Predicting missing biomarker data in a longitudinal study of Alzheimer disease

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ABSTRACT

Objective: To investigate predictors of missing data in a longitudinal study of Alzheimer disease (AD).

Methods: The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a clinic-based, multicenter, longitudinal study with blood, CSF, PET, and MRI scans repeatedly measured in 229 participants with normal cognition (NC), 397 with mild cognitive impairment (MCI), and 193 with mild AD during 2005–2007. We used univariate and multivariable logistic regression models to examine the associations between baseline demographic/clinical features and loss of biomarker follow-ups in ADNI.

Results: CSF studies tended to recruit and retain patients with MCI with more AD-like features, including lower levels of baseline CSF $A\beta_{42}$. Depression was the major predictor for MCI dropouts, while family history of AD kept more patients with AD enrolled in PET and MRI studies. Poor cognitive performance was associated with loss of follow-up in most biomarker studies, even among NC participants. The presence of vascular risk factors seemed more critical than cognitive function for predicting dropouts in AD.

Conclusion: The missing data are not missing completely at random in ADNI and likely conditional on certain features in addition to cognitive function. Missing data predictors vary across biomarkers and even MCI and AD groups do not share the same missing data pattern. Understanding the missing data structure may help in the design of future longitudinal studies and clinical trials in AD. *Neurology*® 2012;78:1376–1382

GLOSSARY

AD = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–Cognitive Subscale; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CDR** = Clinical Dementia Rating; **MAR** = missing at random; **MCAR** = missing completely at random; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MNAR** = missing not at random; **NC** = normal cognition; **OR** = odds ratio.

Missing data are common in cohort studies, particularly in Alzheimer disease (AD) research.[1] Higher mortality risk and cognitive impairment hinder older adults from staying in studies requiring multiple visits and thus result in incomplete data.[2] Although statistical methods have been developed to handle missing data in repeated-measures studies,[3–5] the underlying mechanism for missing data is rarely examined in actual studies.

Most longitudinal studies of AD use complete data for analysis and ignore missing data, assuming the complete data are a random sample drawn from the entire study population, so-called missing completely at random (MCAR).[6] A less stringent assumption, missing at random (MAR),[6] may be satisfied if missingness does not depend on the variable itself, conditional on observed covariates. If missingness does depend on the variable itself, even after accounting for observed covariates, then data are said to be missing not at random (MNAR).[6] Analysis methods should be used which are appropriate to the type of missingness at work.

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Supplemental data at www.neurology.org

Supplemental Data

From the Division of Epidemiology (R.Y.L., W.J.J.) and Helen Wills Neuroscience Institute (W.J.J.), University of California, Berkeley; and Department of Neurology (R.Y.L.), Buddhist Tzu Chi General Hospital, Hualien, Taiwan.

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Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI or provided data but did not participate in analysis or writing of this report.

Table 1 Baseline characteristics of 819 participants in ADNI

	ADNI diagnostic group		
	NC	MCI	AD
Sample size	229	397	193
Demographic features			
Mean age, y (SD)	75.1 (5.0)	74.0 (7.5)	74.6 (7.5)
M: F, n	119: 110	256: 141	102: 91
Education, y (SD)	16.0 (2.9)	15.7 (3.0)	14.7 (3.1)
Occupation, n (%)			
I[a]	138 (60.3)	190 (47.9)	75 (38.9)
II[b]	54 (23.6)	115 (29.0)	59 (30.6)
III[c]	37 (16.2)	92 (23.2)	59 (30.6)
Smoker, n (%)	85 (37.1)	163 (41.1)	75 (38.9)
AD family history, n (%)	59 (25.8)	101 (25.4)	45 (23.3)
ANART error, n, mean (SD)	9.5 (8.8)	13.6 (9.9)	15.8 (10.0)
*APOE*4 carrier, n (%)	61 (26.6)	212 (53.4)	127 (65.8)
Clinical features			
Body mass index, mean (SD)	26.7 (4.4)	26.0 (4.0)	25.6 (3.9)
Comorbidity, n, mean (SD)	5 (3.0)	5 (3.0)	5 (3.3)
CVD risk score, mean (SD)	18.9 (3.6)	18.4 (3.9)	18.7 (4.1)
FAQ score, mean (SD)	0.1 (0.6)	3.9 (4.5)	13.0 (6.8)
GDS score, mean (SD)	0.8 (1.1)	1.6 (1.4)	1.7 (1.4)
NPI-Q score, mean (SD)	0.4 (0.9)	1.9 (2.7)	3.5 (3.3)
Abnormal gait, n (%)	12 (5.2)	36 (9.1)	35 (18.1)
Cognitive performance			
CDR scale, mean (SD)	0 (0)	0.5 (0.03)	0.7 (0.3)
MMSE score, mean (SD)	29.1 (1.0)	27.0 (1.8)	23.3 (2.1)
ADAS-Cog, mean (SD)	6.2 (2.9)	11.5 (4.4)	18.6 (6.3)
Mean biomarker value			
Blood homocysteine, μM/L	10.0 (n = 227)	10.6 (n = 393)	10.8 (n = 193)
CSF Aβ42, pg/mL	205.6 (n =114)	163.7 (n = 198)	143.0 (n = 102)
CSF tau, pg/mL	69.7 (n =114)	103.6 (n = 195)	121.6 (n = 100)
FDG-PET ROIs, normalized intensity	1.28 (n =103)	1.20 (n = 203)	1.08 (n = 97)
MRI hippocampal volume, mm^3	3,633 (n =228)	3,233 (n = 393)	2,895 (n = 193)
Year of last visit			
Within 1st year, n	16	59	37
Within 2nd year, n	8	45	140
Within 3rd year, n	91	152	14
After 3rd year, n	114	141	2

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADNI = Alzheimer's Disease Neuroimaging Initiative; ANART = American National Adult Reading Test; CDR = Clinical Dementia Rating; CVD = cardiovascular disease; FAQ = Functional Assessment Questionnaire; FDG-PET ROIs = [^{18}F]fluorodeoxyglucose–PET region of interest; GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NC = normal cognition; NPI-Q = Neuropsychiatric Inventory Questionnaire.
[a] Professional/managerial.
[b] Skilled.
[c] Partly skilled/unskilled.

However, it is important to note that it is not possible to distinguish between MAR and MNAR based on observed data, suggesting sensitivity analyses ought to ideally be performed.

In this study we examined the missing data structure of the Alzheimer's Disease Neuroimaging Initiative (ADNI), an AD longitudinal study with multiple biomarkers repeatedly measured, in an attempt to understand the direction of bias due to dropouts, which we believe is essential to developing strategies to retain cases in future longitudinal studies and to inform how the ADNI data themselves are analyzed.

METHODS

Study population. This is a cohort study with 3 subgroups. A total of 819 research participants (NC: 229; MCI: 397; AD: 193) were enrolled in the ADNI study from 59 centers in the United States and Canada during 2005–2007. Full inclusion/exclusion criteria are detailed at www.adni-info.org. Briefly, screening criteria for entry into the study included the Mini-Mental State Examination score (MMSE), Clinical Dementia Rating scale (CDR), and an education-adjusted cutoff score on delayed recall of 1 paragraph from the Logical Memory subtest of the Wechsler Memory Scale–Revised.[7] All participants were recruited between the ages of 55 and 90, and had at least 6 years of education and a study partner able to provide an independent evaluation of functioning. Specific psychoactive medications or other neurologic disorders were excluded.

Standard protocol approvals, registrations, and patient consents. The study procedures were approved by institutional review boards of all participating institutions. Written informed consents to blood sampling, lumbar puncture, neuropsychological testing, and neuroimaging were obtained from all research participants or their representatives.

Follow-up timeline. Detailed schedules of assessment for NC, MCI, and AD are posted in the general procedure manual on the ADNI Web site (http://adni.loni.ucla.edu/wpcontent/uploads/2010/09/ADNI_GeneralProceduresManual.pdf).

Briefly, after the baseline visit, subsequent visits took place at 6- or 12-month intervals in person. Participants with NC or MCI were followed up for 3 years, while those with AD for 2 years at maximum. The visit schedules for collecting biomarkers were similar but not the same for NC, MCI, and AD groups. Participants might visit the research clinic for other assessments without consenting or completing certain biomarker tests. We used the data from ADNI up to April 19, 2011.

Biomarkers. Missing data for blood homocysteine, CSF Aβ_{42} and tau proteins, [^{18}F]fluorodeoxyglucose PET (FDG-PET), and volumetric MRI were examined in ADNI.

Biofluids. Serum and plasma samples from blood were prepared separately for all participants at each visit. Blood and CSF samples were collected and analyzed using a standardized protocol.[8] Biochemical profiles including homocysteine in blood samples and Aβ_{42}, total-tau, and phosphorylated-tau in CSF were measured. The study was targeted to acquire baseline CSF samples for at least 20% of total participants by approaching any potential subject who might be interested.

PET. The protocol to acquire ADNI PET data at sites nationwide is detailed at www.loni.ucla.edu/ADNI/Data/ADNI_Data.shtml, and methods for FDG-PET analysis have been described previously.[9] The study was targeted to acquire baseline PET scans for 50% of total participants. While inclusion in the PET protocol was randomly assigned, participants were free to decline to enter this arm of the study.

MRI. The 1.5-T MRI protocol was described elsewhere,[10] which was standardized across all sites and the acquisition time was approximately 30 minutes. The analyses we report here used FreeSurfer software (http://surfer.nmr.mgh.harvard.edu) to obtain bilateral hippocampal volumes in mm^3. The study was targeted to acquire baseline MRI scans for all participants; individuals who refused MRI could not enroll.

Table 2 Univariate association with missing CSF during follow-up[a]

	Odds ratios (95% CI)		
	NC	MCI	AD
Missing n/total	20/116	45/200	28/102
Demographic features			
Age, y	0.99 (0.91–1.10)	0.96 (0.92–1.01)	0.97 (0.92–1.03)
Female	1.04 (0.39–2.76)	1.16 (0.57–2.31)	1.04 (0.43–2.50)
Education, y	1.05 (0.88–1.26)	0.91 (0.81–1.01)	0.95 (0.84–1.09)
Occupation type	0.74 (0.36–1.38)	1.13 (0.75–1.69)	0.74 (0.42–1.25)
Smoking	0.82 (0.29–2.20)	0.97 (0.49–1.91)	0.98 (0.40–2.36)
Family history of AD	0.45 (0.10–1.48)	0.88 (0.41–1.79)	1.20 (0.45–3.02)
*APOE*4 carrier	1.12 (0.33–3.27)	0.97 (0.50–1.89)	0.89 (0.36–2.35)
ANART error, n	1.01 (0.96–1.07)	1.02 (0.99–1.05)	1.01 (0.96–1.06)
General clinical features			
Body mass index	0.94 (0.83–1.06)	1.08 (0.99–1.17)	1.03 (0.92–1.16)
Comorbidity, n	0.94 (0.78–1.11)	1.01 (0.90–1.12)	1.02 (0.90–1.15)
CVD risk score	1.02 (0.89–1.17)	0.98 (0.90–1.07)	1.00 (0.90–1.12)
FAQ score	1.12 (0.45–2.08)	1.03 (0.96–1.11)	0.99 (0.92–1.05)
GDS score	1.20 (0.78–1.79)	1.14 (0.90–1.44)	1.31 (0.95–1.80)
NPI-Q score	1.18 (0.52–2.28)	1.12 (0.98–1.28)	1.09 (0.96–1.25)
Abnormal gait	1.67 (0.23–7.93)	1.17 (0.36–3.22)	0.86 (0.25–2.50)
Cognitive performance			
CDR scale	NA	NA	1.29 (0.22–7.46)
MMSE score	1.06 (0.67–1.79)	1.06 (0.88–1.29)	1.02 (0.81–1.29)
ADAS-Cog	1.22 (1.03–1.45)[b]	0.97 (0.90–1.04)	0.98 (0.91–1.06)
Baseline CSF			
$A\beta_{1-42}$[d]	1.00 (0.92–1.09)	1.08 (1.02–1.15)[b,c]	1.07 (0.96–1.19)
Tau[d]	0.99 (0.83–1.16)	0.99 (0.92–1.04)	0.98 (0.90–1.06)

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ANART = American National Adult Reading Test; CDR = Clinical Dementia Rating; CI = confidence interval; CVD = cardiovascular disease; FAQ = Functional Assessment Questionnaire; GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NA = not applicable; NC = normal cognition; NPI-Q = Neuropsychiatric Inventory Questionnaire.

[a] In logistic regression models, sex: 1 = male, 2 = female; occupation: 1 = professional/managerial, 2 = skilled, 3 = partly skilled/unskilled; gait: 1 = normal, 2 = abnormal. The dependent variable is the indicator (missing = 1; nonmissing = 0) for missing biomarkers. Odds ratios >1 indicate increased probability of missingness for each unit increase of predictors while odds ratios <1 indicate increased probability of remaining in the study for each unit increase of predictors.

[b] $p < 0.05$.

[c] Statistical significance remained in a multivariable model.

[d] Odds ratios for each 10 pg/mL increase.

Predictors of missing biomarkers. Predictors of interest were baseline demographic and clinical features that were likely associated with both cognitive impairment (study outcome) and loss of follow-up (missingness).

Demographic features. Age, sex, years of formal education, smoking, and family history of AD were recorded at enrollment. Occupation types were recorded and classified into 3 levels: 1) professional or managerial; 2) skilled; 3) partly skilled or unskilled occupations according to The National Statistics Socioeconomic Classification.[11] *APOE* genotyping was carried out at the University of Pennsylvania AD Biomarker Laboratory. *APOE*4 gene carriers were participants who had at least 1 *APOE* 4 allele. Premorbid intelligence indicated by number of errors (range 0–50) in American National Adult Reading Test was evaluated at baseline as part of the neuropsychological battery.[12]

Clinical assessments. Body mass index was measured at baseline. The number of comorbid illnesses was documented regardless of severity or chronicity. Cardiovascular risk score was calculated using the office-based cardiovascular risk profile prediction function from the Framingham Heart Study[13]; higher scores indicate higher risks of cardiovascular events. Gait function was assessed as part of the neurologic examination. Functional Assessment Questionnaire,[14] Geriatric Depression Scale,[15] and Neuropsychiatric Inventory Questionnaire[16] were all included to reflect the global function and behavior of participants.

Cognitive measures. CDR scale,[17] MMSE score, and Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) were used to evaluate cognitive performance at enrollment.

Statistical analysis. Predictors were treated as continuous variables, except sex, smoking, family history of AD, *APOE*4 carrier, and gait, which were dichotomous. We first examined factors that influenced whether biomarkers were obtained at baseline. The outcome was the indicator (missing = 1; nonmissing = 0) of missing data for biomarkers (blood, CSF, PET, and MRI) in each diagnostic group (NC, MCI, and AD) and the aforementioned demographic, clinical, and cognitive predictors were entered into the logistic regression model one at a time for univariate analyses. Odds ratios (ORs) were calculated; ORs >1 indicated increased probability of missingness and ORs <1 indicated increased probability of remaining in the study for each unit increase of predictors. Significant predictors in univariate models were subsequently pooled into a multivariable model to test the robustness as some of these predictors might correlate with one another. MCAR assumptions would be violated if the missingness was associated with any of these predictors.

Secondly, we were interested in factors associated with loss to follow-up once participants enrolled in biomarker studies. For participants who had baseline biomarkers, we defined longitudinal missingness as having only baseline without further lumbar puncture for CSF biomarkers and having only measures within the first year for blood, PET, and MRI biomarkers without longer follow-ups. In addition to the predictors above, we included baseline biomarker values (blood homocysteine, CSF $A\beta_{42}$ and tau, FDG-PET ROIs, MRI hippocampal volume) in these longitudinal analyses.

All statistical analyses and graphics were performed in *R* version 2.11.1. All tests of statistical significance were conducted at the 2-tailed α level of 0.05.

RESULTS Baseline demographic and clinical features, biomarker values, and year of last visit in ADNI are shown in table 1. Regardless of whether biomarkers were obtained at the visit, most participants were followed up for over a year (NC: 93%, MCI: 85%, AD: 81%); there were 8 participants (NC: 1; MCI: 4; AD: 3) who died during the first year and 23 who died during the 3-year observation. All participants had at least 1 blood test (819/819, 100%) with the majority having a MRI scan (814/819, 99%), and more than half of participants in each diagnostic group had at least 1 CSF study (418/819, 51%) or 1 PET scan (455/819, 56%). Although the sample size in general shrank over time, the majority of participants who had baseline tests had biomarkers repeatedly measured longer than a year.

Table 3 Univariate association with missing PET during follow-up[a]

	Odds ratios (95% CI)		
	NC	MCI	AD
Missing n/total	46/133	62/224	39/98
Demographic features			
Age, y	0.97 (0.88–1.06)	0.99 (0.95–1.05)	0.98 (0.92–1.03)
Female	3.47 (1.41–9.19)[b]	0.68 (0.31–1.40)	0.82 (0.35–1.87)
Education, y	0.92 (0.79–1.06)	0.93 (0.83–1.04)	0.99 (0.88–1.13)
Occupation type	1.64 (0.95–2.81)	1.00 (0.64–1.53)	0.92 (0.56–1.50)
Smoking	1.13 (0.45–2.74)	1.83 (0.93–3.59)	2.70 (1.15–6.51)[b]
Family history of AD	0.31 (0.07–0.97)	0.48 (0.19–1.09)	0.15 (0.02–0.58)[b,c]
APOE4 carrier	0.37 (0.08–1.18)	1.45 (0.74–2.89)	0.40 (0.17–0.95)[b]
ANART error, n	1.04 (0.99–1.09)	0.99 (0.95–1.02)	1.01 (0.97–1.05)
General clinical features			
Body mass index	1.06 (0.95–1.19)	1.03 (0.95–1.12)	0.94 (0.84–1.05)
Comorbidity, n	0.94 (0.80–1.08)	0.98 (0.87–1.10)	0.90 (0.78–1.02)
CVD risk score	1.07 (0.95–1.23)	1.02 (0.94–1.11)	1.13 (1.01–1.28)[b]
FAQ score	NA	1.05 (0.96–1.13)	1.01 (0.95–1.08)
GDS score	1.04 (0.72–1.45)	1.34 (1.07–1.67)[b,c]	0.97 (0.72–1.29)
NPI-Q score	0.92 (0.51–1.38)	1.06 (0.95–1.19)	1.05 (0.93–1.18)
Abnormal gait	NA	1.33 (0.36–3.98)	0.42 (0.13–1.19)
Cognitive performance			
CDR scale	NA	NA	1.20 (0.23–6.42)
MMSE score	0.68 (0.46–1.01)	0.94 (0.77–1.15)	0.93 (0.77–1.12)
ADAS-Cog	1.14 (0.99–1.32)	1.10 (1.02–1.20)[b,c]	1.04 (0.98–1.11)
Baseline FDG uptake, normalized intensity	0.29 (0.00–19.8)	0.47 (0.03–6.71)	0.13 (0.01–2.90)

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ANART = American National Adult Reading Test; CDR = Clinical Dementia Rating; CI = confidence interval; CVD = cardiovascular disease; FAQ = Functional Assessment Questionnaire; FDG = fludeoxyglucose; GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NA = not applicable; NC = normal cognition; NPI-Q = Neuropsychiatric Inventory Questionnaire.

[a] In logistic regression models, sex: 1 = male; 2 = female; occupation: 1 = professional/managerial; 2 = skilled; 3 = partly skilled/unskilled; gait: 1 = normal; 2 = abnormal. The dependent variable is the indicator (missing = 1; nonmissing = 0) for missing biomarkers. Odds ratios >1 indicate increased probability of missingness for each unit increase of predictors while odds ratios <1 indicate increased probability of remaining in the study for each unit increase of predictors.

[b] $p < 0.05$.

[c] Statistical significance remained in a multivariable model.

In CSF studies, a family history of AD was associated with having CSF measured at baseline for participants with MCI or AD, but no evidence was found against MCAR for the NC group at enrollment (table e-1 on the *Neurology*® Web site at www.neurology.org). During follow-ups for CSF biomarkers, higher baseline ADAS-Cog scores (worse cognitive performance) predicted dropouts for NC and higher levels of baseline β-amyloid in CSF predicted dropouts for MCI (table 2). Thus the NC group tended to keep cognitively normal participants while the MCI group tended to recruit individuals with an AD family history and retain those who were more AD-like in the longitudinal CSF study.

In PET studies, we found no evidence against MCAR for the NC group at enrollment. MCI participants with lower ADAS-Cog scores (better cognitive performance) as opposed to AD participants with more neuropsychiatric complaints and higher CDR scores were more likely to be included in PET studies (table e-2). During follow-ups for PET, female normal participants were more likely to drop out, depression and lower cognitive performance predicted missing data in the MCI group, while family history of AD, *APOE4* carrier, and higher cardiovascular risk scores were associated with dropouts in the AD group (table 3). Baseline FDG-PET results did not predict missing data in subsequent visits for all 3 groups.

During follow-ups for MRI after the first year, poor cognitive performance (lower MMSE scores and higher ADAS-Cog scores) was predictive of missing data even for the NC group; depression stood out among all other factors in a multivariable model to be associated with dropouts in MCI; and a family history of AD and higher CDR scores characterized AD participants who stayed in the study. Baseline MRI hippocampal volume was not predictive of missing data during follow-ups (table 4).

For blood tests, lower cognitive performance predicted missing data for NC and MCI during follow-ups. Higher cardiovascular risk scores and higher baseline levels of serum homocysteine were associated with dropouts in AD (table 5).

DISCUSSION The missing data structure varied across different biomarkers that were repeatedly measured in ADNI. For at least some of the measured parameters we show that missingness is not MCAR, although whether it is MAR or MNAR cannot be determined based on the observed data. Our findings

indicate that using complete data analysis may result in biased estimates and that handling missing data must be tailored to the target biomarker.

MCI participants with positive family histories of AD and lower premorbid verbal intelligence were more likely to be included in CSF studies and a similar pattern was also seen in AD; these findings suggest that MCI/AD recruitment for CSF donation likely captured people with more AD characteristics. Subjects with positive family histories of AD may have learned about AD from family experience and thus be more motivated to participate in AD studies even though the study procedure is invasive. The motivation may be further enhanced when subjects themselves are cognitively impaired, have hopes of finding effective treatments, or in the case of MCI are apprehensive about converting to dementia. During CSF follow-ups, poor cognitive performance in NC and higher baseline CSF $A\beta_{42}$ in MCI predicted missingness, suggesting the NC group tended to retain relatively normal subjects and the MCI group would retain subjects with lower CSF $A\beta_{42}$ who have a higher likelihood of converting to AD. Thus using CSF biomarkers to track clinical progression in MCI would be predicted to result in an overestimation of the proportion of converters in longitudinal studies or clinical trials.

Better cognitive function was associated with PET enrollment in MCI. This association, however, did not extend to the AD group who were more likely to enroll if more impaired. The AD group tended to retain *APOE4* positive individuals, those with positive family histories, and those with lower cardiovascular risk, suggesting that following up patients with AD using PET scans may capture more purely AD than those with more vascular risk factors. This demonstrates that the missing data structure in MCI and AD should not be assumed to be the same.

Cognitive impairment, particularly decision-making impairment, may reduce the willingness to participate in research[18]; this may explain our observations in the MCI group. But for patients with AD who have overt dementia, surrogates may have more involvement in the decision-making process,[19] which would explain the associations between greater impairment and participation and retention in the PET and MRI components. However, for patients with comorbid illnesses, such as cardiovascular diseases, surrogates may be concerned that the overall benefit/risk ratio does not favor longer participation[20] or such subjects may be more likely to drop out due to medical illness. We cannot confirm these explanations without interviewing both patients and study partners, but our observation at least demonstrates that retained patients with MCI and patients with AD in a follow-up study belong to 2 selected groups. These data suggest that caution is required when assuming that MCI and AD represent the same cognitive spectrum, especially when using PET scans to track disease progression.

Loss of follow-up in MRI studies was conditional on poor cognitive performance in both NC and MCI but not in AD, which again suggests that cognitive impairment may have differential influence on following participants with MCI and AD. In line with CSF studies, baseline cognitive performance despite

Table 4 Univariate association with missing MRI during follow-up[a]

	Odds ratios (95% CI)		
	NC	MCI	AD
Missing n/total	47/228	85/393	86/193
Demographic features			
Age, y	1.03 (0.97–1.10)	1.01 (0.98–1.05)	0.99 (0.96–1.03)
Female	1.15 (0.61–2.20)	0.87 (0.52–1.44)	1.04 (0.59–1.84)
Education, y	0.93 (0.83–1.04)	0.93 (0.86–0.99)[b]	0.93 (0.85–1.02)
Occupation type	1.29 (0.85–1.93)	1.12 (0.83–1.50)	1.24 (0.88–1.76)
Smoking	0.84 (0.42–1.62)	1.28 (0.78–2.07)	1.15 (0.64–2.06)
Family history of AD	0.36 (0.13–0.85)[b,c]	0.67 (0.36–1.18)	0.36 (0.17–0.74)[b,c]
APOE4 carrier	0.59 (0.25–1.25)	1.15 (0.71–1.88)	0.59 (0.32–1.08)
ANART error, n	1.01 (0.98–1.05)	1.01 (0.98–1.03)	0.99 (0.97–1.02)
General clinical features			
Body mass index	0.93 (0.86–1.01)	1.02 (0.96–1.08)	0.96 (0.89–1.04)
Comorbidity, n	0.99 (0.88–1.10)	0.97 (0.89–1.05)	0.96 (0.88–1.05)
CVD risk score	0.97 (0.89–1.06)	1.02 (0.96–1.09)	1.04 (0.97–1.12)
FAQ score	0.67 (0.20–1.29)	1.01 (0.96–1.06)	0.99 (0.95–1.03)
GDS score	1.03 (0.77–1.35)	1.23 (1.03–1.45)[b,c]	0.97 (0.79–1.19)
NPI-Q score	0.96 (0.63–1.34)	1.09 (1.01–1.19)[b]	1.02 (0.94–1.11)
Abnormal gait	0.76 (0.11–3.01)	1.04 (0.43–2.27)	0.51 (0.23–1.08)
Cognitive performance			
CDR scale	NA	NA	0.28 (0.09–0.89)[b,c]
MMSE score	0.69 (0.51–0.93)[b,c]	0.93 (0.81–1.06)	1.01 (0.88–1.16)
ADAS-Cog	1.21 (1.08–1.36)[b,c]	1.06 (1.01–1.12)[b]	0.99 (0.95–1.04)
Baseline MRI hippocampal volume, mm^3	1.00 (0.99–1.00)	1.00 (0.99–1.00)	0.99 (0.99–1.00)

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ANART = American National Adult Reading Test; CDR = Clinical Dementia Rating; CI = confidence interval; CVD = cardiovascular disease; FAQ = Functional Assessment Questionnaire; GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NA = not applicable; NC = normal cognition; NPI-Q = Neuropsychiatric Inventory Questionnaire.

[a] In logistic regression models, sex: 1 = male; 2 = female; occupation: 1 = professional/managerial; 2 = skilled; 3 = partly skilled/unskilled; gait: 1 = normal; 2 = abnormal. The dependent variable is the indicator (missing = 1; nonmissing = 0) for missing biomarkers. Odds ratios >1 indicate increased probability of missingness for each unit increase of predictors while odds ratios <1 indicate increased probability of remaining in the study for each unit increase of predictors.

[b] $p < 0.05$.

[c] Statistical significance remained in a multivariable model.

Table 5 Univariate association with missing blood sample during follow-up[a]

	Odds ratios (95% CI)		
	NC	MCI	AD
Missing n/total	27/229	100/397	66/193
Demographic features			
Age, y	1.03 (0.95–1.11)	0.99 (0.96–1.02)	1.02 (0.98–1.06)
Female	1.19 (0.53–2.69)	1.22 (0.76–1.95)	0.99 (0.54–1.80)
Education, y	0.95 (0.83–1.10)	0.93 (0.87–1.00)	1.02 (0.92–1.12)
Occupation type	1.49 (0.90–2.43)	1.12 (0.85–1.48)	1.12 (0.78–1.61)
Smoking	0.68 (0.27–1.59)	1.05 (0.66–1.66)	1.52 (0.83–2.79)
Family history of AD	0.33 (0.08–0.98)	0.78 (0.45–1.32)	0.63 (0.29–1.30)
*APOE*4 carrier	0.59 (0.19–1.53)	1.15 (0.73–1.82)	0.64 (0.34–1.19)
ANART error, n	1.01 (0.97–1.06)	1.01 (0.98–1.03)	0.97 (0.94–1.00)
General clinical features			
Body mass index	0.91 (0.81–1.01)	1.01 (0.95–1.07)	0.99 (0.92–1.07)
Comorbidity, n	0.99 (0.86–1.12)	0.96 (0.88–1.04)	1.02 (0.93–1.11)
CVD risk score	0.98 (0.88–1.10)	1.02 (0.97–1.09)	1.09 (1.01–1.17)[b]
FAQ score	NA	1.02 (0.96–1.07)	1.02 (0.98–1.07)
GDS score	1.01 (0.69–1.40)	1.15 (0.98–1.35)	0.99 (0.81–1.23)
NPI-Q score	0.98 (0.55–1.43)	1.05 (0.97–1.14)	1.03 (0.94–1.12)
Abnormal gait	1.54 (0.23–6.26)	0.69 (0.27–1.55)	0.73 (0.31–1.59)
Cognitive performance			
CDR scale	NA	NA	0.72 (0.22–2.36)
MMSE score	0.72 (0.50–1.04)	0.86 (0.75–0.98)[b]	0.99 (0.86–1.15)
ADAS-Cog	1.24 (1.08–1.42)[b]	1.09 (1.03–1.14)[b,c]	1.01 (0.96–1.06)
Baseline blood Hcyt, μmol/L	0.87 (0.73–1.02)	1.02 (0.94–1.10)	1.10 (1.01–1.21)[b]

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ANART = American National Adult Reading Test; CDR = Clinical Dementia Rating; CI = confidence interval; CVD = cardiovascular disease; FAQ = Functional Assessment Questionnaire; GDS = Geriatric Depression Scale; Hcyt = homocysteine; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NA = not applicable; NC = normal cognition; NPI-Q = Neuropsychiatric Inventory Questionnaire.

[a] In logistic regression models, sex: 1 = male; 2 = female; occupation: 1 = professional/managerial; 2 = skilled; 3 = partly skilled/unskilled; gait: 1 = normal; 2 = abnormal. The dependent variable is the indicator (missing = 1; nonmissing = 0) for missing biomarkers. Odds ratios >1 indicate increased probability of missingness for each unit increase of predictors while odds ratios <1 indicate increased probability of remaining in the study for each unit increase of predictors.

[b] $p < 0.05$.

[c] Statistical significance remained in a multivariable model.

the limited variability among people considered cognitively normal is still associated with long-term dropouts in MRI studies. Similar to PET studies, depression was also associated with missingness in follow-up MRI scans, suggesting that depression is the major factor driving longitudinal missingness of imaging markers among all covariates considered in the study.

Since repeated blood tests are the standard source of biomarkers in population health studies, blood biomarkers can serve as a control variable to compare missing data patterns across different biomarkers. Poor cognitive function seemed to affect participation in long-term follow-ups in NC and MCI groups. After a diagnosis of AD, cognitive function was no longer critical in determining the missingness. Interestingly, similar to the results from the PET studies, higher baseline homocysteine and higher cardiovascular risk in AD were associated with loss of follow-up, suggesting that patients with AD with vascular risk factors may be more likely to drop out of longitudinal studies per se.

Our study has several strengths. First, the design of ADNI emulates a typical clinical trial in terms of case enrollment criteria, multicenter setting, standardized outcome measures, and follow-up protocols, making our results generalizable to other AD clinical trials. However, we recognize that ADNI is not a clinical trial; missingness related to adverse drug effects or hope of improvement cannot be addressed in this observational study. Second, biomarkers in ADNI have been demonstrated to be useful in tracking AD progression. Future clinical trials for AD will likely incorporate these biomarkers to track cognitive decline and similar missing data challenges may be encountered; therefore our ADNI case study is of high reference value. Third, the ADNI study provides comprehensive data on demographic features, laboratory tests, and clinical assessments, allowing us to systematically examine the missing data structure and plausibly test MCAR and MAR assumptions.

There are also several limitations in the study. First, despite the comprehensive approach taken in ADNI, we can never be certain whether missing data are MAR or MNAR based on the observed data. Second, we acknowledge that some ORs were just barely statistically significant and results might be due to multiple comparisons as we included more than a dozen potential predictors in the models. However, all of these predictors were selected based on a priori hypotheses and most of these significant predictors were coherent with the missingness across biomarkers and diagnostic groups rather than reflecting a random set of variables. Third, although one can hypothesize plausible reasons why certain predictors might predict dropout, we could not confirm these, being neither able to interview the individuals nor to collect information on the reasons for missingness. Fourth, 3 diagnostic groups had different visit schedules, making the missing data structures of NC, MCI, and AD less comparable. Thus we should be conservative in making inferences about intergroup difference.

How best to handle missing data is the subject of considerable interest and debate. Ideally the method chosen should be based on the assumptions one is willing to make regarding missingness. For example, popular methods such as multiple imputation, maxi-

mum likelihood, or weighted estimating equation methods are typically based on the missing at random assumption.[3,6,21] A possible alternative is to stratify by biomarker-specific missingness predictors and perform a complete case analysis, although this increases the complexity of trial design, and assumes that predictors of missingness are consistent across studies.

Longitudinal missingness in ADNI is not completely at random and CSF and imaging markers may bias longitudinal parameters in different directions. Poor cognitive performance at baseline is predictive of missingness even for cognitively normal participants but may be less critical for patients with AD. Depression is a strong predictor for missingness of imaging biomarkers. Patterns of longitudinal missingness may reflect their different levels of accessibility, invasiveness, public awareness, and surrogate decision-making in relation to dementia. Dealing with the missing data in a cohort study or clinical trial for dementia should be tailored to the target biomarker and cognitive stage.

AUTHOR CONTRIBUTIONS

Study concept and design: Dr. Lo and Dr. Jagust. Data interpretation: Dr. Lo and Dr. Jagust. Drafting of the manuscript: Dr. Lo. Statistical analysis: Dr. Lo. Critical revision of the manuscript: Dr. Jagust.

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DISCLOSURE

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