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Change in body mass index before and after Alzheimer's disease onset

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Abstract

Objectives—A high body mass index (BMI) in middle-age or a decrease in BMI at late-age has been considered a predictor for the development of Alzheimer's disease (AD). However, little is known about the BMI change close to or after AD onset.

Methods—BMI of participants from three cohorts, the Washington Heights and Inwood Columbia Aging Project (WHICAP; population-based) and the Predictors Study (clinic-based), and National Alzheimer's Coordinating Center (NACC; clinic-based) were analyzed longitudinally. We used generalized estimating equations to test whether there were significant changes of BMI over time, adjusting for age, sex, education, race, and research center. Stratification analyses were run to determine whether BMI changes depended on baseline BMI status.

Results—BMI declined over time up to AD clinical onset, with an annual decrease of 0.21 ($p=0.02$) in WHICAP and 0.18 ($p=0.04$) kg/m^2 in NACC. After clinical onset of AD, there was no significant decrease of BMI. BMI even increased ($b=0.11$, $p=0.004$) among prevalent AD participants in NACC. During the prodromal period, BMI decreased over time in overweight(BMI ≥25 and <30) WHICAP participants or obese (BMI≥30) NACC participants. After AD onset, BMI

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tended to increase in underweight/normal weight (BMI<25) patients and decrease in obese patients in all three cohorts, although the results were significant in NACC study only.

Conclusions—Our study suggests that while BMI declines before the clinical AD onset, it levels off after clinical AD onset, and might even increase in prevalent AD. The pattern of BMI change may also depend on the initial BMI.

Keywords

Body mass index; weight; Alzheimer's disease; prospective study

INTRODUCTION

The role of weight or BMI in predicting Alzheimer's disease (AD) has been widely explored in epidemiological studies. In general, these studies have found higher mid-life weight or BMI is associated with increased risk for the development of AD [1-7]. In late life, higher baseline BMI has been shown to be related with a decreased risk of AD, while faster declining of BMI or weight in late life is associated with higher risk of AD [8-16].

Weight loss was included as a “clinical feature consistent with the diagnosis of AD” in the original version of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group report [17]. As weight loss is frequently observed in AD patients in clinical practice, it has been claimed or assumed that the decrease of BMI or weight loss continues after AD onset. This is often hypothesized to be due to loss of the sense of taste and/or smell, depression, decreased ability to prepare meals, dental problems, forgetting to eat or neurobiological changes related to accumulating AD pathology [18]. Even more, weight loss is often used as a clinical aid in the differential diagnosis of AD from other related conditions such as frontotemporal dementia (which is often accompanied by weight gain). However, there have been few reports from large population-based studies confirming weight loss in AD [19-28]. Furthermore, previous studies [19-28] were based on prevalent patients only, while BMI change during the period around diagnosis has not been examined. This would require tracking BMI in incident AD patients. Finally, most previous studies used weight but not BMI as a measurement of adiposity.

Using BMI assessments from participants in three, well-established, large cohorts of AD patients, we examined BMI change over time during the prodromal (shortly pre-clinical onset) and post-onset periods among incident AD patients, as well as BMI change among prevalent AD patients.

MATERIAL AND METHODS

Study Participants

Predictors study—The recruiting and evaluation procedures of the Predictors Study have been described in more detail elsewhere [29]. Briefly, participants in the Predictors Study II were recruited and studied at four sites: Columbia University, New York; Johns Hopkins University, Baltimore; Massachusetts General Hospital, Boston; and Paris, France.

Enrollment required a modified Mini-Mental State Examination (mMMSE) score of ≥30 (maximum = 57) which is equivalent to a score of approximately 16 or more on the Folstein MMSE [30]. All participants met DSM-III-R criteria for primary degenerative dementia of the Alzheimer type and NINCDS-ADRDA criteria for probable AD at enrollment. Neurologic and mental status examinations were conducted at study entry and repeated at 6-month intervals. Subjects who had at least two BMI evaluations were included in the current study. The study was reviewed and approved by the participating institutions' review boards, and written informed consent was obtained from all subjects.

Washington Heights/Hamilton Heights Inwood Columbia Aging Project (WHICAP)—The WHICAP participants were identified (via ethnicity and age stratification processes) from a probability sample of Medicare beneficiaries aged 65 or older, residing in northern Manhattan [31]. Briefly, at entry, a physician elicited each participant's medical and neurological history, and conducted standardized physical and neurological examinations. Each participant was also administered a structured in-person interview, including an assessment of health and function, and a neuropsychological battery [32]. The diagnosis of any type of dementia or its absence was based on standard research criteria, using all available information at a consensus conference of physicians, neurologists, neuropsychologists and psychiatrists. Participants were followed every 1.5 years, repeating the baseline examination and consensus diagnosis [33, 34]. For the diagnosis of probable or possible AD, the criteria of the NINCDS-ADRDA were used. All WHICAP participants who met the criteria for probable or possible AD at baseline (prevalent AD) or follow-up (incident AD) and had at least two BMI assessments were included in the study. The Columbia University Institutional Review Board has reviewed and approved this project. All individuals provided written informed consent.

National Alzheimer's Coordinating Center (NACC)—The study population was composed of subjects from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) [35], gathered prospectively from 33 Alzheimer's Disease Centers (ADCs) (29 active and 4 inactive) between September 2005 and June 2011. Subjects underwent annual clinical exams, which included cognitive and functional testing. Standardized forms were used at all Centers and informed consent was given by all subjects and their informants. Research using the NACC database was approved by the Institutional Review Board at the University of Washington. To be eligible for the current study, the NACC participants had to meet the criteria for probable or possible AD at baseline (prevalent AD) or follow-up (incident AD), have at least two BMI assessments, and be age 65 or older at the first visit with BMI assessment.

BMI measurement

BMI was measured in a similar way in three cohorts. With the participant standing, body weight was measured to the nearest 0.1 kg with a balance scale, and height was measured without shoes to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by height in square meters [kg/m^2]) [36].

Covariates

Age at baseline (years) and education (years) were used as continuous variables. Participants were assigned to one of three race groups: White, Black (African American), or Other based on self-report. Race was used as a dummy variable with White as the reference. Sex was a dichotomous variable with male as the reference. Weight-gaining medication included neuroleptics and other antipsychotics[37], weight-losing medicine included cholinesterase inhibitors[38]. Ever use of these medication was considered as a dichotomous variable with never-used as the reference. Type of residence was categorized as regular home or retirement community (as reference) vs. any assisted living facilities including assisted living/boarding home/adult family home, rehabilitation center, skilled nursing facility, or nursing home. APOE ε4 was used as a dichotomous variable, with carrying 1 or 2 ε4 allele as 1 and not carrying ε4 allele as 0 (the reference).

Statistical analyses

To fully describe the dynamic change of BMI over time along the AD course, primary analyses were conducted separately for the following analytical groups: 1) Before AD onset: BMI before AD onset among incident AD participants, 2) On and after AD onset: BMI on and after AD onset among incident AD participants, and 3) Prevalent AD: BMI among prevalent AD participants, presumably representing a later stage of the disease. All three analytical groups were available for WIHCAP and NACC, while the Predictors study (by design) included prevalent AD patients only. Time of the first BMI evaluation among each analytical group was treated as the baseline visit.

Baseline characteristics of patients were described. Follow-up time was years from the baseline BMI assessment to the last BMI assessment. Generalized estimating equations (GEEs) with BMI as the outcome variable and time from baseline as the main predictor variable were used to determine if there was a significant decrease (negative β coefficient of time) or increase (positive β coefficient of time) of BMI over time. The GEE models were initially unadjusted (Model 1) and then adjusted (Model 2) for covariates including age, gender, race, and education. In Model 3, research center and type of residence (both for Predictors study and NACC study only), and medication use were additionally adjusted, as previous studies have found these factors may affect the modes of weight loss in AD patients [39].

To examine whether rate of change in BMI depended on initial BMI status (underweight and normal weight BMI<25, overweight BMI ≥25 and <30, and obese BMI≥30), we included an interaction term (time × initial BMI status) in Model 3. Stratification analysis by initial BMI status was done subsequently to estimate the rate of BMI change in each subgroup.

Sensitivity analysis—To examine change in BMI up to the time of AD diagnosis, we included the BMI assessment at the same visit of AD onset in the ‘before onset’ group, rather than in the ‘on or after onset’ group. The NACC cohort includes subjects who were less than 65 years old when they entered the study but were included in the primary analyses if they had the first BMI assessments at or after age 65. Sensitivity analyses were done by limiting NACC subjects to those who were 65 or older at their first visit to NACC. As

APOE ε4 genotype has been shown to be associated with weight loss in patients with AD [40], we further adjusted for APOE ε4 genotype in a final Model 4 that also included all the covariates of Model 3. We also examined whether rate of change in BMI depended on APOE ε4 genotype by including the interaction term of time × APOE ε4 genotype in the Model 4.

All analyses were conducted using PASW Statistics (IBM, Chicago, IL). All *p* values were based on 2-sided tests. The significance level was set at 0.05 for all tests.

RESULTS

Characteristics of the study population

Demographic characteristics of the analytic samples are presented in Table 1. All baseline characteristics are evaluated at the first BMI visit where the subject met all inclusion criteria. Overall, the populations of Predictors study and NACC study shared similar demographic characteristics: they were both in late 70's at the baseline BMI assessment, the majority of the study population was White, they both included slightly more females than males, and participants they had approximately college level education. The WHICAP population was multi-ethnic, including mainly Hispanics, but also Black and White. The WHICAP population also had lower education, and included more females than males.

Change of BMI over time

BMI during the prodromal (pre-onset) phase of incident AD—In models adjusted for basic covariates, we found a significant decrease of BMI before the clinical disease onset in WHICAP (Table 2, Model 2, β= −0.21, p=0.02; i.e., about 0.21 kg/m^2 decline per year, or approximately 0.6 kg decline per year for people with a height of 1.7 m; Figure 1). We found an almost identical magnitude of annual BMI decline before clinical onset in the NACC data (Table 2, Model 2, β= −0.18, p=0.04; Figure 1).

BMI on and after the onset of incident AD—During the on average 4.67 years of follow-up after AD onset, we found that BMI did not seem to change in incident AD patients of WHICAP or NACC (Table 2, Model 2, β= −0.06, p=0.51; Figure 1) in WHICAP participants. Similarly, during the on average 1.88 years of follow-up after AD onset in NACC participants, we found that BMI did not change (β=0.09, p=0.24; Figure 1).

BMI among prevalent AD participants—We found a marginally significant increase (Table 2, Model 2, β= 0.17, p=0.06) in BMI among prevalent AD participants of the Predictors study, but the increase was no longer significant after adjusted for covariates. In prevalent AD participants of WHICAP, though, the BMI did not change (Table 2, Model 2, β= −0.07, p=0.50; Figure 1) Among NACC participants who entered the study with prevalent AD, the BMI increased significantly (Table 2, Model 2, β= 0.11, p=0.004; Figure 1).

BMI change over time by initial BMI status

BMI during the prodromal (pre-onset) of incident AD—In WHICAP, we found no difference in rate of BMI decline according to initial BMI status (interactions between initial BMI status and time: β for overweight*time= −0.06, p=0.56; and β for obesity*time= −0.07, p=0.74). In NACC, we found that obese subjects experienced a faster decline of BMI than normal weight subjects prior to AD onset, with a significant interaction between initial BMI and time (β for obesity*time interaction= −0.93, p=0.02). Subsequent stratification analysis showed that BMI decreased significantly over time in obese subjects only (Table 3, β= −0.82, p<0.0001).

BMI on and after the onset of incident AD—In WHICAP, subjects who were obese at baseline had a faster decline of BMI (β for obesity*time =−0.5, p=0.002) compared to normal-weight subjects. In NACC, we found a significant interaction between initial BMI and time (β for overweight*time= −0.25, p=0.004; and β for obesity*time= −0.62, p<0.0001). Subsequent stratification analysis showed that BMI increased in underweight/normal-weight subjects, was stable in originally overweight subjects, and continued to decrease in originally obese subjects (Table 3).

BMI among prevalent AD participants—In Predictors study, there was a significant interaction between initial BMI status and time, with overweight (β for overweight*time= −0.38, p=0.015) and obese (β for obese*time= −0.59, p=0.001) subjects having less increase of BMI overtime compared to underweight/normal weight subjects. Indeed, we saw a marginally significant increase of BMI (β=0.21, p=0.06) in underweight/normal weight patients, while a stable BMI in overweight (β = −0.06, p=0.59) and tended to decrease in obese (β = −0.21, p=0.14) subjects. Similar to the Predictors study findings, there was a significant interaction between initial BMI status and time, with overweight (β for overweight*time= −0.21, p<0.0001) and obese (β for obese*time= −0.55, p<0.0001) subjects had less increase of BMI overtime in the NACC study. More interestingly, the overall pattern and magnitude of BMI change over time in NACC prevalent AD patients were very similar to those of the Predictors study: subjects with an initial underweight/normal profile had a significant increase of BMI (β=0.21, p<0.0001) and obese subjects had a significant decrease of BMI (β= −0.26, p=0.001), while the overweight subjects maintained a stable BMI (β = 0.01, p=0.82). In WHICAP, BMI status at baseline did not modify the rate of BMI change over time.

Sensitivity analyses

When the visit of AD onset was categorized as ‘before onset’ rather than ‘after onset’, the results were similar to those in the primary analysis (data not shown). When analysis was limited to NACC subjects who were 65 years or older at their first visit, the results did not change materially (data not shown). When APOE ε4 genotype was additionally adjusted, the results did not change much (Model 4 in Table 2). There seemed to be no interaction between APOE ε4 genotype in the WHICAP and NACC cohorts. However, in Predictors’ study, there was a significant decline of BMI in APOE e4 non-carriers (B=−0.44, P=0.006) while a non-significant increase of BMI (b=0.13, p=0.24) was found in APOE e4 positive subjects (p for interaction = 0.03).

DISCUSSION

In this longitudinal analysis of data from three large cohorts, we found BMI decreased prior to clinical AD onset. Following the onset of clinical AD, there was no longer a significant decrease of BMI. Furthermore, BMI seemed to increase in prevalent AD patients.

Our findings of decreasing BMI before onset of AD are consistent with existing epidemiological studies showing that weight loss may precede the diagnosis of dementia [8-16]. The mechanism for late-life decline of BMI preceding AD diagnosis is unknown, but likely to be associated with the underlying pathological change of dementia. Brain areas that participate in weight control (i.e., mesial temporal cortex, MTC) [41] are affected during the preclinical dementia phase, thereby leading to weight loss. Disrupted release of hormones and neuropeptides in predementia can also interact with brain centers to induce physiological responses leading to weight reduction before the onset of dementia [42]. Weight loss may also result from predementia apathy [43], reduced olfactory function [44], difficulty in eating (both feeding apraxia and impaired swallowing) [45], and/or inadequate nutrition [46] due to cognitive impairment. Alternatively, it is possible that weight loss might also be a potential risk factor for developing AD via several potential biological mechanisms [47]. For example, long-term weight loss could contribute to a deficiency of some micronutrients such as antioxidative vitamins or fatty acids [46], which have been quite often associated with reduced risk of AD [48]. In addition, recent evidence indicates that leptin, an adipokin produced by subcutaneous and visceral adipose tissue, could be neuroprotective by enhancing neuronal survival, protecting against oxidative damage, and promoting the proliferation of hippocampal progenitor cells [49]. Thus, persons who lose weight may have a decrease in leptin and thus have a lower level of neuroprotection.

A few earlier prospective studies have reported that weight loss frequently occurs in the AD patients [19-25]. However, more recently, several studies found AD patients may not necessarily experience weight loss. One study found that 79 AD and 26 non-demented institutionalized subjects maintained stable body weights throughout their institutional stay over 48 months [26]. In another prospective study of 395 prevalent AD patients, weight loss of 4% or more in 1 year was observed in about one third of the study sample [39], indicating that the majority of patients did not experience significant weight loss over one year. In another study, about 22% of the 362 AD patients lost 5% of their weight per year, but AD patients were also more likely to gain ≥5% of their initial weight than controls [27]. Finally, a study following 50 AD patients for 30 months found that 26 of them gained weight and 24 lost weight [28]. In our study, we did not find an overall significant loss or gain of weight among AD patients during the first several years following the diagnosis. When the BMI change was examined in prevalent AD patients, presumably representing a later stage of AD, we found a trend of increase of BMI in two clinic-based studies, or a stable BMI in the population-based WHICAP study. Thus, our data do not support the earlier reports of weight loss or BMI drop in AD patients, but rather echoed the more recent studies by noticing that BMI does not drop in prevalent AD patients.

We also found overweight or obese participants had a decline of BMI prior to AD diagnosis, but those who were normal/underweight did not. This could be due to a ‘floor effect’, as

subjects who were normal/underweight may not have as much weight to lose as those who were obese or overweight. The overall increase of BMI in prevalent AD patients may be driven by the large number of normal/underweight subjects, who started to gain weight shortly after diagnosis. Obese patients, in contrast, may continue to lose weight even long after the diagnosis, although the rate of decrease slowed down compared to before onset. It is unclear why the BMI change pattern after AD onset differs by the initial BMI. One hypothesis is that once patients are diagnosed with AD, especially in clinic-based patients cohorts (NACC and Predictors study), they may receive more intensive health care, such as increased supervision and more careful monitoring of weight and food intake. Therefore, after AD onset, obese patients may lose weight because they may receive a better controlled amount of foods from caregivers, while the normal/underweight patients may receive increased foods intake, both in an effort to help the patient reach a normal weight. It can be noted (by examining the β values in the models) that, no matter what initial BMI status is, the trend seems to be that the decrease of BMI gradually slows down over time, or even switches to an increase at certain stage for subjects with low BMI. This suggests that before the AD onset, those physiological changes such as reduced olfactory function, apathy, and others may play key roles in the BMI decrease, while at a later stage when the patients are more severely impaired, factors such as lower mobility due to functional impairments or use of weight-increase medications begin to play a more important role, contributing to the increase of BMI.

We found additional adjustment of APOE status did not change the results much. We also found BMI decreased in APOE ε4 negative but not in ε4 positive prevalent patients according to the data from Predictors' study. However, no such difference was found in the WHICAP or NACC cohorts. Very few studies have examined the relationship of APOE ε4 status and weight loss, and the results seemed to be inconsistent. One study found APOE ε4 was associated with associated with weight loss[40], while other studies found the presence of the 4 allele was not associated with weight loss[9, 50]. Further studies are needed to examine whether APOE genotype is associated with change of BMI or weight.

Our study has certain limitations. Although we considered many potential confounding factors that can influence weight in our analyses, it is still possible that our results are explained by residual confounding, including those due to other medications, dose and duration of medication use, physical activity, and other disease conditions that could affect mobility and thus less energy expenditure or dietary caloric intake. We also lack detailed information about family support structure, which could influence eating patterns and, hence, weight loss or gain.

Confidence in our findings is high for several reasons. To our knowledge, this is the first study to describe trends of BMI change among AD patients, especially at different stages of the disease. The current study contains both population-based and clinic-based cohorts and has large sample size overall or in each cohort. The WHICAP cohort is a multi-ethnic sample, including a large number of Hispanics. The diagnosis of AD in all three cohorts was based on comprehensive assessment and standard research criteria. We adjusted for some potential confounders including many demographic and clinical factors, and these factors were carefully collected according to standard research protocol in all three cohorts. It is not

uncommon that associations noted in single studies are not observed in subsequent investigations. Thus, one of the most important elements of this report is the replication of the BMI change pattern in more than one cohort.

Overall, the current study confirmed prior evidence regarding an observable decrease of BMI prior to AD onset, but found stability or an increase in BMI among patients after clinical diagnosis of AD. Our findings, if replicated in future studies, may have important implications for AD diagnosis, prognosis, or management. Our findings of BMI change after AD onset suggest that a longitudinal tracking of BMI may be one of the useful factors to consider for early diagnosis of AD. Monitoring the BMI may also useful for prognosis. For example, a recent study among 414 patients with a diagnosis of probable AD found that weight loss was predictive of subsequent rapid cognitive decline[51], which has consistently been reported to predict worse prognosis. Finally, monitoring weight and BMI may also help caregivers plan for the nutritional needs of patients at different points of the illness.

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List of Abbreviations

AD	Alzheimer's disease
ADCs	Alzheimer's Disease Centers
BMI	body mass index
UDS	Uniform Data Set
GEEs	Generalized estimating equations
mMMSE	modified Mini-Mental State Examination
NACC	National Alzheimer's Coordinating Center
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

REFERENCE

1. Rosengren A, Skoog I, Gustafson D, Wilhelmsen L. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. Arch Intern Med. 2005; 165:321–326. [PubMed: 15710796]
2. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Archives of neurology. 2005; 62:1556–1560. [PubMed: 16216938]
3. Whitmer RA, Gunderson EP, Quesenberry CP Jr. Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res. 2007; 4:103–109. [PubMed: 17430231]

4. Hassing LB, Dahl AK, Thorvaldsson V, Berg S, Gatz M, Pedersen NL, et al. Overweight in midlife and risk of dementia: a 40-year follow-up study. Int J Obes (Lond). 2009; 33:893–898. [PubMed: 19506566]
5. Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk: a population-based twin study. Neurology. 2011; 76:1568–1574. [PubMed: 21536637]
6. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr. et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Archives of neurology. 2009; 66:336–342. [PubMed: 19273752]
7. Gustafson DR, Backman K, Joas E, Waern M, Ostling S, Guo X, et al. 37 years of body mass index and dementia: observations from the prospective population study of women in Gothenburg, Sweden. J Alzheimers Dis. 2012; 28:163–171. [PubMed: 21965312]
8. Power BD, Alfonso H, Flicker L, Hankey GJ, Yeap BB, Almeida OP. Changes in body mass in later life and incident dementia. Int Psychogeriatr. 2013; 25:467–478. [PubMed: 23151427]
9. Johnson DK, Wilkins CH, Morris JC. Accelerated weight loss may precede diagnosis in Alzheimer disease. Arch Neurol. 2006; 63:1312–1317. [PubMed: 16966511]
10. Hughes TF, Borenstein AR, Schofield E, Wu Y, Larson EB. Association between late-life body mass index and dementia: The Kame Project. Neurology. 2009; 72:1741–1746. [PubMed: 19451529]
11. Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. Journal of the American Geriatrics Society. 2008; 56:111–116. [PubMed: 18028342]
12. Luchsinger JA, Mayeux R. Adiposity and Alzheimer's disease. Curr Alzheimer Res. 2007; 4:127–134. [PubMed: 17430235]
13. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. Neurology. 2005; 65:892–897. [PubMed: 16186530]
14. Barrett-Connor E, Edelstein SL, Corey-Bloom J, Wiederholt WC. Weight loss precedes dementia in community-dwelling older adults. Journal of the American Geriatrics Society. 1996; 44:1147–1152. [PubMed: 8855991]
15. Gao S, Nguyen JT, Hendrie HC, Unverzagt FW, Hake A, Smith-Gamble V, et al. Accelerated weight loss and incident dementia in an elderly African-American cohort. Journal of the American Geriatrics Society. 2011; 59:18–25. [PubMed: 21054328]
16. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Archives of neurology. 2005; 62:55–60. [PubMed: 15642850]
17. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
18. Tamura BK, Masaki KH, Blanchette P. Weight loss in patients with Alzheimer's disease. Journal of nutrition for the elderly. 2007; 26:21–38. [PubMed: 18285291]
19. Sandman PO, Adolfsson R, Nygren C, Hallmans G, Winblad B. Nutritional status and dietary intake in institutionalized patients with Alzheimer's disease and multiinfarct dementia. Journal of the American Geriatrics Society. 1987; 35:31–38. [PubMed: 3098821]
20. Tavares AR, Rabins PV. Weight loss in Alzheimer's disease: a longitudinal study. ZfA Zeitschrift fur Alternsforschung. 1987; 42:165–167.
21. Singh S, Mulley GP, Losowsky MS. Why are Alzheimer patients thin? Age and ageing. 1988; 17:21–28. [PubMed: 3364307]
22. Franklin CA, Karkeck J. Weight loss and senile dementia in an institutionalized elderly population. Journal of the American Dietetic Association. 1989; 89:790–792. [PubMed: 2723301]
23. Wolf-Klein GP, Silverstone FA, Levy AP. Nutritional patterns and weight change in Alzheimer patients. International psychogeriatrics / IPA. 1992; 4:103–118. [PubMed: 1391666]
24. Du W, DiLuca C, Growdon JH. Weight loss in Alzheimer's disease. Journal of geriatric psychiatry and neurology. 1993; 6:34–38. [PubMed: 8422270]

25. Cronin-Stubbs D, Beckett LA, Scherr PA, Field TS, Chown MJ, Pilgrim DM, et al. Weight loss in people with Alzheimer's disease: a prospective population based analysis. BMJ (Clinical research ed). 1997; 314:178–179.
26. Wang SY, Fukagawa N, Hossain M, Ooi WL. Longitudinal weight changes, length of survival, and energy requirements of long-term care residents with dementia. Journal of the American Geriatrics Society. 1997; 45:1189–1195. [PubMed: 9329479]
27. White H, Pieper C, Schmader K. The association of weight change in Alzheimer's disease with severity of disease and mortality: a longitudinal analysis. Journal of the American Geriatrics Society. 1998; 46:1223–1227. [PubMed: 9777903]
28. Gillette-Guyonnet S, Nourhashemi F, Andrieu S, de Glisezinski I, Ousset PJ, Riviere D, et al. Weight loss in Alzheimer disease. The American journal of clinical nutrition. 2000; 71:637S–642S. [PubMed: 10681272]
29. Stern Y, Folstein M, Albert M, Richards M, Miller L, Bylsma F, et al. Multicenter study of predictors of disease course in Alzheimer disease (the “predictors study”). I. Study design, cohort description, and intersite comparisons. Alzheimer disease and associated disorders. 1993; 7:3–21. [PubMed: 8481224]
30. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research. 1975; 12:189–198. [PubMed: 1202204]
31. Tang MX, Cross P, Andrews H, Jacobs DM, Small S, Bell K, et al. Incid ence of Alzheimer's disease in African-Americans, Caribbean Hispanics and Caucasians in northern Manhattan. Neurology. 2001; 56:49–56. [PubMed: 11148235]
32. Stern Y, Andrews H, Pittman J, Sano M, Tatemichi T, Lantigua R, et al. Diagnosis of dementia in a heterogeneous population. Development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. Archives of neurology. 1992; 49:453–460. [PubMed: 1580806]
33. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol. 2006; 59:912–921. [PubMed: 16622828]
34. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA. 2009; 302:627–637. [PubMed: 19671904]
35. Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. Alzheimer disease and associated disorders. 2007; 21:249–258. [PubMed: 17804958]
36. Kuczmarski R, Carroll M, Flegal K, Troiano R. Varying body mass index cutoff points to describe overweight prevalence among U.S. adults: NHANES III (1988 to 1994). Obes Res. 1997; 5:542–548. [PubMed: 9449138]
37. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS drugs. 2005; 19(Suppl 1):1–93. [PubMed: 15998156]
38. Gillette-Guyonnet S, Cortes F, Cantet C, Vellas B. Long-term cholinergic treatment is not associated with greater risk of weight loss during Alzheimer's disease: data from the French REAL.FR cohort. J Nutr Health Aging. 2005; 9:69–73. [PubMed: 15791348]
39. Guerin O, Andrieu S, Schneider SM, Milano M, Boulahssass R, Brocker P, et al. Different modes of weight loss in Alzheimer disease: a prospective study of 395 patients. The American journal of clinical nutrition. 2005; 82:435–441. [PubMed: 16087990]
40. Vanhanen M, Kivipelto M, Koivisto K, Kuusisto J, Mykkanen L, Helkala EL, et al. APOE-epsilon4 is associated with weight loss in women with AD: a population-based study. Neurology. 2001; 56:655–659. [PubMed: 11245719]
41. Grundman M, Corey-Bloom J, Jernigan T, Archibald S, Thal LJ. Low body weight in Alzheimer's disease is associated with mesial temporal cortex atrophy. Neurology. 1996; 46:1585–1591. [PubMed: 8649553]
42. Gustafson D. Adiposity indices and dementia. Lancet neurology. 2006; 5:713–720.
43. Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members.

Proceedings of the National Academy of Sciences of the United States of America. 2001; 98:3440–3445. [PubMed: 11248097]

44. Devanand DP, Michaels-Marston KS, Liu X, Pelton GH, Padilla M, Marder K, et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. The American journal of psychiatry. 2000; 157:1399–1405. [PubMed: 10964854]
45. Chang CC, Roberts BL. Feeding difficulty in older adults with dementia. Journal of clinical nursing. 2008; 17:2266–2274. [PubMed: 18705703]
46. Shatenstein B, Kergoat MJ, Reid I. Poor nutrient intakes during 1-year follow-up with community-dwelling older adults with early-stage Alzheimer dementia compared to cognitively intact matched controls. Journal of the American Dietetic Association. 2007; 107:2091–2099. [PubMed: 18060894]
47. Sergi G, De Rui M, Coin A, Inelmen EM, Manzato E. Weight loss and Alzheimer's disease: temporal and aetiologic connections. The Proceedings of the Nutrition Society. 2013; 72:160–165. [PubMed: 23110988]
48. Luchsinger JA, Mayeux R. Dietary factors and Alzheimer's disease. Lancet neurology. 2004; 3:579–587.
49. Tang BL. Leptin as a neuroprotective agent. Biochemical and biophysical research communications. 2008; 368:181–185. [PubMed: 18222172]
50. Jefferson MF, Burlinson S, Burns A, Mann D, Pickering-Brown S, Owen F, et al. Clinical features of dementia associated with apolipoprotein epsilon4: discrimination with a neural network genetic algorithm. Int J Geriatr Psychiatry. 2001; 16:77–81. [PubMed: 11180489]
51. Soto ME, Secher M, Gillette-Guyonnet S, Abellan van Kan G, Andrieu S, Nourhashemi F, et al. Weight loss and rapid cognitive decline in community-dwelling patients with Alzheimer's disease. J Alzheimers Dis. 2012; 28:647–654. [PubMed: 22045479]
52. Manly JJ, Tang MX, Schupf N, Stern Y, Vonsattel JP, Mayeux R. Frequency and course of mild cognitive impairment in a multiethnic community. Ann Neurol. 2008; 63:494–506. [PubMed: 18300306]

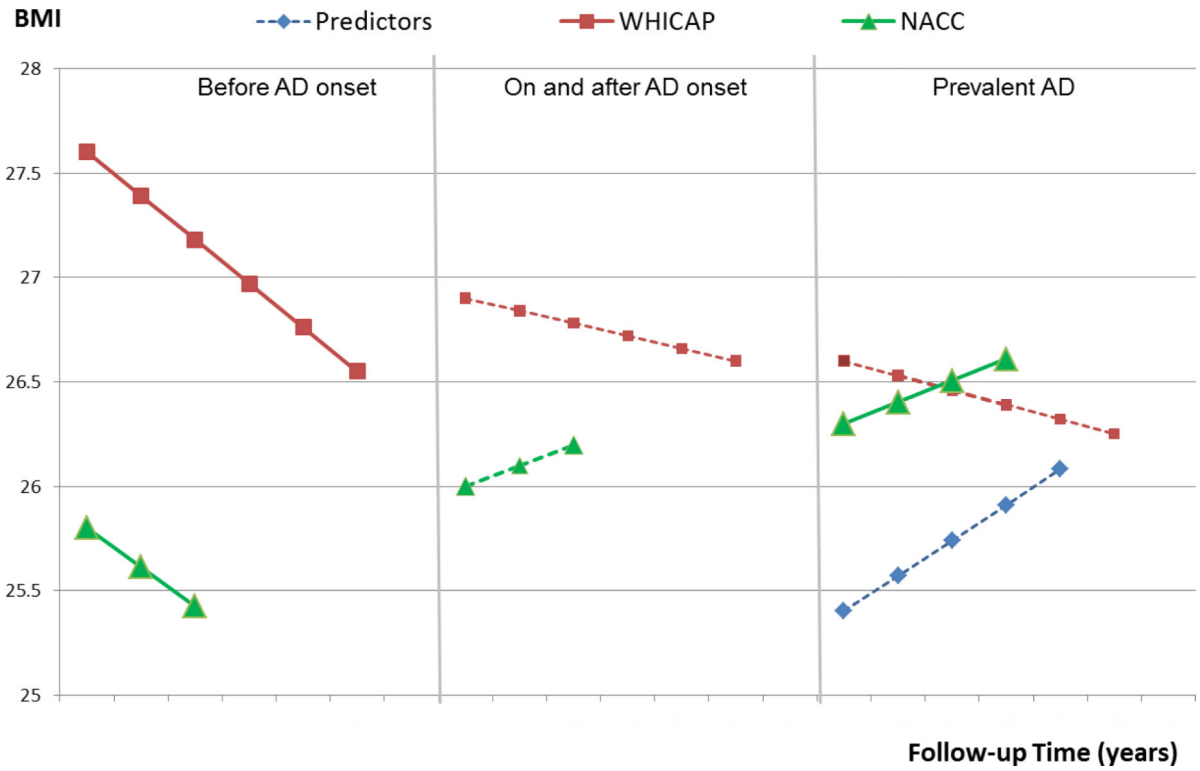

Figure 1. GEE-predicted BMI during the course of follow-up among three cohorts of Alzheimer's disease (AD) patients

Figure 1 shows GEE-predicted BMI (y-axis) during the course of follow-up in years (x-Axis) among three cohorts of Alzheimer's disease (AD) patients. The figure is derived from models that are adjusted for age, sex, ethnicity, and education. Duration of follow-up is based on the average number of follow-up years in each phase (before onset, after and on AD onset, prevalent AD), separately for the three cohorts. Dotted lines indicate non-significant trends while solid lines indicate significant increase or decrease of BMI

Table 1

Characteristics of study populations.

	Predictors Study	WHICAP		NACC			
	Prevalent AD	**Before AD onset**	**On or after AD onset**	**Prevalent AD**	**Before AD onset**	**On or after AD onset**	**Prevalent AD**
Total number of subjects, N	190	176	144	118	593	600	3191
Total number of visits, N	1025	508	377	329	1563	1616	9396
Number of visits, mean(SD)	5.39 (2.78)	2.89 (0.95)	2.62 (0.84)	2.79 (0.88)	2.64 (0.85)	2.69 (0.88)	2.94 (1.10)
Follow-up time[//], years, mean(SD; range)	3.4 (2.2)	4.78 (2.67)	4.67 (2.75)	4.17 (2.4)	1.88 (0.94)	1.88 (0.96)	2.34 (1.26)
Age at initial BMI visit, years	76 (7.7)	78.9 (6.4)	80.8 (6.1)	81.9 (6.6)	78.7 (8.5)	79.3 (7.1)	77.9 (6.8)
Female, N (%)mean(SD)	114 (60)	130 (73.9)	101 (70.1)	85 (72)	312 (53)	294 (49)	1668 (52)
Education, years	13.8 (3.5)	8.5 (4.8)	5.8 (4.8)	5.5 (4.2)	14.9 (3.3)	15.4 (3.1)	14.0 (3.8)
Race, N (%)		/	/	/	/	/	/
White	142 (96)	38 (22)	11 (8)	9 (8)	514 (87)	523 (87)	2593 (81)
Black	17 (4)	48 (27)	28 (19)	33 (28)	58 (10)	49 (8)	401 (13)
Others	/	90 (51)	103 (72)	76 (64)	20 (3)	28 (5)	190 (6)
BMI at initial visit, kg/m^2	25.4 (4.2)	27.6 (5.8)	26.9 (5.1)	26.6 (4.8)	25.8 (4.1)	26.0 (4.4)	26.3 (4.5)
Cognition[*] at initial visit	21.9 (4.0)	−0.12 (1.7)	−1.7 (1.6)	−2.8 (1.4)	27.7 (7.3)	24.8 (6.8)	22.3 (11.8)

[//]Follow-up time were years from the baseline BMI assessment to the last BMI assessment.

[*]Cognition measured by Mini-Mental State Examination (MMSE) in Predictors study and NACC. A composite cognitive Z-score[32, 52] was used to measure cognition in WHICAP.

Table 2

Change of BMI over time in three cohorts.

		Before AD onset BMIs			On or after AD onset BMIs			Prevalent AD BMIs		
	Model *	**N subjects/visits**	**β**	**p**	**N subjects/visits**	**β**	**p**	**N subjects/visits**	**β**	**p**
Predictors	Model 1	/			/			190/1025	**0.19**	**0.05**
	Model 2	/			/			188/1016	**0.17**	**0.06**
	Model 3	/			/			188/1016	0.08	0.36
	Model 4	/			/			137/ 769	0.01	0.93
WHICAP	Model 1	176/508	−0.08	0.45	144/377	−0.08	0.32	118/329	−0.02	0.87
	Model 2	175/506	**−0.21**	**0.02**	141/ 368	−0.06	0.51	118/329	−0.07	0.50
	Model 3	172/498	**−0.19**	**0.03**	141/368	−0.06	0.46	115/323	−0.08	0.41
	Model 4	156/457	**−0.19**	**0.04**	136/354	−0.05	0.52	103/294	−0.08	0.43
NACC	Model 1	593/1563	**−0.27**	**0.002**	600/1616	0.05	0.55	3191/9396	**0.07**	**0.05**
	Model 2	589/1550	**−0.18**	**0.04**	597/1609	0.09	0.24	3167/9323	**0.11**	**0.004**
	Model 3	572/1388	**−0.27**	**0.005**	590/1489	−0.03	0.74	3116/8620	**0.12**	**0.004**
	Model 4	447/1108	−0.17	0.07	468/1212	0.06	0.50	2263/6519	**0.15**	**0.002**

* Model 1 was unadjusted. Model 2 was adjusted for age, gender, race, education. Model 3 was adjusted for all the covariates of Model 2, plus research center, residence (assisted living facilities vs. home or retirement home), and medication use (including both weight-gaining medicine and weight-losing medicine). Model 4 was adjusted for all the covariates in Model 3 as well as APOE e4 genotype.

Table 3

Change of BMI over time in three cohorts, by initial BMI level [*].

Predictors study	Before AD onset BMIs			After and on AD onset BMIs			Prevalent AD BMIs		
	N	β	p	N	β	p	N	β	p
Underweight/ normal							95/482	0.21	0.06
Overweight							68/377	−0.06	0.59
Obese							25/154	−0.21	0.14

WHICAP	Before AD onset BMIs			After and on AD onset BMIs			Prevalent AD BMIs		
	N	β	p	N	β	p	N	β	p
Underweight/ normal	62/176	−0.10	0.12	52/137	0.06	0.49	41/114	−0.002	0.97
Overweight	**61/182**	**−0.13**	**0.05**	50/136	−0.12	0.06	51/139	−0.07	0.51
Obese	49/140	−0.18	0.34	39/95	−0.18	0.34	23/70	−0.12	0.52

NACC	Before AD onset BMIs			After and on AD onset BMIs			Prevalent AD BMIs		
	N	β	p	N	β	p	N	β	p
Underweight/ normal	260/630	−0.06	0.52	**259/665**	**0.31**	**<0.0001**	**1297/3532**	**0.21**	**<0.0001**
Overweight	237/580	−0.09	0.23	237/608	0.04	0.66	1238/3471	0.01	0.82
Obese	**75/178**	**−0.82**	**<0.0001**	**94/216**	**−0.40**	**0.05**	**581/1617**	**−0.26**	**0.001**

[*] The analysis was based on Model 3, which was adjusted for age, gender, ethnicity, education, study center (for NACC data and Predictors study), plus residence (nursing home or full-term care facilities vs. home or retirement home), medication use (including both weight-gaining medicine and weight-losing medicine).