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Longitudinal Examination of Obesity and Cognitive Function: Results from the Baltimore Longitudinal Study of Aging

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Key Words

Obesity · Cognition · Aged · Longitudinal · Age-associated cognitive change

Abstract

Background: Obesity indices (i.e. BMI, waist-to-hip ratio) show differential relationships to other health outcomes, though their association to neurocognitive outcome is unclear. ***Methods:*** We examined whether central obesity would be more closely associated with cognitive function in 1,703 participants from the Baltimore Longitudinal Study of Aging. ***Results:*** Longitudinal mixed-effects regression models showed multiple obesity indices were associated with poorer performance in a variety of cognitive domains, including global screening measures, memory, and verbal fluency tasks. Obesity was associated with better performance on tests of attention and visuospatial ability. An obesity index by age interaction emerged in multiple domains, including memory and attention/executive function. ***Conclusion:*** Obesity indices showed similar associations to cognitive function, and further work is needed to clarify the physiological mechanisms that link obesity to poor neurocognitive outcome.

Introduction

Obesity is a leading preventable cause of death in the United States, accounting for an estimated 400,000 deaths each year [1]. Some researchers predict obesity will cause the first decline in life expectancy in 100 years [2, 3]. This risk is largely attributable to the many health consequences of obesity, including cardiovascular disease, type 2 diabetes, sleep apnea, and cancer [4]. For example, obese adults are five times more likely to have high blood pressure and forty times more likely to have type 2 diabetes than their normal weight peers [5–8].

Recent research indicates that obesity is also associated with poor neurocognitive outcome. Elevated BMI has been linked with increased risk of Alzheimer's disease and structural brain changes, including excess age-related atrophy and white matter disease [9–14]. Consistent with these findings, excess weight is also associated with reduced cognitive function in a growing number of cross-sectional studies [15–20].

Little is known about the prospective relation between obesity and cognitive decline in non-demented individuals. For example, longitudinal data from the Framingham Heart Study have shown that obesity is associated

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with accelerated cognitive decline in aging men [21, 22]. However, most prospective studies have relied upon BMI as their sole index of obesity. BMI can be influenced by a number of factors and indices, such as waist circumference and waist-to-hip ratio (WHR), which are more closely linked to some adverse health outcomes than BMI [23, 24]. As a result, it is possible that obesity indices are differentially related to changes in cognitive function over time.

To test this hypothesis, we examined the prospective relation between three obesity indices and neuropsychological test performance in non-demented participants from the Baltimore Longitudinal Study of Aging. Based on findings for other adverse health outcomes, we hypothesized that measures of central obesity (e.g. waist circumference, WHR) would be more highly related to cognitive decline than BMI.

Subjects and Methods

All methods were approved by the local human subject's protection boards prior to data collection and analysis of data.

Participants

The Baltimore Longitudinal Study of Aging is a prospective study of community-dwelling volunteers largely from the Baltimore-Washington area. Participants return to the National Institute on Aging at Harbor Hospital in Baltimore, Maryland, about every 2 years to undergo medical, psychological, and cognitive testing. Beginning in 1986, older adult participants (>60 years of age) completed an expanded neuropsychological test battery to better delineate age-related cognitive changes. Participants for the present study included 1,703 individuals aged 19–93 years. Table 1 shows demographic characteristics, baseline anthropometric characteristics, and selected health status indicators. Participants return every 2–3 years for repeated examinations, including neuropsychological testing. There was considerable variability in numbers of visits and intervals between visits (table 2). Participants had an average of 3.1 (SD = 2.0; range = 1–11) visits, and the average time between visits was 2.0 (SD = 0.8) years. Women had fewer visits than men because they joined the study in 1978, 20 years after the study began in 1958. Participants were excluded for medical conditions likely to impact cognitive function, including stroke (n = 50). For individuals with dementia (n = 29), myocardial infarction (n = 25), and atrial fibrillation (n = 118), only visits completed prior to diagnoses were included. Although some participants experienced 10% or more weight loss or change in obesity index during the study, none of these fluctuations were attributable to health conditions that might cause significant weight loss.

Measures

Obesity Indices. BMI was calculated as the ratio of weight (in kilograms) to height (in meters) squared. Height and weight were measured objectively with a clinical calibrated scale. Weight and hip circumferences were obtained with a flexible tape measure, manipulated to maintain close contact with the skin without compression of underlying tissues. Waist circumference was defined as the minimal abdominal perimeter located halfway between the rib cage and the pelvic crest. Hip circumference was defined as the point of maximal protrusion of the gluteal muscles and, in the anterior plane, the symphysis of the pubis. Waist and hip circumference were then used to compute the WHR. Obesity indices were measured at every examination visit.

Neuropsychological Tests. Trained examiners administered tests in the following neuropsychological domains:

(1) Global Cognitive Function: Mini-Mental State Examination total score (n = 643), Blessed Information-Memory-Concentration (IMC) test – errors (n = 1,703).
(2) Attention and Executive Function: Wechsler Adult Intelligence Scale – Revised (WAIS-R) digit span forward (n = 559), WAIS-R digit span backward (n = 560), Trail Making Test A (n = 636) and B (n = 599) times to completion.
(3) Memory: California Verbal Learning Test (n = 461) indices (including words recalled at trial 1, list a, list b, short free recall, and long free recall), Prospective Memory Test total score (n = 357), Benton Visual Retention Test total score (n = 989).

Table 1. Demographic characteristics, baseline anthropometric characteristics, and selected health status indicators

	Values	Min.	Max.
Age, years	55.5 ± 16.9	19	93
Education, years	16.7 ± 2.5	4	24
Females, %	50.3		
Non-Hispanic white, %	75.4		
Hypertension, %	35.0		
Type 2 diabetes/glucose intolerance, %	41.9		
BMI	25.8 ± 4.3	16.2	48.8
Waist circumference, cm	86.0 ± 13.2	58.5	141
Waist-to-hip ratio, cm	0.9 ± 0.1	0.6	1.1
Anti-lipid medication, %	3.6		

Data presented as means ± SD or %.

Table 2. Sample size by number of visits measuring obesity indices and neuropsychological test performance

Number of visits	n (% of sample)
1	1,703 (100.0)
2	1,257 (73.8)
3	887 (52.1)
4	602 (35.3)
5	385 (22.6)
6	241 (14.2)
7	119 (7.0)
8+	72 (3.9)

Table 3. Coefficients from longitudinal mixed-effects regression models for the adjusted relation between BMI and cognitive function in 1,703 adults in the Baltimore Longitudinal Study of Aging

	Intercept	Age	BMI	Sex	Years of education	Hyper-tension	Glucose-diabetes	Anti-lipid meds	Age × BMI
Global									
MMSE	27.36**	–0.70*	–0.03**	–0.25**	0.13**	0.04	0.06	–0.00	0.01
Blessed IMC errors	3.23**	0.049	0.03**	–0.17**	–0.14**	0.04	–0.15*	–0.13	0.00
Attention/executive									
Digit span forward	6.85**	–0.34	–0.03*	0.38**	0.10**	–0.06	0.18	0.03	0.00
Digit span backward	6.52**	–0.38	–0.02	0.43**	0.10**	0.03	0.18	–0.13	0.00
Trails A	55.64**	13.71**	–0.24**	–0.35	–0.71**	0.39	0.18	–1.64*	–0.31**
Trails B	148.32**	40.54**	0.25	–0.79	–3.78**	–0.27	0.98	–4.76	–0.54
Memory									
CVLT trial 1	7.03**	–0.51*	–0.00	–1.12**	0.05*	0.02	–0.01	0.08	–0.00
CVLT A	45.83**	–3.37**	–0.02	–6.40**	0.54**	1.47**	0.28	0.58	0.01
CVLT B	5.66**	–0.49*	–0.02	–0.99**	0.09**	0.32**	0.04	0.23	–0.01
CVLT short free	8.27**	–1.05**	0.00	–1.25**	0.14**	0.48**	–0.02	0.15	0.01
CVLT long free	8.70**	–0.90**	0.01	–1.27**	0.14**	0.41**	–0.02	0.13	0.00
Prospective memory	4.01**	–0.27*	0.02*	–0.10	0.04**	0.03	0.00	0.14*	0.00
BVRT	8.11**	0.45**	0.03	–0.11	–0.18**	0.00	–0.30**	0.32*	0.02**
Language									
Letter Fluency	10.42**	–1.78**	–0.11**	–0.54	0.45**	–0.11	0.43	–0.10	0.03
Category Fluency	13.64**	–2.65**	–0.08**	–1.56**	0.28**	0.26**	0.35	0.13	0.04
Boston Naming	44.59**	–2.84**	–0.00	0.60	0.55**	–0.10	0.03	0.10	0.07
Visuospatial									
Card Rotations	44.87**	–13.39**	0.31	16.23**	1.30**	–0.70	–3.57	1.32	0.21

CVLT = California Verbal Learning Test; BVRT = Benton Visual Retention Test. Age was employed as both a fixed and random factor with the age × BMI interaction term denoting change over time. * $p < 0.05$; ** $p < 0.01$.

(4) Language: Letter Fluency total score (n = 647; letter F, A, and S), Category Fluency total score (n = 647; fruits, animals, and vegetables), Boston Naming Test total score (n = 87).
(5) Visuospatial: Card Rotations total score (n = 467).

Data Analysis

Data were analyzed using mixed-effects regression models. This approach is the most appropriate statistical method for repeated measurements in the Baltimore Longitudinal Study of Aging because of the non-uniformity of measurement intervals both within and across participants. Mixed-effects regression accounts for these inconsistencies in measurement intervals, remains unaffected by differences in number of repeated assessment among individuals, and accounts for the correlation among repeated measurements on the same participants. We examined separate longitudinal models for each neuropsychological test as a dependent measure for each obesity measure: BMI, waist circumference, and WHR. In addition to the obesity index, age, sex, years of education, hypertension status, glucose intolerance or diabetes status, and anti-lipid medication use were included as covariates. We included an age × obesity index interaction term in each analysis to assess differential change over time associated with obesity. We centered age on 60 years and rescaled into a decade metric. Obesity indices were not centered prior to analyses. In these analyses, age represents both a fixed and random effect in the models, allowing a determination of change over time. We analyzed these data using SAS version 9.1.3 (SAS Institute, Cary, N.C., USA). We created graphs of the model-predicted scores to visualize the pattern of age-related change at pre-selected levels of obesity for each index.

Results

Global Cognitive Function

Cross sectional analyses showed that multiple obesity indices were associated with poorer cognitive test performance. Among the global cognitive function tests, obesity indices were associated significantly with lower performance on the Mini-Mental State Examination and Blessed IMC test (tables 3–5). Higher BMI was associated with poorer performance on both mental status tests. Higher waist circumference and WHR were associated with the Blessed IMC (fig. 1a–c). Longitudinal analyses showed that BMI did not interact with age on either test,

Table 4. Coefficients from longitudinal mixed-effects regression models for the adjusted relation between waist circumference and cognitive function in 1,703 adults in the Baltimore Longitudinal Study of Aging

	Intercept	Age	Waist circumference	Sex	Years of education	Hypertension	Glucose-diabetes	Anti-lipid meds	Age × waist
Global									
MMSE	26.97**	–0.44	–0.00	–0.20*	0.13**	0.02	0.03	0.01	0.00
Blessed IMC errors	3.39**	–0.12	0.01*	–0.18**	–0.15**	0.06	–0.13	–0.12	0.00*
Attention/executive									
Digit span forward	6.66**	–0.05	–0.01	0.45**	0.11**	–0.06	0.17	0.02	–0.00
Digit span backward	6.25**	0.01	–0.00	0.48**	0.11**	0.02	0.16	–0.18	–0.00
Trails A	60.61**	11.99**	–0.14**	1.04	–0.69**	0.66	0.27	–1.47	–0.07*
Trails B	144.69**	16.94	0.14	–1.66	–3.87**	–0.30	0.95	–4.13	0.09
Memory									
CVLT trial 1	7.29**	–0.20	–0.00	–1.08**	0.05*	0.00	–0.03	0.04	–0.00
CVLT A	46.50**	–2.02	–0.02	–6.33**	0.55**	1.41**	0.24	0.43	–0.01
CVLT B	5.54**	–0.58*	–0.01	–0.92**	0.09**	0.35**	0.02	0.15	–0.00
CVLT short free	8.47**	–0.71*	–0.00	–1.25**	0.15**	0.48**	–0.02	0.14	–0.00
CVLT long free	8.99**	–0.52	–0.00	–1.30**	0.15**	0.41**	–0.02	0.18	–0.00
Prospective memory	3.95**	–0.25	0.01*	–0.14*	0.04**	0.03	–0.01	0.17*	0.00
BVRT	7.27**	–0.03	0.02**	–0.10	–0.18**	–0.03	–0.25*	0.29	0.01**
Language									
Letter Fluency	9.64**	–0.77	–0.02**	–0.22	0.44**	–0.11	0.41	–0.15	–0.00
Category Fluency	12.45**	–1.32*	–0.01	–1.43**	0.28**	0.25**	0.31	0.14	–0.00
Boston Naming	43.47**	–0.93	0.01	0.52	0.56**	–0.15	–0.12	0.18	–0.00
Visuospatial									
Card Rotations	43.62**	–6.25	0.12*	15.12**	1.26**	–1.35	–4.19	1.94	–0.03

CVLT = California Verbal Learning Test; BVRT = Benton Visual Retention Test. Age was employed as both a fixed and random factor with the age × waist circumference interaction term denoting change over time. * $p < 0.05$; ** $p < 0.01$.

but larger waist circumference and WHR interacted with age and were associated with poorer performance on the Blessed IMC over time (fig. 1a–c).

Attention and Executive Function

Cross-sectional analyses showed that higher BMI, waist circumference, and WHR were associated with faster performance on the Trail Making Test A (fig. 1d–f). No associations emerged for Trail Making Test B. In terms of longitudinal analyses, BMI and waist circumference had significant interactions with Trails A, such that increasing obesity was associated with faster performance as age increased. For Trails B, higher WHR was associated with slower performance as age increased.

Memory

Cross-sectional analyses showed that obesity indices were associated with Prospective Memory and the Benton Visual Retention Test, though no subtests of the California Verbal Learning Test. More specifically, BMI and waist circumference were associated with significantly poorer performance on Prospective Memory. Waist circumference and WHR were associated with significantly poorer performance on the Benton Visual Retention Test. Longitudinal analyses revealed a significant interaction between age and all 3 obesity indices on the Benton Visual Retention Test, such that performance declined over time as function of increasing obesity.

Language

Cross-sectional analyses on language measures showed that BMI was associated with significantly poorer performance on the Letter and Category Fluency tests. Waist circumference was associated with poorer performance on only Letter Fluency, and WHR was associated with poorer performance on only Category Fluency. Boston Naming was not associated with any obesity index. Longitudinal analyses showed no obesity × age interaction.

Table 5. Coefficients from longitudinal mixed-effects regression models for the adjusted relation between WHR and cognitive function in 1,703 adults in the Baltimore Longitudinal Study of Aging

	Intercept	Age	WHR	Sex	Years of education	Hyper-tension	Glucose-diabetes	Anti-lipid meds	Age × WHR
Global									
MMSE	26.74**	–0.19	–0.11	–0.24*	0.13**	0.01	0.01	–0.01	–0.25
Blessed IMC errors	3.23**	–0.20	0.88*	–0.19*	–0.15**	0.06	–0.13	–0.13	0.39*
Attention/executive									
Digit span forward	6.44**	–0.07	–0.50	0.42**	0.11**	–0.05	0.16	0.01	–0.26
Digit span back	5.74**	–0.01	0.11	0.40**	0.11**	0.03	0.15	–0.19	–0.37
Trails A	63.03**	12.39**	–16.35**	1.46	–0.70**	0.66	0.01	–1.59	–7.09
Trails B	148.55**	–12.51	7.23	0.93	–3.89**	–0.06	1.86	–3.65	42.01**
Memory									
CVLT Trial 1	7.67**	–0.14	–0.83	–1.04**	0.05*	0.01	–0.02	0.04	–0.41
CVLT A	46.80**	–2.87*	–1.98	–6.14**	0.55**	1.44**	0.27	0.42	–0.32
CVLT B	5.87**	–0.88**	–1.00	–0.84**	0.09**	0.36**	0.03	0.15	0.29
CVLT short free	8.40**	–0.87*	–0.22	–1.23**	0.15**	0.48**	–0.01	0.13	–0.02
CVLT long free	8.83**	–0.71	–0.09	–1.29**	0.15**	0.42**	–0.01	0.17	–0.17
Prospective memory	4.33**	–0.22	0.16	–0.10	0.03**	0.04	0.01	0.18**	0.01
BVRT	6.73**	–0.14	2.37**	–0.15	–0.18**	–0.05	–0.27**	0.31*	1.23**
Language									
Letter Fluency	8.69**	–0.40	–1.22	–0.34	0.44**	–0.12	0.34	–0.17	–0.49
Category Fluency	11.80**	–0.76	–0.37	–1.51**	0.28**	0.24**	0.27	0.12	–0.98
Boston Naming	43.35**	–0.59	1.17	0.51	0.56**	–0.15	–0.10	0.18	–0.48
Visuospatial									
Card Rotations	45.63**	0.98	10.41	14.39**	1.28**	–1.50	–4.08	1.94	–10.98*

CVLT = California Verbal Learning Test; BVRT = Benton Visual Retention Test. Age was employed as both a fixed and random factor with the age × WHR interaction term denoting change over time. * $p < 0.05$; ** $p < 0.01$.

Visuospatial

In the visuospatial domain, cross-sectional analyses indicated that higher waist circumference was associated with better performance on Card Rotations, though no association emerged for BMI or WHR. Longitudinal analyses showed that persons with smaller WHR declined faster over time and no effect emerged for other obesity indices.

Discussion

Results from the present study provide further evidence for an independent association between obesity and cognitive test performance. Cross-sectional analyses showed that larger body composition was associated with poorer performance on measures of global cognitive function, memory, and language. This pattern is consistent with the growing number of studies demonstrating that obesity is an independent risk factor for poor neurocognitive outcome [9–14]. However, in contrast to hypotheses and other medical outcomes [23, 24], no clear pattern of cognitive differences emerged between measures of central obesity and BMI. The exact reason for this finding is unclear, as the mechanisms for obesity-related cognitive impairment (discussed later) remain poorly understood.

Interestingly, cross-sectional analyses found no association between body composition and executive function, and those higher indices were actually associated with better performance on tests of attention/psychomotor speed and visuospatial skills. Several recent studies have also found higher BMI is associated with better cognition, causing some to hypothesize that weight loss in older adults may reflect reduced functional abilities in a prodromal stage of Alzheimer's disease or a common neurological pathway [25, 26]. This possibility appears less likely in the current sample, as the average age (55 years) is younger than the usual onset for Alzheimer's disease and the pattern of impaired test performance

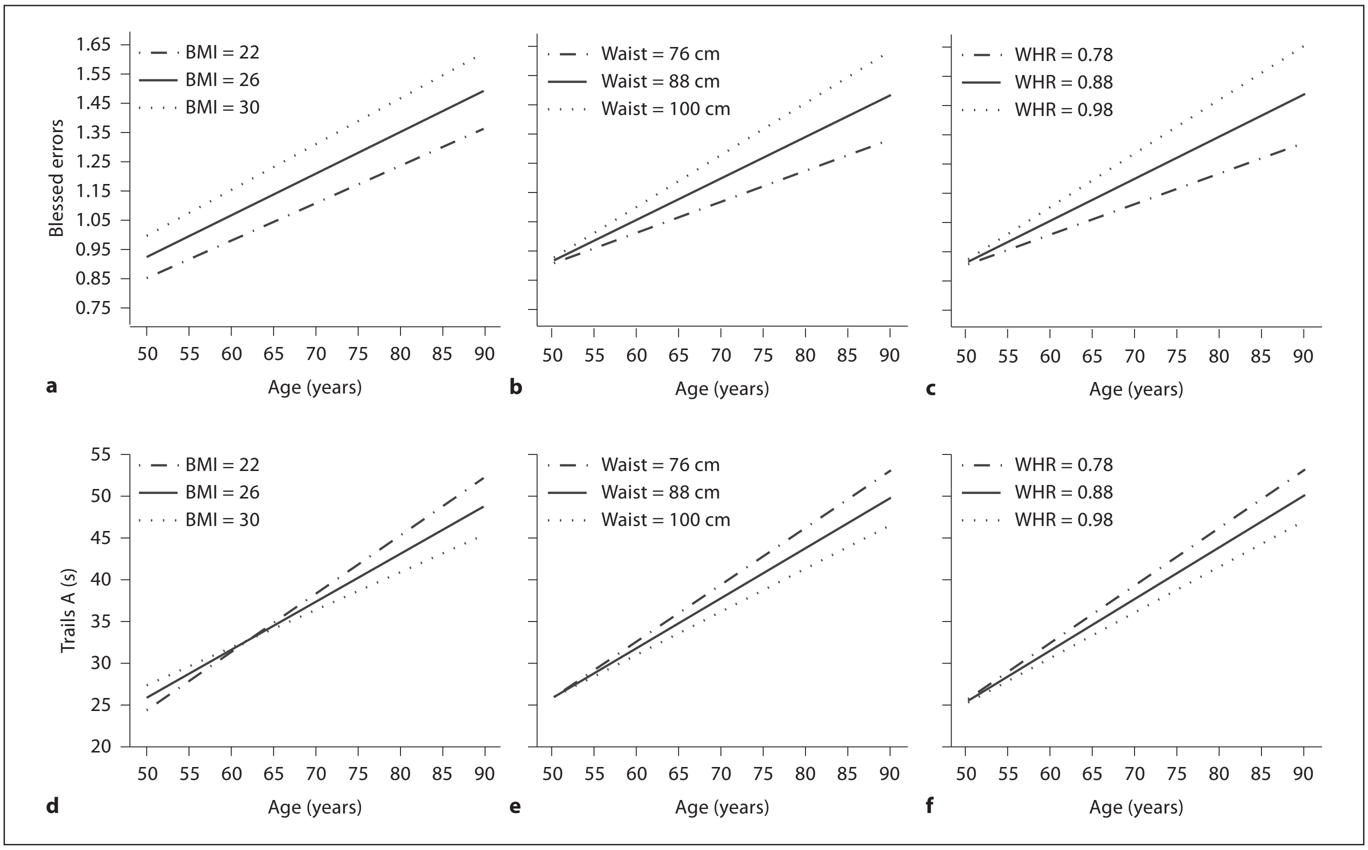

Fig. 1. Longitudinal rate of change in cognitive performance as a function of age for number of errors on the Blessed IMC Test by BMI (**a**), waist circumferences (**b**), and waist-hip ratio (**c**), and Trail Making Test A time to completion by BMI (**d**), waist circumferences (**e**), and waist-hip ratio (**f**).

does not involve significant amnestic and naming impairments. Further work is much needed to better delineate the association between obesity and cognitive function across the lifespan.

In the current study, longitudinal analyses showed higher body composition was associated with more rapid decline on measures of global functioning, executive function, and memory over time. Such findings are consistent with past studies showing elevated risk of cognitive decline in obese individuals. However, the etiology of the finding that larger body composition indices were associated with better performance on a test of attention/psychomotor speed while also associated with poorer executive function over time is unclear. Attention and executive function are largely mediated by frontal brain regions and highly correlated [27]. Given that the overall sample exhibits a pattern generally consistent with age-associated cognitive decline, the current findings raise the possibility that obesity produces differential effects on attention and executive function. Some evidence for this notion may already exist in the literature, as a cross-sectional study of otherwise healthy individuals showed higher BMI was associated with deficits in executive function but not attention [15]. This speculation requires confirmation in other samples, particularly studies using functional neuroimaging to better understand cognitive function in obese individuals.

Closely related, the observed pattern of findings from the current study also poses interesting questions about the mechanisms by which obesity is associated with cognitive function. Though medical conditions frequently comorbid to obesity (e.g. hypertension, type 2 diabetes) are known contributors to cognitive decline and dementia [28–30], many studies adjust for these conditions and suggest an independent effect for obesity [14, 15, 21]. There are several alternative explanations that might better account for these findings, including vascular pathology (e.g. endothelial dysfunction), reduced cardiovascular fitness, inflammatory processes, and neuroendocrine dysregulation. Each of these conditions is prevalent in obese individuals and associated with poor neurocognitive function [31–37]. Recent studies also indicate a possible link between obesity and levels of amyloid-β, which may help account for these cognitive findings and the increased risk of Alzheimer's disease in obese individuals [10, 29, 38–40]. In addition, both obesity and cognitive performance are correlated with dopamine pathway dysregulation, which may negatively affect cognition in older individuals [41, 42]. Finally, obesity is associated with alterations in levels of brain-derived neurotrophic factor and leptin – biomarkers that have recently been linked to cognitive function in human studies [43, 44]. Each of these mechanisms, in isolation or combination, may contribute to the observed cognitive performance.

However, the current results also revealed that lower BMI was associated with better function and reduced decline on Trail Making Test A, and perhaps on another, Card Rotations. This finding initially appears to contradict the proposed neuroprotective qualities of caloric restriction [45, 46] and encourage other explanations. As noted above, the average age and cognitive profile argue against low BMI being a marker of prodromal Alzheimer's disease in the current sample. An alternate explanation is the possible cognitive impact of intentional dieting in older adults. The few existing studies have examined the association between dieting and cognitive function in younger adults, with findings ranging from mild decline to mild improvement [47–50]. Data regarding dieting status were not available for the current study and could not be directly analyzed. Another possibility is that the long-term neurocognitive impact of obesity is at least partly determined by an individual's weight history across the lifespan. Recent work shows inconsistent effects of obesity on cognitive function in children and adolescents [51–53] and it is possible that this trajectory continues through adulthood. Studies that incorporate lifetime weight history will provide key insight into this possibility.

The present findings are limited in several ways. First, the current sample is relatively well-educated (average >16 years of education) and this high level of cognitive reserve may limit the observed rate of cognitive decline [54, 55]. Similarly, a comprehensive IQ estimate (e.g. WAIS-IV) was not available for analyses and may help account for patterns of decline over time. However, the present sample's relative homogeneity is also a strength because it may minimize the confounding effects of demographic variables such as occupational status, socioeconomic status, and educational attainment. In addition, the present sample was relatively healthy: none of the observed weight changes were attributable to acute or chronic diseases.

In summary, findings from the current study indicate that multiple indices of body composition show cross-sectional and longitudinal associations with cognitive function. Further work is much needed to identify etiological mechanisms for these associations, particularly those that can directly examine underlying physiological processes.

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References

1 Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Actual causes of death in the United States, 2000. JAMA 2004;291:1238–1245.

2 Flegal KM, Graubard BI, Williamson DF, Gail MH: Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293:1861–1867.

3 Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al: A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005; 352:1138–1145.

4 Bray GA: Medical consequences of obesity. J Clin Endocrinol Metab 2004;89:2583–2589.

5 Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961–969.

6 Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, et al: Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132:501–513.

7 Harris MM, Stevens J, Thomas N, Schreiner P, Folsom AR: Associations of fat distribution and obesity with hypertension in a biethnic population: the ARIC study. Atherosclerosis Risk in Communities Study. Obes Res 2000;8:516–524.

8 Rosenberg L, Palmer JR, Campbell LL, Rao RS: Obesity and hypertension among college-educated black women in the United States. J Hum Hypertens 1999;13:237–241.

9 Gustafson D, Lissner L, Bengtsson C, Bjorkelund C, Skoog I: A 24-year follow-up of body mass index and cerebral atrophy. Neurology 2004;63:1876–1881.

10 Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I: An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 2003;163:1524–1528.

11 Gustafson DR, Steen B, Skoog I: Body mass index and white matter lesions in elderly women: an 18-year longitudinal study. Int Psychogeriatr 2004;16:327–336.
12 Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC: The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol 2005;5:23.
13 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. Arch Neurol 2005;62:1556–1560.
14 Jagust W, Harvey D, Mungas D, Haan M: Central obesity and the aging brain. Arch Neurol 2005;62:1545–1548.
15 Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E: Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr Psychiatry 2007;48:57–61.
16 Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E: Obesity is associated with memory deficits in young and middle-aged adults. Eat Weight Disord 2006;11:e15–e19.
17 Jeong SK, Nam HS, Son MH, Son EJ, Cho KH: Interactive effect of obesity indexes on cognition. Dement Geriatr Cogn Disord 2005;19:91–96.
18 Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, Morris JN, 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. J Am Geriatr Soc 2006;54:97–103.
19 Waldstein SR, Katzel LI: Interactive relations of central versus total obesity and blood pressure to cognitive function. Int J Obes 2006;30:201–207.
20 Cournot M, Marquie JC, Ansiau D, Martinaud C, Fonds H, Ferrieres J, et al: Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurol 2006;67:1208–1214.
21 Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB: Lower cognitive function in the presence of obesity and hypertension: the Framingham Heart Study. Int J Obes Relat Metab Disord 2003;27:260–268.
22 Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB: Obesity, diabetes and cognitive deficit: The Framingham Heart Study. Neurobiol Aging 2005;(suppl 1):11–16.
23 Lindqvist P, Andersson K, Sundh V, Lissner L, Bjorkelund C, Bengtsson C: Concurrent and separate effects of body mass index and waist-to-hip ratio on 24-year mortality in the Population Study of Women in Gothenburg: evidence of age-dependency. Eur J Epidemiol 2006;21:789–794.
24 Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S: Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. Am Heart J 2005;149:54–60.
25 Barrett-Connor E, Edelstein S, Corey-Bloom J, Wiederholt W: Weight loss precedes dementia in community-dwelling older adults. J Nutr Health Aging 1998;2:113–114.
26 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. Arch Neurol 2005;62:55–60.
27 Tanji J, Hoshi E: Role of the lateral prefrontal cortex in executive behavioral control. Physiol Rev 2008;88:37–57.
28 Skoog I, Gustafson D: Update on hypertension and Alzheimer's disease. Neurol Res 2006;28:605–611.
29 Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al: Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord 2006;20:93–100.
30 Halling A, Berglund J: Association of diagnosis of ischaemic heart disease, diabetes mellitus and heart failure with cognitive function in the elderly population. Eur J Gen Pract 2006;12:114–119.
31 Ylikoski R, Ylikoski A, Raininko R, Keskivaara P, Sulkava R, Tilvis R, et al: Cardiovascular diseases, health status, brain imaging findings and neuropsychological functioning in neurologically healthy elderly individuals. Arch Gerontol Geriatr 2000;30:115–130.
32 Rahmouni K, Correia ML, Haynes WG, Mark AL: Obesity-associated hypertension: new insights into mechanisms. Hypertension 2005;45:9–14.
33 Convit A, Wolf OT, Tarshish C, de Leon MJ: Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proc Natl Acad Sci USA 2003;100:2019–2022.
34 Teunissen CE, van Boxtel MP, Bosma H, Bosmans E, Delanghe J, De BC, et al: Inflammation markers in relation to cognition in a healthy aging population. J Neuroimmunol 2003;134:142–150.
35 Colcombe S, Kramer AF: Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14:125–130.
36 Bjorntorp P, Rosmond R: Neuroendocrine abnormalities in visceral obesity. Int J Obes Relat Metab Disord 2000;(suppl 2):S80–S85.
37 Sapolsky RM: Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. Exp Gerontol 1999;34:721–732.
38 Balakrishnan K, Verdile G, Mehta PD, Beilby J, Nolan D, Galvao DA, et al: Plasma Abeta42 correlates positively with increased body fat in healthy individuals. J Alzheimers Dis 2005;8:269–282.
39 Razay G, Vreugdenhil A, Wilcock G: Obesity, abdominal obesity and Alzheimer disease. Dement Geriatr Cogn Disord 2006;22:173–176.
40 Leahey T, Myers T, Gunstad J, Glickman E, Spitznagel M, et al: Abeta40 is associated with cognitive function, body fat, and physical fitness in healthy older adults. Nutr Neurosci 2007;10:205–209.
41 Nieoullon A, Coquerel A: Dopamine: a key regulator to adapt action, emotion, motivation and cognition. Curr Opin Neurol 2003;(suppl 2):S3–S9.
42 Noble EP: D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet B Neuropsychiatr Genet 2003;116:103–125.
43 Gunstad J, Benitez A, Smith J, Glickman E, Spitznagel MB, et al: Serum brain-derived neurotrophic factor is associated with cognitive function in healthy older adults. J Geriatr Psychiatry Neurol 2008;21:166–170.
44 Gunstad J, Spitznagel MB, Keary TA, Glickman E, Alexander T, et al: Serum leptin levels are associated with cognitive function in older adults. Brain Res 2008;1230:233–236.
45 Pasinetti GM, Zhao Z, Qin W, Ho L, Shrishailam Y, Macgrogan D, et al: Caloric intake and Alzheimer's disease: experimental approaches and therapeutic implications. Interdiscip Top Gerontol 2007;35:159–175.
46 Mattson MP: Will caloric restriction and folate protect against AD and PD? Neurol 2003;60:690–695.
47 Bryan J, Tiggemann M: The effect of weight-loss dieting on cognitive performance and psychological well-being in overweight women. Appetite 2001;36:147–156.
48 Pollitt E, Leibel RL, Greenfield D: Brief fasting, stress, and cognition in children. Am J Clin Nutr 1981;34:1526–1533.
49 Pollitt E, Lewis NL, Garza C, Shulman RJ: Fasting and cognitive function. J Psychiatr Res 1982;17:169–174.
50 Green MW, Rogers PJ, Elliman NA, Gatenby SJ: Impairment of cognitive performance associated with dieting and high levels of dietary restraint. Physiol Behav 1994;55:447–452.
51 Gunstad J, Spitznagel MB, Paul RH, Cohen RA, Kohn M, et al: Body mass index and neuropsychological function in healthy children and adolescents. Appetite 2008;50:246–251.
52 Li Y, Dai Q, Jackson JC, Zhang J: Overweight is associated with decreased cognitive functioning among school-age children and adolescents. Obesity 2008;16:1809–1815.
53 Lokken KL, Boeka AG, Austin HM, Gunstad J, Harmon CM: Evidence of executive dysfunction in extremely obese adolescents: a pilot study. Surg Obes Relat Dis 2009;5:547–552.
54 Stern Y: Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord 2006;20:112–117.
55 Corral M, Rodriguez M, Amenedo E, Sanchez JL, Diaz F: Cognitive reserve, age, and neuropsychological performance in healthy participants. Dev Neuropsychol 2006;29:479–491.