BODY COMPOSITION IN EARLY ALZHEIMER'S DISEASE

By
Jeffrey M. Burns, MD

Submitted to the graduate degree program in Clinical Research
and the Graduate Faculty of the University of Kansas
in partial fulfillment of the requirements for the degree of
Master's of Science.

_____
Chairperson: Won Choi Ph.D.

Gary Gronseth, MD _____
Russell Swerdlow, MD_____
David Johnson Ph.D._____

Date Defended: _____

The Thesis Committee for Jeffrey M. Burns, MD certifies
that this is the approved Version of the following thesis:

BODY COMPOSITION IN EARLY ALZHEIMER'S DISEASE

_____
Chairperson: Won Choi Ph.D.

Gary Gronseth, MD _____
David Johnson Ph.D._____
Russell Swerdlow, MD_____

Date Approved: _____

Acknowledgments

This study was supported by grants R03AG026374 and R21AG029615 from the National Institute of Aging, K23NS058252 from the National Institute on Neurological Disorders and Stroke and with generous support from the University of Kansas Endowment Association. The University of Kansas General Clinical Research Center (M01RR023940) provided essential space, expertise, and nursing support. The Hoglund Brain Imaging Center is supported by grant C76 HF00201 and Dr. Brooks is supported by NS039123 and AG026482. Dr. Swerdlow is supported by R01AG022407. This study utilized the LONI Pipeline environment (http://pipeline.loni.ucla.edu), which was developed by the Laboratory of Neuro Imaging and partially funded by NIH grants P41 RR013642, R01 MH71940 and U54 RR021813. We would also like to acknowledge and thank Hal Oppenheimer and the Oppenheimer Foundation for financial support.

Table of Contents

Abstract

Background: Alzheimer's disease (AD) is associated with unintended weight loss. We examined body composition in early AD and nondemented aging and its relation to brain volume and cognition.

Methods: Brain magnetic resonance imaging (MRI) and neuropsychological testing were performed on nondemented (CDR 0, n=70) and early-stage AD (CDR 0.5 or 1, n=70) subjects. Dual energy x-ray absorptiometry (DEXA) determined whole-body fat mass and lean mass. Body mass index (BMI) was determined from height and weight. Linear regression analyses controlling for age and sex assessed the relationship between body composition, cognition, and brain volume.

Results: Lean mass was reduced in early AD compared to nondemented controls ($F=7.73$, $p=0.006$) after controlling for sex. Lean mass was associated with whole-brain volume (beta=0.20, $p<0.001$) and white matter volume (beta=0.19, $p<0.001$) when controlling for age and sex. Lean mass was also associated with global cognitive performance (beta=0.12, $p=0.007$) when controlling for age and sex. Total body fat and percent body fat were not different across groups or related to cognition and brain volume.

Conclusion: Loss of lean mass is accelerated in AD and associated with brain atrophy. AD and sarcopenia may share common underlying mechanisms or sarcopenia may be a direct or indirect consequence of AD pathophysiology.

Introduction

Alzheimer's disease (AD) is commonly associated with unintended weight loss[1] that begins years prior to the recognition of AD-related clinical symptoms.[2-4] Weight loss in those with AD is associated with dementia severity and faster clinical progression.[1] AD-related brain changes including medial temporal lobe atrophy[5] and neuropathological burden (plaques and tangles)[6] are associated with reduced body mass index (BMI) suggesting that neurodegenerative processes may contribute to alterations in body composition.

Epidemiological studies suggest a complex relationship between body composition and cognitive outcomes that may be variable across the age-spectrum. Obesity in midlife is a risk factor for the future development of dementia,[7, 8] an observation that is strengthened by neuroimaging evidence suggesting that obesity is associated with temporal lobe atrophy[9, 10] and abnormal spectroscopic measures of brain integrity.[11] Obesity in late-life, however, has been variably associated with dementia risk, with some studies reporting a lower dementia risk in overweight and obese older adults[12, 13] perhaps explained by weight loss associated with the preclinical and early stages of AD.[2-4]

Most studies of body composition in dementia and AD are limited by relatively nonspecific measures of body composition such as total body weight or BMI rather than more specific measures of body fat and muscle mass. To further examine body

composition in AD, we used dual emission x-ray absorptiometry (DEXA) to examine group differences in body composition in early-stage AD and nondemented subjects. Additionally, we examined predictors of body composition, including examining the hypothesis that imaging measures of neurodegeneration (i.e., brain atrophy) would be associated with lower BMI, lean mass, and percent body fat. We also examined whether cognitive dysfunction was associated with body composition, expecting that cognitive function would be positively correlated with measures of body composition.

Methods

Sample and Recruitment: Participants were 60 years and older and either nondemented (Clinical Dementia Rating (CDR) 0, n = 70) or diagnosed with early-stage AD (CDR 0.5 [n=56] and 1 [n=14]). Participants were recruited from a referral-based memory clinic and by media appeals. Study exclusions include neurologic disease other than AD, diabetes mellitus (defined as a clinical diagnosis and use of an anti-diabetic agent), history of ischemic heart disease (acute coronary artery event, angina), schizophrenia, clinically-significant depressive symptoms, abnormalities in vitamin B12, RPR, or thyroid function, use of antipsychotic and investigational medications, and significant visual or auditory impairment, systemic illness, or orthopedic issues that could impair completion of the study. We have previously reported results on sub-samples of this cohort.[14-16]

Clinical Assessment: All subjects were evaluated using a semi-structured interview of the participant and a knowledgeable collateral source to determine the presence or absence of dementia, and its severity if present, using the Clinical Dementia Rating (CDR).[17] Diagnostic criteria for AD require the gradual onset and progression of impairment in memory and in at least one other cognitive and functional domain.[18] These diagnostic methods have an accuracy for AD of 93%[19] and sensitively detect the earliest stages of AD by focusing on intra-individual change rather than comparison with group norms.[20] Additionally, they accurately identify the subset of individuals meeting criteria for MCI who have early stage AD.[21] A global CDR score is derived from individual ratings in each domain with CDR 0 indicating no dementia, CDR 0.5 very mild dementia, CDR 1 mild dementia. Subjects with moderate (CDR 2) or severe (CDR 3) dementia were not enrolled in the study. The CDR sum of boxes was used as a measure of dementia severity.

Medications, past medical history, education, and demographic information were collected from the collateral source by a nurse clinician. A standard physical and neurological examination was performed to assess abnormalities in visual fields, cranial nerves, motor strength, sensation, reflexes, plantar responses, coordination, praxis, and gait. Functional activity level was estimated using the Mild Cognitive Impairment Activities of Daily Living Scale (MCI-ADL) scale with information collected from the collateral source.[22] The scale evaluates 18 domains and ranges from zero (worst performance) to 57 (best performance).

Neuropsychological Assessment: A trained psychometrician administered a standard psychometric battery to all participants as previously described.[14-16] The battery included standard measures of memory (WMS-R Logical Memory I and II, Free and Cued Selective Reminding Task), language (Boston Naming Test – 15 item), working memory (WMS III Digit Span Forwards and Backwards, WAIS Letter-number sequencing), executive function (Trailmaking A and B, Verbal Fluency (animals, fruits and vegetables), and Stroop Color-Word Test), and visuospatial ability (WAIS Block Design). Cognitive performance scores for each test were converted to z-scores (with higher scores representing better performance) based on the mean and standard deviation of nondemented subjects. The mean of each participant's z-scores was determined to create an index of global cognitive performance. The mini-mental status examination (MMSE) was also administered as a measure of global cognition.

Body Composition: Dual energy x-ray absorptiometry (DEXA; Lunar Corp.) was used to determine regional and total body measures of lean mass and fat mass. Percent body fat represents the percent of total body mass (determined by DEXA) composed of fat (i.e., total body fat / total body mass). We utilized total body weight determined by DEXA. DEXA determined weight was highly correlated with our manually measured (by scale) body weight ($r=0.999$, $p<0.001$) yet minimizes the influence of clothing. Height was measured using a standard stadiometer. Body mass index (BMI) was determined by dividing total body weight (in kg) by the square of height in meters (m^2). Total lean

mass was also normalized by height (lean mass index) by dividing total body lean mass (in kg) by the square of height (m^2).

Neuroimaging: Structural MRI was obtained on all participants using a Siemens 3.0 Tesla Allegra MRI scanner at the Hoglund Brain Imaging Center. High-resolution T1-weighted anatomic images were acquired to provide detailed gross anatomy with high gray-white matter contrast (MP-RAGE; 1x1x1mm^3 voxels; TR=2500, TE=4.38, TI=1100, FOV 256X256mm^2 with 18% oversample, 1mm slice thickness, flip angle=8 degrees). Normalized Whole Brain Volume was computed for each image session using a validated set of imaging tools from the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl) as previously described[15] utilizing the Laboratory of Neuroimaging Pipeline (University of California Los Angeles, www.pipeline.loni.ucla.edu). Briefly, the images were pre-processed and skull-stripped using Brain Extraction Tool. The skull-stripped images were then segmented into white matter, gray matter, and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (FAST) by registering them to the Montreal Neuroimaging Institute avg152 template. Normalized volumes for white matter, gray matter, and whole brain (sum of white and gray matter) were calculated by dividing each by the total intracranial volume (the sum of white, gray, and cerebrospinal fluid volumes) and expressed as the percent of total intracranial volume. Normalized brain volumes minimize sex differences and produce an estimate of brain atrophy.

Other Clinical Measures: We also examined potential covariates that may mediate brain and body composition relationships including habitual level of physical activity, depressive symptoms, frailty, and laboratory assessments of insulin, lipids, inflammation and apolipoprotein E4 allele status as previously described.[14-16] Each participant's level of habitual physical activity was estimated using the Physical Activity Scale in the Elderly (PASE), a reliable and valid measure of physical activity and physical function developed specifically for older individuals.[23] The PASE provides an estimate of an individual's level of physical activity within the last seven days by assessing the frequency and duration of participation in activities such as walking, yard work, household activities, and sports and recreational activities such as golf, tennis, dancing, jogging, weight lifting, etc. The PASE is administered to both the subject and the study partner. For individuals with AD, data collected from the study partner was used in the analyses. We assessed peripheral insulin levels (by radioimmunoassay, Diagnostic Systems Laboratories, Webster, TX) using a standard 14-sample, three-hour intravenous glucose tolerance test performed at 8:30AM after a 12-hour overnight fast, as previously described.[16] Total 3-hour area-under-the-curves (AUC) for glucose and insulin served as overall indices for glucose and insulin levels. The Physical Performance Test (PPT) was used as a measure of physical performance and frailty.[24] Fasting venous blood samples were assessed using commercial enzymatic assays for total cholesterol (Diagnostic Chemicals, Ltd.). Highly-sensitive C-reactive protein (CRP) was determined in fasting blood by turbidimetric assay (Roche Diagnostics Systems).

Statistical Analyses: Analyses were conducted using SPSS 16.0. Continuous variables were summarized by means and standard deviations and categorical variables were summarized by frequency and percent. The Student's T-test was used to compare continuous demographic and imaging variables in early AD and nondemented groups. A chi square test was used to compare categorical variables. Pearson's correlation coefficients were calculated to assess simple relationships between variables. Linear regression was used to examine the relationship of variables of interest (i.e., whole brain volume, cognition) with body composition (i.e., BMI, lean mass, and fat mass as dependent variables). All analyses were controlled for age and sex. Secondary analyses controlled for additional covariates that correlated with body composition (i.e., dementia status, physical activity, insulin and glucose levels [3-hour AUC], and CRP). Additional models examined for the presence of interactions (e.g., dementia x sex). A final exploratory multiple linear regression model examined the influence of all variables of interest and covariates on body composition. Age and sex were forced into the model with covariates entered as stepwise regression retaining variables with $p<0.05$.

Results

Descriptives

Table 1 summarizes the characteristics of the non-demented and early AD groups. The mean age of the cohort (n=140) was 74.1 (6.8) years with no difference between non-demented and early stage AD groups. Individuals with early AD had a mean MMSE score of 26.0 (out of 30 points), indicating mild global cognitive dysfunction. Early-AD

participants demonstrated impairments in daily function, lower whole brain volume, and reduced habitual levels of physical activity.

To identify potentially important covariates, we examined the relationship of body composition measures with age and other clinical measures. Age was inversely associated with total lean mass (beta==-0.18, p<0.001) and lean mass index (beta=-0.014, p=0.02) when controlling for sex. Controlling for age and sex, total lean mass was associated with habitual physical activity (beta=0.14, p<0.001) and insulin AUC (beta=0.11, p=0.02). Percent body fat was associated with insulin AUC (beta=0.28, p<0.001), glucose AUC (beta=0.19, p=0.007), and CRP (beta=0.17, p=0.01) when controlling for age and sex. There were no ApoE4-related differences in total lean mass and percent body fat. Given these associations, we performed all analyses controlling for age and sex and secondary analyses controlling for potential confounding by physical activity, CRP, insulin, and glucose.

Body Composition in AD and Nondemented Subjects

Total lean mass was reduced in individuals with early AD compared to nondemented controls after controlling for known sex differences in lean mass (F=7.73, p=0.006). There were no dementia group x sex interactions, suggesting AD-related differences in lean mass were not different in men and women. Normalizing lean mass for height (lean mass index) slightly attenuated the differences in lean mass across early AD and nondemented groups (p=0.09), likely driven by lower height in the men with early AD

compared to nondemented men (table 2). BMI, body weight and body fat measures were not different across dementia groups. Given known differences in body composition in men and women, body composition data is presented in table 2 for the overall group and stratified by sex.

Brain Atrophy and Body Composition

We examined the association of brain atrophy measures with body composition controlling for age and sex. Whole brain volume was predictive of total lean mass (beta=0.20, p<0.001) and lean mass index (0.19, p=0.009). Controlling for dementia status and additional covariates of physical activity, CRP, and insulin and glucose levels (3-hour AUC) did not alter the results. Whole brain volume was also associated with BMI (beta = 0.20, p=0.05) but this relationship was attenuated when controlling for dementia status (p=0.11). Whole brain volume was not associated with total body fat (beta=0.14, p=0.21) and percent body fat (beta=0.01, p=0.89). There were no dementia status x whole brain volume or sex x whole brain volume interactions, suggesting that the positive relationship between whole brain volume and body composition was similar in AD vs. nondemented and men vs. women.

We next examined the relationship between components of whole brain volume (gray and white matter volume) and body composition when controlling for age and sex. White matter volume was associated with lean mass (beta=0.19, p<0.001), lean mass index (beta=0.23, p<0.001), and BMI (beta=0.23, p=0.01) but not total body fat or

percent body fat. These associations were unchanged when controlling for dementia status and additional covariates of physical activity, CRP, insulin and glucose measures. Gray matter volume was not associated with any measures of body composition.

We next examined an overall model that included all variables of interest (whole brain volume, global cognition, dementia status) and covariates (age, sex, physical activity, CRP, and insulin and glucose) to assess which variables were most strongly related to lean mass. Age and sex were forced into the model (step 1) with all covariates assessed in step 2 using stepwise regression. In this model, whole brain volume (beta=0.13, p=0.01), insulin (3-hour AUC; beta=0.10, p=0.02), and physical activity level (beta=0.13, p=0.01) were each independently predictive of lean mass.

Cognitive Performance and Body Composition

We next assessed the relationship of global measures of cognitive performance (global cognitive index and MMSE) with body composition controlling for age and sex. Total lean mass was associated with global cognitive performance (beta=0.12, p=0.007) and MMSE (beta=0.11, p=0.009). As global cognition is a composite measure of performance on individual cognitive tests, we next assessed the relationship of lean mass on performance of individual cognitive tests controlling for age and sex. Lean mass was associated with performance on logical memory I (beta=0.12, p=0.007), logical memory II (beta=0.09, p=0.04), trailmaking A (beta=-0.09, p=0.05), trailmaking B

(beta=-0.11, p=0.01), category fluency (beta=0.09, p=0.05), block design (beta=0.13, p=0.005), and digit span forward (beta=0.10, p=0.03). There were no dementia status x cognitive performance interactions in predicting lean mass or lean mass index suggesting that the relationship between lean mass and cognition is similar in AD and nondemented participants. Additional analyses controlling for dementia status resulted in attenuation of these results, suggesting that group differences in cognition and lean mass were driving the results. Total body fat and percent body fat were not related to global cognitive performance in any analyses.

Discussion

Our findings are consistent with prior reports that alterations in body composition are apparent in the earliest clinical stages of AD.[2-4] Our study extends these reports by suggesting that AD-related alterations in body composition may be predominantly related to loss of lean mass (i.e., sarcopenia), consistent with at least one large, epidemiological study that found an association between cognitive impairment and reduced muscle mass.[25] Although measures of adiposity have been linked with an increased risk for AD,[13] we found no relationship of total body fat measures with brain volume, cognition, or dementia status. The study design (cross-sectional, case-control) limits our ability to infer causal relationships but our data suggests that loss of lean mass (i.e., sarcopenia) may be accelerated in the earliest stages of AD.

We observed a direct correlation between whole brain volume (an estimate of brain atrophy) and lean mass suggesting that brain atrophy and loss of muscle mass may co-occur. Our data are consistent with other studies suggesting that brain pathology may contribute to decline in body composition[6] perhaps by disrupting CNS regulation of energy metabolism and food intake.[26] Brain atrophy is considered a neuroimaging marker reflective of AD pathology,[27] although we observed a strong relationship between lean mass and white matter volume, rather than gray matter volume which is more strongly linked with neurodegeneration. This, and the similar lean mass – brain volume relationship observed in nondemented and AD participants, suggests that mechanisms other than AD processes may underlie these relationships.

Additionally, we observed modest correlations between lean mass and cognitive performance. Previous studies have demonstrated that higher BMI is associated with better cognitive performance[28] and less cognitive decline;[29] thus, our results extend these studies by suggesting that lean mass, rather than adiposity, may be a more specific factor relating body composition with cognitive outcomes in older adults.

Our observations also suggest that AD and sarcopenia may share common underlying mechanisms. Sarcopenia in normal aging is most strongly associated with age-related reductions in physical activity[30] and alterations in anabolic and inflammatory stimuli.[31] AD is associated with reduced physical activity[14] and systemic anabolic and inflammatory abnormalities that are implicated in sarcopenia.[32-34] While our measures

of anabolic and inflammatory processes are limited in this study, we observed a correlation between lean mass and insulin, a well-known anabolic hormone[35] that may have neurotrophic[36] and neuroprotective[37] affects. We previously reported that insulin levels are associated with cognition and brain volume in early AD and that this association is strongest for white matter.[16] Additionally, insulin signaling preferentially affects the development of white matter structures.[38] Thus, our observation that white matter volume, lean mass, and insulin levels are inter-related suggests that loss of anabolic support to both muscle and brain may be a potential mechanism underlying the observed relationships.

Individuals with early AD had reduced physical activity levels compared to the nondemented cohort. Additionally, an individual's physical activity level was predictive of lean mass, with lower physical activity associated with less lean mass. These observations suggest that the AD clinical syndrome may indirectly influence lean mass through associated reductions in physical activity. Physical activity and exercise have well-described anti-inflammatory[39] and anabolic effects and result in increased lean mass. Accumulating animal and human studies link exercise and fitness with brain health[15, 40-42] although the mechanisms relating exercise with brain health remain imprecisely defined. While the cross-sectional, case-control design limits the ability to infer causality, these data suggest that factors associated with the preservation lean muscle, such as exercise, may attenuate structural and functional brain changes associated with AD and aging.

The current study is limited by its cross-sectional design and relatively small sample size. We utilized validated clinical methods for diagnosing the earliest stages of AD although these methods are imperfect in predicting AD pathology. Additionally, study participants were part of a convenience sample which limits generalizability and may have introduced sampling bias that could impact the results. Further longitudinal and interventional studies will be necessary to more precisely define the nature and mechanisms of body composition changes in AD. Our data suggest that loss of lean mass may be accelerated in AD perhaps through underlying mechanisms common to both AD and sarcopenia or as a direct or indirect consequence of AD pathophysiology.

Table 1: Sample Characteristics

	Nondemented (n = 70)	Early AD (n = 70)	p value
Age, years	73.3 (7.3)	74.9 (6.7)	0.17
Education, years	16.5 (2.7)	15.2 (3.3)	0.01
Female % (n)	57.2 (40)	58.6 (41)	0.86
Apolipoprotein E4 Carrier % (n)	27.9 (19)	59.1 (39)	<0.001
MMSE	29.4 (0.8)	26.0 (3.5)	<0.001
Global Cognitive Performance, Z-score	0.1 (0.6)	-1.7 (1.1)	<0.001
Activities of Daily Living	48.5 (3.3)	40.2 (7.8)	<0.001
Geriatric Depression Scale	0.49 (0.79)	3.3 (2.9)	<0.001
Whole Brain Volume, %ICV	78.0 (2.9)	75.3 (3.3)	<0.001
White Matter Volume, %ICV	35.0 (1.9)	34.6 (2.4)	0.32
Gray Matter Volume, %ICV	43.0 (2.5)	40.6 (2.4)	<0.001
Physical Activity Level (PASE Score)	130.4 (51.8)	88.9 (56.7)	<0.001

Physical Performance Test	30.5 (3.4)	27.6 (3.9)	<0.001
Total Cholesterol (ml/dl)	182.6 (34.0)	188.1 (37.4)	0.37
C-reactive Protein (mg/L)	2.3 (2.4)	1.8 (1.5)	0.11
Insulin Area-Under-the-Curve**	2540 (1361)	2903 (1747)	0.18
Glucose Area-Under-the-Curve**	22475 (2851)	23049 (4541)	0.38

* Peak oxygen consumption normalized by total lean mass.

**Area-under-the-curve generated from a three-hour intravenous glucose tolerance test.

All data represent means (SD) except when otherwise noted.

MMSE: Mini-Mental State Examination; %ICV: percent intracranial volume

Table 2: Body Composition in Early AD compared to Nondemented Controls

	Nondemented	Early AD	p-value
Body Mass Index			
Overall*	25.7 (3.6)	25.0 (3.9)	0.29
Men	25.7 (3.6)	25.6 (3.5)	0.94
Women	25.7 (3.7)	24.5 (4.2)	0.20
Body Weight (kg)			
Overall*	70.5 (13.4)	66.7 (12.5)	0.06
Men	78.4 (13.0)	74.4 (11.4)	0.22
Women	64.5 (10.5)	61.1 (10.1)	0.14
Total Lean Mass (kg)			
Overall*	44.6 (10.4)	41.9 (9.3)	**0.009**
Men	54.6 (7.0)	51.5 (5.9)	0.07
Women	37.1 (4.5)	35.2 (3.5)	**0.03**
Lean Mass Index (kg/m2)			
Overall*	15.5 (2.0)	15.0 (2.2)	0.09
Men	17.2 (1.6)	17.0 (1.7)	0.70
Women	14.2 (1.3)	13.6 (1.3)	**0.03**

Height (cm)			
Overall*	169.6 (11.2)	166.2 (9.1)	0.07
Men	178.3 (8.3)	174.0 (7.0)	**0.04**
Women	161.4 (6.6)	160.8 (6.1)	0.69
Fat Mass (kg)			
Overall*	25.8 (8.3)	24.7 (8.7)	0.41
Men	23.8 (8.5)	22.8 (8.8)	0.67
Women	27.4 (7.8)	25.9 (8.4)	0.43
Percent Body Fat			
Overall*	36.8 (9.0)	36.7 (9.9)	0.87
Men	30.0 (7.5)	30.0 (8.5)	0.99
Women	41.8 (6.3)	41.4 (7.9)	0.81

All data represent means (SD).

*Group comparison by general linear model controlling for sex; all other group comparisons were tested using Student's t-test.

Figure 1: Relationship between Lean Mass and Whole Brain Volume

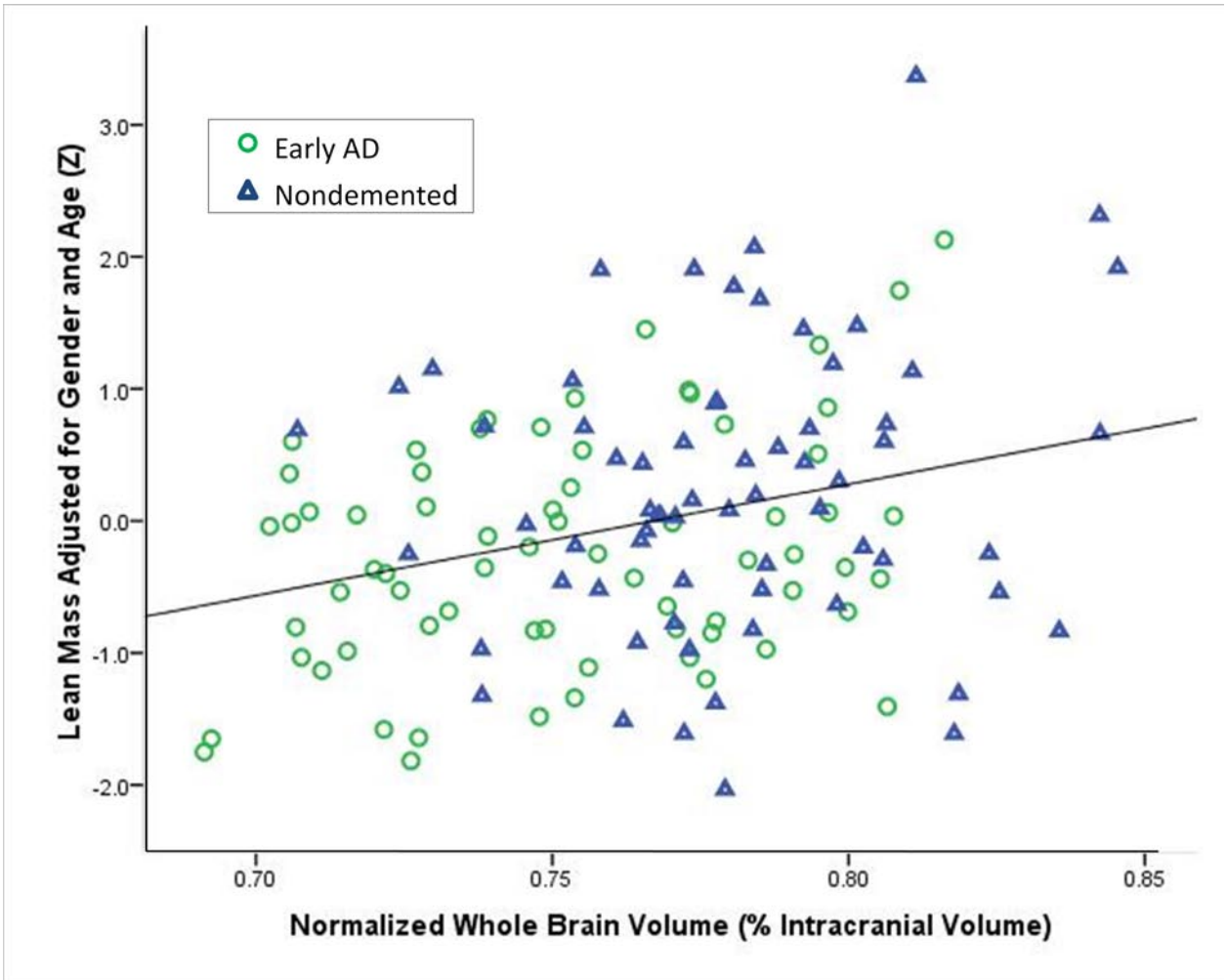

Figure Legend: Whole brain volume is positively associated with lean mass in early AD and nondemented controls. Whole brain volume is normalized to account for differences in head size and provide an estimate of brain atrophy. For illustrative purposes in the figure, lean mass was adjusted for gender and age and presented in standardized units [Z]. This positive association was not different across AD and nondemented groups and was independent of age, gender, dementia severity, inflammation, insulin, and glucose measures.

REFERENCES

1. 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
2. Johnson DK, Wilkins CH, Morris JC. Accelerated Weight Loss May Precede Diagnosis in Alzheimer Disease. Arch Neurol. 2006;63:1312-1317
3. Knopman DS, Edland SD, Cha RH et al. Incident dementia in women is preceded by weight loss by at least a decade. Vol. 69, 2007:739-746
4. BarrettConnor E, Edelstein SL, CoreyBloom J, Wiederholt WC. Weight loss precedes dementia in community-dwelling older adults. Journal of the American Geriatrics Society. 1996;44:1147-1152
5. Grundman M, Corey-Bloom J, Jernigan T et al. Low body weight in Alzheimer's disease is associated with mesial temporal cortex atrophy. Neurology. 1996;46:1585-1591
6. Buchman AS, Schneider JA, Wilson RS et al. Body mass index in older persons is associated with Alzheimer disease pathology. Vol. 67, 2006:1949-1954
7. Whitmer RA, Gunderson EP, Barrett-Connor E et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ. 2005;330:1360
8. Gustafson D, Rothenberg E, Blennow K et al. An 18-Year Follow-up of Overweight and Risk of Alzheimer Disease. Archives of Internal Medicine. 2003;163:1524-1528
9. Gustafson D, Lissner L, Bengtsson C et al. A 24-year follow-up of body mass index and cerebral atrophy. Neurology. 2004;63:1876-1881
10. Jagust W, Harvey D, Mungas D, Haan M. Central Obesity and the Aging Brain. Archives of Neurology. 2005;62:1545-1548
11. Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. 2008;63:652-657
12. Atti AR, Palmer K, Volpato S et al. Late-Life Body Mass Index and Dementia Incidence: Nine-Year Follow-Up Data from the Kungsholmen Project. Vol. 56, 2008:111-116
13. Luchsinger JA, Patel B, Tang M-X et al. Measures of Adiposity and Dementia Risk in Elderly Persons. Vol. 64, 2007:392-398
14. Burns JM, Mayo MS, Anderson HS et al. Cardiorespiratory Fitness in Early-Stage Alzheimer’s Disease. . Alzheimer Dis Assoc Disord. 2008;22:39-46
15. Burns JM, Donnelly JE, Anderson HS et al. Cardiorespiratory Fitness and Brain Atrophy in Early Alzheimer's Disease. Neurology. 2008;In Press
16. Burns JM, Donnelly JE, Anderson HS et al. Peripheral insulin and brain structure in early Alzheimer disease. Neurology. 2007;69:1094-1104
17. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43:2412b-2414
18. McKhann G, Drachman D, Folstein M et al. 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
19. Berg L, McKeel DW, Jr., Miller JP et al. Clinicopathologic Studies in Cognitively Healthy Aging and Alzheimer Disease: Relation of Histologic Markers to Dementia Severity, Age, Sex, and Apolipoprotein E Genotype. Archives of Neurology. 1998;55:326-335
20. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology. 2006;67:467-473
21. Morris JC, Storandt M, Miller JP et al. Mild Cognitive Impairment Represents Early-Stage Alzheimer Disease. Archives of Neurology. 2001;58:397-405
22. Galasko D, Bennett D, Sano M et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Disease & Associated Disorders. Suppl 2:S33-9, 1997. 1997;11:S33-39
23. Washburn RA, McAuley E, Katula J et al. The physical activity scale for the elderly (PASE): evidence for validity. J Clin Epidemiol. 1999;52:643-651
24. Shah KR, Carr D, Roe CM et al. Impaired Physical Performance and the Assessment of Dementia of the Alzheimer Type. Alzheimer Disease and Associated Disorders. 2004;18:112-118
25. Fati Nourhashémi SASG-GERJ-LAHGBV. Is There a Relationship Between Fat-Free Soft Tissue Mass and Low Cognitive Function? Results From a Study of 7,105 Women. Vol. 50, 2002:1796-1801
26. Schwartz MW, Woods SC, Porte D et al. Central nervous system control of food intake. Nature. 2000;404:661-671
27. Silbert LC, Quinn JF, Moore MM et al. Changes in premorbid brain volume predict Alzheimer's disease pathology. Neurology. 2003;61:487-492
28. Kuo H-K, Jones RN, Milberg WP et al. Cognitive Function in Normal-Weight, Overweight, and Obese Older Adults: An Analysis of the Advanced Cognitive Training for Independent and Vital Elderly Cohort. Journal of the American Geriatrics Society. 2006;54:97-103
29. Deschamps V, Astier X, Ferry M et al. Nutritional status of healthy elderly persons living in Dordogne, France, and relation with mortality and cognitive or functional decline. European journal of clinical nutrition. 2002;56:305-312
30. Roubenoff R. Catabolism of aging: is it an inflammatory process? Current opinion in clinical nutrition and metabolic care. 2003;6:295-299
31. Doherty TJ. Invited Review: Aging and sarcopenia. Journal of Applied Physiology. 2003;95:1717-1727
32. Álvarez A, Cacabelos R, Sanpedro C et al. Serum TNF-alpha levels are increased and correlate negatively with free IGF-I in Alzheimer disease. Neurobiology of Aging. 2007;28:533-536
33. Gasparini L, Xu H. Potential roles of insulin and IGF-1 in Alzheimer's disease. Trends in Neurosciences. 2003;26:404-406
34. Cacabelos R, Alvarez XA, Franco-Maside A et al. Serum tumor necrosis factor (TNF) in Alzheimer's disease and multi-infarct dementia. Methods Find.Exp.Clin.Pharmacol. 1994;16:29-35

35. Chow LS, Albright RC, Bigelow ML et al. Mechanism of insulin's anabolic effect on muscle: measurements of muscle protein synthesis and breakdown using aminoacyl-tRNA and other surrogate measures. Vol. 291, 2006:E729-736
36. Tanaka M, Sawada M, Yoshida S et al. Insulin prevents apoptosis of external granular layer neurons in rat cerebellar slice cultures. Neuroscience Letters. 1995;199:37-40
37. Schubert M, Gautam D, Surjo D et al. Role for neuronal insulin resistance in neurodegenerative diseases. Proceedings of the National Academy of Sciences. 2004;101:3100-3105
38. Beck KD, Powell-Braxtont L, Widmer H-R et al. Igf1 gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons. Neuron. 1995;14:717-730
39. Timmerman KL, Flynn MG, Coen PM et al. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? Journal of Leukocyte Biology. 2008;84:1271-1278
40. Kramer AF, Hahn S, Cohen NJ et al. Ageing, fitness and neurocognitive function. Nature. 1999;400:418-419
41. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. Psychological Science. 2003;14:125-130
42. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary Exercise Decreases Amyloid Load in a Transgenic Model of Alzheimer's Disease. Journal of Neuroscience. 2005;25:4217-4221