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Relative Contributions of Biomarkers in Alzheimer's Disease

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Abstract

Purpose—To assess relationships between biomarkers for Alzheimer's Disease (AD) and their potential contributions to AD.

Methods—Biomarkers and cognitive evaluations were assessed longitudinally for 179 patients with mild cognitive impairment (MCI), from the Alzheimer's Disease Neuroimaging Initiative (ADNI) from 2003–2006, and were used to examine, at any given time, the joint contributions of hippocampal volume, whole brain volume, and brain glucose metabolism on clinical AD progression, using the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog). Marginal structural models (MSMs) were applied, and inverse-probability of treatment weight (IPTW) estimation was utilized to account for time-dependent confounding between study variables.

Results—At any given time, population-level differences (e.g. 1-standard deviation (SD) increase) in brain glucose metabolism (−1.036 95% CI: −1.608, −0.464) and hippocampal volume (−1.537 95% CI: −2.399, −0.674) independently reduced mean ADAS-Cog, whereas a 1-SD increase in whole brain volume did not (0.372 95% CI: −0.283, 1.027). Effects of brain glucose metabolism differed in subgroups defined by baseline covariates (e.g., age), but no subgroup effects were observed for hippocampal volume and brain volume.

Conclusions—Brain glucose metabolism and hippocampal volume represent relevant biological markers in subjects at risk for AD.

Medical Subject Headings (MeSH)

biological markers; causality; dementia; longitudinal studies

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INTRODUCTION

Alzheimer's Disease (AD) represents a major public health concern given aging populations in the U.S. and worldwide (1, 2). Efforts to better understand the disease have included epidemiologic studies, some of which have utilized different biomarkers for AD (3–7). Developments in neuroimaging have led to the availability of additional markers, representative of anatomical, metabolic, and biochemical aspects of the disease (8–10). These different biomarkers could be used to clarify further the causal pathways that contribute to AD.

Relationships between various biomarkers, which measure structural and functional brain changes, and their relationship to AD are not well understood. Individual biomarkers have been studied extensively with respect to the disease (e.g., brain atrophy). Other studies have investigated multiple biomarkers and their interrelationships with regard to AD (11–14). However, few studies, if any, have examined the joint relationships of multiple biomarkers and their respective contributions to AD over time.

Assessment of the individual effects of biomarkers that account for other biomarkers (e.g., contribution of whole brain volume independent of hippocampal volume) and other factors would improve understanding of the disease process. However, standard statistical methods may result in biased estimates of such effects given time-dependent confounders—i.e., variables that need to be adjusted but which occur on the causal pathway for the effect of interest (Figure 1). Causal inference methods have been developed and applied previously to evaluate effects given time-dependent confounders (15–17).

Amnestic mild cognitive impairment (MCI) represents an intermediate clinical stage in AD (18). Subjects with MCI are classified as having memory impairment without additional cognitive and functional impairments that characterize individuals with AD (18). While MCI subjects are at increased risk of AD (i.e., 12% annual rate vs. 1–2% in non-MCI subjects), not all transition to AD (9). Levels of different biomarkers in MCI vary considerably, and a joint examination of these biomarkers would allow for investigation of their relative effects on changes in disease status in MCI.

We applied causal methods to examine the relative contributions of different biomarkers on AD progression in subjects with MCI. Moreover, we examined the contributions of these biomarkers in different subpopulations at variable risk for AD (e.g., age groups). A broader understanding of the relationships between individual biomarkers and AD could be informative with regard to AD progression and potential interventions to the disease.

METHODS

Subjects

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal study to develop and examine biomarkers of AD progression (9). Subjects were recruited from multiple clinical sites in the U.S. and Canada. Subjects were between ages 55 and 90, and were free of other significant neurologic diseases. Further details about inclusion criteria and other information are available (19, 20).

At baseline, all subjects received a clinical evaluation and a brain MRI scan. Subjects diagnosed with MCI (n=398) had evaluations repeated over follow-up at 6, 12, 18, 24, and 36 month intervals. In addition to clinical and MRI evaluations, half of the subjects received [^{18}F]fluro-deoxyglucose position emission tomography (FDG-PET) scans, to assess brain glucose metabolism, at baseline and follow-up. Cerebrospinal fluid (CSF) samples were

obtained for half of the subjects at baseline. Therefore, the number of subjects available for analysis differed depending on the set of biomarkers examined.

MCI subjects with baseline MRI and FDG-PET data (n=179) were selected for the study. Available follow-up data varied across subjects. In the 179 subjects, 739 observations from different subject-visit times were available for analysis (i.e., complete FDG-PET and MRI data). For 30 subjects with missing data at one of the time points, FDG-PET and MRI measures were imputed by taking the average of the extant values of these measures at the adjoining time points to the records with missing data. Similarly, values were imputed for one subject with missing values at two consecutive time points. Records where FDG-PET and MRI data were missing at a patient's final follow-up visit were excluded. A subset of subjects with CSF samples (89 subjects, 389 total observations) were available for a separate analysis, which examined CSF beta-amyloid (CSF-Aβ) as an additional biomarker of AD.

Study Measures

Study outcome—The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) is a measure of cognitive dysfunction in AD. It has primary functions similar to the Mini-Mental State Examination (MMSE) for evaluation of language, memory, and a variety of other cognitive functions (21). A 70-point version of the test was used—i.e., 11 item test that excluded number cancellation and delayed word recall(21). Total score ranges are 0 to 70, with a higher score indicative of poorer cognitive function.

Magnetic resonance imaging (MRI)—Structural magnetic resonance scans (1.5-T) were acquired at multiple ADNI sites based on a standardized protocol(22). Bilateral hippocampal volume and whole brain volume measures were obtained by scan processing using FreeSurfer software(23). Left and right hippocampal volume were averaged to create a summary measure for the analysis. Brain volume encompasses gray and white matter volume.

Brain glucose metabolism—[^{18}F]Fluro-deoxyglucose positron emission tomography (FDG-PET) represents a quantitative *in-vivo* measure of brain glucose metabolism. Data were acquired at sites nationwide using a standardized protocol (24). Details of image processing of the PET scans are provided elsewhere (25, 26).

A composite measure of FDG-PET was used, based on an average of five brain regions that were found to differentiate AD patients and healthy controls in a meta-analysis (25).

Cerebrospinal fluid beta-amyloid(1-42) (CSF-Aβ)—Details of CSF collection and processing are given elsewhere (27). CSF-Aβ was used as a surrogate measure of brain amyloid pathology. Studies comparing CSF-Aβ with autopsy-based as well *in-vivo* based assessments of brain amyloid pathology, based on brain imaging, are available elsewhere (12, 28).

Other covariates—Different variables independently associated with ADAS-Cog were considered in the analysis as potential confounders and/or effect modifiers. Baseline variables(units) included: age (years); sex; height (cm); education (years); apolipoprotein e4 allele (ApoE4) status (categorized as 0,1, 2 alleles); modified Hachinski score; cardiovascular disease (yes/no (y/n)); diabetes (y/n); smoking (y/n); and hypertension (y/n). Time-dependent variables included: white matter hyperintensities (% total brain volume); systolic and diastolic blood pressure (mmHg); blood glucose (mg/dL); plasma homocysteine (μmol/L); geriatric depression score (range: 0–15); and neuropsychiatric inventory questionaire score (range: 0–5). In addition, FDG-PET, based on frontal-lateral brain

regions, not included in the composite measure above, and previous ADAS-Cog, from *t-1*, were included as potential confounders.

Statistical Analysis

Descriptive analysis—Variables were plotted to evaluate their change over time. The relationship of brain volume and hippocampal volume was examined in plots, and Spearman correlations were generated to assess the respective variability of each variable and its potential contribution to the analysis. Associations of the different covariates described above ("Other covariates") and ADAS-Cog were examined to assess these covariates as potential confounders.

Causal inference analysis—The analysis sought to examine the relative short-term effects of FDG-PET, hippocampal volume, and brain volume on expected ADAS-Cog, at given time *t*, as represented in Figure 1.

Based on Figure 1, changes in hippocampal volume and brain volume are assumed to produce immediate short-term effects on ADAS-Cog, both directly and indirectly (through FDG-PET) at any given time. Prior glucose metabolism (i.e., neuronal dysfunction and synaptic dysfunction reflected in reduced glucose utilization, measured by FDG-PET at *t-1*) is assumed to affect brain and hippocampal volume, which in turn are assumed to affect subsequent FDG-PET at *t* (e.g., brain atrophy), based on previous biological data and the most current model of AD biomarker change (10). The effect of FDG-PET on ADAS-Cog is assumed to be an average of FDG-PET effects at *t* and *t-1* representative of short and longer-tem metabolic patterns on changes in ADAS-Cog. Other covariates described above and measured at *t* (not included in graph) are assumed to affect volumetric and FDG-PET variables at *t*, and could be affected potentially by prior levels of FDG-PET and volumetric measures at *t-1* (e.g., depression score and various metabolic changes (e.g., blood glucose) that could occur indirectly from reduced function).

Marginal structural models (MSMs) were used to evaluate: 1) overall marginal effects of FDG-PET, hippocampal volume and brain volume on ADAS-Cog; and 2) independent (i.e., direct) effects of these biomarkers not mediated by other biomarkers in the causal pathway (e.g., effect of FDG-PET independent of volumetric effects). Additionally, MSMs were used to examine modification of these effects by baseline age, ApoE4 status, and CSF-Aβ.

Briefly, causal inference methodology can provide unbiased estimates of MSMs in the presence of time-dependent confounders as depicted in Figure 1—i.e., confounders of an exposure of interest that are affected by previous levels of that exposure. By comparison, standard analytical methods are likely to produce biased estimates of effects under these conditions(29). To identify and estimate effects from MSMs requires a set of assumptions and estimation procedures. Details are provided in the Appendix. Models were fit with linear regression using generalized estimating equations (GEE) that included weights that were derived for each subject (15). Given that short-term effects of different biomarkers were of interest, the available data for given subjects were pooled (e.g., up to 6 time points per subject) to improve precision. Analyses were implemented with standard software (SAS version 9.1.3 and R version 2.4.1).

RESULTS

Characteristics of the study group are presented in Table 1. Of the group, 65.9% were men. Subjects' mean baseline age was 75, and ages ranged from 56 to 90 years. Subjects were well-educated: 95.0% and 65.4% reported completion of high school and college, respectively. Of the 179 subjects, 66 (36.9%) were diagnosed with AD within 3 years. Mean

follow-up was 1.6 years, and 50% of the group completed at least 2 years of the study. Over half of the subjects were ApoE4 carriers. Mean ADAS-Cog at any given time was 11.7, and was greater (i.e., worse) in subjects who converted to AD. 89 of the 179 subjects had recorded baseline CSF-Aβ measures (mean (range)): 159.8 (48.3–281.8)), which differed significantly between subjects who did and did not convert to AD.

Individual and joint marginal effects of each of the biomarkers assessed in the study on ADAS-Cog are presented in Table 2. The individual effect of each biomarker (Table 2, left) represents the change in mean ADAS-Cog at any time *t* if everyone in the study population experienced an increase in one of the respective biomarkers (e.g., 1 standard deviation (SD) increase based on distribution of a particular biomarker in the study population). These effects indicate that a short-term increase in any one of the three biomarkers individually (FDG-PET, hippocampal volume, brain volume) would contribute to a significant reduction (i.e., improvement) in mean ADAS-cog. For example, an increase the equivalent of 1 SD (~520 mm^3) in hippocampal volume in all subjects would result in a 15% reduction in mean ADAS-Cog from 11.8 to 10.0.

Joint models examined the relative, independent effects of the different biomarkers –i.e., relative to one another---on ADAS-Cog (Table 2, right). For any particular model, the effects represent the independent contributions of the correspondent biomarkers with respect to change in mean ADAS-Cog at any time *t*, if, contrary to fact, the levels of the other biomarkers in the model were fixed for everyone in the population. For example, based on the model of FDG-PET and hippocampal volume, the effect of FDG-PET (-1.193 95% CI: −1.795, −0.591) represents the reduction in mean ADAS-Cog for a 1 SD population-level increase in FDG-PET if, contrary to fact, everyone had the same hippocampal volume. An independent effect of hippocampal volume (−1.375 95% CI: −2.206, −0.544) was observed in the same model. In a separate model that examined all three biomarkers simultaneously (including brain volume), increases in FDG-PET (−1.036 95% CI: −1.608, −0.464) and hippocampal volume (−1.537 95% CI: −2.399, −0.674) reduced ADAS-Cog, but the same relative increase (i.e., 1 SD) in brain volume did not (0.372, 95% CI: −0.283, 1.027). These results indicate that higher FDG-PET and hippocampal volume confer benefits independently with respect to lower ADAS-Cog, at a population-level, whereas greater brain volume, separately from FDG-PET and/or hippocampal volume, does not.

Other models evaluated effects of the various biomarkers for subpopulations defined by differences in baseline age, Apoe4 status, and CSF-Aβ levels (Tables 3–5). Mean ADAS-Cog did not differ by these groups (Tables 3–5, left column). By contrast, the effects of FDG-PET on ADAS-Cog differed significantly for the different subpopulations based on the covariates considered (Tables 3–5, middle column, top). For example, if everyone in the population experienced higher FDG-PET (i.e. 1 SD), the effect was lower mean ADAS-Cog in older vs. younger subjects (for each year: −0.076 95% CI −0.152, 0.000); in subjects with one additional ApoE4 allele vs. subjects with one less E4 allele (−1.159 95% CI: −2.163, −0.156); and subjects with higher CSF-Aβ vs. subjects with lower CSF-Aβ (per 1 pg/mL: −0.014 95% CI: −0.026, −0.002).

Of the three biomarkers, only subgroup effects of FDG-PET were observed; there were no observed significant differences in effects of hippocampal volume or brain volume (Tables 3–5, middle column) in the same subpopulations examined with FDG-PET.

Estimates from joint models that included interactions of FDG-PET and the baseline covariates (Tables 3–5, right column) were attenuated slightly compared to the estimates in the univariable models with FDG-PET alone (Tables 3–5, middle column, top). Interactions

between the volumetric biomarkers and the baseline covariates were not significant and are not presented.

DISCUSSION

We examined the causal relations of three biomarkers, representative of different pathways that could contribute to AD progression in subjects with MCI. FDG-PET, a marker of brain glucose utilization, and hippocampal volume were independently related to ADAS-Cog, which was used as a marker of AD progression. Brain volume was not independently related to ADAS-Cog after accounting for the other two markers. Moreover, FDG-PET was the only biomarker for which subgroup effects, based on age, apoE4 status, and CSF-Aβ, were observed.

Investigators have underscored the importance of examining multiple biomarkers for better assessment of the relationships of these biomarkers with AD (12–14). The current study builds on previous work by employing methods which allowed for modeling the joint dependencies between different biomarkers over time and quantifying the marginal effects of these biomarkers to better clarify their individual relationships to disease progression.

The study is compelling for a number of reasons. First, FDG-PET appears to represent a pathway exclusive of hippocampal atrophy, which is strongly associated with cognitive decline in AD (30–32). This result suggests that MCI subjects with reduced hippocampal volume, but with greater glucose metabolism, may experience less (or delayed) cognitive decline compared to if the same subjects experienced less glucose metabolism. An independent effect of FDG-PET could have implications for AD progression at a population-level given the wide variability of its distribution in MCI. Moreover, FDG-PET, in addition to MRI, could be utilized in studies for investigation of the relationships between these markers and other factors (e.g., diabetes, physical activity), for improved specification of pathways to AD.

Subgroup effects for FDG-PET were observed in groups at risk for AD. These results suggest that greater metabolic activity may be protective in such groups (i.e., older age, presence of ApoE4 allele), though the effects were relatively small. Effects of FDG-PET were observed in subjects with higher CSF-Aβ, who are at less risk of AD than those with lower CSF-Aβ. It is possible that CSF-Aβ is a more specific marker of AD than age or ApoE4, such that any protective effects of metabolic activity are outweighed by greater brain beta-amyloid, which lower CSF-Aβ represents.

Greater brain volume did not improve ADAS-Cog independently of the other biomarkers considered. Although brain volume represents a global measure of both disease progression (i.e., atrophy) and reserve, it may not be as specific to AD as the other biomarkers. Others have shown overall brain atrophy to be predictive of AD onset in MCI subjects after accounting for hippocampal volume (33), however, this may be related this study's outcome measure (AD onset) compared to ADAS-Cog, which measures cognitive function. Also, it is possible that our methodology, which accounted for dependence between study variables over time, may explain in part the reduced effects of brain volume, as well the independent effects observed for the other biomarkers.

One of the strengths of the study includes its use of causal inference methods to summarize and relate effects of biomarkers assessed over time on ADAS-Cog. It is possible, however, that the MSM models used to examine these effects were not entirely accurate nor that our estimation of these MSMs effectively controlled for, or included, all potential confounders of the effects examined (See Appendix). We applied model selection tools that have been shown to provide improved model fits, over typical ad-hoc assumptions, to better specify

models used in MSM estimation (34, 35). We assumed a temporal order between biomarkers (See Figure 1), which may have not been fully realized in the actual data—i.e., volume measures were obtained simultaneously, based on the same MRI scan, and in some instances were measured subsequently to FDG-PET. However, the assumption should be satisfied based on the biologic plausibility of the relationships between the variables (i.e., reduced volume affects FDG-PET, brain volume encompasses hippocampal volume). Still, it is possible that effect estimates may be biased due to violations of this assumption or others related to model misspecification or unmeasured confounding.

MCI subjects represent an increasingly important population for study given their transitory status with respect to further cognitive decline and AD, and their potential responsiveness to intervention (9). It is unclear whether the findings of the study are applicable to a wider population of MCI subjects at risk of AD. Subjects with stroke and other underlying neurologic abnormalities were excluded from ADNI. The rate of AD conversion in this MCI group (i.e., annual rate of 12%) is comparable to rates reported for different population studies, although these rates varied considerably (36, 37).

In summary, this study found that population-level increases in markers of brain metabolism and hippocampal volume, in subjects diagnosed with MCI, independently improved cognitive function at any given time, and appeared to reduce risk of progressive AD. These measures should be considered in future studies given their potential for specifying AD pathways and informing therapeutic and public health strategies against the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease assessment scale-cognitive subscale
ADNI	Alzheimer's disease neuroimaging initiative
ApoE4	Apolipoprotein e4 allele

CSF-AB	Cerebrospinal fluid beta-amyloid
CI	Confidence interval
FDG-PET	Fluro-deoxyglucose positron emission tomography
MRI	Magnetic resonance imaging
MCI	Mild cognitive impairment
MSM	Marginal structural model
SD	Standard Deviation

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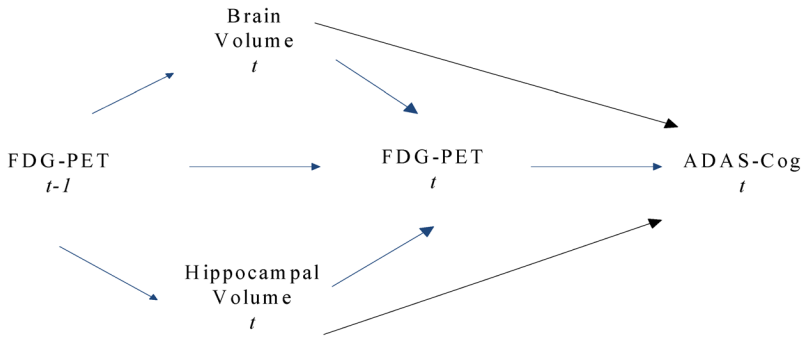

FIGURE 1.

Brain volume and hippocampal volume can directly affect ADAS-Cog as well as through reduction in brain glucose metabolism, as measured by FDG-PET. These measures are affected also by reduction in glucose metabolism which is the result of reduced neuronal/synaptic activity. Marginal structural models were applied and estimated to assess the independent effects of the different biomarkers with respect to ADAS-Cog.

Hypothetical pathways by which different biomarkers for Alzheimer's Disease (AD) affect cognitive function (ADAS-Cog), a marker of AD progression, at any given time *t.*

Table 1

Distributions of Baseline Characteristics in Study Participants

Characteristic	MCI Combined	MCI-AD Converters	MCI-Non-Converters	*P* Value[3]
N	179	66	113	
Age, years	75.1 (7.2) [1]	74.8 (6.9)	75.3 (7.4)	0.66
Gender: male	65.9	60.6	69.0	0.25
Education, years	15.7 (2.9)	16.0 (2.6)	15.5 (3.1)	0.27
Follow-up, years	1.6 (0.7)	1.8 (0.7)	1.5 (0.8)	0.012
ADAS-Cog	10.9 (4.0)	12.6 (3.8)	9.8 (3.8)	<0.001
FDG-PET, CMRglc	1.2 (0.1)	1.1 (0.1)	1.2 (0.1)	<0.001
Hippocampal Volume, mm^3	3290 (520)	3134 (532)	3382 (492)	<0.01
Brain Volume ($\times 10^3$), mm^3	996.6 (107.7)	993.0 (121.2)	998.7 (99.4)	0.73
CSF-Aβ, pg/dL [2]	159.8 (52.1)	147.9 (45.8)	168.2 (55.0)	0.012
ApoE4 Status				
1 allele	41.3	48.5	37.2	0.028
2 allele	12.9	18.2	9.7	

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ApoE4, apolipoprotein e4 allele; CMRglc=cerebral metabolic rate for glucose; FDG-PET= fluro-deoxyglucose positron emission tomography; MCI=mild cognitive impairment.

[1] Values are expressed as mean (standard deviation), or %.

[2] 89 participants with CSF-$A\beta_{1-42}$ measure at baseline.

[3] Group differences between converters and non-converters based on the *t*-test for continuous data and the χ^2 test for categorical data.

Table 2

Overall and Joint Marginal Effects of FDG-PET, Hippocampal Volume and Brain Volume on Mean ADAS-Cog

Univariable[1]			**Multivariable**[1]		
	Coefficient	**95% CI**		**Coefficient**	**95% CI**
Intercept[2]	11.798	11.139, 12.456	Intercept	11.713	11.086, 12.340
Hippocampal Volume[3]	−1.833	−2.671, −0.994	Hippocampal Volume	−1.375	−2.206, −0.544
			FDG-PET	−1.193	−1.795, −0.591
Intercept	11.018	10.226, 11.809			
Brain Volume	−0.742	−1.452, −0.033	Intercept	11.152	10.373, 11.930
			Brain Volume	−0.331	−0.978, 0.316
			FDG-PET	−1.321	−1.950, −0.692
Intercept	11.505	10.911, 12.098			
FDG-PET	−1.604	−2.243, −0.965	Intercept	11.873	11.055, 12.690
			Brain Volume	0.171	−0.476, 0.818
			Hippocampal Volume	−1.831	−2.678, −0.984
			Intercept	11.946	11.115, 12.777
			Brain Volume	0.372	−0.283, 1.027
			Hippocampal Volume	−1.537	−2.399, −0.674
			FDG-PET	−1.036	−1.608, −0.464

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CI=confidence interval; FDG-PET=fluro-deoxyglucose positron emission tomography; SD=standard deviation.

[1]Univariable models reflect effects of individual biomarkers; multivariable model reflects effects of biomarkers that account for other biomarkers.

[2]Intercept represents mean ADAS-Cog when biomarkers centered at median values—i.e., if contrary to fact, everyone's values equal the median values of the different biomarkers. [3]Marginal effect of a 1 SD increase in biomarkers— i.e., if contrary to fact, all subjects experienced an increase the equivalent of 1 SD in the distributions of the different biomarkers.

Table 3

Overall and Joint Marginal Effects of FDG-PET, Hippocampal Volume and Brain Volume on Mean ADAS-Cog Examined With Age

Univariable[1]						Multivariable[1]		
	No Interaction			Interaction			Interaction	
	Coefficient	95% CI		Coefficient	95% CI		Coefficient	95% CI
Intercept[2]	11.511	10.905, 12.117	Intercept	11.500	10.900, 12.100	Intercept	11.739	11.100, 12.378
FDG-PET[3]	−1.622	−2.259, −0.985	FDG-PET	−1.828	−2.475, −1.181	Hippoc Vol	−1.461	−2.286, −0.636
Age[4]	0.045	−0.028, 0.117	Age	0.038	−0.036, 0.112	FDG-PET	−1.363	−1.975, −0.751
			FDG-PET × Age	−0.076	−0.152, 0.000	Age	−0.053	−0.121, 0.016
						FDG-PET × Age[5]	−0.081	−0.154, −0.008
Intercept	11.827	11.166, 12.487	Intercept	11.768	11.113, 12.423	Intercept	11.138	10.389, 11.887
Hippoc Vol	−1.924	−2.774, −1.073	Hippoc Vol	−1.936	−2.836, −1.120	Brain Vol	−0.446	−1.171, 0.279
Age	−0.066	−0.138, 0.007	Age	−0.059	−0.132, 0.013	FDG-PET	−1.643	−2.260, −1.026
			Hippoc Vol × Age	−0.024	−0.114, 0.066	Age	0.011	−0.067, 0.089
						FDG-PET × Age	−0.087	−0.167, −0.010
Intercept	11.042	10.223, 11.861	Intercept	11.219	10.290, 12.148	Intercept	11.789	10.995, 12.583
Brain Vol	−0.764	−1.519, −0.009	Brain Vol	−0.675	−1.516, 0.166	Brain Vol	0.061	−0.639, 0.760
Age	0.001	−0.083, 0.085	Age	0.032	−0.082, 0.145	Hippoc Vol	−1.446	−2.380, −0.670
			Brain Vol × Age	0.043	−0.049, 0.135	FDG-PET	−1.246	−1.834, −0.658
						Age	−0.054	−0.131, 0.022
						FDG-PET × Age	−0.078	−0.152, −0.002

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; Brain Vol=brain volume; CI=confidence interval; FDG-PET=fluro-deoxyglucose positron emission tomography; Hippoc Vol=hippocampal volume; SD=standard deviation.

[1]Univariable models reflect effects of individual biomarkers; multivariable model reflects effects of biomarkers that account for other biomarkers.

[2]Intercept represents mean ADAS-Cog when biomarkers and covariates centered at median values—i.e., if contrary to fact, everyone's values equal the median values of the different biomarkers, and age is set to its median value (75 years).

[3]Marginal effect of a 1 SD increase in biomarkers—i.e., if contrary to fact, all subjects experienced an increase the equivalent of 1 SD in the distributions of the different biomarkers.

[4]Age coefficient represents the expected difference in mean ADAS-Cog for a 1-year age increase.

[5]Interaction of FDG-PET and age represents an additional reduction in mean ADAS-Cog if subjects experience a higher FDG-PET (1 SD) for each additional year of age—i.e., −1.363 (effect of FDG-PET for age 75) + (−0.081*years of age>75).

Table 4

Overall and Joint Marginal Effects of FDG-PET, Hippocampal Volume and Brain Volume on Mean ADAS-Cog Examined With ApoE4 Status

	Univariable[1]					**Mulitivariable**[1]		
	No Interaction			**Interaction**			**Interaction**	
	Coefficient	**95% CI**		**Coefficient**	**95% CI**		**Coefficient**	**95% CI**
Intercept[2]	11.284	10.379, 12.190	Intercept	11.361	10.471, 12.251	Intercept	11.704	10.711, 12.698
FDG-PET[3]	−1.664	−2.301, −1.027	FDG-PET	−1.148	−1.947, −0.394	Hippoc Vol	−1.345	−2.213, − 0.476
ApoE4[4]	0.411	−0.469, 1.291	ApoE4	0.125	−0.739, 0.990	FDG-PET	−0.813	−1.577, − 0.049
			FDG-PET × ApoE4	−1.159	−2.163, −0.156	ApoE4	−0.139	−1.070, 0.792
						FDG-PET × ApoE4[5]	−1.044	−1.981, −0.013
Intercept	11.485	10.493, 12.477	Intercept	11.490	10.510, 12.470	Intercept	11.144	10.029, 12.259
Hippoc Vol	−1.830	−2.671, −0.989	Hippoc Vol	−1.447	−2.879, −0.059	Brain Vol	−0.253	−0.984, 0.480
ApoE4	0.462	−0.461, 1.385	ApoE4	0.450	−0.489, 1.389	FDG-PET	−1.007	−1.760, − 0.254
			Hippoc. Vol × ApoE4	−0.630	−2.006, 0.735	ApoE4	0.105	−0.791, 1.001
						FDG-PET × ApoE4	−0.990	−1.980, −0.013
Intercept	10.555	9.447, 11.662	Intercept	10.561	9.234, 11.888	Intercept	12.109	11.114, 13.105
Brain Vol	−0.807	−1.512, −0.101	Brain Vol	−0.800	−1.846, 0.247	Brain Vol	0.442	−0.162, 1.045
ApoE4	0.643	−0.261, 1.546	ApoE4	0.635	−0.598, 1.867	Hippoc Vol	−1.462	−2.675, −0.249
			Brain Vol × ApoE4	−0.011	−1.104, 1.083	FDG-PET	−0.704	−2.994, −0.023
						ApoE4	−0.282	−1.234, 0.671
						FDG-PET × ApoE4	−1.070	−3.847, − 0.081

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ApoE4=apolipoprotein e4 allele; Brain Vol=brain volume; CI=confidence interval; FDG-PET=fluro-deoxyglucose positron emission tomography; Hippoc Vol=hippocampal volume; SD=standard deviation.

[1]Univariable models reflect effects of individual biomarkers; multivariable model reflects effects of biomarkers that account for other biomarkers.

[2]Intercept represents mean ADAS-Cog when biomarkers and covariates centered at median values—i.e., if contrary to fact, everyone's values equal the median values of the different biomarkers, and ApoE4 is set to its reference (0 alleles).

[3]Marginal effect of a 1 SD increase in biomarkers—i.e., if contrary to fact, all subjects experienced an increase the equivalent of 1 SD in the distributions of the different biomarkers.

[4]ApoE4 coefficient represents the expected difference in mean ADAS-Cog in subjects with 1 additional E4 allele.

[5] Interaction of FDG-PET and ApoE4 represents an additional reduction in mean ADAS-cog if subjects experience a higher FDG-PET (1 SD) for each additional E4 allele—i.e., −0.813 (effect of FDG-PET for 0 alleles) + (−1.044*additional allele).

Table 5

Overall and Joint Marginal Effects of FDG-PET, Hippocampal Volume and Brain Volume on Mean ADAS-Cog Examined with CSF-Aβ

	Univariable[1]					Mulitivariable[1]		
	No Interaction			Interaction			Interaction	
	Coefficient	95% CI		Coefficient	95% CI		Coefficient	95% CI
Intercept[2]	11.718	10.907, 12.529	Intercept	11.853	11.024, 12.682	Intercept	11.768	10.988, 12.548
FDG-PET[3]	−1.516	−2.394, −0.638	FDG-PET	−1.604	−2.458, −0.749	Hippoc Vol	−1.407	−2.183, −0.631
CSF-Aβ[4]	−0.008	−0.021, 0.006	CSF-Aβ	−0.005	−0.019, 0.009	FDG-PET	−1.263	−2.084, −0.442
			FDG-PET × CSF-Aβ	−0.014	−0.026, −0.002	CSF-Aβ	−0.007	−0.020, 0.007
						FDG-PET × CSF-Aβ[5]	−0.010	−0.021, 0.002
Intercept	11.761	11.032, 12.490	Intercept	11.777	11.030, 12.524	Intercept	11.721	10.659, 12.783
Hippoc Vol	−1.708	−2.419, −0.996	Hippoc Vol	−1.628	−2.472, −0.925	Brain Vol	−0.129	−1.042, 0.784
CSF-Aβ	−0.013	−0.025, −0.002	CSF-Aβ	−0.014	−0.027, 0.000	FDG-PET	−1.436	−2.267, −0.605
			Hippoc Vol × CSF-Aβ	−0.006	−0.020, 0.008	CSF-Aβ	−0.005	−0.020, 0.001
						FDG-PET × CSF-Aβ	−0.014	−0.023, 0.001
Intercept	11.469	10.457, 12.480	Intercept	11.468	10.425, 12.511	Intercept	12.356	11.372, 13.340
Brain Vol	−0.441	−1.227, 0.345	Brain Vol	−0.442	−1.255, 0.372	Brain Vol	0.887	−0.001, 1.775
CSF-Aβ	−0.014	−0.028, 0.000	CSF-Aβ	−0.014	−0.032, 0.004	Hippoc Vol	−1.878	−2.746, −1.108
			Brain Vol × CSF-Aβ	0.000	−0.016, 0.016	FDG-PET	−1.183	−1.937, −0.428
						CSF-Aβ	−0.006	−0.020, 0.008
						FDG-PET × CSF-Aβ	−0.007	−0.017, 0.002

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; Brain Vol=brain volume; CSF-Aβ=cerebrospinal fluid amyloid beta(1-42); CI=confidence interval; FDG-PET=fluro-deoxyglucose positron emission tomography; Hippoc Vo=hippocampal volume; SD=standard deviation.

[1]Univariable models reflect effects of individual biomarkers; multivariable model reflects effects of biomarkers that account for other biomarkers.

[2]Intercept represents mean ADAS-Cog when biomarkers and covariates centered at median values—i.e., if contrary to fact, everyone's values equal the median values of the different biomarkers, and CSF-Aβ is set to its median value (150 pg/dL).

[3]Marginal effect of a 1 SD increase in biomarkers—i.e., if contrary to fact, all subjects experienced an increase the equivalent of 1 SD in the distributions of the different biomarkers.

[4]CSF-Aβ coefficient represents the expected difference in mean ADAS-Cog for a 1 pg/dL increase in CSF-Aβ.

[5] Interaction of FDG-PET and CSF-Aβ represents an additional reduction in mean ADAS-Cog if subjects experience a higher FDG-PET (1 SD) for each additional 1 pg/dL of CSF-Aβ—i.e., −1.263 (effect of FDG-PET for CSF-Aβ 150) + (−0.010* CSF-Aβ >150).