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Body mass index is associated with biological CSF markers of core brain pathology of Alzheimer's disease

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Abstract

Weight changes are common in aging and Alzheimer's disease (AD) and postmortem findings suggest a relation between lower body mass index (BMI) and increased AD brain pathology. In the current multicenter study, we tested whether lower BMI is associated with higher core AD brain pathology as assessed by cerebrospinal fluid (CSF)-based biological markers of AD in 751 living subjects: 308 patients with AD, 296 subjects with amnestic mild cognitive impairment (MCI), and 147 elderly healthy controls (HC). Based upon a priori cutoff values on CSF concentration of total tau and beta-amyloid ($A\beta_{1-42}$), subjects were binarized into a group with abnormal CSF biomarker signature (CSF+) and those without (CSF−). Results showed that BMI was significantly lower in the CSF+ when compared with the CSF− group ($F = 27.7$, $df = 746$, $p < 0.001$). There was no interaction between CSF signature and diagnosis or apolipoprotein E (ApoE) genotype. In conclusion, lower BMI is indicative of AD pathology as assessed with CSF-based biomarkers in demented and nondemented elderly subjects.
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Keywords: Alzheimer's disease; Body mass index; Cerebrospinal fluid; Tau protein; $A\beta_{1-42}$

1. Introduction

Alzheimer's disease (AD) is the most common form of age-related dementia, accounting for about 60%–80% of all cases and shows a prevalence of 14% in people at the age of about 70 years in the United States (Plassman et al., 2007). Weight loss, in addition to cognitive and behavioral

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changes, is one of the major clinical manifestations of AD, occurring in about 30%–40% of all AD patients (Gillette-Guyonnet et al., 2007). However, before the onset of dementia, measures of weight such as the body mass index (BMI) have been reported to be changed in those subjects who subsequently progress to AD (Barrett-Connor et al., 1998).

Previous longitudinal studies have revealed a complex relation between predementia weight status and risk of AD. Both lower and higher BMI have been associated with the development of AD, where especially during midlife, obesity or higher BMI have been associated with increased risk of AD (Fitzpatrick et al., 2009; Kivipelto et al., 2005; Whitmer et al., 2005). At older ages, the findings are more mixed with some studies reporting higher (Gustafson et al., 2003; Luchsinger et al., 2007) or lower BMI (Cronin-Stubbs et al., 1997) associated with progression to AD. A recent population-based study showed that a higher BMI was associated with higher risk of AD at an age of about 50 years, but lower BMI was associated with higher risk of AD when assessed at more advanced ages ($>$ 65 years) (Fitzpatrick et al., 2009).

It has been proposed that lower BMI may represent an early noncognitive sign of AD pathology rather than constitute a risk factor for the development of AD (Nourhashemi et al., 2003). A recent postmortem study showed for the first time that lower BMI is related to increased AD pathology including neuritic plaques and neurofibrillary tangles in the brain of elderly subjects with AD and without dementia, independently of possible conditions of imminent death (Buchman et al., 2005, 2006).

In the current multicenter study including a large number of subject samples recruited in prospective studies at 2 European centers and the North American "Alzheimer's Disease Neuroimaging Initiative" (ADNI), we tested the relation between BMI and core feasible cerebrospinal fluid (CSF) biomarkers of AD neuropathology (Blennow et al., 2006; Hampel et al., 2004). These CSF biomarkers have been previously shown to correlate with amyloid-beta (Aβ) load in the brain (CSF Aβ_{1-42}) (Strozyk et al., 2003) and neurofibrillary pathology as assessed by CSF measures of phosphorylated tau (p-tau) and total tau (Buerger et al., 2006; Tapiola et al., 1997) in AD dementia patients. We hypothesized that lower BMI levels are associated with abnormal CSF biomarker pattern of AD pathology regardless of clinical manifestation of dementia symptoms (Blennow and Hampel, 2003).

2. Methods

2.1. Subjects

The study included a total of 751 subjects including 305 patients with AD, 296 subjects with mild cognitive impairment (MCI), and 147 elderly healthy control subjects (HC). The data were collected within the prospective US multicenter ADNI biomarker program contributing 100 patients with AD, 193 subjects with amnestic MCI, and 113 elderly HC, and the Neuropsychiatric Clinic Malmoe University Hospital, Malmö, Sweden, contributing 147 patients with AD, 103 subjects with amnestic MCI, and 34 HC, and the Alzheimer Memorial Center, Department of Psychiatry, Ludwig Maximilian University contributing 61 patients with AD.

Note that ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

All subjects received cognitive testing, apolipoprotein E (ApoE) genotyping, and cerebrospinal fluid (CSF) lumbar puncture. BMI was calculated according to the formula: BMI = (body weight in kg)/(body height in meters^2). The diagnosis of AD was made at all centers according to the criteria for probable AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). All MCI subjects were of the amnestic type diagnosed according to the Mayo Clinic criteria. In general this included the presence of subjective memory complaint, objective evidence of memory impairment by psychometric testing of recall or recognition memory, and normal activities of daily living (Petersen et al., 1999; Winblad et al., 2004). The data from ADNI was a subset of the full ADNI data set with amnestic MCI (n = 397), mild AD (n = 193), and HC (n = 229), selected on the basis that CSF measures, ApoE genotype characterization, and BMI must have been obtained. The subsample included in the current study was virtually the same in terms of age, Mini Mental State Examination (MMSE) score, education, and Alzheimer's Disease Assessment Scale (ADAS) and Auditory Verbal Learning Test (AVLT) compared with the remainder of subjects within the whole ADNI subject population. Thus, no selection bias was evident on the basis of this analysis. All collected ADNI data are online freely accessible to researchers (downloaded on 29 September 2008 and updated on 18 August 2009 for MRI measures at www.loni.ucla.edu/ADNI). General inclusion criteria included an age between 55 and 90 years, a modified Hachinski score $\leq$ 4,

education of at least 6 grade level, and stable treatment of at least 4 weeks in the case of treatment with permitted medication (for full list see www.adni-info.org, Procedures Manual). Inclusion criteria for AD encompassed subjective memory complaint, memory impairment as assessed by an education-adjusted score on delayed recall of a single paragraph recall from the Wechsler Logical Memory II Subscale as follows: 0–7 years of education: ≤ 2; for 8–15 years: ≤ 4; for 16 years or more: ≤ 8; a MMSE score between 20 and 26, and a clinical dementia rating (CDR) score of 0.5 or 1. For the diagnosis of amnestic MCI, the subjects had to show subjective memory impairment and objective memory impairment identical to that for AD, a clinical dementia rating score of 0.5 including the memory box score of 0.5 or greater, and an MMSE score between 24 and 30, with unimpaired general cognitive ability and functional performance such that they did not meet criteria for dementia. Healthy control subjects had to show normal performance on the Logical Memory II Subscale adjusted for education as follows: 0–7 years: ≥ 3; 8–15 years: ≥ 5; 16 or more years: ≥ 9; and absence of significant impairment on cognitive function or activities of daily living.

For the study samples that were recruited at the memory disorder clinic, Malmö University Hospital, Sweden, and the memory clinic at Ludwig Maximilian University of Munich, physicians who specialized in cognitive disorders performed a thorough physical, neurological and psychiatric examination, as well as a clinical interview of each patient at baseline. Furthermore, analysis of ApoE genotype and computed tomography (CT) or MRI scans of the brain were done. The MCI criteria advocated by Petersen and colleagues were applied, including: (1) memory complaint, preferably corroborated by an informant; (2) objective memory impairment adjusted for age and education, as judged by the physician; (3) preservation of general cognitive functioning, as determined by the clinicians judgment based on a structured interview with the patient and an MMSE score greater than or equal to 24; (4) no or minimal impairment of daily life activities; and (5) not fulfilling the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-IIIR) criteria of dementia. Patients with other causes of cognitive impairment, including brain tumor, subdural hematoma, central nervous system (CNS) infection, major depressive episode, schizophrenia, and current alcohol abuse were excluded. However, it is very important to include a clinically relevant population of subjects with MCI, which reflects the normal clientele in a memory clinic, even though such an MCI population is heterogeneous. Therefore, the MCI subjects were allowed to exhibit white matter changes or silent brain infarcts, because these changes are common in elderly subjects with or without cognitive deficits. Similarly, mild to moderate depressive symptoms and low plasma concentrations of vitamin B12 or folate were treated at baseline, but we did not exclude these patients from the study.

The patients with MCI that did not develop dementia during follow-up had to be cognitively stable for at least 4 years to be considered as stable MCI subjects. Patients receiving an AD diagnosis during follow-up had to meet the DSM-IIIR criteria of dementia and the criteria of probable AD defined by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).

The control population consisted of healthy elderly volunteers, who were recruited in the city of Malmö, Sweden. Inclusion criteria were: (1) absence of memory complaints or any other cognitive symptoms; (2) preservation of general cognitive functioning; and (3) no active neurological or psychiatric disease. The control subjects were followed clinically for 4.5 years in order to rule out development of cognitive decline.

All subjects were recruited after written informed consent. The studies were approved by the respective universities' ethics committees.

2.2. ApoE genotyping

For the ADNI and Malmö data sets, ApoE genotyping was performed using TaqMan polymerase chain reaction (PCR) assays (Life Technologies Corp., Carlsbad, CA, USA) as described previously (Shaw et al., 2009). In the Munich sample, ApoE genotype was determined by a polymerase chain reaction kit for the Light Cycler (Roche Diagnostics, Mannheim, Germany).

2.3. CSF analysis

Within the ADNI study, all CSF samples collected at the different centers were shipped on dry ice to the Penn ADNI Biomarker Core Laboratory at the University of Pennsylvania, Philadelphia for storage at −80 °C until further analysis at the laboratory. More details on data collection of the CSF samples can be found at (www.adni-info.org, under "ADNI study procedures"). At the Munich and Malmoe centers, samples of CSF were acquired via lumbar puncture between 9 AM and 11 AM according to a routine protocol, and collected in polypropylene tubes on ice. Aliquots (0.5-mL) were centrifuged at 4 °C at 10,000*g* for 10 minutes and stored at −80 °C until analysis.

At the ADNI and Malmoe centers, the CSF concentration of $A\beta_{1-42}$, total tau, and p-tau_{181} were measured in the baseline CSF samples using the INNO-BIA AlzBio3 immunoassay research reagents (Innogenetics, Ghent, Belgium) on the multiplex xMAP Luminex platform (Lumnix Corporation, Austin, TX, USA) at the Penn ADNI Biomarker Core Laboratory. For detailed description see Shaw et al. (2009). For the Malmoe center, data were converted to enzyme-linked immunosorbent assay (ELISA) levels based on previously published conversion factors (Olsson et al., 2005). At the University of Munich, the CSF samples were analyzed using ELISA kits. Specifically, the $A\beta_{1-42}$ ELISA concentration was determined by INNOTEST β-amyloid

(1–42) (Innogenetics). P-tau$_{181}$ and total tau in CSF were measured by ELISA (Innogenetics Kit). The assays and their characteristics have been described in detail previously (Hampel et al., 2004; Vanderstichele et al., 2000; Vanmechelen et al., 2000).

It is important to point out that ELISA test values for tau and Aβ_{1-42} may be approximately 2–4 times higher than with the multiplex xMAP Luminex (Lumnix Corporation) platform using the INNO-BIA AlzBio3 (Innogenetics) immunoassay reagents, but these relative differences notwithstanding, both methods correlate well with each other when CSF is analyzed by both methods (Olsson et al., 2005; Reijn et al., 2007; Shaw et al., 2009). The data were normalized in order to account for these differences and different cutoff values were applied for the ADNI samples and the samples from the other 2 centers (see below).

2.4. Statistics

All data were checked for deviation by normal distribution by quantile-quantile (Q-Q) plots and, if necessary, transformed using the natural logarithm to reach normal distribution properties. In order to render the CSF data that were analyzed at the different centers comparable in terms of the measurement unit, the CSF measurements were normalized by the formula "qnorm ((rank(x) − 0.5)/length(x))," where x is a subject's individual CSF biomarker measurement transformed by the natural logarithm. Based upon raw CSF measures, the subjects were classified according to published CSF cutoff values into those showing abnormal AD pathology-type abnormalities (CSF+) and with normal CSF profile (CSF−). For the Malmö and the Munich data samples, the CSF+ signature of AD pathology was defined based on the ELISA concentration levels of total tau $>$ 350 and Aβ_{1-42} $<$ 530 (Hansson et al., 2006), and for the ADNI samples, the criteria for CSF+ included the xMAP-Luminex-immunoassay (Lumnix Corporation) concentrations of total tau $>$ 93 and Aβ_{1-42} $<$ 192. These cutoff values were derived from CSF-based measurements in postmortem-verified AD cases and living healthy controls as previously published (Shaw et al., 2009).

In order to test for differences of BMI between the CSF+ and CSF− signatures a cumulative Bayesian analysis was conducted to combine evidence from the different data sets. Briefly, Bayesian analysis combines prior knowledge with new data in order to get an updated confidence for the model parameter of interest in the form of a posterior probability distribution (Spiegelhalter et al., 1999). The Bayesian approach allows for updating prior evidence as one gains more knowledge, e.g., by accumulating data from different studies. In the current multicenter study, Bayesian analysis is applied to combine data sets from different centers to evaluate the association between CSF-based biomarkers and BMI. In all analyses, BMI was treated as a continuous variable.

The regression model determining the difference of BMI between CSF+ and CSF− controlled for age, gender, and MMSE score. The interaction between ApoE genotype and CSF-profile was evaluated. In addition, separate regression analyses were run for each CSF biomarker (total tau, p-tau$_{181}$, Aβ_{1-42}) as predictors, controlling again for age, gender, and MMSE score. Data were combined in a Bayesian manner by informing the prior of the distribution of the regression coefficient as data from the different studies were successively entered. Specifically, the largest data set (i.e., ADNI data set) was analyzed first in the regression analysis, using a wide prior distribution for the parameters, which can be interpreted as noninformative priors. The resulting posterior distribution was subsequently implemented as prior knowledge for the Malmö data, and in the same way the resulting posterior was used as a prior for the analysis of the data from the Munich study. The final posterior distribution reflects the combined evidence from all 3 studies. The analysis was done in R (version 2.10.0, www.r-project.org) and WinBUGS (version 1.4.1, www.mrc-bsu.cam.ac.uk/bugs/) (Lunn et al., 2000).

3. Results

3.1. Association between BMI and CSF biomarker signature

The mean BMI and the percentage of subjects who were underweight (BMI $<$ 18.50) or were obese (BMI $>$ 30)

Table 1
Demographic variables, MMSE and ApoE genotype for CSF− signatures and diagnostic groups

Study	Group	Sample size	BMI	*n* with BMI $<$ 18.5 $>$ 30	Age	Gender (f/m)	MMSE	ApoE genotype (ApoE e4+/−)
CSF−	HC	132	26.4 (5.5)	10/33	74.1 (6.0)	71/61	29.0 (1.0)	27/105
	MCI	155	27.4 (5.2)	4/50	71.2 (9.5)	48/107	27.0 (1.8)	69/86
	AD	77	25.9 (4.4)	2/17	76.3 (6.8)	40/37	22.5 (3.6)	41/36
	Total	364	26.7 (5.2)	16/100	73.4 (8.0)	159/205	26.8 (3.1)	137/227
CSF+	HC	15	26.0 (7.4)	2/4	76.6 (4.5)	6/9	29.2 (0.7)	9/6
	MCI	141	24.4 (4.5)	8/18	73.3 (6.6)	76/65	26.8 (1.6)	100/41
	AD	231	24.0 (4.4)	21/23	74.3 (7.5)	158/73	21.2 (4.5)	173/58
	Total	387	24.2 (4.6)	31/45	74.1 (7.1)	240/147	23.6 (4.6)	282/105

Mean (and SD) is indicated for continuous variables. Study according to subjects with abnormal CSF biomarker signature (CSF+) and those without (CSF−).
Key: ApoE, apolipoprotein E; BMI, body mass index; f, female; m, male; MMSE, Mini Mental State Examination.

Table 2
BMI and standardized CSF concentration of each biomarker for the different diagnostic groups

Group	Sample size	BMI	Total tau	P-tau$_{181}$	Aβ_{1-42}
HC	147	26.5 (5.8)	−0.62 (0.79)	−0.54 (0.86)	0.67 (0.97)
MCI	296	26 (5.2)	0.02 (1.06)	0.08 (0.94)	−0.12 (1.06)
AD	308	24.5 (5.1)	0.28 (0.9)	0.19 (1.02)	−0.22 (0.79)

Data are mean (SD).
Key: Aβ, amyloid beta; AD, Alzheimer's disease; BMI, body mass index; CSF, cerebrospinal fluid; HC, healthy control; MCI, mild cognitive impairment; P-tau, phosphorylated tau.

according to the World Health Organization (WHO) criteria along with demographic, genetic, and clinical data are displayed for both CSF biomarker signatures and the diagnostic groups in Table 1. BMI was significantly lower in the CSF+ when compared with the CSF− group ($F = 27.7$, $df = 746$, $p < 0.001$). Age and MMSE did not differ between CSF+ and CSF− signatures. There was a higher proportion of ApoE e4 carriers ($\chi^2 = 94.4$, $df = 1$, $p < 0.001$) and females ($\chi^2 = 25.3$, $df = 1$, $p < 0.001$) in the CSF+ group than in the CSF− group. When BMI was compared between different diagnostic groups, there was an overall analysis of covariance (ANCOVA) assessed group effect ($F = 4.9$, $df = 744$, $p = 0.008$), with AD subjects showing a lower BMI compared with HC or MCI subjects (for both comparisons $p = 0.001$) as tested by Tukey post hoc tests (Table 2). There was no interaction between diagnosis and CSF signature with respect to the association with BMI (Fig. 1). Controlling for MMSE score did not alter the result pattern. Bayesian regression analysis controlled for gender and age showed a significantly decreased BMI associated with a CSF+ signature ($\beta = -0.06$; 95% confidence interval [CI], −0.09 to −0.03]), i.e., subjects with a CSF profile indicative of AD brain pathology (Shaw et al., 2009).

Fig. 2 illustrates the Bayesian analysis, demonstrating that the variance of the regression coefficient of CSF signature as a predictor of BMI becomes smaller and the regression coefficient converges on the value of −0.06 during the accumulation of an increasing amount of data, i.e., combining data across the different studies. Thus, as data from different studies were added, the confidence of a true difference between the population means of the CSF signatures increased.

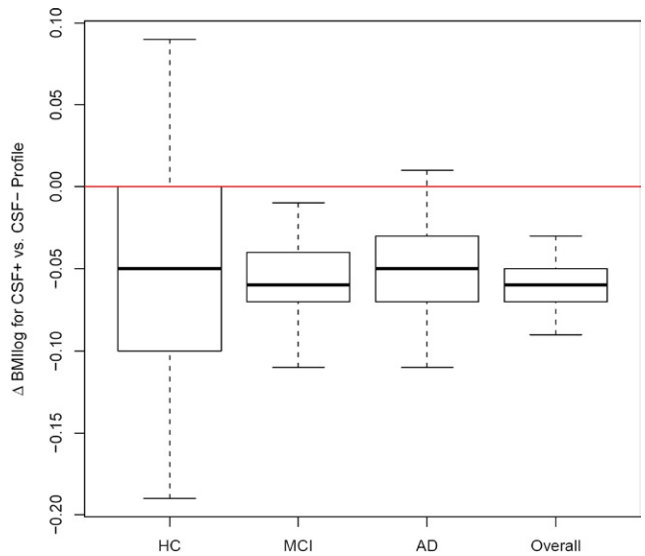

Fig. 1. The box plot of the difference in body mass index (BMI) (log transformed) between subjects with abnormal (CSF+) and those without (CSF−) cerebrospinal fluid (CSF) biomarker signatures as a function of the different diagnostic groups as well as for the total sample is displayed. Subjects with a CSF+ had on average a smaller BMI than subjects with a CSF− signature across the different diagnostic groups.

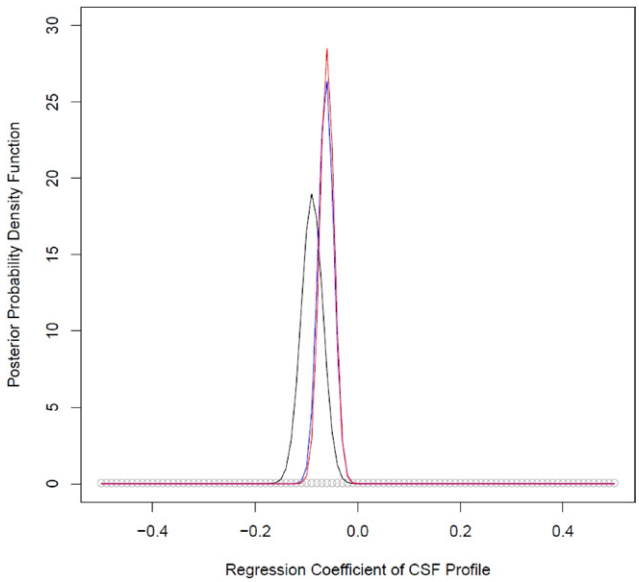

Fig. 2. The Bayesian posterior probability distribution of the regression coefficient of the difference between subjects with abnormal (CSF+) and those without (CSF−) cerebrospinal fluid (CSF) biomarker signatures in body mass index (BMI) (log) based upon increasing amount of data is shown. The estimate of the regression coefficient is improved at the different stages of successively entering data, starting with no data (empty circles), data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study (black), and Malmö (red). It becomes apparent that the mean difference between CSF signatures becomes more and more settled around the value of −0.06 (see results) and the distribution variance is decreased as the model "learns", i.e., becomes successively informed by more data.

3.2. Test of difference in BMI between MCI-AD converters and MCI nonconverters

Among the amnestic MCI patients, 124 out of 296 subjects (41.9%) converted to AD after a mean follow-up time interval of 2.8 years (annual conversion rate = 15.0%). The ANCOVA did not detect a difference in BMI between MCI subjects who converted to AD and those subjects who either remained stable (n = 124) or reversed to HC status (n = 6) (F = 0.6, df = 290), controlled for age, gender, and MMSE. Importantly, Bayesian linear regression analysis showed no interaction between MCI conversion status and CSF signature with respect to BMI (β = −0.04; 95% CI, −0.14 to 0.05).

3.3. Test of the influence of ApoE genotype on the association between BMI and CSF signature

We also assessed the potential influence of the ApoE genotype on the observed association between CSF biomarker concentration and BMI. CSF signature did not show an interaction with ApoE genotype (β = −0.01; 95% CI, −0.06 to 0.04) nor was there a main effect of ApoE genotype on BMI (β = 0.01; 95% CI, −0.03 to 0.06), when controlled for age, gender, and MMSE score. CSF profile remained marginally significant in this extended model controlling for ApoE genotype (β = −0.04; 95% CI, −0.09 to 0).

3.4. Association between BMI and different CSF biomarkers

In addition to the composite CSF signature, the association between each CSF biomarker and BMI was tested. An increase in the concentration of CSF total tau concentration (β = −0.03; 95% CI, −0.05 to −0.02) or CSF p-tau (β = −0.02; 95% CI, −0.04 to −0.01) was associated with lower BMI, controlled for MMSE score, age, and gender (Fig. 3A and B). For the CSF concentration of $A\beta_{1-42,}$ a decrease of the biomarker concentration was marginally associated with lower BMI (β = 0.02; 95% CI, 0–0.03; Fig. 3C).

4. Discussion

The major results of the current multicenter study show that the CSF biomarker signature of AD pathology is associated with decreased BMI in elderly subjects. These results are not dependent upon the presence of clinical manifestation of dementia but were observed across subjects including elderly healthy, amnestic MCI, and AD subjects. To our knowledge, this is the first study to examine an association between core feasible CSF biomarkers of Aβ and tau pathology of AD and differences in BMI.

4.1. BMI and neuropathology of AD

Our results are in striking agreement with previous postmortem findings of the association between lower BMI and higher composite score of the amount of histochemical AD-type pathology including plaques and neurofibrillary tangles in brains from demented and nondemented subjects (Buchman et al., 2006, 2008). We have used a composite CSF signature combining total tau and $A\beta_{1-42}$ that has previously been shown to detect early AD (Hansson et al., 2006) and separates autopsy confirmed AD cases from living elderly healthy control subjects (Shaw et al., 2009). The combination of such CSF biomarkers shows a superior accuracy for the detection of AD when compared with the use of single CSF measures alone (Hansson et al., 2006; Herukka et al., 2007; Vemuri et al., 2009). Because CSF biomarkers have been found to correlate well with AD pathology in the brain (Fagan et al., 2006; Strozyk et al., 2003; Tapiola et al., 1997), this approach may lend itself to indirectly assess the extent of AD pathology in the brain. Note that the proportion of subjects with an abnormal CSF signature is increased in MCI and AD, but can still be as high as 30% in cognitively elderly HC (Shaw et al., 2009; Visser et al., 2009). The CSF total tau:$A\beta_{1-42}$ ratio predicts accelerated cognitive decline in healthy controls (Fagan et al., 2007), suggesting that subclinical AD pathology is present to a substantial degree in nondemented subjects. In the current study, an abnormal CSF signature was found in 10% of the HC subjects and 48% of the MCI subjects. Thus, an AD-typical CSF signature is also present in nondemented subjects and the current findings support the notion that AD pathology is associated with lower BMI within both demented and nondemented elderly subjects.

4.2. Possible biological mechanisms underlying the association between BMI and neuropathology as detected by CSF biomarkers

Possible biological mechanisms of the relation between BMI and AD pathology may include AD-related dysfunction of cortical and subcortical brain regions including the hypothalamic circuit of the arcuate nucleus and perfornicular area adjacent to the hippocampal fornix, which have been proposed to be involved in body fat regulation and energy homeostasis (Schwartz et al., 2000). AD associated pathology and neuronal degeneration (Grundman et al., 1996) may afflict these brain regions that could lead to altered food intake and body weight (Buchman et al., 2006). Furthermore, reduced weight may reflect hypermetabolism that could lead to energy deficiency related to AD pathology as suggested by recent findings in a transgenic mouse model of AD (Morgan and Gordon, 2008; Vloeberghs et al., 2008). Such approaches may prove fruitful in delineating a mechanistic link between weight reduction and AD pathologies. Lower weight may also result within the context of generally increased frailty. Core features of physical frailty include lower grip strength, gait speed, BMI (body composition), and increased fatigue (Buchman et al., 2008; Ferrucci et al., 2004). Physical frailty is associated with increased AD pathology in the brain of el-

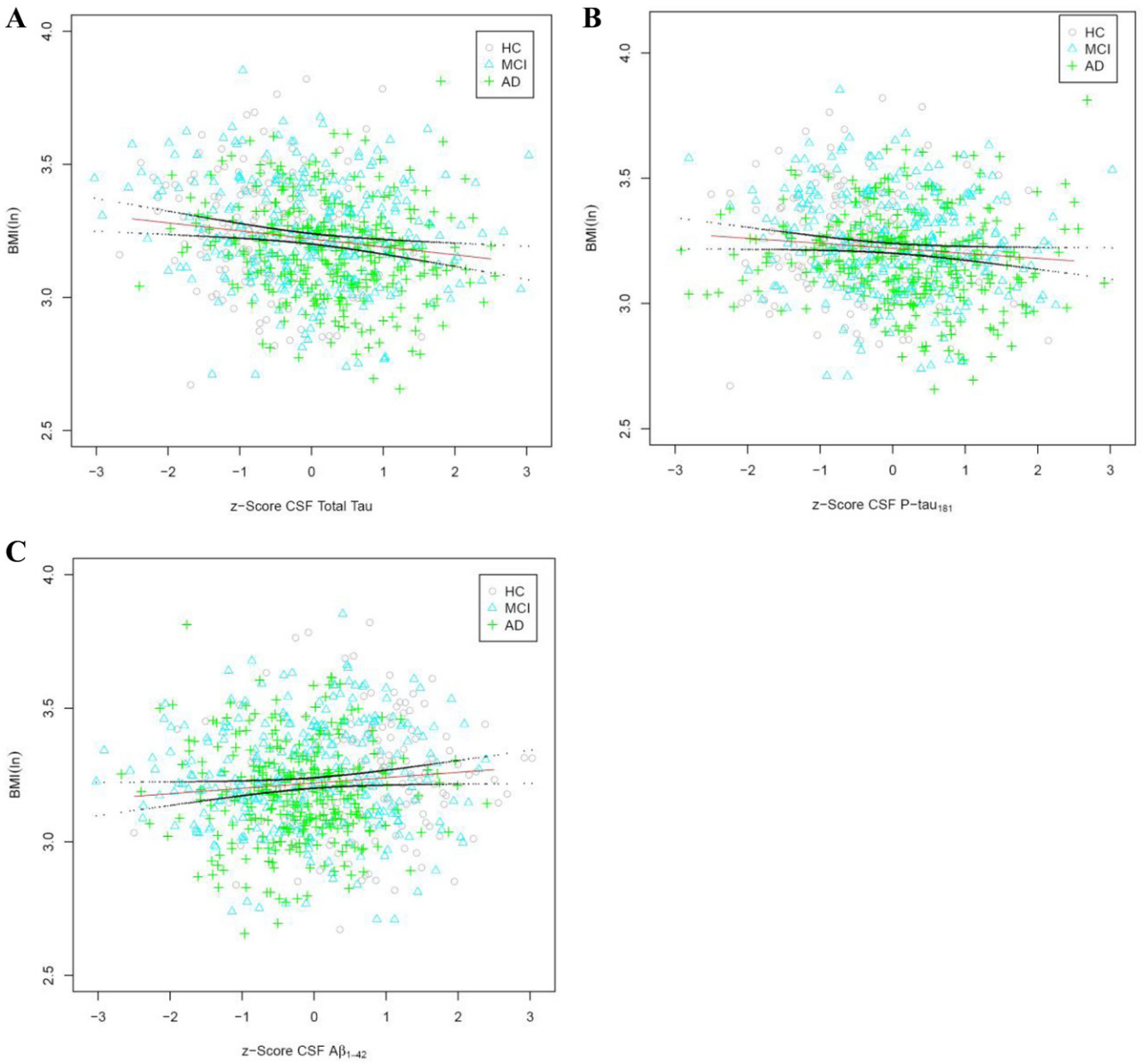

Fig. 3. The scatter plots show body mass index (BMI) as a function of the standardized cerebrospinal fluid (CSF) concentration of total tau (A), phosphorylated tau (p-tau)$_{181}$ (B), or beta-amyloid (Aβ)$_{1-42}$ (C). The data points are labeled according to diagnostic group. The regression line and associated 95% confidence interval (CI) (curved lines) are displayed. The CSF concentration normalized to a standard normal distribution with a mean of 0 and SD of 1 is displayed for each CSF biomarker.

derly subjects with or without presence of dementia (Buchman et al., 2008) and was found to be predictive of dementia and rapid cognitive decline (Dumont et al., 2005; Wang et al., 2006). Sarcopenia, i.e., the reduction in the mass and strength of muscles, is increased in aging, is related to BMI, and may result from AD-related risk factors and pathological mechanism such as inflammation and oxidative stress (Rolland et al., 2008). Thus, BMI may be an expression of declining physical health and presence of AD pathology in the brain even in absence of clinical manifestation of dementia (Buchman et al., 2008).

It should be noted that lower BMI could be a proxy measure of other pathological conditions that are related in a mechanistic way to the generation of neurofibrillary pathology including neuritic plaques and neurofibrillary tangles. Other factors such as a change in behavior in form of loss of appetite, reduced activity, or apathy as correlates of cognitive deficits may influence dietary intake and contribute to loss of weight (Berlinger and Potter, 1991; Doty et al.,

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