Adiposity, Change in Adiposity, and Cognitive Decline in Mid- and Late-Life

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Abstract

OBJECTIVES—To examine associations of adiposity and adiposity change (loss, stable, gain) with subsequent longitudinal cognitive performance among African Americans in mid- and late-life.

DESIGN—Cohort study using linear mixed models.

SETTING—Genetic Epidemiology Network of Arteriopathy

PARTICIPANTS—African American hypertensive sibships (n=1108) in Jackson, Mississippi.

MEASUREMENTS—Waist circumference and body mass index (BMI) were measured at two exams, five years apart. Stable adiposity was defined as values within ±5% of the first measure. A

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composite cognitive Z-score was derived from individual cognitive test Z-scores at two study visits, six years apart.

RESULTS—Higher waist circumference was associated with a greater rate of cognitive decline during follow-up (beta= −0.0009 per year, p=0.001); neither BMI, change in waist circumference, nor change in BMI was associated with rate of decline. Loss of adiposity in mid-life was associated with a higher cognitive Z-score among the middle-aged, while loss of adiposity in late-life was associated with a lower Z-score among the older adults (p=0.01 for waist circumference-x-age group interaction and p=0.04 for BMI-x-age group interaction). Simultaneous inclusion of waist circumference and BMI measures in the cross-sectional model suggests an association between higher waist circumference and poorer cognitive performance (beta= −0.009; p=0.006) and between higher BMI and better cognitive performance (beta= 0.014; p=0.06).

CONCLUSION—Results suggest a differential pattern of the adiposity-cognition relationship by age (mid- or late-life) and regional distribution of adiposity.

Keywords

body mass index; waist circumference; cognitive decline; ethnicity; longitudinal

INTRODUCTION

Obesity is an emerging but complex factor associated with cognitive decline and dementia. Accumulating evidence from epidemiological studies suggests a link between increased adiposity at mid-life and dementia (1). In contrast, elevated body mass index (BMI) measured in late-life has been associated with reduced dementia risk (2–4). A well-known prodromal weight loss phenomenon preceding a diagnosis of dementia (5) suggests that the timing of adiposity measures during the lifecourse complicates the relationship between adiposity and cognitive decline.

Another important consideration in the relationship between body adiposity and cognitive decline is the regional distribution of adiposity, such as central versus overall adiposity. Increasing evidence suggests that waist circumference, a measure of central adiposity, better estimates risk of obesity-related disease than measures of overall adiposity such as BMI (6).

African Americans are disproportionately affected by both obesity and late-onset dementia (7, 8). Despite the higher prevalence of dementia and obesity in this race/ethnic population, few studies of adiposity and dementia have included substantial numbers of African Americans.

The likely modification of obesity and dementia risk by age, the potential divergent relationships of waist circumference and BMI, and the increased risk of dementia and greater prevalence of obesity among African Americans highlight the need for longitudinal studies of adiposity and cognitive function among African Americans across the adult life span. The aim of this study was to investigate the relationship of central and overall adiposity as well as longitudinal changes in adiposity to cognitive decline in African American adults in mid- and late-life.

METHODS

Study Population

Data are from the African American cohort of the Genetic Epidemiology Network of Arteriopathy (GENOA) study, a community-based study of hypertensive sibships; although whites were recruited in GENOA, they were not offered repeat measures of cognition so cognitive decline was not available. The GENOA study enrolled hypertensive African Americans and their siblings from Jackson, Mississippi between 1997 and 1999 (Visit 1). At least two siblings were required to have essential hypertension before age 60 years; non-hypertensive siblings were also invited to participate. Detailed neurocognitive testing was conducted on the cohort concurrent with and shortly after GENOA Visit 2 (2001–2006) and repeated in 2009 to 2011 (Visit 3).

Adiposity measurements for this analysis were obtained at Visit 1 and Visit 2. Cognitive function tests were obtained at Visit 2 and Visit 3, such that the first cognitive exam coincided with the second adiposity measure. All measures used standardized protocols. Of the 1482 African American participants enrolled at Visit 2 in GENOA, 292 were missing cognitive test results at both time-points, 40 were missing adiposity measures at Visit 2, and 31 were younger than age 35. To reduce possible measurement error, we further excluded 11 outliers with waist circumference measurements < 70 or > 150 cm, resulting in 1,108 for the analytic cohort. The study protocol was approved by the human studies Institutional Review Board at the University of Mississippi Medical Center. All participants provided informed consent.

Cognitive Outcomes

Neurocognitive tests were offered to all participants and were administered in the same sequence using standardized protocols. The test battery assessed global mental status and 4 cognitive domains: memory, language, processing speed, and executive function. The Mini-Mental State Examination was used to assess global cognitive function (9). Processing speed was measured by the Wechsler Adult Intelligence Scale Revised Digit Symbol Substitution Task (10) and the Trail Making Test A (11). The Rey Auditory Verbal Learning Test assessed memory utilizing multiple learning trials of a 15-item word list followed by 30-minute delayed recall of the word list (11). Language was measured by the Word Fluency Test (letters F, A, and S) and the Animal Naming Task (11, 12). The Trail Making Test B test was administered to measure executive function using time and error counts (11). For Trails A and B, because higher (slower) times indicate poorer performance, times were multiplied by −1 for analyses so that higher numbers represented better performance in all measures.

A composite measure was created by converting each individual test within a domain into a Z-score using the mean and standard deviation from the baseline cognitive evaluation of all participants, then averaging the Z-scores as previously described (13–15). The composite global cognitive Z-score was calculated by averaging the Z-scores of each cognitive domain, and then standardizing using the global Z mean and global Z standard deviation from Visit 2. Thus, a global cognitive Z-score of −1 would describe cognitive performance that is 1 standard deviation below the global cognitive Z mean score at Visit 2.

Measures of Adiposity

Standardized protocols for adiposity measurements were followed at Visits 1 and 2. Height was measured by stadiometer and weight by electronic balance. BMI was calculated as weight (kilograms)/height^2 (meters). Waist circumference was measured to the nearest 0.1 centimeter at the umbilicus on the skin or lightweight, non-constricting underwear at the end of exhalation. The tape measure was held horizontal to the floor. A full-length mirror was used to verify the participant was standing erect, tape was horizontal, and weight was equally distributed on both feet.

Waist circumference was analyzed as a continuous variable as well as a categorical variable; with tertiles categorized as 70.0–96.7 cm, 96.7–107.7 cm, and 107.7–150.0 cm.

Change in BMI and change in waist circumference were calculated as difference scores (Visit 2 measure minus Visit 1 measure) and then categorized into three adiposity change groups: lost 5% of their initial adiposity measure, gained 5% of their initial measurement, or remained stable (lost or gained less than 5% of their initial measurement).

Covariates

All covariates were assessed at Visit 2. Age was categorized into two groups to distinguish between mid-life (ages 35–60 years) and late-life (ages 60+ years). Education was categorized as less than high school, high school, some college, or at least a college degree. Blood pressure, measured three times in a seated, rested state with appropriately sized cuffs, was defined as the average of the 2nd and 3rd measurements. A diagnosis of diabetes was self-reported. History of stroke was self-reported. 'Ever' smoked was defined as having smoked more than 100 cigarettes during lifetime.

Statistical Analysis

Linear mixed models with random intercepts were used to examine the association of Visit 2 adiposity or adiposity change with longitudinal cognitive performance. The linear mixed model accounts for correlation between multiple visits and between sibships. Separate models were fit for waist circumference, BMI, change in waist circumference, and change in BMI. We included a two-way interaction term (adiposity-by-age group) in each model to examine differences in cognitive performance associated with adiposity in mid-life compared to late-life. After stratifying the models by age group, we also fit each model with a two-way interaction term (adiposity-by-time) to determine if the rate of cognitive decline differed among the adiposity groups. Models were adjusted for baseline age (continuous), education, sex, duration of time between the measures of adiposity, and the duration of time between cognitive testing. In a second model, we further adjusted for baseline systolic blood pressure, diabetes status, history of stroke, and smoking status which may be mediators between adiposity and cognitive performance.

RESULTS

Participant characteristics for the analytic sample at Visit 2 (the first cognitive exam) and by age group (mid- or late-life) are shown in Table 1. The age range was 35–86 years (mean=58

years). Participants were predominantly women (71%), had limited to intermediate education (68% had a high school degree or less), were obese (mean BMI = 31.3), and, by study design, predominantly hypertensive (73%). There was an average of 5.1 years between adiposity measures and an average of 6.2 years between cognitive measures. Compared to mid-life participants, late-life participants had less education, smaller BMI, larger waist circumference, higher systolic blood pressure, greater prevalence of hypertension, lower baseline Mini-Mental State Examination scores, and a shorter duration between the study visits. Late-life individuals were also less likely to have gained >5% of their initial waist circumference or BMI. There were no significant differences between the mid- and late-life participants in sex distribution, smoking status, diabetes or stroke prevalence. The rate of cognitive decline in late-life was significantly greater than the rate in mid-life (0.08 SD vs 0.06 SD per year, p=0.002).

Waist circumference

Higher waist circumference at Visit 2 was associated with a greater rate of cognitive decline during follow-up (beta= −0.0009 per year, p=0.001) for all participants (mid- and late-life combined). The test of the interaction term between age group and waist circumference yielded p=0.87, suggesting no modification of this association by age. Persons in the lowest waist circumference tertile had slower rates of decline compared to persons in the middle or highest tertiles (Figure 1, low vs high tertile: beta= 0.026, p=0.001; low vs middle tertile: beta= 0.025, p=0.002; middle vs high tertile: beta= 0.001, p=0.88). These results were essentially unchanged after further adjustment for systolic blood pressure, diabetes status, history of stroke, and smoking history (data not shown).

Among the waist circumference change groups (lost, stable, or gained), the rate of cognitive decline was not significantly different in either mid- or late-life (p > 0.10 for each change group-by-time interaction term). The test of the interaction term between age group and waist circumference change group yielded beta= 0.17 and p= 0.01 suggesting that loss of waist circumference in mid-life was associated with a higher Z-score among the middle-aged, while loss of waist circumference in late-life was associated with a lower Z-score among the older adults (Table 2). During mid-life, the test for trend of decreasing cognitive Z-scores across the ordered levels of lost, stable, and gain in waist circumference yielded p=0.08. The test for trend of increasing cognitive Z-scores across the ordered change groups in late-life yielded p=0.13. Pairwise comparisons between the waist circumference change groups showed no significant differences in mid-life. In late-life, significantly lower cognitive Z-scores were observed among the loss group compared to the stable group (difference in Z-scores= −0.18, p= 0.05) and in the loss group compared to the gain group (difference in Z-scores= −0.21, p= 0.04).

Body mass index

BMI at Visit 2 was not significantly associated with rate of cognitive decline in mid- or late-life (BMI-by-time interaction: p>0.10 in both mid- and late-life). The BMI change group-by-age group interaction yielded beta=0.17 and p=0.04 suggesting that loss of BMI in mid-life was associated with a higher Z-score among the middle-aged, while loss of BMI in late-life was associated with a lower Z-score among the older adults (Table 2). During mid-life,

the test for trend of decreasing cognitive Z-scores across the ordered levels of loss, stable, and gain in BMI yielded p=0.11. The test for trend of increasing cognitive Z-scores across the ordered change groups in late-life yielded p=0.14. Pairwise comparisons between the BMI change groups in mid-life showed a significantly higher mean Z-score among the stable BMI group compared to the gain group (difference in Z-scores = 0.13; p=0.05). In late-life, significantly lower cognitive Z-scores were observed among the BMI loss group compared to the stable group (difference in Z-scores= −0.36, p<0.001) and moderately lower Z-scores among the loss group compared to the gain group (difference in Z-scores= −0.24, p=0.06).

Joint associations of waist circumference and body mass index

In another set of analyses, both the waist circumference and BMI variables (obtained at Visit 2) were simultaneously included in the model to examine associations of abdominal obesity with cognitive performance while accounting for overall obesity. Table 3 shows a significant inverse relationship between waist circumference and baseline cognitive Z-score at mid-life, at late-life, and among the combined age groups after adjustment for BMI. In contrast, there was a weak positive association with BMI and baseline cognitive Z-score after adjustment for waist circumference.

DISCUSSION

Results from this population-based study of African Americans with prevalent cardiovascular risk factors suggest the following three key findings: First, higher central adiposity in mid- or late-life was associated with a significantly greater rate of cognitive decline; neither overall adiposity nor changes in central or overall adiposity were associated with the rate of decline. Second, change in adiposity (loss, stable, or gain) showed divergent relationships with cognitive performance in mid-life vs late-life such that loss (gain) of adiposity in mid-life was associated with a higher (lower) cognitive Z-score among the middle-aged, while loss (gain) of adiposity in late-life was associated with a lower (higher) Z-score among the older adults. Third, cross-sectional analysis suggested that central and overall adiposity had independent and divergent relationships with cognitive performance. Simultaneous inclusion of waist circumference and BMI measures in our model suggests an association of higher waist circumference with significantly poorer baseline cognitive performance, while those with higher BMI had better baseline cognitive performance. The combination of waist circumference and BMI might be more predictive of cognitive performance than either measure alone.

Studies of adiposity with cognitive outcomes in African Americans are limited and have primarily focused on overall adiposity in late-life, finding higher risk for dementia with losses in adiposity (16, 17). This is in agreement with our results and with the well-known prodromal weight loss phenomenon that precedes a diagnosis of dementia (5, 18). We expand upon existing studies by contrasting relationships of overall and central adiposity and investigating changes in adiposity as well as the joint associations of overall and central adiposity with cognitive performance in mid- and late-life. The importance of these results is accentuated by the relatively short follow-up period for cognitive decline, especially among

our middle-aged subcohort, as longer periods of follow-up are often required during younger ages to detect relationships with cognitive decline.

Our findings that central adiposity is associated with risk of subsequent cognitive decline is in agreement with extant literature (19–21). A potential explanation for more robust associations of central compared to overall adiposity with cognitive decline include a greater relevance of central adiposity to stroke, diabetes, and cardiovascular disease (22), which may lie on the causal pathway between obesity and cognitive decline. However, our adjustment for systolic blood pressure, diabetes, and stroke did not substantially abate the association between central adiposity and cognitive decline, suggesting that something inherent to central adiposity may increase the risk of cognitive decline. Adiposity and the trajectory of adiposity over the life course have been associated with brain atrophy, white matter changes, and blood brain barrier integrity, which in turn, have been associated with increased risk of cognitive decline and late-onset dementia (23–27). Other proposed candidate mediators that link adiposity and dementia are inflammatory markers and adipokines. Inflammatory markers are closely linked with adiposity and adipokines (28, 29) and are associated with poorer cognitive function (30–35). This requires further study, particular in African Americans who are reported to have more adverse adipokineprofiles than whites despite having similar adiposity levels (36).

Our finding of no difference in cognitive performance between individuals in late-life who gained adiposity or whose adiposity remained stable is in in agreement with the Women's Health Initiative Study of Cognitive Aging, which also reported no difference between weight and waist circumference gain and stable groups and subsequent mean levels of global or domain-specific cognitive performance during follow-up among older women (37). One explanation could be that higher central adiposity poses persisting risk for poorer cognition regardless of additional changes in central adiposity. Additionally, the follow-up period may have been too short to observe substantial cognitive change.

Fewer studies have reported on the joint effects of central and overall adiposity on cognitive function or decline. Our findings show a positive association of overall adiposity and, simultaneously, a negative association of central adiposity with baseline cognitive performance in both mid- and late-life. This result suggests that the combination of BMI and waist circumference might be more predictive of cognitive performance than either measure alone. Similar results were reported for a cohort of older Mexican-Americans in a longitudinal study of cognitive impairment (20) and in the Women's Health Initiative Memory Study where central adiposity, defined by waist-to-hip ratio, was associated with greater risk of cognitive impairment among normal-weight or overweight but not obese postmenopausal women (38).

This study has several strengths including longitudinal assessments of cognitive performance and adiposity and the ascertainment of two clinically available measures of adiposity, waist circumference and BMI, in African Americans, a group disproportionately burdened by dementia. Many participants also had cardiovascular risk factors associated with risk of dementia and cognitive decline; this may have enabled detection of relationships even in middle-age. Cognitive performance was evaluated with a standard battery of cognitive tests

across several domains. Potentially confounding and possible mediators were considered in the analyses.

A limitation of this study is that cognitive function was not an initial focus of the GENOA study and currently lacks adjudication of dementia, which restricts interpretations of these findings to cognitive function and cognitive decline as outcomes. Regardless, cognitive decline is a risk factor for incident dementia (39) and a required component of the dementia syndrome (40). We were also unable to differentiate lean and fat components of the anthropometric measurements. The relation of anthropometric measures to cognitive function in mid- and late-life may also be confounded by cancer, HIV, menopausal status (among women) and other conditions that can cause significant weight fluctuations. We had insufficient data to explore the relationships between these conditions, weight change, and cognitive decline. As such, residual confounding may have affected our study results. Additionally, we were only able to measure weight and weight change during mid- and late-life; thus, our results may not be generalizable to adiposity and adiposity change during childhood or early adulthood. Further, because the study population is African American and primarily hypertensive, these findings may not be generalizable to other populations. However, the number of African Americans in the US is projected to increase by over 40% in the next few decades with similar or larger increases in other non-white race/ethnic groups (41), many of whom are at increased risk for dementia (8) and hypertension (42). Therefore these findings could have major public health relevance at the population level. The observational design prohibits causal inferences.

In summary, higher waist circumference, but not BMI, was associated with a faster rate of cognitive decline during both mid- and late-life, even over a relatively brief follow-up period. Loss or gain in adiposity showed divergent relationships with cognitive performance in mid-life vs late-life.

Acknowledgments

REFERENCES

1. Emmerzaal TL, Kiliaan AJ, Gustafson DR. 2003–2013: a decade of body mass index, Alzheimer's disease, and dementia. Journal of Alzheimer's disease : JAD. 2015; 43(3):739–755. [PubMed: 25147111]

2. 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. Journal of the American Geriatrics Society. 2008; 56(1):111–116. [PubMed: 18028342]

3. Luchsinger JA, Patel B, Tang MX, et al. Measures of adiposity and dementia risk in elderly persons. Arch Neurol. 2007; 64(3):392–398. [PubMed: 17353383]

4. Power BD, Alfonso H, Flicker L, et al. Body adiposity in later life and the incidence of dementia: the health in men study. PloS one. 2011; 6(3):e17902. [PubMed: 21464984]

5. Stewart R, Masaki K, Xue Q-L, et al. A 32-year prospective study of change in body weight and incident dementia: The Honolulu-Asia Aging Study. Arch Neurol. 2005; 62(1):55–60. [PubMed: 15642850]

6. Pi-Sunyer, F., Becker, D., Bouchard, C., et al. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. The National Institutes of Health; 1998.

7. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA : the journal of the American Medical Association. 2010; 303(3):235–241. [PubMed: 20071471]

8. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007; 29(1–2):125–132. [PubMed: 17975326]

9. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198. [PubMed: 1202204]

10. Lezak MD. Orientation and attention. Neuropsychological Assessment: Third Edition (Third). 1995

11. Spreen, O., Strauss, E. A compendium of neuropsychological tests: administration, norms, and commentary. 2nd. Vol. xvi. New York: Oxford University Press; 1998. p. 736

12. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989; 39(9):1159–1165. [PubMed: 2771064]

13. Chibnik LB, Shulman JM, Leurgans SE, et al. CR1 is associated with amyloid plaque burden and age-related cognitive decline. Annals of neurology. 2011; 69(3):560–569. [PubMed: 21391232]

14. Massaro JM, D'Agostino RB Sr, Sullivan LM, et al. Managing and analysing data from a large-scale study on Framingham Offspring relating brain structure to cognitive function. Statistics in medicine. 2004; 23(2):351–367. [PubMed: 14716734]

15. Wilson RS, Beckett LA, Barnes LL, et al. Individual differences in rates of change in cognitive abilities of older persons. Psychology and aging. 2002; 17(2):179–193. [PubMed: 12061405]

16. Gao S, Nguyen JT, Hendrie HC, et al. Accelerated weight loss and incident dementia in an elderly African-American cohort. Journal of the American Geriatrics Society. 2011; 59(1):18–25. [PubMed: 21054328]

17. Liu H, Gao S, Hall KS, et al. Optimal blood pressure for cognitive function: findings from an elderly African-American cohort study. Journal of the American Geriatrics Society. 2013; 61(6): 875–881. [PubMed: 23647314]

18. 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(10): 1147–1152. [PubMed: 8855991]

19. Gustafson DR, Backman K, Waern M, et al. Adiposity indicators and dementia over 32 years in Sweden. Neurology. 2009; 73(19):1559–1566. [PubMed: 19901247]

20. West NA, Haan MN. Body adiposity in late life and risk of dementia or cognitive impairment in a longitudinal community-based study. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2009; 64A(1):103–109.

21. Whitmer RA, Gustafson DR, Barrett-Connor E, et al. Central obesity and increased risk of dementia more than three decades later. Neurology. 2008; 71(14):1057–1064. [PubMed: 18367704]

22. Balkau B, Deanfield JE, Despres JP, et al. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. Circulation. 2007; 116(17):1942–1951. [PubMed: 17965405]

23. Debette S, Beiser A, Hoffmann U, et al. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Annals of neurology. 2010; 68(2):136–144. [PubMed: 20695006]

24. Ho AJ, Raji CA, Becker JT, et al. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiology of Aging. 2010; 31(8):1326–1339. [PubMed: 20570405]

25. Isaac V, Sim S, Zheng H, et al. Adverse associations between visceral adiposity, brain structure and cognitive performance in healthy elderly. Frontiers in Aging Neuroscience. 2011; 3

26. Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. Arch Neurol. 2005; 62(10):1545–1548. [PubMed: 16216937]

27. Ward M, Carlsson C, Trivedi M, et al. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurology. 2005; 5(1):23. [PubMed: 16321166]

28. Barinas-Mitchell E, Kuller LH, Sutton-Tyrrell K, et al. Effect of weight loss and nutritional intervention on arterial stiffness in type 2 diabetes. Diabetes Care. 2006; 29(10):2218–2222. [PubMed: 17003296]

29. Goldberg Y, Boaz M, Matas Z, et al. Weight loss induced by nutritional and exercise intervention decreases arterial stiffness in obese subjects. Clinical Nutrition. 2009; 28(1):21–25. [PubMed: 19019502]

30. Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam Study. Arch Neurol. 2004; 61(5):668–672. [PubMed: 15148142]

31. Galimberti D, Fenoglio C, Lovati C, et al. Serum MCP-1 levels are increased in mild cognitive impairment and mild Alzheimer's disease. Neurobiol Aging. 2006; 27(12):1763–1768. [PubMed: 16307829]

32. Ravaglia G, Forti P, Maioli F, et al. Blood inflammatory markers and risk of dementia: The Conselice Study of Brain Aging. Neurobiol Aging. 2007; 28(12):1810–1820. [PubMed: 17011077]

33. Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Annals of neurology. 2002; 52(2):168–174. [PubMed: 12210786]

34. Trollor JN, Smith E, Baune BT, et al. Systemic inflammation is associated with MCI and its subtypes: the Sydney Memory and Aging Study. Dementia and geriatric cognitive disorders. 2010; 30(6):569–578. [PubMed: 21252552]

35. Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003; 61(1):76–80. [PubMed: 12847160]

36. Degawa-Yamauchi M, Dilts JR, Bovenkerk JE, et al. Lower serum adiponectin levels in African-American boys. Obesity research. 2003; 11(11):1384–1390. [PubMed: 14627760]

37. Driscoll I, Espeland MA, Wassertheil-Smoller S, et al. Weight change and cognitive function: Findings from the Women's Health Initiative Study of Cognitive Aging. Obesity. 2011; 19(8): 1595–1600. [PubMed: 21394095]

38. Kerwin DR, Gaussoin SA, Chlebowski RT, et al. Interaction between body mass index and central adiposity and risk of incident cognitive impairment and dementia: Results from the Women's Health Initiative Memory Study. Journal of the American Geriatrics Society. 2011; 59(1):107–112. [PubMed: 21226681]

39. Tifratene K, Robert P, Metelkina A, et al. Progression of mild cognitive impairment to dementia due to AD in clinical settings. Neurology. 2015; 85(4):331–338. [PubMed: 26136516]

40. American Psychiatric Association., American Psychiatric Association. Diagnostic and statistical manual of mental disorders : DSM-5. 5th. Vol. xliv. Washington, D.C.: American Psychiatric Association; 2013. DSM-5 Task Force; p. 947

41. Colby, SL., Ortman, JM. Projections of the Size and Composition of the U.S. Population: 2014 to 2060. Washington, DC: U.S. Census Bureau; 2015.

42. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association. Circulation. 2015; 131(4):e29–e322. [PubMed: 25520374]
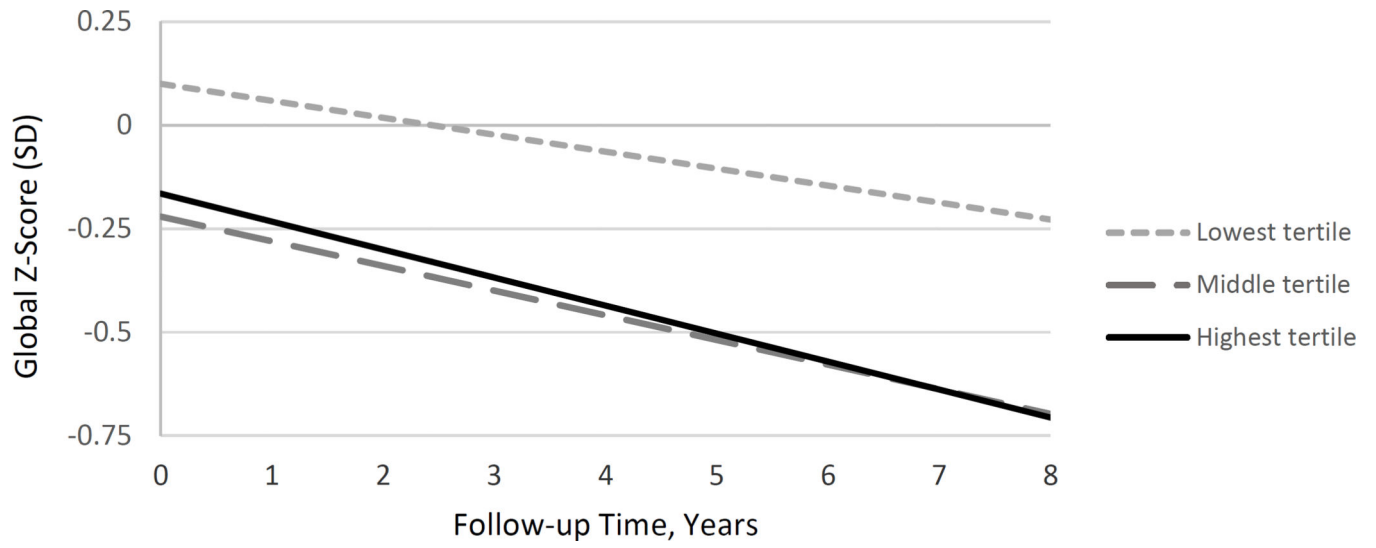
Figure 1.
Decline in cognitive Z-score by waist circumference tertile, adjusted for age, sex, and education.

Table 1

Characteristics of study participants at the baseline cognitive exam (Visit 2) by age group (mid-life = 35–60 years and late-life = 60+ years).

Characteristic	Total (N=1108)	Mid-life (N=653)	Late-life (N=455)	P
Age, years	57.9 (9.0)	52.1 (6.1)	66.3 (4.7)	<0.001
Female, n (%)	888 (71%)	470 (72%)	318 (70%)	0.45
Education level, n (%)				<0.001
No high school	358 (37%)	137 (25%)	221 (53%)	
High school	305 (31%)	213 (38%)	92 (22%)	
Some college	28 (3%)	17 (3%)	11 (3%)	
College degree +	280 (29%)	187 (34%)	93 (22%)	
Waist circumference, cm, median (IQR)	101.9 (17.8)	101.2 (18.2)	103.0 (16.9)	0.05
Change in waist circumference				0.02
Lost 5%	213 (19%)	114 (17%)	99 (22%)	
Stable Gained 5%	546 (49%)	319 (49%)	227 (50%)	
	349 (32%)	220 (34%)	129 (28%)	
Body mass index, kg/m^2, median (IQR)	30.6 (7.7)	30.8 (8.0)	30.0 (7.5)	0.04
Change in BMI				<0.001
Lost 5%	127 (11%)	65 (10%)	62 (14%)	
Stable	688 (62%)	379 (58%)	309 (68%)	
Gained 5%	293 (26%)	209 (32%)	84 (18%)	
Weight, kg	88.8 (17.6)	90.5 (18.2)	86.5 (16.4)	<0.001
Weight change/year, kg	0.2 (1.0)	0.3 (1.0)	0.0 (1.1)	<0.001
Ever smoked, n (%)	436 (39.8%)	265 (41.2%)	171 (37.8%)	0.27
Systolic blood pressure, mmHg	134 (22)	131 (20)	138 (23)	<0.001
Hypertension, n (%)	808 (73%)	425 (68%)	363 (80%)	<0.001
Diabetes, n (%)	297 (27%)	176 (27%)	121 (27%)	0.89
Stroke, n (%)	54 (5%)	28 (4%)	26 (6%)	0.28
Time between adiposity measures, years	5.1 (1.3)	5.6 (1.1)	4.4 (1.2)	<0.001
Time between cognitive tests, years	6.2 (1.2)	6.4 (0.9)	5.9 (1.5)	<0.001
MMSE score	27.0 (2.5)	27.5 (2.1)	26.2 (2.9)	<0.001

Data are means (standard deviation) unless otherwise stated.

MMSE: Mini Mental State Examination

Table 2

Associations between adiposity change groups (loss, stable, or gain) and their subsequent mean cognitive Z-scores in mid- and late-life.

Change group	Mean Z-score* (95% CI)	Pairwise comparison	Difference in Z-scores between groups* (95% CI)	p
Waist Circumference in Mid-life				
Loss (n=114)	−0.15 (−0.32, 0.02)	Loss vs stable	0.04 (−0.14, 0.21)	0.67
Stable (n=319)	−0.19 (−0.30, −0.07)	Loss vs gain	0.12 (−0.06, 0.31)	0.20
Gain (n=220)	−0.27 (−0.40, −0.14)	Stable vs gain	0.08 (−0.05, 0.22)	0.23
P for trend	0.08			
Waist Circumference in Late-life				
Loss (n=99)	−0.35 (−0.52, −0.17)	Loss vs stable	−0.18 (−0.36, 0.0009)	0.05
Stable (n=227)	−0.16 (−0.30, −0.03)	Loss vs gain	−0.21 (−0.42, −0.01)	0.04
Gain (n=129)	−0.13 (−0.29, 0.03)	Stable vs gain	−0.03 (−0.20, 0.14)	0.71
P for trend	0.13			
Body Mass Index in Mid-life				
Loss (n=65)	−0.18 (−0.38, 0.03)	Loss vs stable	−0.01 (−0.22, 0.20)	0.92
Stable (n=379)	−0.17 (−0.27, −0.06)	Loss vs gain	0.12 (−0.10, 0.35)	0.27
Gain (n=209)	−0.30 (−0.44, −0.16)	Stable vs gain	0.13 (−0.00, 0.27)	0.05
P for trend	0.11			
Body Mass Index in Late-life				
Loss (n=62)	−0.47 (−0.68, −0.27)	Loss vs stable	−0.36 (−0.57, −0.16)	<0.001
Stable (n=309)	−0.11 (−0.23, 0.01)	Loss vs gain	−0.24 (−0.49, 0.01)	0.06
Gain (n=84)	−0.24 (−0.42, −0.05)	Stable vs gain	0.13 (−0.06, 0.31)	0.18
P for trend	0.14			

*
Adjusted for baseline age (continuous), sex, education, time between cognitive tests, and time between adiposity measures.

Table 3

The association of adiposity measures with baseline global cognitive Z-score in mid-life, late-life, and combined age groups.

Model term[*]	Mid-life	Late-life	Combined age groups
	beta (SE); *p*	beta (SE); *p*	beta (SE); *p*
Model 1			
Waist circumference, cm	−0.004 (0.002); 0.08	−0.004 (0.003); 0.20	−0.004 (0.002); 0.03
Model 2			
Body mass index, kg/m^2	−0.004 (0.005); 0.47	−0.002 (0.007); 0.81	−0.004 (0.004); 0.40
Model 3			
Waist circumference, cm	−0.010 (0.005); p=0.03	−0.010 (0.005); p=0.06	−0.009 (0.003); p=0.006
Body mass index, kg/m^2	0.014 (0.010); p=0.15	0.017 (0.013); p=0.17	0.014 (0.008); p=0.06
Model 4			
Waist circumference, cm	−0.008 (0.005); p=0.07	−0.010 (0.005); p=0.06	−0.009 (0.003); p=0.008
Body mass index, kg/m^2	0.014 (0.010); p=0.17	0.020 (0.013); p=0.11	0.016 (0.008); p=0.04

[*] Model 1: waist circumference only, with adjustment for age, education, and sex

Model 2: body mass index only, with adjustment for age, education, and sex

Model 3: both waist circumference and body mass index, with adjustment for age, education, and sex

Model 4: model 3 plus systolic blood pressure, diabetes, stroke, and smoking status