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Research Article

Obesity and Structural Brain Integrity in Older Women: The Women's Health Initiative Magnetic Resonance Imaging Study

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Abstract

Background: Midlife obesity has been linked to age-related brain atrophy and risk of dementia, but the relationships are less clear for older individuals. These associations may be explained by changes in appetite or metabolism in the dementia prodrome; thus, prospective studies with adequate follow-up are needed. We examined the associations that obesity (body mass index, BMI) and change in BMI over an average of 6.6 (1.0–9.1) years have with global and regional brain and white matter lesion volumes in a sample of 1,366 women aged 65–80.
Methods: Least square means for regional brain volumes and white matter lesion loads for women grouped by BMI and changes in BMI were generated from multivariable linear models with and without adjustment for demographic and health covariates.
Results: Both global obesity and increase in BMI were associated with lower cerebrospinal fluid and higher specific brain volumes ($ps < .05$), after controlling for diabetes and other cerebrovascular disease risk factors. Obesity, but not change in BMI, predicted lower lesion loads for the total, parietal, and occipital white matter ($ps < .05$).
Conclusions: Obesity in this cohort is associated with less brain atrophy and lower ischemic lesion loads. The findings are consistent with our previous report of worse cognitive performance in association with weight loss (probably not due to frailty) in this cohort and in line with the idea of the "obesity paradox" as differences in dementia risk vary across time, whereby midlife obesity seems to be a predictor of dementia, whereas weight loss seems to be a better predictor at older ages.

Keywords: Brain volume—Lesion volume—White matter hyperintensities—Aging—BMI

Obesity is related to a variety of unfavorable health outcomes, including cardiovascular, pulmonary, and endocrine diseases (1). Accumulating evidence suggests that midlife obesity is associated with higher risk for dementia later in life (2–5), while studies exploring this association in the elderly remain conflicting (6–9). Obesity prevalence in the United States is currently higher than 30% and growing rapidly (10), especially in adults aged 50 or older (1). Given that the prevalence of both obesity (1) and dementia (10) are approaching epidemic proportions, the prevention of obesity may contribute to reduction of dementia burden and thereby have significant public health implications.

Both age and obesity have been linked to unfavorable structural brain changes. A certain amount of global and regionally specific brain atrophy is common even in normally aging adults (11,12). Obesity in its own right has been associated with such structural brain changes, including loss of global and regional brain volume

and white matter (WM) integrity (13–16). In parallel, white matter hyperintensities (WMH), visible on brain imaging scans of older individuals (17), are more common and extensive in patients with cardiovascular risk factors (18). Obesity is an independent risk factor associated with numerous indices of cardiovascular disease (CVD) (19). Evidence suggests a relatively greater burden of WMH in obese older adults (17); however, studies of WMH in obesity are limited.

Examinations of the effects of obesity on brain morphology are also limited in number. In addition, cross-sectional studies in older adults may be misleading because loss of appetite and hyperphagia are common in the dementia prodrome. Therefore, studies in which adiposity parameters are obtained early in the follow-up and over time are necessary to clarify the relationships between obesity and structural brain aging. The Women's Health Initiative Memory Study (WHIMS)-MRI (12,20) offers an unprecedented opportunity to examine these relationships in a large and well-defined cohort. We ask whether either global obesity (body mass index, BMI) or change in BMI is associated with specific global and regional brain or lesion volumes, with and without adjustment for demographic and health factors.

Materials and Methods

Participants

We analyzed data from 1,366 women, 65–80 years of age, who were enrolled between January 2005 and April 2006 in WHIMS-MRI, which was designed to contrast MRI outcomes among women who had been assigned to active versus placebo hormone therapy (HT) during the WHIMS trials in 14 of its sites (20). Women were free of dementia at enrollment based on the ascertainment of probable dementia and cognitive impairment. A detailed description of the four-phase protocol for detecting probable dementia and cognitive impairment has been previously published (20,21). MRI scans were obtained, on average, 8.02 (Conjugate Equine Estrogens (CEE) + Medroxyprogesterone Acetate (MPA) arm of the trial) or 7.97 (CEE-alone arm of the trial) years following randomization and 3.0 (CEE + MPA) or 1.4 (CEE-alone) years following termination of HT. WHIMS-MRI also obtained measurements of subclinical CVD (22). Studies were approved by the National Institutes of Health and Institutional Review Boards of participating institutions. All participants provided written informed consent.

MRI Protocol

The MRI acquisition and image processing protocols were developed, standardized and validated by the investigators at the MRI Quality Control Center, Department of Radiology at the University of Pennsylvania and implemented centrally (22–25). Scanning sequences were performed with a FOV = 22 cm and matrix size of 256 × 256 as follows: (i) 3D-plane gradient echo localizer; (ii) sagittal T1-weighted spin echo mid-slice image to obtain the anatomic location of the AC/PC for slice angle and slice positioning; (iii) oblique axial spin density/T2-weighted spin echo images (TR = 3,200 ms, TE = 30/120 ms, slice thickness = 3 mm); (iv) oblique axial fluid attenuation inversion recovery (FLAIR) T2-weighted spin echo images (TR = 8,000 ms, TI = 2,000 ms, TE = 100 ms, slice thickness = 3 mm); and (v) axial 3D spoiled gradient recalled T1-weighted gradient echo images parallel to the AC/PC plane (TR = 21 ms, TE = 8 ms, flip angle = 30, slice thickness = 1.5 mm).

T1-weighted images underwent preprocessing to a standardized protocol for alignment, removal of extracranial material, and segmentation of tissue into white and gray parenchyma and cerebrospinal fluid (CSF). An automated computer-based template warping method, which sums the number of voxels within each anatomical region of interest, provided regional volumes. Intracranial volume was defined as total cerebral volume plus ventricular CSF. The ischemic lesion segmentation algorithm was applied following additional preprocessing, including standardization and coregistration, based on local signal features extracted from coregistered multiparametric MRI sequences. A trained support vector machine classifier was used to classify ischemic lesion volume generally corresponding to small vessel ischemic disease (SVID = ischemic WM disease and lacunar infarction) (12,22). SVID was operationally defined as nonmass lesions with FLAIR signal greater than that of normal gray matter (GM) in a vascular distribution. The automated method was validated against manual segmentation by an expert (22) and has been applied to other cohorts (23,24). Supratentorial tissue was then classified as normal or ischemic WM and assigned to one of 92 anatomical regions of interest (22).

Anthropometric Measurements

Weight to the nearest 0.1 kg and height to the nearest 0.1 cm were recorded annually with calibrated scales by trained technicians. BMI is defined as weight in kilograms divided by the square of height in meters. The baseline measurements were obtained at entry into the parent WHI study. Change in BMI was calculated at the last visit prior to MRI compared with baseline over an average of 6.6 (range 1.0–9.1) years.

Statistical Analysis

General linear models were used to examine bivariate relationships between BMI at the last visit prior to the MRI and age at MRI, education, race/ethnicity, hypertension, prior CVD, diabetes, if on a low calorie diet, and HT assignment. Due to their highly skewed distribution, lesion volumes were log transformed. Least square means for select regional brain and lesion load volumes for categories of BMI were generated from multivariable linear models controlling for intracranial volume, HT, race/ethnicity, education, alcohol use, prior use of HT, self-reported dieting at WHI baseline, hypertension, CVD history, diabetes, age at MRI, caloric intake at WHI baseline, and time from WHI enrollment to MRI. These same models were used for calculation of least square means for various regional brain or lesion load volumes and BMI percent change from baseline to visit prior to MRI.

Categories based on BMI included those with BMI less than 25 (<25), 25–29, 30–35, and higher than 35 (35+). Categories based on change in BMI from baseline included a group for which decrease in BMI was larger than 5% (decrease >5%), a group that remained largely stable (change between −5% and +5%), and a group for which BMI increased more than 5%. The regional volumes examined included whole brain, CSF, and volumes of total WM, total GM, frontal, temporal, parietal, and occipital WM or GM, respectively, basal ganglia, orbitofrontal cortex, cingulate gyrus, precuneus, and the hippocampus.

Results are reported as significant for regional brain volume associations if $p \leq .003$, and $p \leq .01$ for regional WM lesion volumes, after employing stringent Bonferroni corrections for multiple comparisons. Given that large effects of obesity on brain volume are not expected in healthy adult women, all results are reported in the tables in order to help guide future research, as many comparisons were significant at $p < .05$ but did not survive the more stringent corrections for multiple comparisons.

Results

The sample was predominantly Caucasian (91%) and women were between 70 and 89 years of age at the time of the MRI scan. Most women had either some college education or a college degree (72%); fewer than 5% had not completed high school. Most women (~87%) had no prior history of CVD or diabetes and were not on a low calorie diet. Sample characteristics are presented in Table 1. For analyses purposes, the sample was further separated into four groups based on baseline BMI and into three groups based on change in BMI from baseline. More participants in the obese and overweight groups were hypertensive and diabetic at follow-up ($p < .05$), and no such differences were observed between groupings based on change in BMI from baseline. There were no significant differences in global cognitive status or in depressive symptoms among any of the groups ($p > .05$).

Significant relationships between global obesity measured at the last visit prior to MRI and regional brain volumes after correcting for multiple comparisons were observed for the following (Table 2): whole brain ($p = .0004$), CSF ($p = .004$), total, frontal, and temporal WM ($ps < .003$), and the hippocampus ($p < .0001$), such that higher BMI was associated with higher volumes in these regions, with the exception that lower CSF volume was seen in the obese.

Significant relationships between change in BMI (from baseline to last visit prior to MRI) and brain volumes after corrections for multiple comparisons were observed only for women who experienced a BMI decrease of 5% or more from baseline for the following regions

Table 1. Characteristics of Women at WHI Enrollment or Last Visit Prior to MRI (Hypertension, CVD, and Diabetes) and Relationships With BMI at Last Visit Prior to MRI

		BMI	Weight Change
Variable	*N*	Mean (*SE*)	Mean (*SE*)
Age at MRI—years (missing = 11)			
70–75	388	29.08 (0.28)	−0.14 (0.41)
76–81	723	27.90 (0.19)	−1.33 (0.28)
82–89	255	27.09 (0.32)	−2.70 (0.62)
p value		<.0001	.0005
Education (missing = 11)			
<High school	61	29.54 (0.76)	1.13 (0.85)
High school/GED	316	28.56 (0.30)	−1.17 (0.35)
>High school < 4-year college	541	27.94 (0.21)	−1.34 (0.38)
>4-year college	448	27.72 (0.27)	−1.50 (0.41)
p value		.0223	.13
Ethnicity (missing = 11)			
American Indian/Alaskan native	4	31.15 (1.62)	−0.93 (1.70)
Asian/Pacific Islander	21	23.85 (0.94)	−0.29 (0.57)
Black/African American	63	30.28 (0.82)	2.16 (1.45)
Hispanic/Latino	20	30.63 (1.05)	−1.35 (1.64)
White, non-Hispanic	1,247	28.02 (0.15)	−1.44 (0.23)
Other	11	25.15 (1.19)	−0.73 (2.18)
p value		<.0001	.04
Hypertension (missing = 11)			
No	395	26.70 (0.23)	−0.95 (0.34)
Yes	971	28.64 (0.18)	−1.36 (0.28)
p value		<.0001	.40
Prior CVD (missing = 11)			
No	1,190	28.06 (0.16)	−1.20 (0.24)
Yes	176	28.20 (0.37)	−1.52 (0.49)
p value		.7544	.63
Diabetes (missing = 11)			
No	1,217	27.80 (0.15)	−1.24 (0.22)
Yes	149	30.40 (0.49)	−1.30 (0.99)
p value		<.0001	.93
Low calorie diet (missing = 11)			
No	1,236	27.93 (0.15)	−1.40 (0.23)
Yes	130	29.49 (0.52)	0.27 (0.80)
p value		.0015	.03
Intervention assignment (missing = 11)			
E-alone placebo	256	28.56 (0.34)	−1.25 (0.63)
E-alone HT	249	28.58 (0.34)	−2.61 (0.54)
E + P HT	428	27.92 (0.24)	−0.77 (0.36)
E + P placebo	433	27.67 (0.26)	−0.92 (0.35)
p value		.0661	.03

Notes: BMI = body mass index; CVD = cardiovascular disease; E = estrogen; E + P = estrogen + progesting; HT = hormone therapy; MRI = magnetic resonance imaging; *SE* = standard error; WHI = Women's Health Initiative.

(Table 3): temporal GM ($p < .05$), cingulate cortex ($p = .002$), and the hippocampus ($p = .0002$). There were no statistically significant associations between BMI and brain volume for those who maintained or gained weight ($ps > .05$). Moreover, those with relatively stable weight over follow-up (change between −5% and +5%) had the highest basal ganglia and total and regional GM volumes.

Lower regional lesion loads were observed in relation to global obesity only in parietal WM ($p = .01$; Table 4). Relationships between change in BMI from baseline (>5%) and regional lesion loads were largely absent (Table 5).

Discussion

The goal of the study was to determine whether there is a relationship between either global obesity or change in BMI during follow-up and either volumes of specific brain regions or regional lesion

Table 2. Relationships Between Regional Brain Volumes and BMI Measured at the Last Visit Prior to MRI, With Covariate Adjustment for ICV and the Risk Factors in Table 1

Region/Group by BMI	<25 (*N* = 427)	25–29 (*N* = 525)	30–34 (*N* = 298)	35+ (*N* = 142)	*p* Value
Whole brain volume	798.9 (5.1)	807.0 (4.9)	807.2 (5.2)	812.4 (5.7)	**.0004**
CSF	291.5 (5.1)	283.4 (4.9)	283.3 (5.2)	278.0 (5.7)	**.0004**
Total WM	415.1 (5.1)	420.6 (4.9)	422.7 (5.2)	430.5 (5.7)	**.0003**
Total GM	347.9 (4.8)	350.5 (4.7)	348.8 (4.9)	346.2 (5.7)	.50
Basal ganglia	383.8 (4.9)	386.4 (4.8)	384.5 (4.9)	381.9 (5.5)	.49
WM					
Frontal	**166.8 (2.3)**	**169.6 (2.3)**	**170.1 (2.4)**	**173.4 (2.6)**	**.001**
Temporal	**97.6 (1.3)**	**98.9 (1.3)**	**99.9 (1.4)**	**101.7 (1.5)**	**.0001**
Parietal	92.8 (1.3)	93.8 (1.3)	93.9 (1.3)	95.9 (1.5)	.01
Occipital	48.5 (1.0)	48.9 (1.0)	49.4 (1.0)	49.8 (1.2)	.25
GM					
Frontal	115.5 (1.9)	115.6 (1.9)	115.7 (1.9)	113.6 (2.1)	.46
Temporal	85.1 (1.3)	86.3 (1.3)	85.7 (1.3)	85.9 (1.5)	.28
Parietal	61.4 (1.2)	61.6 (1.1)	60.4 (1.2)	60.1 (1.3)	.12
Occipital	53.9 (0.8)	54.3 (0.8)	54.4 (0.8)	54.1 (0.9)	.72
Orbitofrontal cortex	20.4 (0.3)	20.6 (0.3)	20.6 (0.3)	20.3 (0.4)	.23
Cingulate gyrus	17.3 (0.4)	17.7 (0.4)	17.8 (0.4)	17.9 (0.4)	.01
Hippocampus	**5.9 (0.1)**	**6.1 (0.1)**	**6.2 (0.1)**	**6.3 (0.1)**	**<.0001**
Precuneus	3.6 (0.1)	3.7 (0.1)	3.7 (0.1)	3.7 (0.1)	.08

Notes: BMI = body mass index; CSF = cerebrospinal fluid; GM = gray matter; ICV = intracranial volume; MRI = magnetic resonance imaging; WM = white matter. Bold font indicates significant results after correcting for multiple comparisons.

Table 3. Relationships Between Regional Brain Volumes and % Change in BMI From Baseline to Last Visit Prior to MRI, With Covariate Adjustment for the Risk Factors in Table 1 and ICV

Region/Group by BMI % Change	Decrease > 5% (*N* = 376)	Change −5% and 5% (*N* = 745)	Increase > 5% (*N* = 282)	*p* Value
Whole brain	799.2 (5.1)	806.3 (4.9)	807.0 (5.1)	.005
CSF	291.2 (5.1)	284.1 (4.9)	283.4 (5.1)	.005
Total WM	418.9 (5.2)	418.7 (4.9)	423.2 (5.1)	.21
Total GM	344.9 (4.8)	351.9 (4.6)	347.7 (4.8)	.01
Basal ganglia	380.3 (4.9)	387.7 (4.7)	383.9 (4.9)	.004
WM				
Frontal	168.4 (2.4)	168.5 (2.3)	170.7 (2.3)	.12
Temporal	98.5 (1.4)	98.7 (1.3)	99.8 (1.3)	.17
Parietal	93.7 (1.3)	93.2 (1.3)	94.4 (1.3)	.22
Occipital	49.1 (1.0)	48.9 (0.9)	48.8 (1.0)	.92
GM				
Frontal	114.6 (1.9)	116.4 (1.8)	114.8 (1.9)	.06
Temporal	**84.4 (1.3)**	**86.5 (1.3)**	**85.6 (1.3)**	**.002**
Parietal	60.3 (1.2)	61.7 (1.1)	60.7 (1.2)	.02
Occipital	53.8 (0.8)	54.6 (0.8)	53.9 (0.8)	.07
Orbitofrontal cortex	20.3 (0.3)	20.7 (0.3)	20.5 (0.3)	.01
Cingulate gyrus	**17.2 (0.4)**	**17.7 (0.3)**	**17.8 (0.4)**	**.002**
Hippocampus	**5.9 (0.1)**	**6.1 (0.1)**	**6.2 (0.1)**	**.0002**
Precuneus	3.6 (0.1)	3.7 (0.1)	3.7 (0.1)	.01

Notes: BMI = body mass index; CSF = cerebrospinal fluid; GM = gray matter; ICV = intracranial volume; MRI = magnetic resonance imaging; WM = white matter. Bold font indicates significant results after correcting for multiple comparisons. Group differences are driven by those who lost 5% or more of their body weight; there were no significant differences between women who maintained or gained weight ($ps > .05$).

Table 4. Relationships Between Regional Lesion Loads and BMI Measured at the Last Visit Prior to MRI, With Covariate Adjustment for the Risk Factors in Table 1 and ICV

Region/Group by BMI	<25 (*N* = 427)	25–29 (*N* = 525)	30–34 (*N* = 298)	35+ (*N* = 142)	*p* Value
Total WM	5.1 (0.8)	4.8 (0.7)	4.2 (0.7)	3.8 (0.7)	.02
WM					
Frontal	2.3 (0.3)	2.2 (0.3)	1.9 (0.3)	1.9 (0.3)	.16
Temporal	1.2 (0.2)	1.1 (0.2)	0.9 (0.2)	0.9 (0.2)	.05
Parietal	1.4 (0.2)	1.4 (0.2)	1.1 (0.2)	0.9 (0.2)	.01
Occipital	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.3 (0.1)	.04

Notes: BMI = body mass index; ICV = intracranial volume; MRI = magnetic resonance imaging; WM = white matter.

Table 5. Relationships Between Regional Lesion Loads and % Change in BMI From Baseline to Last Visit Prior to MRI, With Covariate Adjustment for the Risk Factors in Table 1 and ICV

Region/Group by BMI % Change	Decrease > 5% (*N* = 376)	Change –5% and 5% (*N* = 745)	Increase > 5% (*N* = 282)	*p* Value
Total WM	4.7 (0.7)	4.5 (0.7)	4.8 (0.7)	.65
WM				
Frontal	2.2 (0.3)	2.1 (0.3)	2.2 (0.3)	.55
Temporal	1.1 (0.2)	1.0 (0.2)	1.1 (0.2)	.63
Parietal	1.3 (0.2)	1.7 (0.2)	1.3 (0.2)	.81
Occipital	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	.59

Notes: BMI = body mass index; ICV = intracranial volume; MRI = magnetic resonance imaging; WM = white matter.

loads. Specific regional brain volume associations with global obesity were observed for the whole brain volume, CSF, total, frontal, and temporal WM, and the hippocampus. Specific regional brain volume associations with increase in BMI from baseline were observed for the temporal GM, cingulate cortex, and the hippocampus.

Prior cross-sectional studies have suggested reduced brain volumes in nondemented obese individuals. These regions include the whole brain volume (14,15,26,27), GM (28,29), prefrontal regions (14,27,29), and the temporal lobe (13). Little in terms of relationships between obesity and the rates of regional brain atrophy, both when employing an obesity cutoff or when looking across the range of BMI values, was observed however in the nondemented participants from the Baltimore Longitudinal Study of Aging (BLSA) who undergo consensus diagnosis and are prospectively screened for impairment similarly to WHIMS participants (30). In the BLSA studies, associations between obesity and brain volumes only emerged when individuals who developed cognitive impairment over the follow-up were included in analyses. These findings suggest that cross-sectional studies may overestimate associations between brain volumes and obesity due to inclusion of individuals who eventually develop cognitive impairment.

Obesity in our sample of women aged 65 and older seems to be associated with better brain integrity as indexed by higher regional brain volumes, lower CSF, and lower lesion load volumes. Although our findings may seem counterintuitive, they seem to be in line with a number of studies supporting the idea that differences in dementia risk vary across time whereby higher BMI in midlife is a predictor of dementia (2–5), whereas weight loss seems to be a better predictor at older ages (31–34). The term "obesity paradox" was coined recently to capture the predictive ability of BMI changes over time after several studies reported excess weight, which traditionally has been considered detrimental for health, to predict survival in the elderly (9,33). Our present findings are also in line with our previous report of worse cognitive performance in association with all-cause weight loss in the WHIMS cohort (34). Lower BMI or weight loss in this older sample potentially signals increased risk for impairment, as weight loss is common in predementia stages and is one of the principal manifestations of AD (35). There is some literature to suggest, however, that the late life obesity paradox does not exist when earlier trajectories can be taken into account (33).

Given the link between obesity and a variety of unfavorable health outcomes, including CVD, our secondary goal was to assess the relationships between either most current BMI measurement (closest to MRI visit) or change in BMI from baseline and regional lesion volumes. In our sample, global BMI predicted lesion loads for the parietal WM only after correcting for multiple comparisons. Little was observed in terms of change in BMI from baseline predicting current lesion load. Our results support the assertion that age-related differences in WMH volumes are significantly increased in the presence of comorbidities, including obesity, especially after 50 years of age (36). Although the literature on the associations between WM lesion load and BMI is rather limited, we are in agreement with the reports of associations between elevated BMI and increased risk of WM lesions (37).

This study comes with some inherent limitations. The sample is drawn from participants in a randomized clinical trial and is not population based. All participants are older, postmenopausal females; hence, we cannot generalize the findings to men or younger post- or premenopausal women. Some biases may have arisen due to differential survivorship. Also, we cannot infer from our data whether the changes in weight are a consequence of or predate changes in regional brain volumes or lesion loads. We are not able to distinguish between intentional and nonintentional weight loss or gain, which may have different relationships with brain health. It is also impossible to infer whether there was an increase in morbidity or mortality associated with weight change, as opposed to being a part of normal aging process, that might signal some underlying pathology, such as frailty.

Frailty is conceptualized as a loss of physiologic integrity associated with loss of lean mass, neuroendocrine dysregulation, and immune dysfunction. Although a common perception of a frail person is small and thin, recent evidence suggests that frailty in later life may start as early as middle age, with midlife obesity (38) and midlife CVD (39) as potential underlying causes. Moreover, frail health is not only associated with increased likelihood of CVD but also associated with many

noninvasive measures of CVD in those without a CVD history (40). Hence, it is not entirely surprising that frailty also relates to several obesity-related health conditions and that the development of frailty and associated weight loss could potentially contribute to the "obesity paradox"—where those overweight or obese seem to have a better prognosis. Additionally, although unlikely to be a major cause of weight gain in this age group, the possibility also remains that increased BMI, at least in some, is a result of increased lean mass due to physical activity.

The limitations, however, should not undermine many unique aspects of the study, including the large number of extensively screened and characterized community-dwelling, older women with prospective follow-ups, and validated image processing methods. The magnitude of associations between regional brain volumes and obesity in our community-dwelling cohort of generally healthy, older women were small and most do not survive conservative adjustments for multiple comparisons. Our study adds information to the literature on changes in obesity over a period of several years preceding the MRI measurements. Although cross-sectional studies comparing currently obese and lean people provide a useful glimpse into the neurobiology of obesity, they also highlight the need for studies with extended follow-up, which would allow us to infer whether neurological abnormalities precede, accompany, or follow the obese state. Clarification of the consequences of intentional versus unintentional weight loss is also needed to help guide clinical recommendations for older adults.

Supplementary Material

Supplementary material can be found at: http://gerontologist.oxfordjournals.org

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