Brain MRI markers and dropout in a longitudinal study of cognitive aging

The Three-City Dijon Study

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ABSTRACT

Objective: Longitudinal studies of dementia rely on the assumption that individuals who drop out are comparable to those who remain in the study, adjusting for measured covariates. Existing methods to handle dropouts account for differences based on past health and cognitive measures. We assess whether such adjustments fully account for differences in future dementia risk.

Methods: Among Three-City Study participants in Dijon, France, with 1 (n = 1,633) or 2 (n = 1,168) brain MRI scans, we tested whether white matter lesion volume (WMLV), hippocampal volume, or brain CSF volume predicted dropout ("unable to contact" or "refused interview") in repeated-measures logistic regression with up to 4 follow-ups (average 3.5 waves). Using linear regression, we also estimated differences in MRI volumes and MRI changes by subsequent dropout status and estimated plausible ranges for selective attrition bias based on these associations. Models were adjusted for demographic, health, and cognitive score covariates.

Results: Baseline greater WMLV predicted increased odds of dropping out (adjusted odds ratio = 1.71; 95% confidence interval [CI] 1.20−2.43). Among participants with 2 MRI scans, individuals who subsequently dropped out had significantly worse declines in hippocampal volume (−0.30 SD difference; 95% CI −0.43 to −0.17) between the first and second MRI scans.

Conclusions: Higher future dementia risk, indicated by worse past brain MRI findings, predicted future study dropout. Adjustment for selective attrition, based on MRI markers when available, may help reduce bias in estimates of dementia incidence and improve research on dementia risk factors. MRI findings may also help prospectively identify cohort members at elevated risk of attrition. *Neurology*® **2012;79:1340-1348**

GLOSSARY

BVRT = Benton Visual Retention Test; **CI** = confidence interval; **IADL** = instrumental activities of daily living; **ICV** = intracranial volume; **ISAAC** = Isaacs' test of verbal/category fluency; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **TMTB** = Trail Making Test B; **WMLV** = white matter lesion volume.

Cognitive impairment strongly predicts dropout in longitudinal studies of aging.[1,2] Longitudinal analyses may therefore differentially exclude cohort members with severe cognitive decline, although this is arguably the population of greatest interest for dementia research. Correctly accounting for such selective attrition might strengthen efforts to identify the effects of cardio-metabolic, behavioral, or clinical factors on the incidence or progression of dementia.[3] Statistical approaches that account for selective attrition using past measured characteristics, such as health and cognitive test scores, are therefore increasingly being adopted in longitudinal research.[4−7] However, such adjustments are insufficient if future dementia risk differs for dropouts even after controlling for measured covariates.[3] Specifically, inferences rest on the

Supplemental Data

assumption that outcome values are missing at random, conditional on measured variables.[3] Although past cognitive scores predict future performances, most cognitive measures have imperfect reliability and only moderate correspondence with underlying progression of Alzheimer or cerebrovascular disease.[8–11] Cerebral MRI data are of special interest for attrition in studies of dementia because MRI markers of subclinical cerebrovascular changes or neurodegenerative disease correlate with future dementia risk over and above current neuropsychological test scores.[12–17] However, few prior studies have examined whether such MRI findings predict dropout (see Note Added in Proof). If so, accounting for selective attrition as patterned by MRI findings could improve our ability to identify factors that increase dementia risk and help prospectively identify cohort members likely to drop out.

Using data from the Dijon cohort of the Three-City Study (3C), we tested the hypothesis that white matter lesion volume (WMLV), hippocampal volume, and brain CSF volume predict loss to follow-up in future assessments, independent of past covariates. We also assessed whether changes in WMLV, hippocampal volume, and CSF volume between the first and second MRI scans were worse for cohort members who subsequently dropped out of the study.

METHODS Sample. The 3C, a population-based prospective study of elderly individuals in Bordeaux, Montpellier, and Dijon, France, has been described in detail previously.[18] We report here results from Dijon only. Participants (n = 4,931) were enrolled between January 1999 and March 2001 from a sample of noninstitutionalized individuals aged 65 years and older, randomly selected from city electoral rolls. Baseline interviews were conducted at home by trained psychologists. Follow-up interviews were conducted approximately 2, 4, 7, and 9 years after enrollment.

MRI scans were offered to participants aged ≤80 years, enrolled from April 1999 to July 2000 (funding precluded performing MRI scans for everyone); the MRI scan consent rate was 83%.

From 1,923 participants who completed baseline MRIs, we excluded from analyses participants with missing assessments of WMLV, hippocampal volume, or CSF volume(n = 123), participants who died before the year 2 interview (n = 18), participants with dementia at baseline (n = 4), or participants with missing data on baseline cognitive assessments or other covariates (n = 141). In all analyses, respondents were censored at death, so individuals who died after completing an MRI scan but

before the next scheduled interview wave were excluded from analyses. These exclusions resulted in a final sample of 1,633 individuals available for analyses involving only baseline MRI scans. Our analytic sample is compared with the age-eligible 3C sample in table e-1 on the *Neurology*® Web site at www.neurology.org. For analyses involving data from the second MRI scan, we additionally excluded 377 individuals who dropped out in the first 2 follow-ups or did not complete the second MRI scan, 37 without valid brain volume findings at the second MRI scan, and 51 who died after the second MRI scan but before the year 7 interview wave, leaving 1,168 respondents for final analyses.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre, and all subjects signed legal consent forms.

Dropout status. At each wave, we categorized as a dropout any cohort member who was alive but could not be contacted or who was contacted but refused to participate in the interview.

MRI protocol. The protocol for cranial MRI, using a 1.5-T Magnetom (Siemens, Erlangen, Germany), has been described in detail previously.[19] Fully automatic image processing software was developed for tissue segmentation and to detect and quantify white matter lesions.[19] WMLV was calculated by summing the volumes of all the lesions detected. Using voxel-based morphometry techniques, total intracranial volume (ICV) was computed by summing gray matter, white matter, and CSF volumes.

We considered 3 MRI biomarkers: WMLV, hippocampal volume, and CSF volume. Of the available MRI markers in 3C, we prioritized indicators that are commonly assessed with a standardized protocol in other studies, show a substantial variability in our sample, and have been implicated in the development of dementia and related cognitive outcomes.[12–17] Each volume was divided by ICV at the concurrent MRI scan and multiplied by 100. Annualized rates of change in volumes were calculated as volume at the second MRI scan (as % of ICV) minus volume at the first MRI scan (as % of ICV) divided by years elapsed between the 2 MRI scans. All MRI measures were capped at the 1st and 99th percentile (i.e., values below or above these percentiles were recoded to the 1st or 99th percentile value) to reduce the influence of outliers (sensitivity analyses indicated that findings were not sensitive to this trimming). For analyses in which MRI findings were the dependent variable, they were converted to z scores by subtracting the mean value for that outcome (i.e., volume at baseline, volume at second MRI scan, or annualized rate of change in volume) and dividing by the SD.

Covariates. Our goal was to assess whether MRI findings were independent predictors of dropout after adjustment for measured covariates. We considered 4 covariate sets, which we expected would have increasingly better explanatory power for dropout. Basic models were adjusted for demographics only: age, age squared, sex, educational attainment (assessed in 6 categories: none; primary school; middle school; technical or professional short degree; secondary level without diploma, technical or professional long degree; and baccalaureate and above) and assessment wave. Our second models were additionally adjusted for self-assessed indicators of health as reported at the most recent prior interview, including self-rated health (ordinal 1−5),[20] elevated depressive symptoms (17+ on the Center for Epidemiologic Studies Depression scale[21]), and limitations in instrumental activities of daily living (IADLs), including using the phone, using public transportation, managing medications, and managing a budget (0−4)[22] We next added baseline cognitive test

scores: Isaacs' test of verbal/category fluency (ISAAC)[23]; the Benton Visual Retention Test (BVRT)[24]; Trail Making Test B (TMTB) expressed as seconds to task completion [maximum 300] divided by number of correct connections, capped at 35 [99th percentile])[25]; and the Mini-Mental State Examination (MMSE).[11,26] Cognitive scores were z score–transformed using baseline mean and SD; we recoded extreme values more than 3 SDs above or below the mean to a z score of 3 (or −3). ISAAC, BVRT, and MMSE were assessed at all follow-up interviews (years 2, 4, 7, and 9); TMTB was not assessed at the year 2 follow-up. Our fourth set of covariates also included changes in test scores (for the ISAAC, BVRT, and MMSE only), defined as the raw difference between the 2 most recent prior z-scored test values (i.e., change from baseline to second interview to predict dropout at the third interview).

Analyses. We used logistic regression to predict dropout at each of 4 follow-up waves, based on the 4 hierarchical covariate sets. First, we used each MRI finding one by one in the models; in the final model, we included the full covariate set and adjusted

simultaneously for WMLV, hippocampal volume, and CSF volume. Models including change in cognitive scores as predictors were estimated in a smaller subset of observations because we could only calculate change scores for those with 2 prior cognitive assessments.

Respondents were censored at death or after their first dropout. Use of repeated observations on study participants maximized statistical power to detect associations between MRI findings and dropout risk, equivalent to discrete time hazard models. We repeated these models examining death, instead of dropout, as the outcome; estimates were very imprecise, however, due to limited statistical power (tables e-2 and e-3).

We also examined models using MRI findings as dependent variables, rather than predictors. With use of random intercept mixed models with either the first or second MRI volume (as % of ICV and expressed in z scores) as a dependent variable, we estimated the magnitude of difference in each MRI marker between respondents who dropped out and those who did not. For these analyses, we defined "dropout" as a binary variable indicating whether the cohort member participated in all interview

Table 1	Characteristics of the baseline 3-city MRI sample compared with dropouts at each wave[a]				
	Baseline MRI sample	Year 2 dropouts (n at risk = 1,633)	Year 4 dropouts (n at risk = 1,548)	Year 7 dropouts (n at risk = 1,407)	Year 9 dropouts (n at risk = 1,172)
Baseline characteristics, n (%)	1,633 (100)	60	62	200	191
Age, y, mean (SD)	72.3 (4.1)	72.8 (3.7)	72.4 (4.4)	73.8 (4.0)	72.4 (3.8)
Male sex, n (%)	647 (40)	29 (48)	20 (32)	75 (38)	65 (34)
Education level (range:1−6), mean (SD)	3.8 (1.6)	3.9 (1.6)	3.7 (1.6)	3.7 (1.6)	3.7 (1.6)
Self-rated health (range: 1−5), mean (SD)	2.3 (0.6)	2.6 (0.7)	2.5 (0.4)	2.5 (0.7)	2.4 (0.6)
Elevated depressive symptoms (yes/no), n (%)	305 (19)	15 (25)	15 (24)	47 (24)	37 (19)
No. of IADL limitations (range 0−4), mean (SD)	0.07 (0.28)	0.12 (0.32)	0.08 (0.42)	0.11 (0.34)	0.06 (0.26)
Reason for dropout, n (%)					
Refusal		43 (72)	38 (61)	98 (49)	94 (49)
Could not contact		17 (28)	24 (39)	101 (51)	97 (51)
Lagged health characteristics, mean (SD)[b]					
Self-rated health		2.60 (0.74)	2.32 (0.70)	2.4 (1.56)	2.4 (0.7)
Elevated depressive symptoms		15 (25)	8 (13)	36 (18)	50 (26)
No. of IADL limitations (0-4)		0.12 (0.32)	0.16 (0.55)	0.13 (0.49)	0.37 (0.83)
Baseline test scores (z-scored), mean (SD)					
ISAAC	0.00 (0.99)	−0.47 (0.91)	−0.26 (0.98)	−0.26 (1.00)	−0.18 (0.92)
Trailmaking B	0.03 (0.86)	−0.27 (1.02)	−0.11 (0.92)	−0.13 (0.94)	0.02 (0.73)
Benton Visual Retention	0.00 (0.98)	−0.13 (1.05)	−0.15 (1.05)	−0.23 (1.08)	−0.08 (0.98)
Mini-Mental State Examination	0.01 (0.98)	−0.32 (1.15)	−0.40 (1.08)	−0.16 (0.99)	−0.21 (1.07)
Baseline MRI markers, mean (SD)					
White matter lesion volume (% of ICV)	0.39 (0.32)	0.41 (0.28)	0.46 (0.37)	0.49 (0.42)	0.41 (0.31)
Hippocampal volume (% of ICV)	0.49 (0.05)	0.48 (0.05)	0.49 (0.06)	0.47 (0.05)	0.48 (0.05)
CSF volume (% of ICV)	28.19 (3.12)	27.24 (3.23)	26.64 (3.38)	28.75 (3.12)	28.56 (3.19)
Annual % change in MRI markers, n (%)[c]	1168 (72)			131 (66)	156 (82)
White matter lesion volume	0.02 (0.05)			0.02 (0.06)	0.02 (0.05)
Hippocampal volume	0.00 (0.01)			−0.01 (0.01)	−0.01 (0.01)
CSF volume	0.17 (0.27)			0.19 (0.31)	0.20 (0.27)

Abbreviations: IADL = instrumental activities of daily living; ICV = intracranial volume; ISAAC = Isaacs' test of verbal/category fluency.
[a] Number at risk of dropout includes individuals who participated in the prior wave and did not die between the waves.
[b] Undefined at baseline.
[c] Among 1,168 respondents eligible for the analyses of change in MRI scores.

waves for which he or she was alive after the respective MRI scan (i.e., ever dropped out to predict first MRI volumes and dropped out at year 7 or 9 interview to predict second MRI). Patterns in simple linear regression models using the first or second MRI scan separately were similar and are shown in figures e-1 and e-2. We also examined differences in MRI changes between the first and second MRI scans, using z-scored changes in MRI findings as dependent variables in linear regressions. For these models, we considered dropout at the year 7 or 9 interview as the predictor. We compared models for the first 3 covariate sets defined above. These analyses are unconventional because we use temporally later events (dropout) as independent variables to predict temporally prior measures (MRI volumes). The goal is to facilitate incorporation of our findings into sensitivity analyses for the magnitude of bias in other studies; these results should not be interpreted as estimating causal effects of dropout on MRI measures.

Selective attrition may bias estimated effects of risk factors on brain volume or related outcomes, such as dementia. To illustrate the potential impact of selective attrition on effect estimates, we modeled the expected bias in hypothetical studies of a risk factor on change in hippocampal volume under alternative assumptions. The magnitude of bias depends on the difference in brain volume between dropouts and those who remain in the study, the effect of the risk factor on dropout, and the difference in the risk-factor outcome association between dropouts and nondropouts. We also consider situations in which hippocampal volume is associated with dropout only among the exposed. Exact formulas for our estimates are provided in appendix e-1.

RESULTS Average WMLV of the 1,633 subjects in the analytic sample was 0.39% (SD 0.32) of ICV (table 1). Average hippocampal volume was 0.49% (SD = 0.05) of ICV. Average CSF volume was 28.19% (SD = 3.12) of ICV.

In models adjusted only for demographics, each percentage point increase in baseline WMLV (as % of ICV) was associated with 79% higher odds of dropout (table 2, M1; 95% confidence interval [CI] 1.38−2.32). Hippocampal volume was not significantly associated with higher odds of dropout, although the point estimate for the OR was consistent with larger hippocampal volume predicting lower odds of dropout (odds ratio [OR] = 0.14, 95% CI 0.01−1.32, $p = 0.09$). Greater CSF volume was unexpectedly associated with lower odds of dropout (OR = 0.95, 95% CI 0.92−0.99). Results changed little with additional adjustment for self-rated health, depressive symptoms, and IADL limitations (table 2, model 2) and baseline cognitive test scores (table 2, model 3).

Additional adjustment for the change in the most recent 2 prior cognitive test scores (table 2, model 4) required restriction of the sample to those who completed at least 2 cognitive assessments. In this slightly smaller sample, WMLV (OR = 1.81; 95% CI 1.29−2.54) and hippocampal volume (OR = 0.06; 95% CI <0.01−0.87) but not CSF volume ($p = 0.80$) were associated with dropout. In the final model, including WMLV, hippocampal volume, and CSF volume simultaneously in the model, results changed little. Patterns expressing cerebral MRI marker values as quartiles were also similar (table-e 2).

Consistent with the prior models, WMLV was significantly larger (adjusted $b = 0.18$ SD; 95% CI 0.08−0.29) and hippocampal volume was significantly smaller (adjusted $b = -0.12$ SD; 95% CI −0.22 to −0.03) among dropouts (figure 1). CSF volume was not significantly different among future dropouts.

Next, we examined whether individuals who dropped out in the last 2 interview waves, after completing both MRI scans, had experienced worse deterioration between the 2 MRI scans (figure 2). Dropouts did not significantly differ with respect to increase in WMLV. Those who subsequently dropped out had experienced significantly worse deterioration in hippocampal volume between the first and second MRI scans, with a change 0.30 SD (95% CI −0.43 to −0.17) worse than the

| Table 2	Brain MRI markers and odds ratios for dropout[a]		
	Odds ratio	p Value	95% CI
Model 1: Adjusted for demographics			
White matter lesion volume (% of ICV)	1.79	<0.01	1.38-2.32
Hippocampal volume (% of ICV)	0.14	0.09	0.01-1.32
CSF volume (% of ICV)	0.95	<0.01	0.92-0.99
Model 2: Additionally adjusted for prior self-reported health measures			
White matter lesion volume (% of ICV)	1.67	<0.01	1.28-2.17
Hippocampal volume (% of ICV)	0.33	0.34	0.03-3.21
CSF volume (% of ICV)	0.95	<0.01	0.91-0.98
Model 3: Additionally adjusted for baseline test scores			
White matter lesion volume (% of ICV)	1.55	<0.01	1.18-2.02
Hippocampal volume (% of ICV)	0.30	0.30	0.03-2.92
CSF volume (% of ICV)	0.95	<0.01	0.92-0.99
Model 4: Additionally adjusted for change in prior test scores[b]			
White matter lesion volume (% of ICV)	1.80	<0.01	1.27-2.54
Hippocampal volume (% of ICV)	0.09	0.08	0.01-1.37
CSF volume (% of ICV)	0.99	0.80	0.95-1.04
Model 5: Additionally adjusted for other MRI markers[b]			
White matter lesion volume (% of ICV)	1.71	<0.01	1.20-2.43
Hippocampal volume (% of ICV)	0.06	0.08	0.00-1.43
CSF volume (% of ICV)	0.97	0.30	0.92-1.02

Abbreviations: CI = confidence interval; ICV = intracranial volume.
[a] In models 1−4, only one neuroimaging marker is included in each model. In model 5, all 3 neuroimaging markers are included simultaneously. Data for dropout models 1−3 were from 1,633 individuals and >5,760 follow-up attempts (average 3.5 per person), with 513 dropouts.
[b] Restricted to participants with information on the 2 prior cognitive assessments (1,401 individuals and 2,566 follow-up attempts with 390 dropouts). Change in test scores equals raw difference in z-scored test performance between the 2 most recent prior cognitive assessments.

**Figure 1** Pooled estimates of differences in MRI markers, by subsequent dropout status
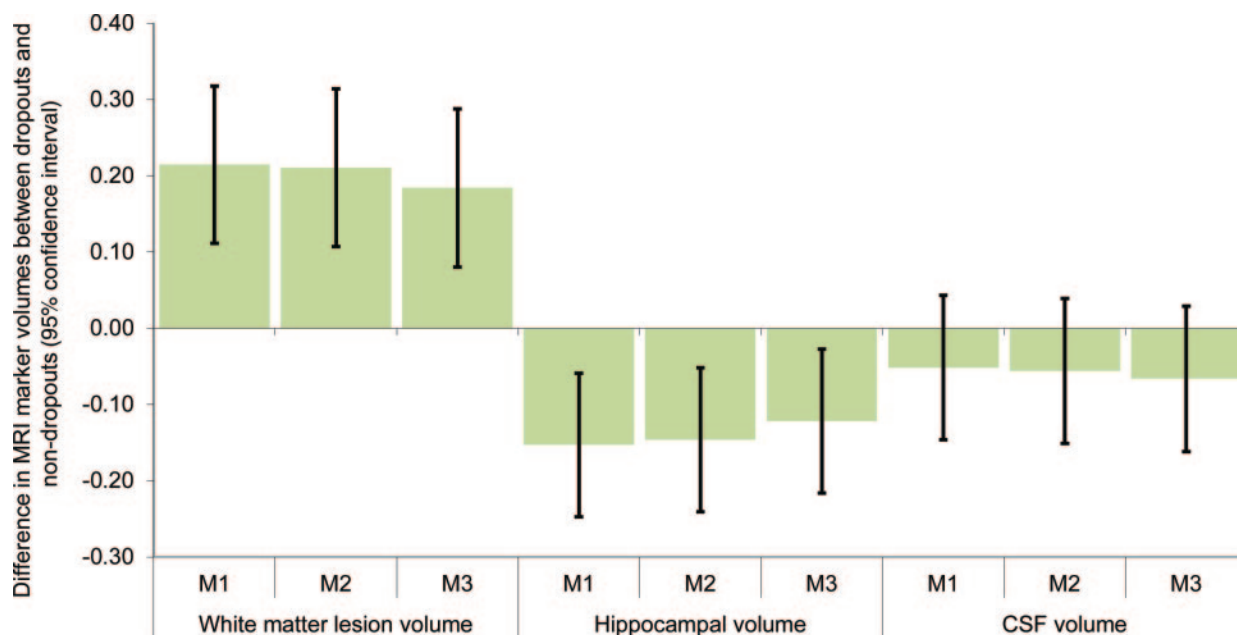
Coefficients are from random intercept mixed models with first or second MRI values on dropout status, with dropout defined as unable to contact or refusal at any interview. All MRI values are % of intracranial volume and normalized so effects are expressed in SDs (n = 1633; observations = 2,801). Model [M] 1, adjusted for demographics only; M2, additionally adjusted for baseline self-reported health measures; M3, additionally adjusted for baseline cognitive test scores.

change experienced by nondropouts (after covariate adjustment). Increases in CSF were also significantly greater for dropouts than for nondropouts: there was a 0.14 SD (95% CI 0.01−0.28) differ-ence, adjusted for demographics. Additional adjustment for self-rated health, elevated depressive symptoms, and baseline cognitive test scores modestly attenuated the CSF difference to 0.10 SD

Figure 2 Annualized rate of change in MRI markers, by subsequent dropout status
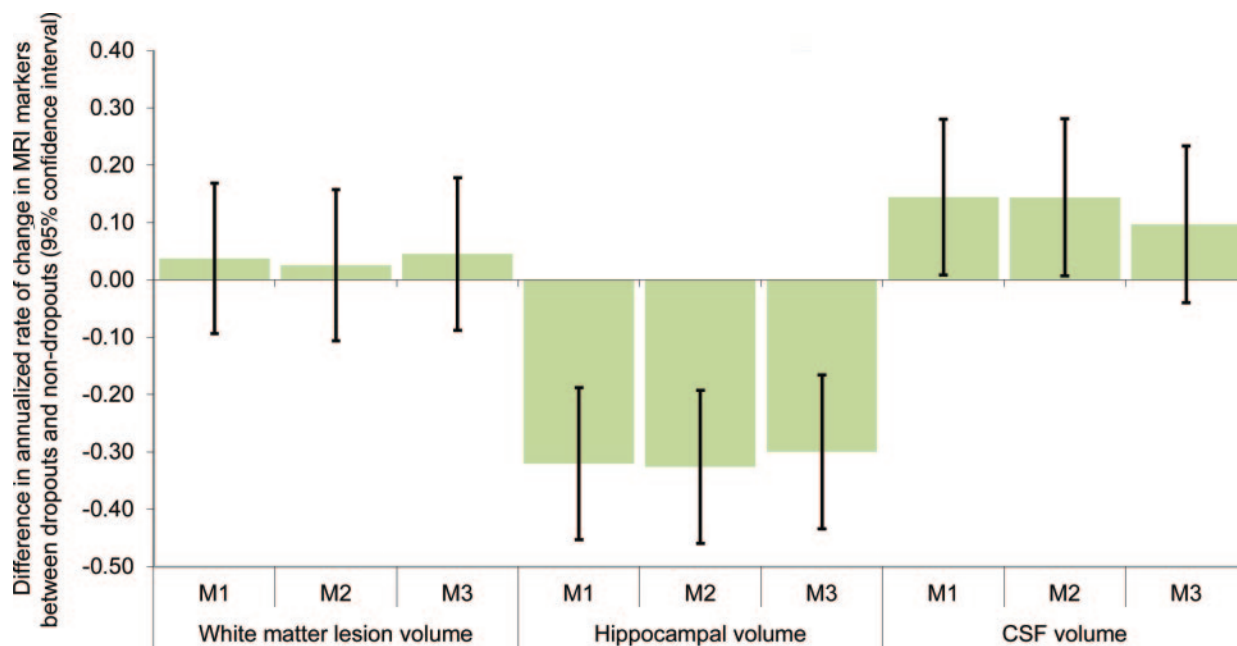
Coefficients are from linear regression models of annualized rate of change in MRI volumes on dropout status, with dropout defined as unable to contact or refusal at the 7- or 9-year interviews (which occurred after the second MRI scan). Annualized rate of change in MRI is defined as % of intracranial volume (ICV) at the second MRI scan minus % of ICV at the first MRI, divided by years elapsed between the MRIs and normalized (n = 1,168). Model [M] 1, adjusted for demographics only; M2, additionally adjusted for baseline self-reported health measures; M3, additionally adjusted for baseline cognitive test scores.

Table 3 Bias in a hypothetical study of the effect of risk factor on hippocampal volume, under alternative assumptions about dropout[a]

	Dropouts as % of sample (ratio of dropout in exposed to dropout in nonexposed)							
	20% (1.0)	20% (1.2)	20% (1.5)	45% (1.5)	20% (2.0)	45% (2.0)	50% (1.5)	45% (2.0)
Scenarios in which hippocampal volume–dropout association is the same for exposed and unexposed[b]								
Dropout difference in hippocampal volume	−0.20	−0.20	−0.20	−0.20	−0.20	−0.30	−0.30	−0.30
Average hippocampal volume of exposed	0.00	0.00	0.00	0.00	0.00	0.00	−0.20	−0.30
Average hippocampal volume of unexposed	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Difference in hippocampal volume, exposed vs nonexposed	0.00	0.00	0.00	0.00	0.00	0.00	−0.20	−0.30
True effect of exposure on hippocampal volume	0.00	0.00	0.00	0.00	0.00	0.00	−0.20	−0.30
Estimated effect of exposure on hippocampal volume	0.00	0.01	0.02	0.04	0.03	0.09	−0.14	−0.21
Bias (equal to estimated effect − true effect)	**0.00**	**0.01**	**0.02**	**0.04**	**0.03**	**0.09**	**0.06**	**0.09**
Scenarios in which hippocampal volume–dropout association differs for exposed and unexposed[b]								
Dropout difference in hippocampal volume among exposed	−0.40	−0.40	−0.40	−0.40	−0.40	−0.60	−0.60	−0.60
Dropout difference in hippocampal volume among unexposed	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Overall dropout difference in hippocampal volume	−0.20	−0.20	−0.20	−0.20	−0.20	−0.30	−0.30	−0.30
Average hippocampal volume of exposed	0.00	0.00	0.00	0.00	0.00	0.00	−0.20	−0.30
Average hippocampal volume of unexposed	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
True effect of exposure on hippocampal volume	0.00	0.00	0.00	0.00	0.00	0.00	−0.20	−0.30
Estimated effect of exposure on hippocampal volume	0.08	0.09	0.10	0.22	0.11	0.36	0.16	0.06
Bias (equal to estimated effect − true effect)	**0.08**	**0.09**	**0.10**	**0.22**	**0.11**	**0.36**	**0.36**	**0.36**

[a] Hippocampal volume is expressed as standard deviations away from the sample mean.

[b] These models assume that hippocampal volume is associated with dropout only among the exposed; for example, if the exposure was "living alone" this implies that among people who live with someone, hippocampal volume is unrelated to dropout risk, but among those who live alone, low hippocampal volume predicts higher dropout risk. These models maintain the overall dropout rates and the full sample differences in hippocampal volume for dropouts vs nondropouts from the models in the same column above.

(95% CI −0.04 to 0.23) and the association was no longer statistically significant.

In a hypothetical study with a moderate dropout of 20%, a ratio of dropout in the exposed to dropout in the unexposed of 1.2, and a difference in hippocampal volume between dropouts and nondropouts of 0.2 SD, attrition bias is quite small (table 3, top panel). However, the bias increases with higher dropout, stronger associations between the risk factor and dropout, and greater differences in hippocampal volume between dropouts and nondropouts. If the association between hippocampal volume and dropout risk differs by level of exposure, effect estimates are biased even in the most optimistic situation (table 3, bottom panel). In the most extreme examples (the rightmost columns of table 3, bottom panel), the bias is so large that a risk factor associated with smaller hippocampal volume appears to be associated with larger hippocampal volume in analyses of nondropouts.

DISCUSSION Individuals who dropped out of this elderly French cohort study had evidence of higher WMLV and lower hippocampal volume compared with those who did not drop out. There was mixed evidence with respect to the association between baseline CSF and subsequent dropout. Furthermore, those who dropped out had a history of greater decreases in hippocampal volume and greater increases in CSF compared with those who did not drop out, suggesting substantial differences in underlying cerebrovascular or neurodegenerative disease. These associations were attenuated but not eliminated by adjustment for demographics, self-rated health, elevated depressive symptoms, IADL limitations, and prior cognitive test scores.

Missing data on a variable are considered missing at random if the values for the variable are unrelated to whether it is missing or observed, conditional on (i.e., adjusted for) observed values of that or any other measured characteristics of the individual. In contrast, data are missing not at random if the value of the variable systematically differs among those for whom it is unobserved, even conditional on the observed characteristics of that person.[3] If data are missing at random and the process that leads to missingness is unrelated to the process determining the outcome, conventional mixed model−based analyses of the data will produce unbiased effect estimates.[27] Our results suggest that this is unlikely to be the case for studies of dementia or cognitive decline.

This finding has 3 critical implications for research on dementia or cognitive aging. First, consistent with previous evidence,[28–30] attrition bias compromises generalizability and results in underestimates of the prevalence of dementia in analyses without correction for dropout. Second, estimates of the effect of any hypothesized risk factor on dementia could be substantially biased in cohort studies with moderate to high dropout. Cohort attrition rates of 10%−40% are common in aging cohorts with demanding cognitive or physical assessments.[31] If the risk factor under consideration directly affects dropout, the bias may either spuriously attenuate or inflate the estimated association between the risk factor and cognitive decline.[32] Many studies do not report whether dropout differs by the primary exposure, but important differences have sometimes been reported[33] and probably prevail in many other studies. Effect estimates of scientific or clinical interest are often not much larger than plausible biases due to attrition. In studies with neuroimaging markers, it may be possible to address potential bias from selective dropout using methods such as inverse probability weighting, principal stratification, multiple imputation, or other statistical tools.[4,27,34–37] The approach of Wang and Hall[27] of using information on an "auxiliary variable" correlated with the unobserved outcome values might be useful. However, most longitudinal studies of cognitive aging do not include MRIs, and even when MRIs are planned, they are typically not available for all or even a representative sample of cohort members. Imputations or sensitivity analyses based on external evidence from studies with MRIs may be valuable to help inform analyses even when MRI measures are not available. For example, we report declines in hippocampal volume approximately 0.3 SD worse among the dropouts compared with those for individuals who did not drop out. If similar associations are established in other cohorts, this finding should inform estimated values of cognitive scores for individuals lost to follow-up. Changes in MRI markers do not perfectly predict future dementia risk, however, so an important future research avenue is to estimate the correspondence between test performance changes and MRI changes.

Finally, our results suggest the possibility of using MRI findings to facilitate follow-up efforts in ongoing cohort studies and reduce attrition. Existing sources of information on dropout risk may be enhanced by incorporating information from MRI scans, when available. The association between MRI markers and attrition is presumably mediated by cognitive skills that facilitate study participation and understanding this process may suggest opportunities to remediate barriers. For example, individuals with incipient memory impairment may be less likely to remember the appointment or to avoid making competing commitments that would preclude participating in the interviews.

Our study has some limitations, including potential generalizability of the 3C sample and possible selection into the MRI sample. CIs for most estimates were wide, so lack of statistical significance does not necessarily imply absence of important associations. Adjustment for a more comprehensive set of background measures might have better accounted for loss to follow-up. Finally, our study had inadequate power to address differential mortality, which could exacerbate dropout bias.[4,38–40]

We show that dropout is associated with MRI measures of brain features that are likely to influence future dementia risk. As a result, estimates of the effects of risk factors on dementia risk may be biased. If these findings are confirmed in other samples, incorporation of adjustments for selective dropout may substantially improve our ability to identify causal determinants of the onset and trajectory of dementia.

NOTE ADDED IN PROOF

Since this paper was accepted for publication, a new article was published in *Neurology*® that is relevant.[41]

AUTHOR CONTRIBUTIONS

DISCLOSURE

REFERENCES

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Thank you, Dr. John F. Kurtzke!

The Neurology online archive has recently been updated to include the following seminal articles related to early research in MS:

Rose AS, Kuzma JW, Kurtzke, JF, et al. Cooperative study in the evaluation of therapy in multiple sclerosis; ACTH vs placebo in acute exacerbations. Neurology 1968 (June); 18 (6 Part 2): 1–10.

Rose AS, Kuzma JW. A protocol for a cooperative study to evaluate the therapeutic effectiveness of ACTH on multiple sclerosis in acute exacerbations. Neurology 1968 (June); 18 (6 Part 2): 1–20 + study forms.

Rose AS, Kuzma JW, Kurtzke, JF, et al. Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs. placebo – final report. Neurology 1970 (May); 20 (5 Part 2) 1–59.

Kurtzke, JF. Multiple Sclerosis: What's in a name? Neurology 1988;38:309–316.

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