BODY WEIGHT AND COGNITIVE DECLINE IN MCI

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Abstract

Objective: To examine body mass index (BMI) and cognitive decline in subjects diagnosed with mild cognitive impairment (MCI).

Methods: Neuropsychological testing was conducted of 286 MCI subjects. General estimating equations (GEE) assessed the relationships of baseline BMI with one-year change in global cognition. Logistic GEE assessed the relationship of BMI with a clinically significant decline in assessments of global cognition and conversion to Alzheimer's disease (AD).

Results: Baseline BMI was associated with a significant decline in cognitive performance in MCI. We observed that a low baseline BMI as associated with an increased risk of a clinically significant decline in global cognition. No association between baseline BMI and conversion to AD was observed.

Conclusions: Lower BMI is associated with a more rapid decline in cognition in MCI. This relationship suggests changes in metabolism are present in MCI or body composition may influence the rate of cognitive decline in MCI.

Introduction

In 2006 there were 37.3 million individuals aged 65 or older living in the United States. This represents an increase of 10.0% in this age group within the last ten years. Additionally, the number of Americans aged 45-64 who will reach 65 over the next two decades is expected to increase by 39% during this decade. As a result of this shifting demographic, by the year 2050 the proportion of the total population with Alzheimer Disease (AD) will double (0.24%), compared to the 1995 population (0.14%).[1] To address this growing concern, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in October 2004 to characterize the earliest clinical signs (imaging and biomarker) of the degenerative process that is likely to develop into AD.[2, 3]

Some of the earliest characterizations of dementia have noted significant weight loss during the progression of the disease. [4-7] Weight loss is associated with more rapid progression of AD and increased mortality.[8] Interestingly, numerous studies have found weight loss to be associated with dementia many years prior to the emergence of clinically apparent symptoms.[9-13] In fact, atrophy of the brain in areas associated with feeding behavior have been found in AD subjects with low BMI. [14] Moreover, recent work in mouse models has shown that the obesity related hormone leptin is negatively related to the hallmark pathological process of AD.[15] These studies are in contrast to previous works that have shown an association between midlife obesity the development of dementia.[16-21]

To address this conflict, the primary focus of this study was to explore the relationship between BMI and cognitive decline. This study is unique in that it examines the role of BMI in subjects diagnosed with mild cognitive impairment (MCI). MCI is characterized as a transition phase between normal aging and Alzheimer disease (AD). Most individuals with the amnesic

form of MCI eventually develop AD, suggesting that, in many cases, MCI may be the earliest clinical phase of AD.[22-24] While the diagnostic precision of MCI has been questioned,[25] the clinical utility of MCI remains promising. Given that AD is a degenerative process, the rationale for this diagnostic construct is to identify individuals early in the disease process who would be most responsive to intervention. Our *a priori* hypothesis was that lower BMI would be associated with a more rapid decline in cognition in the MCI cohort.

Methods

Sample: We compiled demographic, height, weight, and cognitive data on 286 MCI participants enrolled in ADNI. We restricted our analysis to subjects who had complete one-year follow up data as of the February 5th 2008. ADNI criteria for MCI include an MMSE score between 24-30 (inclusive), a memory complaint, have objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a clinical dementia rating (CDR) of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. Baseline, 6 month, and 12-month psychometric and clinical data was collected from 286 individuals diagnosed with MCI. General estimating equations were used to assess the relationship between baseline BMI and one-year cognitive decline in the ADNI Cohort.

Clinical Assessment: ADNI participants were evaluated with standard clinical and psychometric evaluations at baseline, 6-month and 12-months. The CDR [26] was performed at each follow up, a complete battery of clinical and neuropsychological measures were collected. A standardized clinical evaluation was performed collecting information on demographics, vital signs including height and weight, concurrent medications, family history, physical exam, neurological exam,

and the Hachinski-ischemic score. BMI was calculated by dividing subject weight in kg by the square of the subject's height in meters. Subjects were evaluated with the Hamilton Depression Rating Scale, Mini Mental State Examination, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), WMS-R Logical Memory II, Auditory Verbal Learning Test, Boston Naming Test, Trail Making A & B, Digit Symbol, Clock Drawing Test, and Category Fluency. Following each clinical assessment, the evaluating clinician determines diagnostic conversion as well as a "clinically significant" worsening in the ADAS-Cog, MMSE, and the CDR sum of boxes assessments. Per the ADNI protocol, the threshold for "clinically significant" is left to the judgment of the ADNI physician.

Measures of Global Cognition:

We used 4 measures to assess global cognitive performance: z-global, ADAS-Cog, the CDR sum of boxes, and MMSE.

The MMSE is a screening instrument frequently used for Alzheimer's disease drug studies. The scale evaluates orientation to place, orientation to time, registration (immediate repetition of three words), attention and concentration (serially subtracting seven beginning with 100), recall (recalling the previously repeated three words), language (naming, repetition, reading, writing, comprehension), and visual construction (copy two intersecting pentagons). The MMSE measures cognitive impairment with a score ranging from 0 (best) to 30 (worst).[27]

The ADAS-Cog is a structured scale that evaluates memory (word recall, word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, and

ability to remember test instructions are also obtained. The test is scored in terms of errors, with higher scores reflecting poorer performance. Scores can range from 0 (best) to 70 (worse).[28]

A global cognitive z-score was calculated for the following psychometric tests: (Logical Memory-Delayed Recall, Digit Span Forward: Total Correct, Digit Span Backward: Total Correct, Category fluency animals, Category fluency vegetables, Trail Making B, Boston naming test, and Auditory Verbal Learning test, and Digit Score-Total Correct). The composite measure was derived as follows: 9 raw scores were transformed into *z*-scores utilizing the baseline means and standard deviations for each test calculated from baseline means and standard deviations from the cognitively normal subjects within the ADNI cohort. Subtest test *z*-scores for participants with dementia were averaged to create a *z*-score for each cognitive test. If any of the individual test *z*-scores were missing, the global *z*-score was considered missing and was excluded from the analysis.

The CDR describes five degrees of impairment in performance on each of 6 categories of cognitive functioning including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The ratings of degree of impairment obtained on each of the 6 categories of function are synthesized into one global rating of dementia (ranging from 0 to 3).[26]

Statistical Analyses: To characterize baseline demographics, continuous variables were summarized by means and standard deviations while categorical variables were summarized by frequency and percent.

In the longitudinal analysis, we explored the relationship between baseline BMI as a continuous variable and four global markers of cognitive decline, global *z*-score, MMSE, ADAS-

Cog, CDR sum of boxes. Cognitive decline was modeled by linear generalized estimating equations (GEE) analyses as described by Twisk.[29] Generalized estimating equations analysis is analogous to linear regression however, this analysis technique takes into account within-subject correlations found in longitudinal study designs. In the models tested, the dependent variables were the global z-score, ADAS-Cog, MMSE, and the CDR sum of boxes assessments. Predictor variables were baseline BMI, time, and a baseline BMI*time interaction. The interaction between baseline BMI and time modeled the influence of baseline BMI on the rate of cognitive decline.

To examine the clinical significance of any association with cognitive decline and BMI, we modeled relationship between baseline BMI and the determination of a "clinically significant" decline in ADAS-Cog, MMSE, and CDR sum of boxes. We used logistic generalized estimating equations to calculate odds ratios to assess the relationship between BMI and a "clinically significant" progression of MMSE, ADAS-Cog, and CDR box score.

In this analysis, the presence or absence of a clinically significant cognitive decline was used as a dependent variable. Baseline BMI was fit as a continuous variable to estimate the likelihood of "clinically significant" cognitive worsening. Similar logistic generalized estimating equations were used to assess the relationship between baseline BMI and the likelihood of progression from MCI to AD. All predictive models controlled for age, gender, and education. We examined the within-subject correlation structure of the continuous outcome variables and determined that an exchangeable correlation structure would be the most appropriate for this study. All analyses were conducted using SPSS15 using an α-level of 0.05.

Results

Sample characteristic:

Sample characteristics for the MCI cohort are outlined in **Table 1**. The MCI cohort had an average age of 75.0 (SD 7.5) and was 34% female mean baseline BMI of 26.0 (SD 4.0). The cohort's baseline mean MMSE was 26.9 (SD 1.8) and ADAS-Cog was 9.5 (SD 3.7).

Relationship of BMI to Cognitive Performance

General estimating equations were used in adjusted regression models to examine baseline BMI and its association with cognitive decline **Table 2**. Baseline BMI was not associated with any of the global tests of cognition. Baseline BMI was associated with a reduced rate of cognitive decline in ADAS-cog, MMSE, global *z*-score. A one unit decrease in BMI at baseline was associated with a 1.3% decline in ADAS-cog performance (p=0.03), a 3.6% decline in MMSE score (p=<0.001), and a 3.5% decline (p=0.05) in global cognitive performance over a one year interval. No association was observed between CDR sum of boxes and baseline BMI. **Figure 1** graphically represents the expected values of the prediction models and demonstrates the relationship between of baseline BMI and cognitive decline. To illustrate the magnitude of the influence of baseline BMI, the subject's BMI was ranked into tertiles and plotted against time. Subjects in the highest baseline BMI tertile show minimal cognitive decline whereas subjects in the lowest baseline BMI tertile had the most rapid decline.

Baseline BMI and Clinically Significant Cognitive Decline

To assess the clinical significance of the above findings logistic regression models were fit to estimate the odds of the determination of a subject's clinically significant decline as

determined by the evaluating ADNI clinician, **Table 2**. The event indicator in these models was coded as a clinically significantly worsening of the ADAS-Cog, MMSE, and the CDR Sum of Boxes. We observed a protective effect of BMI in reducing the risk of ADAS-Cog decline (n=54, adjusted OR=0.91; CI 0.83-0.99; p=0.03) and a marginally significant protective effect in reducing MMSE decline (n=70, adjusted OR=0.93 CI 0.86-1.0; p=0.06). No association was found between BMI and CDR Box Score (n=86, adjusted OR=0.98 CI 0.91-1.05; p=0.54).

Baseline BMI and Diagnostic Progression

Over the one-year interval, we identified 54 subjects with MCI who converted to AD. Similar logistic regression models were fit to assess the relationship between BMI and clinical progression from MCI to AD, **Table 3**. Baseline BMI was not found to be associated with the MCI cohort's progression to AD (adjusted OR=0.98 CI 0.92-1.05; p=0.62).

Discussion

These results suggest a relationship between BMI and cognitive decline in MCI. We observed that individuals with the lowest levels of BMI were associated with the highest levels of cognitive decline over a one-year interval. Moreover, these results substantiate a clinical relevance of this finding. BMI was not found to be protective of diagnostic conversion to AD although only 52 participants converted to AD over the relatively short time frame of data analyzed. This would suggest that a one-year analysis is sufficient to model the relationship between BMI and cognitive decline, but too short to model the relationship between BMI and the functional decline necessary for the progression from MCI to AD.

These results confirm previous reports which suggest that alterations in body composition may occur months or years before the clinical symptoms of dementia.[9, 10, 13, 30] These data imply

that age differentially modifies the association between BMI and cognitive decline and seemingly contrast reports that have shown that BMI in midlife represents a risk factor for the development of dementia.[31-34] This phenomenon has been observed in other illnesses. For instance, while BMI is a risk factor for cardiovascular disease and certain cancers, the link between obesity and all-cause mortality diminishes with increasing age and is greatly reduced or absent by the time individuals reach their mid-70s to early 80s.[35]

While the mechanism of the weight loss in subjects with MCI is unknown, these findings raise questions about the mechanisms of the weight loss. Body composition change may be related to behavioral changes such as reduced caloric intake due to forgetting to eat or the inability to plan and prepare adequate meals. This issue, however, was addressed in previous work which showed that poor dietary intake alone can not explain weight loss in AD patients.[36] A physiologic mechanism may explain the association of BMI and cognitive decline in MCI. For instance, a higher BMI is associated with higher peripheral insulin which has been found to be associated with higher whole brain volume and better cognitive performance in the early-AD population.[37] Atrophy of the mesial temporal cortex which is involved in feeding behavior and memory, has been shown to be associated with low BMI in AD patients.[14] Finally, recent work as shown that increasing levels of obesity-related leptin negatively regulates Aβ levels in both mouse models and primary cultured neurons.[15]

A major strength of this study is that the sample consisted of well-characterized MCI subjects that allowed us to explore the earliest stages of cognitive decline. The strict diagnosis procedure minimizes the potential for misclassification bias that is common in many neruo-cognitive studies. Other strengths include the use of multiple cognitive assessments and the longitudinal nature of the study. Additionally, depressive symptoms have been shown to be

associated with weight changes in the elderly.[38] Since depressed individuals were excluded from the ADNI study at baseline, this potential confounder did not affect these results.

The primary limitation of the study was the short follow up. We cannot be sure if MCI subjects lost weight prior to diagnosis or if low BMI in MCI correlates with faster cognitive decline. Also, BMI does not differentiate between fat and muscle mass. Future studies should explore the use of more sophisticated measures of body composition to characterize the individual effects and distribution of lean mass and fat mass on cognitive decline. Finally, the MCI patients in the ADNI study were highly educated, non-depressed, community dwelling, and in good general health. These demographic characteristics may influence the generalizability of these results and may have influenced the true relationship of cognitive impairment with BMI in MCI.

These findings indicate a negative association between BMI and cognitive decline in MCI. This suggests systemic alterations occurring some time prior to even the mildest cognitive disturbances. Low BMI or recent changes in BMI may be indicative of worse cognitive outcomes. Given these findings, one of two scenarios would seem plausible. First, low body weight may be a risk factor for the development of cognitive decline, as suggested by previous studies. [39] If so, these data suggest that elderly individuals may be responsive to exercise and dietary interventions designed to delay the onset of dementia.[40] On the other hand, weight loss may be a down stream behavioral or neuro-biologic manifestation of AD related brain pathology. Indeed, there is now increasing evidence that AD related pathology may occur several years before clinical symptoms are present.[41] If this is the case, weight loss may be one of the earliest clinical indicators of dementia in the elderly.

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Table 1. Baseline Characteristics of MCI subjects

Variable	Mild Cognitive Impairment n=286
Demographics	
Age	75.0 (7.5)
Female Gender n (%)	98 (34.1)
Years of Education	15.8 (3.0)
Baseline BMI	26.0 (4.0)
Cognitive Assessments	
MMSE	26.9 (1.8)
ADAS-Cog	9.5 (3.7)
CDR Box Score	1.6 (0.9)
Global Z-Score	-0.97(0.6)

Table 2.

Baseline BMI and "Clinically Significant" Cognitive Decline in MCI (n=286)

Assessment of Global Cognitive Decline	Clinically "Significant" Progression (n)	Effect Estimate (OR)	95% Confidence Interval	P-value
ADAS-Cog	54	0.91	0.83-0.99	0.03
MMSE	70	0.93	0.86-1.0	0.06
CDR Box Score	86	0.98	0.91-1.05	0.54

Table 3.

Baseline BMI and MCI Conversion to AD (n=286)

Diagnostic Conversion (n)	Effect Estimate (OR)	95% Confidence Interval	P-value
52	0.98	0.92-1.05	0.62

Figure 1: