

Which MCI Patients Should be Included in Prodromal Alzheimer Disease Clinical Trials?

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Background: Prodromal Alzheimer disease (AD) clinical trials enroll patients with mild cognitive impairment (MCI) meeting biomarker criteria, but specific enrollment criteria vary among trials.

Methods: We used data from AD Neuroimaging Initiative (ADNI) MCI participants to assess AD biomarker eligibility, variation in trial outcome measures, and statistical power.

Results: Most (65%) participants meet eligibility criteria based on low cerebrospinal fluid amyloid beta (A β). Relative to trials enrolling exclusively based on low cerebrospinal fluid A β , trials including participants with a high ratio of phosphorylated tau to A β would include an additional 15% of participants. Fewer (34% to 62%) participants met criteria for A β and tau. Differences in clinical and demographic characteristics of modeled trial samples were minimal. Those with low A β and high tau showed the greatest change over time on outcome measures.

Conclusions: Eligibility rates for prodromal trials vary depending on the specific biomarker criteria, though differences in demographics and the variation associated with outcome measures are minimal. Broadening inclusion criteria beyond amyloid alone may facilitate recruitment but include patients showing slower progression over time. Biomarker criteria selection should be informed by the goal of enrolling individuals most likely to utilize and benefit from the intervention under investigation in a particular setting.

Key Words: Alzheimer disease, mild cognitive impairment, recruitment

To intervene earlier in Alzheimer disease (AD), clinical trials enroll patients with mild cognitive impairment (MCI).¹ Successful disease slowing in MCI may prolong periods of highest function and lowest cost of care. Because heterogeneous etiologies may underlie MCI, these trials incorporate AD biomarker inclusion criteria, a concept termed prodromal AD.^{2,3} Enrolling only patients meeting AD biomarker criteria ensures on-target activity for candidate treatments with a mechanism of action related to AD pathophysiology, improves placebo group behavior,⁴ and optimizes statistical power.^{5,6}

A query of clinicaltrials.gov reveals that markers of the 42-amino acid peptide beta amyloid (A β), including amyloid positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) measures, are most frequently used as inclusion criteria in prodromal AD trials (Table 1). Fewer trials incorporate markers of neurofibrillary tangles, such as levels of CSF phosphorylated tau (p-Tau) or total tau (t-Tau). In a recently proposed framework, markers of A β are required for a diagnosis of AD.⁷

A guiding principle of clinical trial inclusion criteria is to assess safety and efficacy in a controlled setting among

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TABLE 1. Frequency of Biomarker Criteria Employed by Recruiting or not Yet Recruiting Prodromal AD (or MCI due to AD) Trials Identified Through Clinicaltrials.gov (01/11/18)*

Biomarker Inclusion Criteria	Trials (n)
Amyloid PET only	11
Amyloid PET or CSF A β	5
Amyloid PET or CSF A β or multiple downstream markers (eg, MRI, FDG PET)	2
CSF A β or CSF t-Tau:A β ratio	1
Not reported	4

*On the basis of searches for prodromal AD, MCI due to AD, MCI, mild neurocognitive disorder, or mild cognitive disorder, refined based on reported inclusion criteria.

A β indicates amyloid beta; AD, Alzheimer disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; t-Tau, total tau.

individuals most likely to utilize and benefit from the intervention under investigation. While this implies that precise knowledge of specific drug mechanism of action may mandate more stringent criteria, overly restrictive biomarker criteria may exclude a proportion of otherwise eligible participants who may receive treatment once approved. The use of additional inclusive biomarker criteria may increase prodromal AD trial eligibility rates,⁸ whereas overly restrictive biomarker criteria may add to the already difficult challenge of completing prodromal trial accrual.^{9,10} Alternatively, too broad of enrollment criteria may risk inclusion of participants who are unlikely to progress to AD dementia or are less likely to benefit from the investigational intervention. More restrictive criteria may also increase the probability of cognitive decline during the trial, thereby potentially increasing statistical power.^{11,12}

Few studies to date compare biomarker criteria in the setting of prodromal AD trials. We used AD Neuroimaging Initiative (ADNI) data to assess the impact of using different biomarker enrollment criteria. We first examined rates of prodromal AD trial eligibility and how differing criteria affected modeled trial participant demographics. We then assessed trial statistical power using commonly used clinical trial outcome measures. We did so in the real-world scenario in which the number of available eligible participants is limited.

METHODS

Study Population

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). For up-to-date information, see www.adni-info.org. Data were downloaded on January 14, 2017 from <http://adni.loni.usc.edu/data-samples/access-data/>.

This study included MCI participants in ADNI-1, ADNI-GO (including early and late MCI), and ADNI-2, who had participated in the lumbar puncture aspects of the studies and had available measures of A β , t-Tau, and p-Tau at baseline. All participants had a modified Hachinski scale score of ≤ 4 , a Geriatric Depression Scale (abbreviated 15-item version) score ≤ 6 , were fluent in English or Spanish, had a suitable study partner who could accompany them to study visits, and lived at home. They had no significant neurological or psychiatric disease; no history of alcohol or substance abuse; no clinically significant

laboratory abnormalities; and no contraindication to neuroimaging.¹³ MCI was defined using Petersen criteria.¹⁴ Patients were required to demonstrate objective impairment on psychometric tests without impaired activities of daily living or fulfilling criteria for dementia. In addition, patients were required to score 24 to 30 on the Mini-Mental State Examination (MMSE) and 0.5 on the global Clinical Dementia Rating scale (CDR), with a memory box score ≥ 0.5 . Cognitive impairment was assessed through the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale-Revised. Patients were required to score 0.5 to 1.5 SDs below education-adjusted norms for early MCI and >1.5 SDs below education-adjusted norms for late MCI.

Biomarker Measures

Our analyses focused on CSF and amyloid PET measures as trial inclusion criteria. We applied established cutoffs for identifying AD CSF signatures: A β < 192 pg/mL; t-Tau > 93 pg/mL; tau phosphorylated at threonine 181 (p-Tau) > 23 pg/mL; ratio of t-Tau:A β (t-Tau:A β ratio) ≥ 0.39 ; ratio of p-Tau:A β (p-Tau:A β ratio) ≥ 0.1 and combinations of these criteria.¹⁵ Similarly, we applied a quantitative eligibility criterion for florbetapir amyloid PET, mean standardized uptake value ratios (SUVR) across 4 regions of interest (frontal, temporal, parietal, and cingulate cortex) of 1.11 or greater, using whole cerebellum as a reference region.^{16,17}

Analyses

To examine the impact of varying CSF protein level criteria, we applied specific inclusion criteria to all available MCI participants from the ADNI studies for whom CSF data were available at baseline. We hypothesized that incorporating high ratios of tau to A β , in addition to low CSF A β , as inclusion criteria would increase the proportion of trial eligible participants compared with using A β criteria alone. We explored the relationship between CSF and amyloid PET inclusion criteria by assessing the proportion of eligible participants based on CSF who also met amyloid PET criteria, among those participants with data available for both biomarkers. We investigated the impact of various inclusion criteria on trial population demographics and trial power for 2 clinical outcome measures commonly used in clinical trials: the AD Assessment Scale-cognitive subscale (ADAS-cog)¹⁸ and the CDR.¹⁹ Specifically, because of increased sensitivity demonstrated in MCI,^{5,20} we used the ADAS-cog including additional elements for delayed recall and executive function (ADAS13) and, in line with FDA guidance,²¹ the sum-of-the-boxes score for the CDR (CDRSB). Two-year follow-up data were available for 502 participants for the ADAS13 and 510 participants for the CDRSB.

To assess power relative to the differential inclusion criteria, we considered a hypothetical 2-year, 2-arm randomized clinical trial assessing the within-subject change in CDRSB or ADAS13. We assumed that study resources would be constrained so that only a finite pool of potentially eligible MCI patients would be available for recruitment into the trial (in this case the sample of MCI participants in ADNI). For the varying inclusion criteria, we assessed the variance of CDRSB or ADAS13 after 2 years of follow-up. We estimated the correlation coefficient (ρ) for repeated measures within subjects using a continuous autoregressive covariance model. Using these empirically based estimates of variance and correlation, we computed the minimally

detectable difference in the within-subject change over 2 years between treatment and control groups that a trial would be powered to achieve for a sample size of n per group, where n was taken to be 50% of the number of ADNI MCI participants eligible based on given CSF criteria. Power calculations assumed that the analysis would employ an analysis of covariance (ANCOVA) model²² of the form:

$$E[Y_{1i}] = \beta_0 + \beta_1 Y_{0i} + \Delta Tx_i,$$

where Tx_i denotes the indicator of whether patient i received the experimental treatment or control, $i = 1, \dots, 2n$, and Y_{0i} and Y_{1i} denote pretreatment and posttreatment measurements, respectively. In this case Δ denotes the treatment effect, interpreted as the expected difference in the 2-year within-subject change in response comparing treatment to control. It was further assumed that the pretreatment and posttreatment measurements within a subject followed a bivariate normal distribution with variance σ^2 and 2-year correlation ρ^* . From the above specification, power for detecting a true difference of Δ can be computed as:

Power (D)=

$$\Phi\left(\frac{-\Delta}{\sqrt{\frac{4\sigma^2}{n}(1-\rho^*)}} - z_{1-\alpha/2}\right) + 1 - \Phi\left(\frac{-\Delta}{\sqrt{\frac{4\sigma^2}{n}(1-\rho^*)}} + z_{1-\frac{\alpha}{2}}\right).$$

To illustrate the impact of the varying inclusion criteria on trial power, we plotted absolute power curves, demarcating the necessary true effect size to achieve 90% power. We also computed relative differences between power curves obtained from each of the inclusion criteria, using trials incorporating low CSF A β inclusion criteria as a reference group.

To compare the change over time for subjects satisfying high p-Tau:A β ratio and low A β criteria to those only satisfying one criterion, we fit linear mixed effects models with random slopes and random intercepts to each of the groups. We then compared the fixed effects for the 3 groups for ADAS13 and CDRSB. We also fit a continuation ratio

model to investigate progression to dementia in subjects who satisfy A β and p-Tau:A β ratio, those satisfying only low A β , and subjects satisfying only p-Tau:A β ratio, compared with those meeting no biomarker criteria. We adjusted for age, education, race, sex, and apolipoprotein E (APOE) status (at least one $\epsilon 4$ allele compared with none). Progression was defined as 2 consistent visits with a diagnosis of dementia. Time to progression was taken to be the time from baseline until the first diagnosis of dementia among those who progressed.

RESULTS

Description of the Sample

In total, 623 MCI participants were enrolled in ADNI-1, ADNI-GO, or ADNI-2 and had baseline CSF data available (Table 2). ADNI-1 participants were older and demonstrated slightly poorer performance on the MMSE and ADAS13 at baseline.

Effect of Varying CSF Criteria on Enrollment Eligibility

Table 3 displays the proportion of MCI participants meeting CSF enrollment criteria and combinations of those criteria. Compared with the proportion of participants meeting the low A β criterion (65%), an additional 15% of the sample would qualify for a trial also enrolling participants with adequately high p-Tau:A β ratios. In contrast, only an additional 2% would qualify for a trial also accepting participants with high t-Tau:A β ratios. Approximately 75% of subjects who met the p-Tau:A β ratio criterion but not the A β criterion were within 1 SD of A β eligibility (73/95). Similarly, 65% of subjects who met the t-Tau:A β ratio criterion but not the A β criterion were within 1 SD of A β eligibility (9/14). Restricting to those who met the low A β criterion as well as one of the tau criteria reduced the overall eligible sample by 4% to 48%.

Among participants who had amyloid PET data available, 94% of those eligible based on amyloid PET were

TABLE 2. Baseline Description of the ADNI MCI Participants With CSF

Characteristic	ADNI-1	ADNI-GO	ADNI-2	Combined Sample
N	199	117	307	623
Age [mean (SD)]*	74.37 (7.5)	71.11 (7.8)	71.64 (7.3)	72.41 (7.5)
Female [mean (SD)]	66 (33.2)	52 (44.4)	138 (45.0)	256 (41.1)
White [n (%)]	190 (95.5)	104 (88.9)	292 (95.1)	586 (94.1)
Education [mean (SD)]	15.78 (3.0)	15.67 (2.7)	16.38 (2.6)	16.05 (2.8)
APOE $\epsilon 4$ alleles [n (%)]				
0	92 (46.2)	71 (60.7)	153 (49.8)	316 (50.7)
1	86 (43.2)	38 (32.5)	119 (38.8)	243 (39.0)
2	21 (10.6)	8 (6.8)	35 (11.4)	64 (10.3)
MMSE [mean (SD)]*	26.93 (1.8)	28.3 (1.5)	27.99 (1.8)	27.71 (1.8)
CDRSB [mean (SD)]*	1.56 (0.9)	1.23 (0.7)	1.53 (0.9)	1.48 (0.9)
ADAS13 [mean (SD)]*	18.89 (6.3)	12.33 (5.1)	15.84 (7.1)	16.15 (6.9)
A β CSF Eligible [n (%)]*	147 (73.9)	54 (46.2)	202 (65.8)	403 (64.7)
t-Tau CSF eligible [n (%)]*	90 (45.2)	31 (26.5)	101 (32.9)	222 (35.6)
p-Tau CSF Eligible [n (%)]	141 (70.9)	77 (65.8)	234 (76.2)	452 (72.6)
A β PET eligible [n (%)]	NA	50 (42.7)	178 (58.0)	228 (36.6)
Proportion with visits at 24 mo	0.804	0.855	0.847	0.835

*Statistically significant differences by ADNI study phase after Holm-Bonferroni correction with a family-wise error rate of 0.05. One-way ANOVA tests were used for continuous variables and χ^2 tests were used for categorical variables.

ADAS13 indicates Alzheimer Disease Assessment Scale-cognitive subscale; ADNI, Alzheimer Disease Neuroimaging Initiative; APOE, apolipoprotein; CDRSB, Clinical Dementia Rating Scale Sum of Boxes; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Exam; NA, not available.

TABLE 3. Prodromal Trial Eligibility

		Aβ [n (%)]				Aβ [n (%)]	
		Eligible (≤ 192; N = 403)	Not Eligible (> 192; N = 220)			Eligible (≤ 192; N = 403)	Not eligible (> 192; N = 220)
p-Tau:Aβ ratio	Eligible (≥ 0.10; N = 483)	388 (62)	95 (15)	t-Tau:Aβ ratio	Eligible (≥ 0.39; N = 360)	346 (56)	14 (2)
	Not eligible (< 0.10; N = 140)	15 (3)	125 (20)		Not eligible (< 0.39; N = 263)	57 (9)	206 (33)
p-Tau	Eligible (≥ 23; N = 452)	358 (57)	94 (15)	t-Tau	Eligible (≥ 93; N = 222)	210 (34)	12 (2)
	Not eligible (< 23; N = 171)	45 (7)	126 (20)		Not eligible (< 93; N = 401)	193 (31)	208 (33)

Aβ indicates amyloid beta; p-Tau, phosphorylated tau; SUVR, standardized uptake value ratios; t-Tau, total tau.

also eligible based on low CSF Aβ (Table 4). Among those with discrepant Aβ eligibility, 75% (39/52) were eligible based on CSF but ineligible by PET; 25% (13/52) were eligible by PET but ineligible by CSF. Ninety-one percent of those ineligible based on CSF Aβ who met the p-Tau:Aβ ratio criterion were ineligible based on amyloid PET. Compared with a trial enrolling based only on amyloid PET, incorporating the additional p-Tau:Aβ ratio criterion would increase the pool of eligible participants by 46%.

Effect of Varying CSF Criteria on Trial Populations

Compared with a trial enrolling only those with low CSF Aβ, including patients meeting low Aβ or high p-Tau:Aβ ratio slightly lowered the overall proportion of APOE ε4 carriers and raised the group mean CSF Aβ level (Table 5). No qualitative differences were apparent, however, for sex,

age, race, or performance at baseline on the MMSE, ADAS13, or CDRSB. Trials enrolling only those meeting both Aβ and t-Tau criteria demonstrated the highest proportion of APOE ε4 carriers. These criteria also resulted in the worst mean baseline performance on the ADAS13 and CDRSB, the highest mean levels of p-Tau and t-Tau, and the lowest mean levels of Aβ.

Trial Variance and Power

Table 6 provides the estimated 2-year variances incorporating differing CSF inclusion criteria and employing the CDRSB or ADAS13 as primary outcome measures. No major differences in variance were observed in the trial scenarios. The lowest observed variance for the CDRSB was in trials using p-Tau:Aβ ratio and trials using p-Tau:Aβ ratio or Aβ as inclusion criteria. Trials using the

TABLE 4. Relationship Between CSF and Amyloid PET

		Amyloid PET SUVR < 1.1 (n = 192)				Amyloid PET SUVR > 1.1 (n = 228)	
		Low CSF Aβ [n (%)]				Low CSF Aβ [n (%)]	
		Eligible (N = 39)	Not Eligible (N = 153)			Eligible (N = 215)	Not Eligible (N = 13)
High p-Tau:Aβ ratio	Eligible (N = 105)	30 (15.6)	75 (39.1)	High p-tau ratio	Eligible (N = 220)	213 (93.4)	7 (3.1)
	Not eligible (N = 87)	9 (4.7)	78 (40.6)		Not eligible (N = 8)	2 (0.9)	6 (2.6)
High p-tau	Eligible (N = 97)	20 (10.4)	77 (40.1)	High p-tau	Eligible (N = 211)	204 (89.5)	7 (3.1)
	Not eligible (N = 95)	19 (9.9)	76 (39.6)		Not eligible (N = 17)	11 (4.8)	6 (2.6)
High t-Tau:Aβ ratio	Eligible (N = 27)	17 (8.9)	10 (5.2)	High t-Tau:Aβ ratio	Eligible (N = 193)	192 (84.2)	1 (0.4)
	Not eligible (N = 165)	22 (11.5)	143 (74.5)		Not eligible (N = 35)	23 (10.1)	12 (5.3)
High t-Tau	Eligible (N = 14)	5 (2.6)	9 (4.7)	High t-tau	Eligible (N = 118)	118 (51.8)	0
	Not eligible (N = 178)	34 (17.7)	144 (75.0)		Not eligible (N = 110)	97 (42.5)	13 (5.7)

The proportion of amyloid PET negative and positive participants among those with PET data who were eligible and not eligible based CSF criteria, all cells n (%).

Aβ indicates amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography; p-Tau, phosphorylated tau; SUVR, standardized uptake value ratios; t-Tau, total tau.

TABLE 5. Baseline Description of Trial Samples

Characteristic	Aβ	p-Tau	t-Tau	p-Tau:Aβ ratio	t-Tau:Aβ ratio	Aβ or p-Tau:Aβ ratio	Aβ or t-Tau:Aβ ratio	Aβ and p-Tau	Aβ and t-Tau
N (%)	403 (64.7)	452 (72.6)	222 (35.6)	483 (77.5)	360 (58.1)	498 (79.9)	417 (66.9)	358 (57.5)	210 (33.7)
Age (mean ± SD) (y)	73.29 (7.12)	72.64 (7.5)	73.52 (7.4)	72.66 (7.5)	73.54 (7.2)	72.61 (7.5)	73.39 (7.2)	73.31 (7.3)	73.31 (7.3)
Female [n (%)]	159 (39.5)	192 (42.5)	105 (47.3)	201 (41.6)	147 (40.8)	204 (41.0)	167 (40.1)	145 (40.5)	98 (46.7)
White race [n (%)]	386 (95.8)	427 (94.5)	214 (96.4)	457 (94.6)	347 (96.4)	472 (94.8)	399 (95.7)	343 (95.8)	203 (96.7)
Education (mean ± SD)	16.00 (2.8)	16.04 (2.8)	15.88 (2.8)	16.00 (2.8)	15.99 (2.8)	16.01 (2.8)	16.02 (2.8)	16.01 (2.8)	15.85 (2.8)
ApoE ε4 copies [n (%)]									
0	142 (35.2)	188 (41.6)	67 (30.2)	202 (41.8)	114 (31.7)	211 (42.4)	151 (36.2)	117 (32.7)	58 (27.6)
1	197 (48.9)	206 (45.6)	121 (54.5)	218 (45.1)	185 (51.4)	223 (44.8)	202 (48.4)	183 (51.1)	118 (56.2)
2	64 (15.9)	58 (12.8)	34 (15.3)	63 (13.0)	61 (17.0)	64 (12.9)	64 (15.4)	58 (16.2)	34 (16.2)
MMSE (mean ± SD)	27.42 (1.9)	27.52 (1.9)	27.2 (1.9)	27.54 (1.9)	27.3 (1.9)	27.57 (1.9)	27.42 (1.9)	27.33 (1.9)	27.16 (1.9)
CDRSB (mean ± SD)	1.61 (0.9)	1.53 (0.9)	1.71 (0.9)	1.53 (0.9)	1.62 (0.9)	1.53 (0.9)	1.59 (0.9)	1.62 (0.9)	1.75 (0.9)
ADAS13 (mean ± SD)	17.88 (6.8)	17.26 (6.9)	18.77 (6.4)	17.14 (6.9)	18.47 (6.8)	17.05 (6.9)	17.82 (6.8)	18.29 (6.7)	18.89 (6.3)
CSF Aβ (mean ± SD)	137.7 (24.7)	156.09 (46.0)	139.27 (32.7)	154.09 (43.3)	137.34 (28.9)	154.73 (42.9)	140.47 (29.0)	135.97 (23.7)	133.44 (21.0)
CSF t-tau (mean ± SD)	108.98 (58.0)	106.84 (55.6)	147.80 (52.4)	103.22 (55.7)	119.64 (55.0)	101.16 (56.1)	109.28 (57.4)	116.69 (56.7)	149.01 (53.0)
CSF p-tau (mean ± SD)	46.89 (23.0)	47.26 (21.0)	56.16 (22.5)	45.42 (21.5)	50.00 (22.2)	44.49 (21.8)	46.59 (22.7)	50.55 (21.7)	57.34 (22.4)

Aβ indicates amyloid beta; ADAS13, Alzheimer Disease Assessment Scale-cognitive subscale; APOE, apolipoprotein E; CDRSB, Clinical Dementia Rating Scale Sum of Boxes; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; p-Tau, phosphorylated tau; t-Tau, total tau.

combination of low Aβ and high t-Tau demonstrated the lowest variance for ADAS13. The correlation coefficients of the varying trial scenarios were largely equivalent for each outcome measure. Compared with trials enrolling only those meeting Aβ criteria, none of the more inclusive scenarios sacrificed power (Figs. 1B, E, H, K). In fact, power was increased for the inclusive scenarios (eg, it is estimated that a trial enrolling low Aβ or high p-Tau:Aβ ratio would require a 14% smaller treatment effect on the ADAS13 to achieve 90% power than would a trial enrolling only those with low Aβ). This impact is attributable to the larger sample size afforded by the broader inclusion criteria in the finite population pools being considered. Trials employing more restrictive criteria generally required larger treatment effects to account for smaller sample sizes (eg, it is estimated that compared with a trial using the ADAS13 as an outcome enrolling only participants with low Aβ, a trial enrolling patients meeting both low Aβ and high t-Tau criteria would require a 42% higher treatment effect; Table 6 and Figs. 1C, F, I, L). As expected given the minimal impact that the differing inclusion criteria had on outcome variation and within-subject correlation in the outcome, the smallest minimum detectable difference required for 90% power was afforded by the largest trials, those enrolling patients meeting either low Aβ or high p-Tau criteria or low Aβ or high p-Tau:Aβ ratio criteria.

For trials testing a therapy designed to slow disease progression, trial power will be impacted by the rate of change in the control arm. To explore how specific participants meeting varying criteria differ in disease progression, we plotted change over time for subpopulations of the most inclusive modeled trial, one enrolling either low Aβ or high p-Tau:Aβ ratio. Figure 2 demonstrates the individual and group changes for the outcome measures specifically among those participants meeting only high p-Tau:Aβ ratio, only low Aβ, or both criteria. Those meeting both low Aβ and high p-Tau:Aβ ratio criteria demonstrated greater change over 24 months for the ADAS13, compared with those meeting only low Aβ or only high p-Tau:Aβ ratio criteria. For each additional month, ADAS13 increased by 0.153 [95% confidence interval (CI): 0.130, 0.177], on average, for subjects satisfying both low Aβ and high p-Tau:Aβ ratio. The estimates were 0.040 (95% CI: -0.069, 0.150) and -0.003 (95% CI: -0.057, 0.051) for the low Aβ only and the high p-Tau:Aβ ratio only groups, respectively. For CDRSB, those meeting only low Aβ demonstrated changes equivalent to those meeting both low Aβ and high p-Tau:Aβ ratio criteria; both groups demonstrated greater change than those meeting only high p-Tau:Aβ ratio criteria. For each additional month, CDRSB increased by ~0.057 (95% CI: 0.051, 0.062) for the subjects meeting both criteria. The corresponding estimates were 0.038 (95% CI: -0.007, 0.082) for the low Aβ only group and 0.008 (95% CI: -0.002, 0.018) for the high p-Tau:Aβ ratio only group.

Using our definition of progression, 148 subjects converted to dementia of 601 who had at least one visit after baseline. Subjects who satisfied low Aβ and p-Tau:Aβ ratio were at higher risk for progression [odds ratio (OR) = 5.12; 95% CI: 2.49, 10.53], compared with subjects with a similar age, education, sex, and APOE status who did not satisfy either criteria. The odds of progression were also higher for those who only satisfied low Aβ (OR = 3.7; 95% CI: 1.10, 12.54) but lower for subjects who only satisfied p-Tau:Aβ ratio eligibility (OR = 0.61; 95% CI: 0.19, 2.01), compared with subjects satisfying neither criteria.

TABLE 6. Variance and Power Associated With Trial Design Choices

Enrollment criteria	N	Variance	ρ^* (95% CI)	Minimum Detectable Treatment Effect, Points
CDRSB				
A β	404	5.0	0.48 (0.44, 0.52)	0.74 (0.71, 0.76)
t-Tau	222	5.0	0.46 (0.39, 0.51)	1.02 (0.97, 1.1)
p-Tau	452	4.7	0.50 (0.46, 0.54)	0.67 (0.64, 0.70)
t-Tau:A β ratio	360	5.0	0.48 (0.43, 0.53)	0.79 (0.75, 0.82)
p-Tau:A β ratio	484	4.6	0.50 (0.45, 0.54)	0.64 (0.61, 0.66)
A β or t-Tau	416	4.9	0.49 (0.44, 0.53)	0.72 (0.69, 0.75)
A β or p-Tau	498	4.7	0.50 (0.47, 0.54)	0.63 (0.61, 0.65)
A β or t-Tau:A β ratio	418	4.9	0.49 (0.44, 0.53)	0.72 (0.69, 0.75)
A β or p-Tau:A β ratio	498	4.6	0.50 (0.46, 0.54)	0.63 (0.61, 0.65)
A β and t-Tau	210	4.9	0.45 (0.39, 0.50)	1.05 (1.0, 1.1)
A β and p-Tau	358	5.0	0.47 (0.42, 0.51)	0.79 (0.76, 0.83)
A β and t-Tau:A β ratio	346	5.0	0.47 (0.42, 0.52)	0.81 (0.77, 0.84)
A β and p-Tau:A β ratio	388	4.9	0.48 (0.44, 0.52)	0.75 (0.72, 0.78)
ADAS13				
A β	404	104.7	0.63 (0.58, 0.67)	2.9 (2.7, 3.0)
t-Tau	222	93.0	0.57 (0.51, 0.63)	3.9 (3.6, 4.2)
p-Tau	452	104.6	0.65 (0.61, 0.69)	2.6 (2.5, 2.8)
t-Tau:A β ratio	360	104.3	0.59 (0.53, 0.65)	3.2 (2.9, 3.4)
p-Tau:A β ratio	484	104.9	0.64 (0.58, 0.68)	2.6 (2.4, 2.8)
A β or t-Tau	416	103.7	0.63 (0.59, 0.67)	2.8 (2.6, 3.0)
A β or p-Tau	498	103.2	0.65 (0.61, 0.69)	2.5 (2.3, 2.6)
A β or t-Tau:A β ratio	418	103.9	0.61 (0.55, 0.66)	2.9 (2.7, 3.1)
A β or p-Tau:A β ratio	498	103.7	0.64 (0.58, 0.68)	2.5 (2.4, 2.7)
A β and t-Tau	210	92.5	0.56 (0.49, 0.62)	4.1 (3.8, 4.3)
A β and p-Tau	358	104.8	0.62 (0.57, 0.67)	3.1 (2.9, 3.3)
A β and t-Tau:A β ratio	346	104.5	0.61 (0.56, 0.66)	3.2 (3.0, 3.4)
A β and p-Tau:A β ratio	388	105.8	0.63 (0.58, 0.67)	2.9 (2.8, 3.1)

*Represents the two year within-subject correlation.

A β indicates amyloid beta; ADAS13, Alzheimer Disease Assessment Scale-cognitive subscale; CDRSB, Clinical Dementia Rating Scale Sum of Boxes; CI, confidence interval; p-Tau, phosphorylated tau; t-Tau, total tau.

DISCUSSION

Clinical trial inclusion criteria should ensure participant safety, maximize the probability of trial success, and reflect those patients likely to use and benefit from the investigational intervention if it is efficacious. Overly restrictive criteria may limit generalizability of results and reduce trial feasibility. Recruitment to prodromal AD trials is challenging, due in part to high screen failure rates.^{8,23} Additional barriers to successful recruitment to prodromal AD trials include that the clinical window of eligibility—a current diagnosis of MCI—is temporary,²⁴ limiting the total time a given patient may be trial eligible. Patients must also agree to biomarker testing, as well as randomization to placebo or a drug that may have side effects.¹⁰ Thus, optimizing the probability that patients who are aware, willing, and meet clinical criteria to enroll in prodromal AD trials will also meet biomarker criteria is critical to expediting drug development in this diagnostic category. Here, we found that incorporating a minimum p-Tau level or a minimum p-Tau:A β ratio resulted in eligibility of an additional 15% of MCI participants (a potential 25% boost in enrollment), compared to trials using A β criteria alone. Incorporating additional eligibility based on CSF t-Tau or t-Tau:A β ratio had minimal effects on eligibility rates.

Most prodromal AD trials incorporate a biomarker of A β as an inclusion criterion (Table 1). This practice is due to the stance that A β is an earlier and more specific marker of AD than is tau² and observations in mild-to-moderate AD trials, in which ~20% of participants failed to demonstrate

elevated brain A β .^{25,26} A proposed biological framework specifies that a marker of abnormal A β is necessary for a diagnosis of AD.⁷ Individuals with adequately high p-Tau:A β ratio but subthreshold A β would not be considered AD within this categorization scheme. Recent studies reveal that some individuals with subthreshold A β are at increased risk for cognitive decline and neurofibrillary tangle deposition^{27,28} and >75% of patients eligible based only on p-Tau:A β ratios in this study had CSF A β measures within 1 SD of the eligibility criterion cutoff for that protein. Determining the optimal threshold for AD biomarker criteria will be a critical area of research to identify those most likely to demonstrate disease progression and to benefit from effective AD therapies.

As a group, amyloid negative symptomatic patients do not demonstrate similar disease progression, compared with amyloid positive patients.²⁹ Using a practical model of trial power, one contingent upon a limited pool of MCI patients who can be recruited to trials, we showed that power to demonstrate drug effect is increased in trials incorporating broader inclusion criteria (Fig. 1), primarily as a result of the increased sample size gained through increased eligibility. The specific individuals eligible based on high p-Tau:A β ratios (ie, who were not eligible based on low A β), however, demonstrated less change over time on trial outcomes compared with those with high p-Tau:A β ratio and low A β (Fig. 2) and were less likely to progress to dementia.

Thus, the current results illustrate the challenges faced by investigators designing prodromal AD trials. More

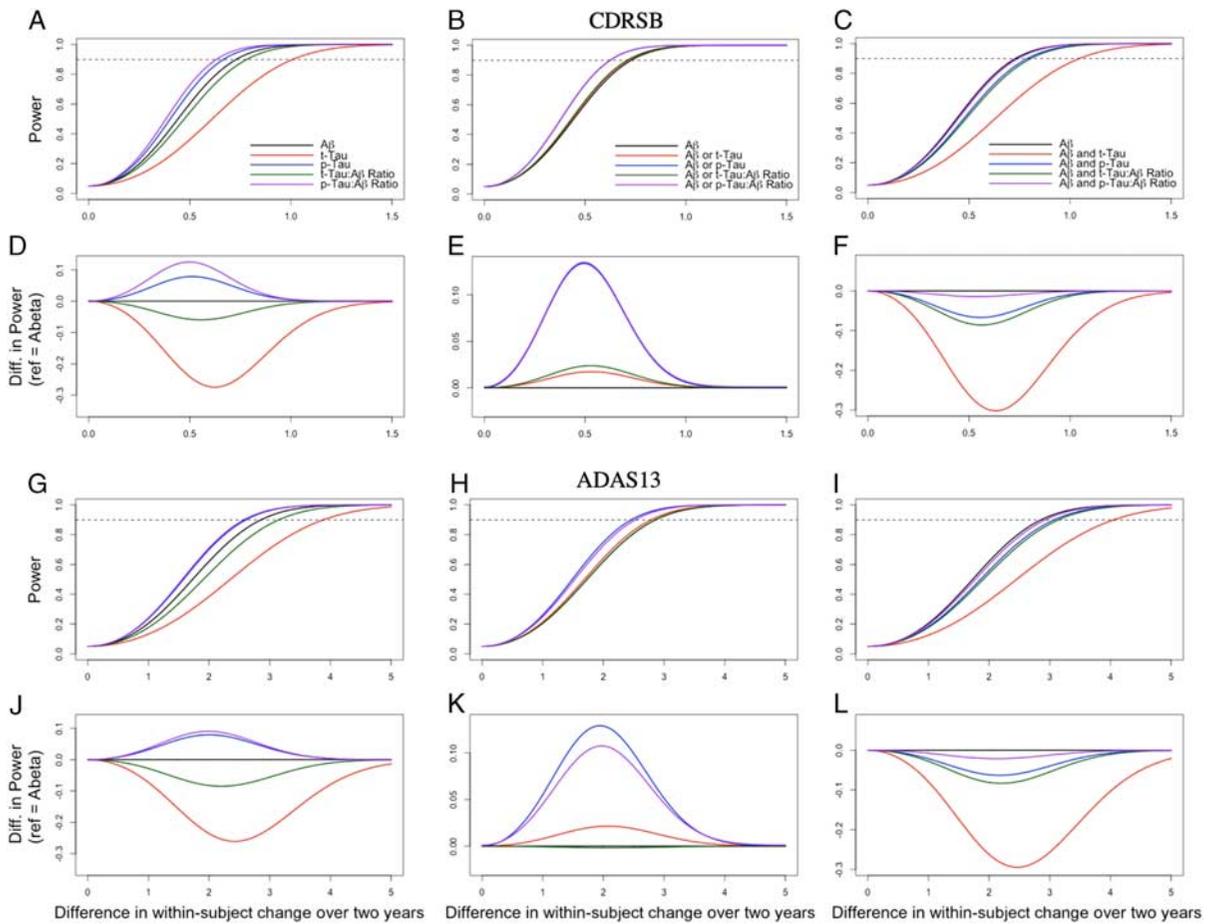


FIGURE 1. Power curves for trials incorporating the CDRSB (A–F) and ADAS13 (G–L) as primary outcomes. In the rows 1 (A–C) and 3 (G–I), power is plotted for trials using indicated biomarker inclusion criteria (and the associated sample sizes based on ADNI) for varying estimated treatment effects. The dotted horizontal line indicates 90% power. In rows 2 (D–F) and 4 (J–L), relative power is plotted, using trials enrolling based only on CSF Aβ as a reference.

inclusive biomarker criteria (eg, permitting participation for those meeting either low Aβ or an adequate ratio) will expedite enrollment by reducing screen failure rates. From a standpoint of instructing future clinical practice, broader

inclusion in prodromal AD clinical trials, with prespecified secondary analyses in biomarker-specific groups, could provide critical information related to drug safety as well as mechanistic pathways for efficacy. Alternatively, more

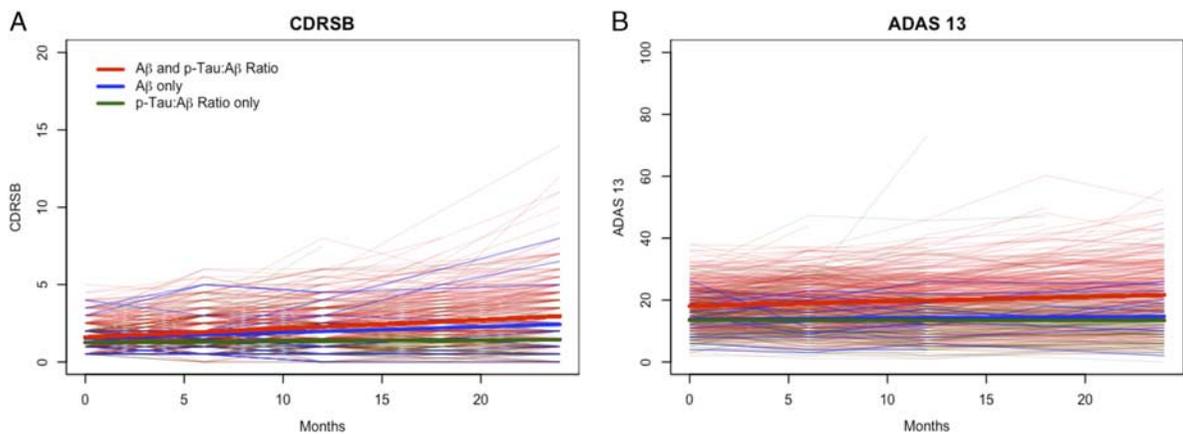


FIGURE 2. Twenty-four month changes in the CDRSB (A) and ADAS13 (B) plotted based on CSF enrollment criteria. Data for individual MCI patients meeting only high p-Tau:Aβ ratio (blue), only low Aβ (green), or both low Aβ and high p-Tau:Aβ ratio criteria (red) are shown, along with smoothed best fit lines for each group.

restrictive criteria (eg, enrolling only those with low A β and high CSF tau) may afford smaller trials due to higher rates of progression but bring more challenging accrual.

Other factors influence trial enrollment criteria selection. Specific drug mechanism of action may mandate more stringent criteria (eg, ensuring fibrillar brain A β is present in participants when testing specific amyloid-lowering therapies or ensuring multiple pathologies are present in combination trials). Trials now most frequently incorporate amyloid PET imaging as biomarker evidence supportive of prodromal AD. Amyloid PET offers some advantages compared with CSF biomarker criteria, including avoiding the reluctance of many patients to undergo lumbar puncture.^{10,30} The current data indicate that using amyloid PET to determine prodromal AD trial eligibility, much like using low CSF A β alone as a criterion, may exclude otherwise eligible participants, here including 15% of those with low CSF A β (Table 4).^{31–33} This finding may represent A β changing earlier in CSF than can be observed by amyloid PET³⁴ or deposition of diffuse but not neuritic plaques in these MCI patients.³⁵ In addition, a third of participants eligible based on p-Tau:A β ratio (and 92% of those with high p-Tau:A β ratio but ineligible based on CSF A β) were ineligible based on amyloid PET. Future research should focus on which biomarker enrollment criteria are associated with greater costs, including the costs of recruitment, time to accrual, and the biomarkers themselves.

Beyond study power and ease of enrollment, there may be ethical implications of these findings. Specifically, if excluded individuals are likely to use the intervention under study were it found to be efficacious (eg, off-label use), then the controlled trial setting would be the only place in which a pure assessment of safety and efficacy in these subpopulations could be performed.

Limitations

Minor differences among the ADNI samples were not controlled for in our analyses. ADNI-2 enrolled early and late stage MCI; we did not incorporate these diagnostic distinctions into our analyses, reflecting current trial practices. Amyloid PET was available for only a subset of participants with CSF data, potentially limiting the generalizability of these results. ADNI is performed nearly exclusively at academic medical centers and may not entirely recapitulate observations from actual trials, which often include a mix of academic and commercial site types.³⁶ We did not apply additional trial exclusion criteria beyond those related to biomarker cutoffs, though ADNI is largely designed to recapitulate trial criteria.³⁷ Moreover, we examined only 1 cutoff for each assessed biomarker and no definitive consensus as yet exists for where these thresholds should be placed.^{38,39} It is possible that setting different cutoffs could reduce or increase the observed discrepancies in eligibility estimates. Finally, there is an imperative to increase the diversity of trial samples⁴⁰ and limited information is available for whether biomarker criteria could differentially affect eligibility among unique racial or ethnic groups.^{41,42} This study lacked adequate diversity to assess for such potential differences.

CONCLUSIONS

Although amyloid PET predominates current prodromal AD trials as a biomarker inclusion criterion, investigators designing these trials may wish to consider additional biomarker eligibility criteria. Including patients

meeting CSF A β criteria, and even more so for CSF p-Tau criteria, may enable enrollment of otherwise ineligible participants. Biomarker criteria selection, however, must be done with specific therapy mechanisms and trial goals in mind. Especially in early phase trials, such decisions may be critical to maximizing accrual and instructing later stage trial decisions.

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