (modified)			x				
Optimism and pessimism: LOT-R			x				
Social support: MSPSS			x				
Self-esteem: SISE			x				
Intolerance of uncertainty: TAS			x				
Perceived AD stigma (newly developed)			x				
Health locus of control: MHLOC			x				
Numeracy			x				
Subjective memory: MIA-R			x		x	x	x
Objective memory: BTACT (shortened)			x		x	x	x
Items from [b]Impact of Genetic Testing for AD (IGT-AD) and Impact of Events Scale-Revised (IES-R)				x			
[b]*Recall/understanding of results*				x	x	x	x
[b]**Impact of Genetic Testing for AD: IGT-AD**					x	x	x
Impact of Events Scale-Revised: IES-R					x	x	x
[b]*Health-related behavior changes*					x	x	x

(Continues)

TABLE 2 (Continued)

Quantitative instrument[a]	Baseline Survey	Introductory Session	Pre-disclosure Survey	Safety Call	Post-disclosure Survey[c] 6-week	9-month	15-month
Psychological Adaptation to Genetic Information Scale: PAGIS					x	x	x
Coping: Brief COPE					x	x	x
[b]Communication of results and support seeking					x	x	

Qualitative topic	Pre-disclosure Interview	Risk Evaluation Session	Post-disclosure Interview[d] 6-week	9-month	15-month
Beliefs about normal aging	x				
Illness representations and beliefs about AD	x		x	x	x
Beliefs about fate/destiny, God, and AD	x		x	x	x
Familiarity with people with AD or dementia	x				
AD worry	x				
Sources of information about AD	x				
Beliefs about health, family history, genes, and disease prevention	x				
Prior experience with genetic testing	x				
Coping with health-related and other stressful problems	x			x	x
Family role in health and caregiving	x			x	
Anticipated reactions to risk information	x				
Risk information interpretation and integration: adapted from the BATHE method		x			
Receipt of risk assessment and/or genetic test results			x	x	x
Appraisal, coping strategies, and impacts			x	x	x

Note: Primary outcomes shown in bold; secondary outcomes shown in italics.
Abbreviations: AD, Alzheimer's disease; BATHE, Background, affect, trouble, handling, and empathy; COPE, Coping Orientation to Problems Experienced Inventory; BTACT, Brief Test of Adult Cognition by Telephone; GAD-7, Generalized Anxiety Disorder-7; IES-R, Revised Impact of Event Scale; IGT-AD, Impact of Genetic Testing in Alzheimer's Disease; LOT-R, Life Orientation Test-Revised; MIA-R, Metamemory in Adulthood Revised; MSPSS, Multidimensional Scale of Perceived Social Support; PAS, Psychological Acculturation Scale; PAGIS, Psychological Adaptation to Genetic Information Scale; PFI; Powe Fatalism Inventory; PHQ-9, Patient Health Questionnaire-9; PSS, Perceived Stress Scale; SISE, Single-Item Self Esteem Scale; TAS, Tolerance for Ambiguity Scale.
[a]The schedule of quantitative instruments with references can be found in Appendix E.
[b]Adapted from REVEAL Study measures.
[c]Follow-up surveys and interviews conducted at 6 weeks, 9 months, and 15 months after Risk Evaluation Session.
[d]Qualitative interviews occur approximately 2 weeks after the corresponding quantitative survey.

useful information from participants at the highest risk, those with two ε4 alleles were placed in the disclosure group.

2.6 | Selection for interviews and Pre-disclosure Interview

After randomization, some participants were selected for a series of up to four 90-min qualitative interviews by videoconference with Abt interviewers trained by the Columbia study team (Table 2). Selection was based on randomization group, *APOE* genotype, AD family history, age, and gender. Participants completed the Pre-disclosure Interview ≈2 weeks after the Pre-disclosure Survey. Participants receive $100.00 for completing this and each subsequent interview.

2.7 | Risk Evaluation Session and Safety Call

Risk estimates for developing AD by age 85 were obtained by analyzing WHICAP[25–28] data for Latino residents of the same communities as the IDEAL Study. Because WHICAP included left-censored and right-censored data, we utilized the Statistical Analysis System (SAS) ICLIFETEST procedure to calculate nonparametric estimates of survival functions.[30] Risk estimates ranged from 21% (0 ε4 alleles, no first-degree family history) to 55% (2 ε4 alleles).

Board-certified genetic counselors provide risk estimates in one-on-one, semi-structured "Risk Evaluation Sessions" by videoconference or in-person upon request (current $N = 8$) using a PowerPoint presentation to discuss the study, AD and genetics, and AD risk-reduction methods (e.g., maintaining a healthy diet and social connections). Risks

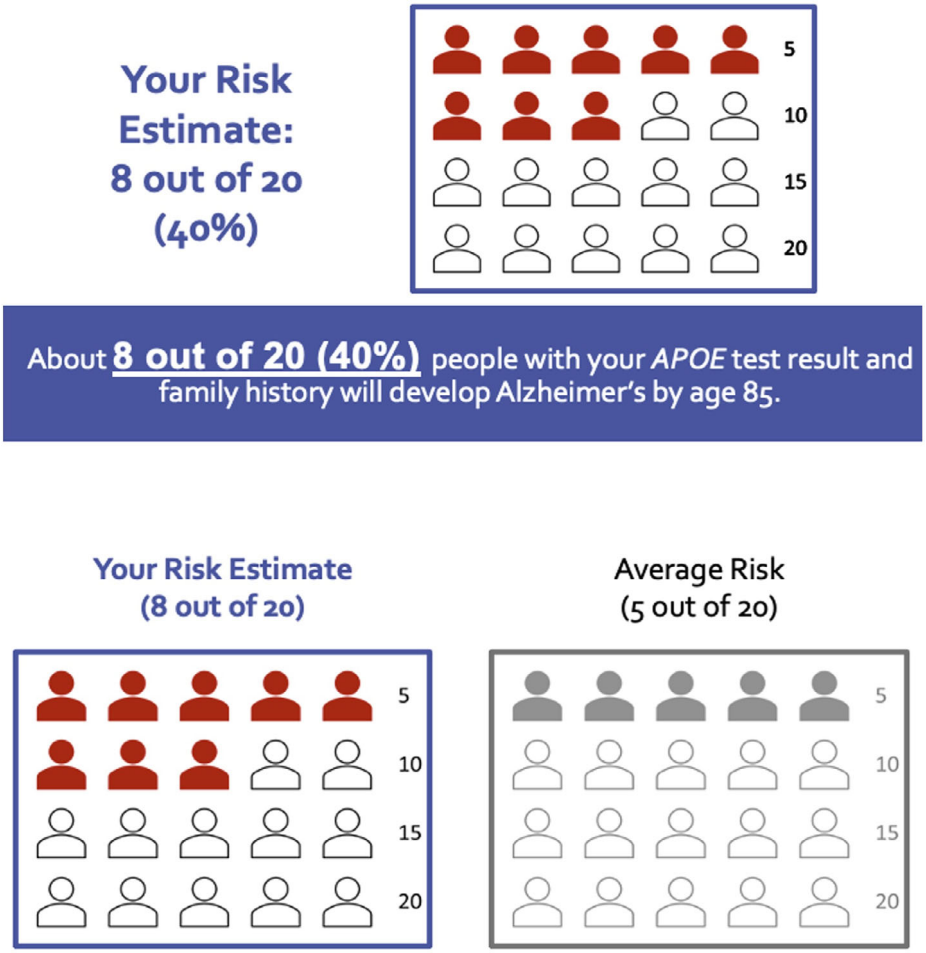

FIGURE 2 Presentation of risk estimate and risk comparison. During the Risk Evaluation Session, participants are first presented with their risk estimate of developing AD by age 85 as a number out of 20, a percentage, and a 5 × 4 icon array (top part of figure). Then they are presented with a comparison of their risk estimate with the average risk for all Latinos residing in northern Manhattan (bottom part of figure). The risk estimate depicted in the figure refers to a Latino resident of northern Manhattan with one *APOE* ε4 allele and a first-degree AD family history. AD, Alzheimer's disease; *APOE*, apolipoprotein E.

are presented as a percentage and a number out of 20 depicted as a 5 × 4 icon array (Figure 2). Risk percentages were converted to fractions using 20 as the common denominator to simplify participant interpretation of risks. Icon arrays depicting 20 people were chosen to visualize risk, allowing the genetic counselors to say, "Imagine yourself in a room with 20 people—this is the number of people in the room who will develop AD by age 85." Directly after receiving their risk estimates, participants are asked open-ended questions adapted from the BATHE method[31] to understand how they integrated and interpreted this information. Participants receive $75.00 for completing this session. They receive a mailed or emailed summary of the information shared. One week later, genetic counselors call participants for a "Safety Call" to assess their recall of the disclosed information and their short-term emotional and psychological reactions to learning their risk.

2.8 | Post-disclosure Surveys and Interviews

Post-disclosure Surveys are completed via CATI 6 weeks, 9 months, and 15 months after the Risk Evaluation Session, and Post-disclosure Interviews are completed ≈2 weeks after each survey (Table 2). Interviewers are blinded to participants' *APOE* genotypes, although they ask participants about their recall of their genotype and risk estimate. Post-disclosure Surveys are attempted with all randomized participants as scheduled, regardless of whether they completed the Risk Evaluation Session or previous Post-disclosure Surveys.

2.9 | Quantitative study component: primary and secondary outcomes (Table 2)

The IDEAL Study has four primary outcomes: (1) positive and negative psychological impacts of risk disclosure, assessed by the Impact of Genetic Testing in AD scale (IGT-AD)[32] (modified to refer to risk disclosure); (2) stress responses to the receipt of risk information (intrusion, avoidance), assessed by the Impact of Event Scale—Revised (IES-R);[33] (3) change in subjective memory from the Pre-disclosure Survey to each Post-disclosure Survey, assessed by the Metamemory in Adulthood Questionnaire-Revised (MIA-R);[34] and (4) change in

objective memory performance from the Pre-disclosure Survey to each Post-disclosure Survey, assessed by a shortened Brief Test of Adult Cognition by Telephone (BTACT).[35,36] We selected the BTACT because it is sensitive to cognitive differences in normal aging as opposed to mild cognitive impairment or dementia, which are unlikely to be observed in the IDEAL Study because of the participants' younger ages. Secondary outcomes are recall/understanding of results,[37] depression and anxiety symptoms,[29,38] health-related behavior changes,[39] and perceived AD threat.[40]

2.10 | Sample size and power

Our target sample size was 400 randomized participants (200 per arm) to ensure we would have 300 randomized participants (150 per arm) for primary analyses at the 15-month assessment, assuming 75% retention. We estimated that ≈2100 Baseline Survey participants would be needed to accrue these numbers, based on assumptions about participation. With 300 participants at last follow-up, a standardized effect size of ≥0.39 standard deviation (SD) is detectable with ≥80% power for comparisons of the *APOE* genotype disclosure versus nondisclosure groups, with Bonferroni adjustment for four comparisons. This detectable difference corresponds to a mean difference of 23% for the IGT-AD (mean = 16.9, SD = 9.9),[32] 24% for the IES-R (mean = 1.8, SD = 1.1),[33] and 9% for the MIA-R (mean = 54.5, SD = 12.1).[34] For the BTACT, a detectable difference of 0.39 SD corresponds to an age difference in memory performance of 5–10 years.[36]

2.11 | Statistical methods

Using publicly-available data from the American Community Survey,[41] we created survey weights to adjust our Baseline Survey sample's distribution of age (40–49, 50–59, 60–64); gender (man, woman); education (high school or less, some college or more); and national origin group (Dominican, Puerto Rican, Mexican or Central American, South American, and other/multiple) to match the population's distribution of age, sex (male, female), education, and national origin group among Latinos living in northern Manhattan 40–64 years of age. Normalized survey weights were computed as the ratio of population to sample proportions for each stratum. Weights were trimmed (lower bound = 0.2, upper bound = 3.5) using the *trimWeight* function in R's *Survey* package.[42]

For each outcome, we will conduct an intent-to-treat analysis using Generalized Linear Models for continuous variables with an identity link using Generalized Estimating Equations (GEEs) to account for within-subject correlation due to repeated measures. In addition, we will also conduct per-protocol and as-treated analyses to evaluate the impact of non-adherence (e.g., skipping the Risk Evaluation Session, refusing to receive *APOE* genotype). We will use multiple imputation methods to impute missing outcomes.

2.12 | Safety and monitoring

The Columbia University Irving Medical Center (CUIMC) Institutional Review Board approved IDEAL. Following secure File Transfer Protocol from Abt, quantitative data are managed using Research Electronic Data Capture (REDCap) tools hosted at Columbia University.[43] Audio recordings of qualitative interviews are transmitted securely for transcription at Datagain, where data are stored on encrypted servers; transcripts are securely returned and stored on a protected server at Columbia University.

We collect information on participants' psychological status using validated survey measures: PHQ-9[29] and the Generalized Anxiety Disorder-7 (GAD-7) scale,[38] in the Baseline Survey and each Post-disclosure Survey. In the Baseline Survey, those who screened positive for suicidality or moderate depression or anxiety (PHQ-9 or GAD-7 sum ≥10) were provided a mental health resources list as a pop-up in the online survey or a script read to them by the CATI interviewer. This list was mailed to everyone who participated in the Baseline Survey.

Post-disclosure Surveys include the IES-R,[33] which ascertains subjective distress in response to receiving an AD risk estimate. Eight IES-R items measuring intrusive thoughts are included in the Safety Call.

Adverse event (AE) and serious AE (SAE) definitions are based on increases in the levels of severity of psychological distress in the Post-disclosure Surveys, compared with levels at baseline. Because participants who indicated suicidality at baseline were excluded from subsequent study steps, new onset of suicidality is an SAE. An increase in depression or anxiety symptoms to the severe category (PHQ-9 score ≥20 or GAD-7 score ≥15) is an AE. An IES-R intrusiveness subscale mean score ≥3 in the Safety Call or a total IES-R score >33 (i.e., optimal cutoff for prediction of post-traumatic stress disorder) in the Post-disclosure Survey is also considered an AE.

Participants who meet criteria for an AE or SAE are contacted by a physician well-known to community members (R.A.L.) to determine their mental state, whether their distress is related to our study, and whether they have support. A genetic counselor contacts them 1 week later. AEs and SAEs are reviewed twice per year by our safety officer.

2.13 | Community engagement

We collaborated with CUIMC's Office of Government & Community Affairs to broadcast a segment about the IDEAL Study on a Manhattan Neighborhood Network television program in Spanish, *Diálogo Democrático*.[45] The segment was live-streamed through Facebook, which facilitated a concurrent question-and-answer portion. We included a link to this broadcast on our website and mailed recruitment materials.

TABLE 3 Relative unweighted and weighted distribution of demographic characteristics for Baseline Survey respondents.

	Unweighted distribution		Weighted distribution[a]		Percent change
	N	%	Wt. N	Wt. %	
Total	2087	100	86685	100	
Variables used in non-response weighting					
Age (years)					
40–49	860	41.2	34213	39.5	−1.7
50–59	835	40.0	36615	42.2	2.2
60–64	392	18.8	15857	18.3	−0.5
Sex					
Male	612	29.5	37581	43.4	13.9
Female	1465	70.5	49104	56.6	−13.9
Education					
High school or less	769	36.8	49591	57.2	20.4
Some college or more	1318	63.2	37094	42.8	−20.4
National origin					
Dominican	1121	53.7	48634	56.1	2.4
Puerto Rican	389	18.6	17171	19.8	1.2
Mexican or Central American	199	9.6	9818	11.3	1.8
South American	211	10.1	6280	7.2	−2.9
Other, multiple, or don't know	167	8.0	4782	5.5	−2.5
Variables not used in non-response weighting					
Nativity					
Foreign born	1290	61.8	55617	64.2	2.4
Born in the United States	797	38.2	31068	35.8	−2.4
Survey completion language					
English	1556	74.6	61934	71.4	−3.2
Spanish	531	25.4	24751	28.6	3.2
Marital status					
Married or in a significant relationship	808	38.7	34492	39.8	1.1
Single, never married	662	31.7	27128	31.3	−0.4
Separated, divorced, or widowed	616	29.5	25038	28.9	−0.6
Religion					
Catholic	1263	60.5	54249	62.6	2.1
Christian non-Catholic	254	12.2	10360	12	−0.2
Non-Christian	44	2.1	1529	1.8	−0.3
None/atheist/agnostic/spiritual but not religious	262	12.6	9575	11.0	−1.6
Other or unknown	264	12.6	10973	12.7	0.1
Employment					
Currently working at paying job	1239	59.4	48758	56.2	−3.2
Unemployed, looking for work	281	13.5	13111	15.1	1.6
Retired	123	5.9	5710	6.6	0.7
Unable to work because of long-term illness or disability	282	13.5	12996	15.0	1.5
Looking after home and family	108	5.2	4273	5.0	−0.3
Self-employed, student, other, or prefer not to say	54	2.6	1837	2.1	−0.5

(Continues)

TABLE 3 (Continued)

	Unweighted distribution		Weighted distribution[a]		Percent change
	N	%	Wt. *N*	Wt. %	
Health insurance					
No insurance	164	7.9	7580	8.7	0.8
Private insurance	868	41.6	31959	36.9	−4.7
Public insurance	991	47.5	44283	51.1	3.6
Other or unknown	64	3.1	2863	3.3	0.2
Education or training in a health-related profession					
No	1811	86.8	77397	89.3	2.5
Yes	275	13.2	9253	10.7	−2.5
Family history of Alzheimer's disease					
No family history	1074	51.5	46164	53.3	1.8
First-degree family history	448	21.5	18108	20.9	−0.6
Other family history	565	27.1	22413	25.9	−1.2
Provided support or help to a family member or close friend with Alzheimer's disease, dementia, or serious memory problems					
No	1061	50.9	45595	52.6	1.7
Yes	1025	49.1	41054	47.4	−1.7

[a]The weighted distribution uses a sample size of 2077, as 10 participants were missing data on at least one of the variables used for weighting.

3 | RESULTS

3.1 | Baseline Survey

IDEAL recruitment spanned June 2021 through September 2023. We sent invitations to 91,433 households and received 5542 (6.1%) responses. Baseline surveys were completed by 2120 participants (78.5% online, 21.5% CATI), and 33 were excluded because the participant or a family member had previously completed a survey, yielding 2087 eligible surveys and a response rate of 2.3%. Of the 3422 participants who responded but did not complete a Baseline Survey, 91.2% did not meet our eligibility criteria and 8.8% declined to participate.

Of eligible participants who completed a Baseline Survey (Table 3), 41% were 40–49 years old, 71% were women, 63% identified as having had some college education, 54% identified as Dominican, 62% were not born in the United States, and 75% completed the survey in English. Comparing unweighted and weighted distributions of demographic characteristics among Baseline Survey participants showed moderate differences (range: 0.5%–20.4%) for age group, sex, education, and national origin (Table 3). Differences for other demographic variables were minimal (range: 0.1%–4.7%).

3.2 | Introductory Session

Among the 2087 eligible Baseline Survey participants, 1628 (88%) were eligible for the clinical trial; the remainder were excluded because they did not provide contact information or declined recontact ($N = 144$) or were otherwise ineligible (i.e., reported suicidality, had previous *APOE* testing, or had a family history consistent with autosomal dominant AD). The Introductory Session was completed by 1030 (63%) of those eligible (1017 online, 13 telephone). Almost all (98%) passed the quiz within three attempts. Results for the first quiz attempt demonstrated that participants largely understood the AD- and study-related concepts presented and could provide informed consent (Table 4). Of those participants who passed the quiz, 820 (82%) signed the consent form.

3.3 | Genetic testing and selection for follow-up

APOE genetic testing was completed by 664 (81%) of participants who signed the consent form, with results of: 2 (0.3%) ε2/ε2, 48 (7.2%) ε2/ε3, 420 (63.2%) ε3/ε3, 11 (1.7%) ε2/ε4, 171 (25.8%) ε3/ε4, and 12 (1.8%) ε4/ε4. We selected 404 participants (61%) for the clinical trial, 374 of whom completed the Pre-disclosure Survey and were randomized (disclosure $N = 194$, 84 with one ε4, 11 with ε4/ε4; nondisclosure $N = 180$, 83 with one ε4, none with ε4/ε4). Data collection for the remaining study steps is ongoing.

4 | DISCUSSION

Building on insights from previous studies,[13–15] the IDEAL Study is novel in its focus on understanding the psychosocial and cognitive impacts of *APOE* genotype disclosure among Latinos. Our study design

TABLE 4 Results from first attempts on the Introductory Session quiz.

Introductory Session quiz item	Percent correct
Multiple choice	(*N* = 1030)
Alzheimer's disease-related questions	
What is Alzheimer's disease?	99.5
In which age group is Alzheimer's disease most common?	90.8
Which form of the *APOE* gene is associated with the greatest risk for Alzheimer's disease?	93.8
Study-related questions	
What gene(s) are we looking at in our study?	81.1
How many months will you be in the study if you are selected for follow-up?	63.7
True/false	
Alzheimer's disease-related questions	
Alzheimer's disease is a normal part of aging.	82.6
Having a parent or sibling with Alzheimer's disease increases the chance you will have Alzheimer's disease.	86.7
Genetics and heart health are two of the factors that affect your chance of having Alzheimer's disease someday.	82.7
If I have an *APOE* ε4 gene, I will definitely develop Alzheimer's disease.	76.7
If I do NOT have an *APOE* ε4 gene, I will never develop Alzheimer's disease.	86.2
Your feelings and your plans for the future could be affected by the results of your *APOE* genetic test.	72.7
Study-related questions	
Everyone who completes today's Introductory Session will be selected for follow-up.	78.9
All follow-up participants will be invited to have interviews.	64.4
Some participants won't get their *APOE* genetic test results until the end of the study.	78.9

provides a framework for future studies of diverse populations using rigorous mixed methods.

The response rate for the Baseline Survey was lower than in other studies of Latinos,[46] and we under-enrolled men and those without college education. Because of COVID-19, we adapted our methods to remote data collection. Participants without digital access are often difficult to reach, resulting in lower participation rates in research; the pandemic exacerbated this issue by further limiting access to public computers and the internet.[47] New economic and familial hardships may have also limited research engagement. Beyond limited digital access and pandemic-related adversity, difficulties in recruiting Latino populations in the United States include the complexity of translating study materials into Spanish, financial and cultural barriers, and concerns about confidentiality.[48,49]

Nonetheless, we demonstrate that the use of remote methods is feasible in this population. For example, 81% of participants completed the genetic testing kit we sent to them. In addition, we created survey weights using census data to mitigate the effects of selection bias related to sex and education on analyses of Baseline Survey data. Our bilingual study team accommodated participants with limited digital access through telephone data collection. We even promoted the IDEAL Study on a local news program.

Diversity of the IDEAL Study team, with good representation of Latinx professionals, allowed us to establish rapport and engage in a culturally competent way with our target community. We improved retention by contacting participants using multiple means (i.e., calls, texts, and emails) and accommodating participants outside of typical business hours. Other studies have achieved further improved engagement within similar communities by providing tablets for home use,[50] but we did not explore this due to prohibitive costs.

Anecdotally, many participants expressed appreciation for their involvement in the study, highlighting a sense of contribution to improved understanding of AD within their community. Their positive feedback underscores the value of our research in a community with high AD incidence[25–28] and emphasizes the crucial role of comprehensive genetic counseling in the era of direct-to-consumer genetic testing, wherein complex genetic risk information is often provided without adequate support or context. Our findings may facilitate the development of culturally-sensitive educational materials about AD and genetic testing and genetic counseling protocols to improve coping and adjustment in response to receiving risk information.

AUTHOR CONTRIBUTIONS

Wendy Uhlmann, Jill Goldman, Cheng-Shiun Leu, Rafael A. Lantigua, Ana Abraído-Lanza, Wendy K. Chung, J. Scott Roberts, Karolynn Siegel, and Ruth Ottman were involved in conception and design of the study. John B. Wetmore, Sophia Rodriguez, Daniela Diaz Caro, and Ruth Ottman drafted the manuscript, which follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist for reporting randomized trials. John B. Wetmore, Sophia

Rodriguez, Daniela Diaz Caro, María Cabán, Wendy Uhlmann, Jill Goldman, Cheng-Shiun Leu, Rebecca Ferber, Rafael A. Lantigua, Ana Abraído-Lanza, J. Scott Roberts, Karolynn Siegel, and Ruth Ottman adapted and finalized the design of the study in a remote setting. Jonathan D. Godinez and Itzel A. Camarillo facilitated education sessions, translated study documents, and conducted recruitment. Cheng-Shiun Leu provided statistical support and created the randomization sequence. Sophia Rodriguez and Daniela Diaz Caro provided the study intervention. Sophia Rodriguez, Daniela Diaz Caro, and Rafael A. Lantigua conducted safety monitoring. Ruth Ottman and Karolynn Siegel obtained study funding. All authors edited the manuscript and read and approved the final version.

ACKNOWLEDGMENTS

The IDEAL Study thanks Safety Officer Dr. Joshua Grill for oversight and Dr. Paul Appelbaum for guidance on our safety-related procedures. We also thank programmer Tsvyatko Dorovski for implementing randomization procedures and assisting in database management. We are grateful to the study participants for devoting time to the research. Data collection and sharing for this project were supported by the Washington Heights-Inwood Columbia Aging Project (WHICAP, R01 AG072474, RF1 AG066107) funded by the National Institute on Aging (NIA) and by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Number UL1TR001873. This study was funded by grants from the NIH (R01AG062528 and T32HG010030). Sponsor: Columbia University, New York, NY (USA). ClinicalTrials.gov Protocol Version: 15 (July 9, 2024).

CONFLICT OF INTEREST STATEMENT

Neither the study's principal investigators (R.O. and K.S.) nor any of the other coauthors has any conflict of interest to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

We confirm that all participants in the IDEAL Study provided either written or electronic informed consent.

ETHICS SATEMENT

The initial IDEAL protocol and all subsequent modifications were approved by the Columbia University Irving Medical Center Institutional Review Board (IRB; AAAR8269). The funder, the National Institute on Aging (NIA), oversees data collection through monthly reports that we upload to their Clinical Research Operations & Management System (CROMS) system. Adverse events (AEs) and serious AEs (SAEs) as well as recruitment and retention rates are reviewed bi-annually by our Safety Officer (Dr. Joshua Grill), who is independent from our sponsor and has no competing interests. The Safety Officer reviewed and approved the Manual of Procedures and Data and Safety Monitoring Plan for the study (including the Study Consent Form) before recruitment began. This protocol is published in the final stages of data collection before analysis of the results. Findings will be disseminated through peer-reviewed journals, presentations at national and international meetings, and summaries shared with participants. De-identified data from all surveys as well as codebooks and interview guides for qualitative interviews will be made available from the principal investigators, after acceptance for publication of the primary data analyses, to qualified researchers who sign a data user agreement.

CLINICAL TRIAL STATEMENT

ClinicalTrials.gov ID: NCT04471779. Registry Name: The IDEAL Study: Information About Alzheimer's Disease for Latinos in New York City. Date Registered: July 15, 2020. Columbia University IRB Protocol Number: AAAR8269.

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SUPPORTING INFORMATION

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

How to cite this article: Wetmore JB, Rodriguez S, Diaz Caro D, et al. Designing and implementing the IDEAL Study: A randomized clinical trial of *APOE* genotype disclosure for late-onset Alzheimer's disease in an urban Latino population. *Alzheimer's Dement*. 2024;10:e70016. https://doi.org/10.1002/trc2.70016