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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 post-mortem findings suggested a relation between lower body mass index (BMI) and increased AD brain pathology. In

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Conflict of interest: Dr. Weiner has been on advisory boards for Lilly, Araclon and Institut Catala de Neurociencies Aplicades, Gulf War Veterans Illnesses Advisory Committee, VACO, Biogen Idec, Elan/Wyeth Alzheimer's Immunotherapy Program North American Advisory Board, Novartis Misfolded Protein Scientific Advisory Board Meeting, Banner Alzheimer's Institute Alzheimer's Prevention Initiative Advisory Board Meeting, and the Research Advisory Committee on Gulf War Veterans' Illnesses. He has been a consultant for Elan/Wyeth, Novartis, Forest, Ipsen, Daiichi Sankyo, Inc., Astra Zeneca, Araclon, Medivation/Pfizer, TauRx Therapeutics LTD, Bayer Healthcare, Biogen Idec, Exonhit Therapeutics, SA, Servier, and Synarc. He serves on the Alzheimer's & Dementia Editorial Board. Dr. Weiner has received research support from Merck, Avid, the NIH, the DOD, and the VA, and holds stock options with Synarc and Elan. All other authors report no conflict of interest.

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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 amnesic 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 to the CSF- group ($F = 27.7$, $df = 746$, $p < 0.001$). There was no interaction between CSF signature and diagnosis or ApoE genotype. In conclusion, lower BMI is indicative of AD pathology as assessed with CSF-based biomarkers in demented and non-demented elderly subjects.

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 changes, is one of the major clinically manifestations of AD, occurring in about 30–40% of all AD patients (Gillette-Guyonnet et al., 2007). However, already prior to 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 higher 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 non-cognitive sign of AD pathology rather than constitute a risk factor for the development of AD (Nourhashemi et al., 2003). A recent post-mortem 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., 2006; Buchman et al., 2005).

In the current multicentre study including a large-scale controlled sample collected in prospective study at two European centers and the of the North American "Alzheimer's Disease Neuroimaging Initiative" (ADNI), we tested the relation between BMI and core feasible 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 ($A\beta$) load in the brain (CSF $A\beta_{1-42}$) (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 controls (HC). The data were collected within the prospective US multicentre ADNI biomarker program contributing 100 patients with AD, 193 subjects with amnesic MCI, and 113 elderly HC, at the Neuropsychiatric Clinic Malmoe University Hospital, Malmoe, Sweden contributing 147 patients with AD, 103 subjects with amnesic 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 non-profit 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 mild cognitive impairment (MCI) and early Alzheimer's disease (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: $BMI = (\text{body weight in kg})/(\text{body height in meters})^2$. 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 amnesic 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 amnesic MCI (N = 397), mild AD (N = 193) and HC (N = 229), selected on the basis that CSF-measures, Apolipoprotein E genotype (ApoE) characterisation, and BMI must have been obtained. The subsample included in the current study was virtually the same in terms of age, MMSE, education, and ADAS and AVLT compared to 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 29/09/2008 and updated on 08/18/09 for MRI measures at <http://www.loni.ucla.edu/ADNI>). General inclusion criteria included an age between 55 to 90 years, a modified Hachinski score ≥ 4 , education of at least 6 grade level, and stable treatment of at least 4 weeks in case of treatment with permitted medication (for full list see <http://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 Mini Mental State Exam (MMSE) score between 20 – 26 and a clinical dementia rating (CDR) score of 0.5 or 1. For the diagnosis of amnesic MCI,

the subjects had to show subjective memory impairment and objective memory impairment identical to that for AD, a CDR of 0.5 including the memory box score of 0.5 or greater, and a MMSE score between 24 and 30, with unimpaired general cognitive ability and functional performance such that they did not meet criteria for dementia. Healthy controls 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 sample that was recruited at the memory disorder clinic, Malmö University Hospital, Sweden, and the memory clinic at Ludwig Maximilian University of Munich, physicians specialised 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 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 a MMSE score greater than or equal to 24; 4) no or minimal impairment of daily life activities; 5) not fulfilling the DSM-III-R criteria of dementia. Patients with other causes of cognitive impairment, including brain tumor, subdural hematoma, 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-III-R criteria of dementia and the criteria of probable AD defined by NINCDS-ADRDA.

The control population consisted of healthy elderly volunteers, who were recruited in the city of Malmö, Sweden. Inclusion criteria were (i) absence of memory complaints or any other cognitive symptoms, (ii) preservation of general cognitive functioning, and (iii) no active neurological or psychiatric disease. The controls 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 as described previously (Shaw et al., 2009a). In the Munich sample, ApoE genotype was determined by a PCR 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 (<http://www.adni-info.org>, under “ADNI study procedures”). At the Munich and Malmoe centres, samples of CSF were acquired via lumbar puncture between 9 and 11 AM according to a routine protocol, and collected in polypropylene tubes on ice. 0.5ml aliquots were centrifuged at 4°C at 10 000g for 10 minutes and stored at –80°C until analysis.

At the ADNI and Malmoe centers, the CSF concentration of A β ₁₋₄₂, total tau, and p-tau₁₈₁ 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 Corp, Austin, TX) at the Penn ADNI Biomarker Core Laboratory. For detailed description see (Shaw et al., 2009a). For the Malmoe center, data were converted to 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 β ₁₋₄₂ ELISA concentration was determined by INNOTEST β -amyloid (1–42) (Innogenetics, Ghent, Belgium). P-tau₁₈₁ 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 A β ₁₋₄₂ may be ~2–4 times higher than with the multiplex xMAP Luminex platform using the INNO-BIA AlzBio3 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., 2009a). The data were normalized in order to account for these differences and different cut-off values were applied for the ADNI samples and the samples from the other two centers (see below).

2.4 Statistics

All data were checked for deviation by normal distribution by QQ plots and, if necessary, transformed using the natural logarithm to reach normal distribution properties. In order to render the CSF data 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 published CSF cut-off values into those showing abnormal AD-pathology type abnormalities (CSF+) and with normal CSF profile (CSF–). For the Malmoe and the Munich data samples, the CSF+ signature of AD pathology was defined based on the Elisa concentration levels of total tau > 350 & A β ₁₋₄₂ < 530 (Hansson et al., 2006), and for the ADNI samples, the criteria for CSF+ included the xMAP-Luminex-immunoassay concentrations of total tau > 93 & A β ₁₋₄₂ < 192. These cut-off values were derived from CSF-based measurements in post-mortem verified AD cases and living healthy controls as previously published (Shaw et al., 2009b).

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 Mini Mental State Examination (MMSE). The interaction between ApoE genotype and CSF-profile was evaluated. In addition, separate regression analysis were run for each CSF biomarker (total tau, p-tau₁₈₁, A β ₁₋₄₂) as predictors, controlling again for age, gender, and MMSE. 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 non-informative priors. The resulting posterior distribution was subsequently implemented as prior knowledge for the Malmoe 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 three studies. The analysis was done in R (version 2.10.0, <http://www.r-project.org>) and WinBUGS (version 1.4.1, <http://www.mcr-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 had underweight (BMI < 18.50) or were obese (BMI > 30) according to the World Health Organisation (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 to 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 ANCOVA assessed group effect ($F = 4.9$, $df = 744$, $p = 0.008$), with AD subjects showing a lower BMI compared to 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 (figure 1). Controlling for MMSE did not alter the result pattern. Bayesian regression analysis controlled for gender and age showed a significantly decreased BMI associated with a CSF+ signature ($B = -0.06$, 95% CI [-0.09, -0.03]), i.e. subjects with a CSF profile indicative of AD brain pathology (Shaw et al., 2009b).

Figure 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.

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

Among the amnesic 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%). ANCOVA analysis 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 ($B = -0.04$, 95% CI [-0.14, 0.05]).

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

We assessed also 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 ($B = -0.01$, 95% CI $[-0.06, 0.04]$) nor was there a main effect of ApoE genotype on BMI ($B = 0.01$, 95% CI $[-0.03, 0.06]$), when controlled for age, gender, and MMSE. CSF profile remained marginally significant in this extended model controlling for ApoE genotype ($B = -0.04$, 95% CI $[-0.09, 0]$).

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 ($B = -0.03$, 95% CI $[-0.05, -0.02]$) or CSF p-tau ($B = -0.02$, 95% CI $[-0.04, -0.01]$) was associated with lower BMI, controlled for MMSE, age, and gender (figure 3A & 3B). For the CSF concentration of $A\beta_{1-42}$, a decrease of the biomarker concentration was marginally associated with lower BMI ($B = 0.02$, 95% CI $[0, 0.03]$, figure 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 subjects, amnesic MCI and AD. To our knowledge, this is the first study to examine an association between core feasible CSF-biomarkers of $A\beta$ and tau pathology of AD and differences in BMI.

4.1 BMI and neuropathology of AD

Our results are in striking agreement with previous post-mortem 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 non-demented subjects (Buchman et al., 2008; Buchman et al., 2006). 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., 2009b). The combination of such CSF biomarkers shows a superior accuracy for the detection of AD when compared to the use of single CSF measures alone (Hansson et al., 2006; Herukka et al., 2007; Vemuri et al., 2009). Since 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 frequency of an abnormal CSF signature is increased in MCI and AD, but can still be in about 30% of cognitively elderly healthy controls (Shaw et al., 2009b; 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 non-demented 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 present in a substantial proportion of non-demented subjects and the current findings to support the notion that AD pathology is associated with lower BMI within both demented and non-demented 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 such as the hypothalamic circuit of the arcuate nucleus and perifornicular 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 elderly 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 behaviour in form of loss of appetite, reduced activity or apathy as correlate of cognitive deficits may influence dietary intake and contribute to loss of weight (Berlinger and Potter, 1991; Doty et al., 1987; Franklin and Karkeck, 1989). However, the fact that the association between the CSF-biomarkers and BMI was found independent of diagnostic status - similar to the findings of the association between BMI and post-mortem brain index of AD pathology (Buchman et al., 2006) - renders the explanation that the observed association of BMI and CSF markers was mediated by dementia related behavioural changes quite unlikely.

4.3 Age-related dynamics of changes of BMI and its association with risk of AD dementia

It should be noted that weight changes show a complex pattern throughout the life span, with both higher and reduced BMI having been found to be associated with increased risk of AD in epidemiological studies. Obesity rather than reduced weight has been found to be predictive of AD, however mostly when assessed midlife (Fitzpatrick et al., 2009; Gustafson et al., 2003; Whitmer et al., 2005; Yaffe et al., 2004), i.e. several decades before the onset of AD. It is thus possible that obesity has an etiological role in the development of AD via metabolic changes that lead to the development of AD pathology (for review see (Craft, 2009)). In fact, obesity has been associated with increased likelihood of diabetes, vascular pathology, hypertension, and increased cholesterol, all of which have been associated with increased likelihood of AD (Expert Panel on Detection, 2001; Gazdzinski et al., 2008). In contrast, lower BMI has been observed in close temporal proximity to the onset of AD. Results from prospective epidemiological studies suggest that significant loss of weight occurs about 3 to 10 year prior to diagnosis of AD (Buchman et al., 2005; Fitzpatrick et al., 2009; Knopman et al., 2007) or dementia (Nourhashemi et al., 2003), although a longer time interval for woman has been observed in a retrospective study (Knopman et al., 2001). The 32-year long Honolulu-Aging study reported that only during the last 6 years before onset

dementia, the weight was significantly lower in subjects to progress to AD (Stewart et al., 2005), and another population based study reported a 3-year interval between weight loss and onset of AD (Nourhashemi et al., 2003). Thus, the emerging pattern is that lower BMI is associated with a pending onset of AD. The current findings encourage future studies to take presence of AD pathology, such as assessed via CSF biomarkers (Buerger et al., 2006; Tapiola et al., 1997) or PIB-PET imaging of brain amyloid deposition (Fagan et al., 2006), into account when estimating the risk of AD associated with BMI.

In conclusion, the current study demonstrated in vivo the relation of lower BMI and higher AD core brain pathology as indicated by core CSF biological markers in patients with AD, in agreement with previously reported post-mortem findings.

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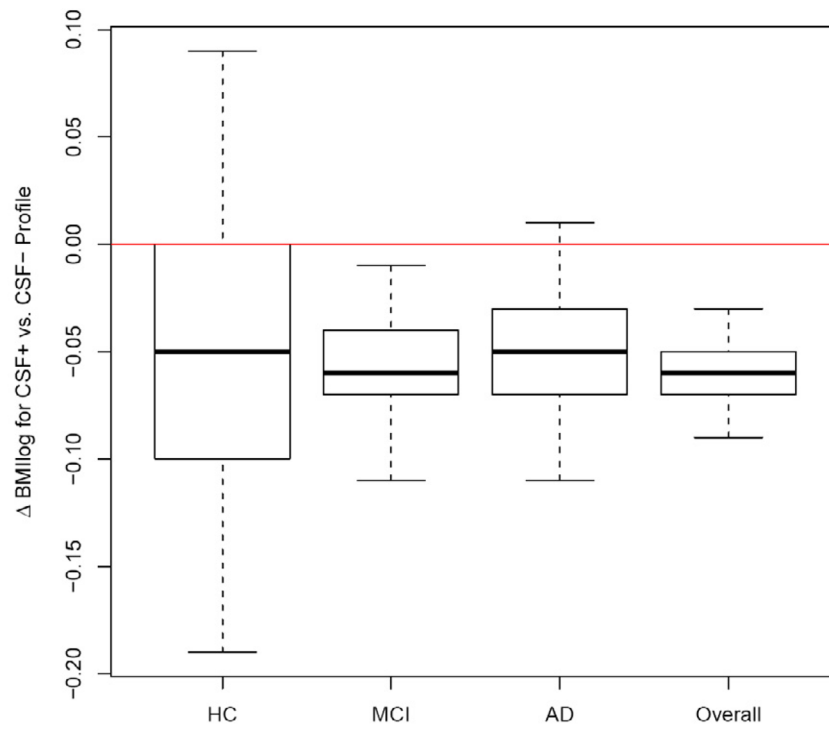


Figure 1. The box plot of the difference in BMI (log transformed) between CSF+ and CSF- signatures as a function of the different diagnostic groups as well as for the total sample is displayed. Subjects with a CSF+ had on average a smaller BMI than subjects with a CSF- signature across the different diagnostic groups.

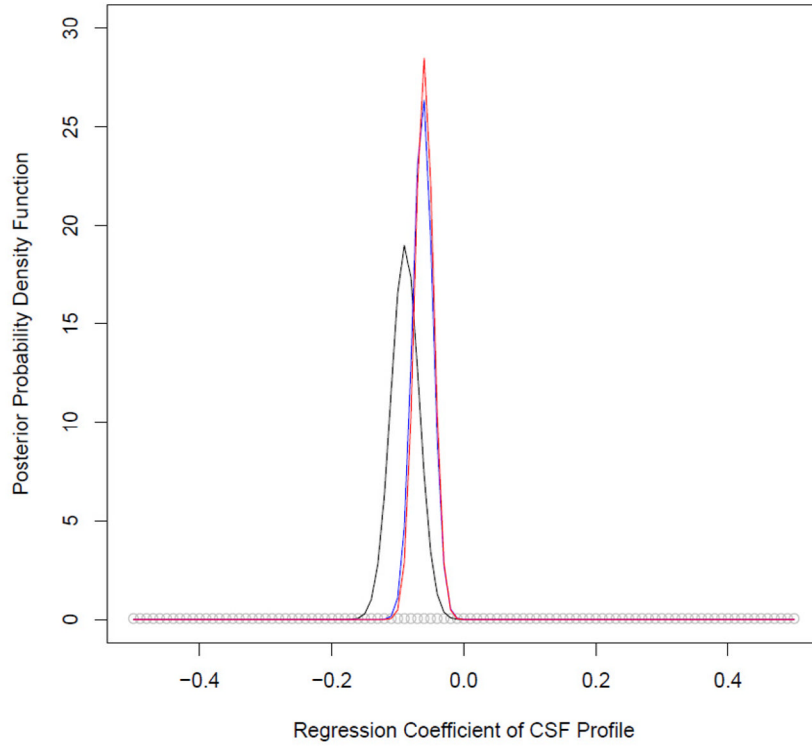


Figure 2. The distribution of Bayesian estimate of probability distribution the regression coefficient of the difference between CSF+ and CSF- in BMI (log) based upon increasing amount of data is shown. The estimate of the regression coefficient is improved at different stages of successive entering of data, starting with no data (empty circles), data from the ADNI study (black), Malmoe (red), and finally the combination of all 3 data sets (yellow). 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. is successively informed by more data.

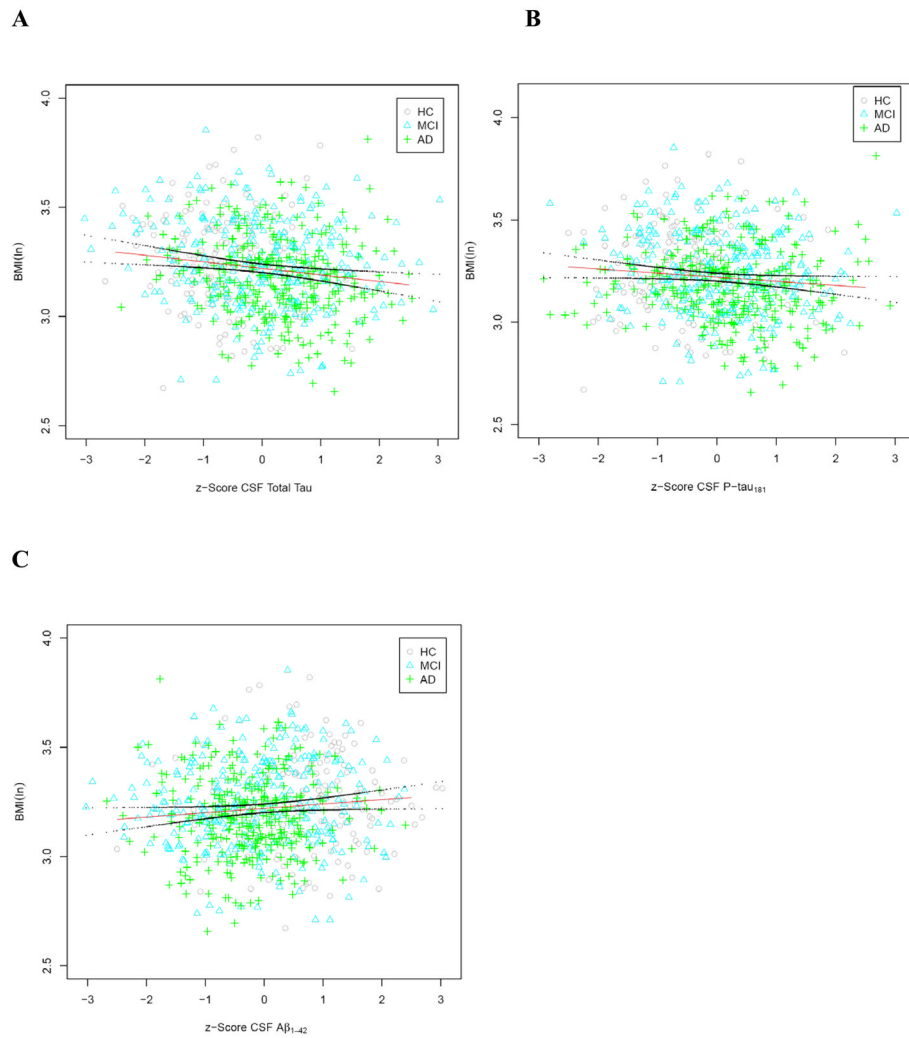


Figure 3. The scatter plots show BMI as a function of the standardized CSF concentration of total tau (A), p-tau₁₈₁ (B), or A β ₁₋₄₂ (C). The data points are labelled according to diagnostic group. The regression line and associated 95% CI (curved lines) are displayed. The CSF concentration normalized to a standard normal distribution with a mean of 0 and SD of 1 is displayed for each CSF biomarker.

Table 1

Demographic variables, MMSE and ApoE genotype for CSF-signatures and diagnostic groups. The mean and standard deviation (in brackets) is shown where pertinent.

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

n = number of subjects; the mean and standard deviation is indicated (in brackets) is indicated for continuous variables

Table 2

Mean and standard deviation (in brackets) of BMI and standardized CSF concentration of each biomarker for the different diagnostic groups.

Group	Sample size	BMI	Total Tau	P-tau ₁₈₁	A β 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)