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Weight trajectory over 20 years and likelihood of mild cognitive impairment or dementia among older women

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Abstract

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Background/Objectives—The association between weight change and cognition is controversial. We examined the association between 20-year weight change and cognitive function in late life.

Design—Cohort study.

Setting—Study of Osteoporotic Fractures (SOF).

Participants—1,289 older, community-dwelling women (mean baseline age 68 [65–81] and 88 [82–102] at cognitive testing).

Measurements—SOF participants had body weight measured repeatedly over 20 years (mean 8 weights). Adjudicated cognitive status was classified as normal (n=775) or mild cognitive impairment (MCI)/dementia (n=514) at Year 20. Logistic models were used to evaluate whether absolute weight change, rate of weight loss per year, presence of abrupt, unrecovered weight loss, and weight variability were associated with MCI or dementia.

Results—Women with greater rate of weight loss over 20 years had increased chance of developing MCI or dementia. In age/education/clinic-adjusted “base” models, each 0.5 kg/year decrease resulted in 30% increased odds of MCI/dementia (OR=1.30 [95% CI: 1.14, 1.49]). After adjustment for age, education, clinic, depression, and walking speed, there was 17% (OR=1.17 [95% CI: 1.02, 1.35]) increased odds of MCI/dementia for each 0.5 kg/year decrease in weight. In base models, variability in weight was significant. Each 1% average deviation from each woman’s predicted weight curve was associated with 11% increased odds of MCI/dementia (OR=1.11 [95% CI: 1.04, 1.18]). The estimate was attenuated after full adjustment (OR=1.06 [95% CI: 0.99, 1.14]). The presence of an abrupt weight decline was not associated with MCI/dementia.

Conclusions—Rate of weight loss over 20 years was associated with development of MCI or dementia in women surviving past 80 years, suggesting that nutritional status, social-environmental factors, and/or adipose tissue function and structure may affect cognitive function with aging.

Keywords

Weight trajectory; dementia; cognitive dysfunction

INTRODUCTION

Weight loss in late life has been linked to cognitive decline and development of dementia.^{1–12} Whether this weight loss is a result of or contributes to that decline is controversial.^{1,13} Weight loss may be an early manifestation of dementia,¹⁴ which could explain the association. However, weight loss has been shown to precede cognitive decline,⁴ suggesting that weight loss itself or the pathological processes behind it could contribute to cognitive decline. There is a paucity of data on whether other aspects of the late-life weight trajectory are associated with cognitive health, among them weight variability and an abrupt decline in weight.

Measuring weight is a simple tool available to all health care providers. Defining whether weight trajectories in older adults are associated with MCI and dementia could inform

efforts to maintain cognitive function. For example, cognitive maintenance interventions could target nutritional status, social-environmental factors, and/or adipose tissue function and structure.

In this study, we sought to determine whether weight trajectories among 1,289 community-dwelling, ambulatory women ages 65 and older were associated with cognitive function after an average of 20 years. We utilized the Study of Osteoporotic Fractures (SOF) cohort, which allowed us to focus our analysis on the oldest old, those who survived into their 80s, 90s and beyond. We hypothesized that among these oldest old women, those with greater weight loss, greater weight variability, and/or an abrupt decline in weight would be more likely to have MCI/dementia.

METHODS

Study Overview and Study Sample

In 1986–88, the Study of Osteoporotic Fractures recruited 9,704 community-dwelling women, ages 65 and older (>99% non-Hispanic white) in four US regions: Baltimore County, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley near Pittsburgh, Pennsylvania.¹⁵ Women unable to walk without assistance and those with bilateral hip replacements were not eligible for inclusion.

The women attended clinic visits, where their weight was measured, every 2 to 4 years. All surviving participants were invited to attend a Year 20 examination between 2006 and 2008; 2,121 women completed the Year 20 clinic or home visit. At the Year 20 visit, 3 of the 4 SOF sites participated in an ancillary study regarding clinical cognitive status. 1,495 women had complete cognitive testing at Year 20. Because there were only 5 women of nonwhite race, they were excluded. 1,289 women (86%) also had weight measurements (mean 8 measurements) taken at baseline and the Year 20 examinations so that a weight trajectory could be determined. These women are the subject of this report (Figure 1).

All women provided written consent, and the SOF was approved by each site's Institutional Review Board.

Weight

Body weight was measured in light clothing with a standard balance beam or digital scale at all 8 visits over the 20-year period (mean 8 visits). A total of 1,068 (83%) women had all measurements; 97% had at least 6 measurements between baseline and the Year 20 exam.

Other Characteristics

Height was measured with a wall-mounted Harpenden stadiometer (Holtain, Dyved, UK). These measures were then used to compute body mass index (BMI).¹⁵ Participants completed questionnaires assessing basic demographics, medical history, and educational history at baseline. Smoking and alcohol consumption, medical history, health behaviors (e.g., walking for exercise), independent activities of daily living, and self-reported health were determined by questionnaire and interview at Year 20. A comorbidity index at Year 20 was calculated by summing self-reported medical conditions (e.g. stroke, diabetes,

congestive heart failure). Depressive symptoms were assessed at the Year 20 visit with the 15-item Geriatric Depression Scale (GDS).¹⁶ Walking speed was assessed at the Year 20 visit as the average time to complete two trials on a 6-meter course. At Year 16, visual acuity was measured with letter charts of Bailey and Lovie.¹⁷

Cognition and Cognitive Diagnosis

At Year 20, centrally trained clinic staff administered the cognitive battery described previously.¹⁸ Briefly, the battery included the Modified Mini-Mental State Examination (3MS),¹⁹ a 100-point extended version of the Mini-Mental State Examination (MMSE), California Verbal Learning Test—II Short Form Immediate and Delayed (CVLT-I and CVLT-D),²⁰ Digit Span—Forward and Digit Span--Backward,²¹ Trail Making Test Part B (Trails B),²² Verbal Associative Fluency (Verbal Fluency) and Category Fluency,²³ and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).²⁴

Clinical cognitive diagnosis of normal cognition, MCI, and dementia were adjudicated from the Year 20 exam testing as previously described.^{25,26} Mild cognitive impairment (MCI) represents an early stage in the neurobiological and neuropathological changes that may culminate in dementia.^{27,28} Therefore, the decision was made *a priori* to combine MCI and dementia in order to be adequately powered. Women were considered cognitively normal if they did not meet any of 5 criteria for more detailed adjudication. The criteria were: 1) 3MS score <88, 2) CVLT delayed recall score <4, 3) IQCODE²⁴ score \geq 3.6, 4) self-reported physician diagnosis of dementia, or 5) nursing home residency. Next, data from women who met *any* of the above criteria were examined by a team of expert clinicians, who reviewed individuals' cognitive test results from Year 20 and all prior cognitive assessment data, functional status, medical history, medications, and depressive symptoms, and then diagnosed individuals as having MCI (based on modified Peterson criteria)²⁹ or dementia (based on DSM-IV criteria), or being cognitively normal.

Statistical Analyses

Baseline characteristics were compared using Chi-square for categorical variables and T-test for continuous variables. For the primary analyses, we examined the association between 20-year weight trajectory and cognition at the Year 20 visit. We considered a number of measures characterizing weight trajectories. Absolute weight change over time was calculated as the difference in weight from baseline to Year 20 (kilogram decrease in weight). For the MCI/dementia outcome, we evaluated weight change continuously, per 10 kg of weight loss. Ten kilograms was chosen based on the standard deviation (SD) (8.99 kg) of the overall population weight change and consideration of clinical relevance. For cognitive testing outcomes we evaluated weight change categorically as: 1) no weight loss (weight gain or no change [change \geq 0]); 2) minimal weight loss (amount of weight loss the same as or slightly greater [within 1 SD] than the population change [1 SD \geq change <0]); or 3) moderate weight loss (amount of weight loss greater than the SD for the population change [change <1 SD]).

Rate of weight loss (kilogram per year) was calculated using the slope estimate from a linear model fit to each woman's weight measures over time. We evaluated rate of loss both

continuously and in categories. For MCI/dementia, we examined Odds Ratio (OR) per 0.5 kg per year decrease in weight. This value was based on the population SD (0.44 kg per year decrease in weight) and clinical relevance. We also compared slope of weight change to the overall population slope: 1) positive slope ([slope ≥ 0] indicating weight gain); 2) minimal negative slope (rate of weight loss the same as or slightly greater [within 1 SD] than the population rate [1 SD \leq slope < 0]); or 3) moderate negative slope (rate of weight loss greater than the SD for the population rate [slope < 1 SD]).

Presence of an unrecovered, abrupt decline in weight indicated a marked loss of weight that was inconsistent with the woman's prior weight trajectory. For this measure, we determined whether the weight trajectory fit a quadratic equation, with a relative maximum, and whether the weight loss continued to Year 20. This measure was evaluated as a dichotomous variable (yes/no).

Variability of weight over time was calculated using the root mean square percentage error (RMSPE) of the estimated linear and quadratic weight curves for each woman. The RMSPE represents the variability around the predicted curve. We used the RMSPE from the linear or quadratic equation that best fit the woman's weight curve. We examined this as a continuous measure as well as quartile categories.

Using logistic regression, we examined the likelihood of developing MCI or dementia (categorized together as the measure of cognitive decline) for each of the individual weight trajectory measures. We evaluated these relationships in unadjusted and age/education/clinic adjusted "base" models.

For our multivariable models, we considered several potentially confounding factors, including baseline body composition (baseline height and body mass index [BMI]), Year 20 lifestyle (alcohol use, smoking), Year 20 health status (self-reported health, depression, walking for exercise, walking speed, comorbidity index), Year 16 visual impairment, and baseline oral estrogen use.³⁰⁻⁴² These factors were chosen because they have been shown to influence cognition and weight. Each potential covariate was added individually to the base model. Covariates individually associated with Year 20 cognition in base models ($p < 0.10$) were further evaluated together in a logistic regression model using manual backwards stepwise selection, where age, education, clinic, and weight variables were forced. Statistically significant variables remained in the final model ($p < 0.05$).^{43,44} Our final, fully adjusted model consisted of the covariates identified above, plus the individual weight measures that remained independently significant at $p < 0.05$.

Finally, we examined the association between weight trajectory measures and individual cognitive testing scores at the Year 20 exam. We used generalized linear models to compare mean scores and test for trend among different categorical weight trajectory measures, adjusting for the same covariates as in the MCI and dementia models. Cognitive measures not normally distributed (MMSE, 3MS and Trails B) were log-transformed for these analyses. Data were back transformed for display of results.

Statistical analyses were completed using SAS v9.4 (SAS, Inc., Cary, NC). We considered $p < 0.05$ to be significant.

RESULTS

Sample Characteristics

SOF participants who survived to the Year 20 exam and had cognitive testing as well as baseline-to-Year-20 weight measurements over the study period were evaluated (n=1,289). Of these, 775 were cognitively normal and 514 were considered to have MCI/dementia. Those who were cognitively normal at Year 20 were younger and more educated at baseline; there was no difference in baseline BMI (26.57 vs 26.90 kg/m²) (Table 1). At the Year 20 exam, women who were cognitively normal were heavier, walked faster, drank more alcohol, and had lower GDS depression scores. They did not differ significantly on baseline estrogen use or on Year 20 comorbidity index, Year 16 visual acuity, baseline smoking history, Year 20 self-reported health, or Year 20 walking for exercise. Women who developed MCI/dementia had greater weight loss, steeper slope of weight loss, and more variability in weight between baseline to Year 20. They did not have a greater likelihood of an abrupt decline in weight. After adjusting for age, education, and clinic, walking speed and depressive symptoms were the only non-weight measures independently associated with MCI/dementia and therefore included in the fully adjusted models.

Association between weight trajectory and MCI/dementia

Overall, the average weight change between baseline and 20-year exams was a loss of 5.38 kilograms (SD=8.99; range loss of 42.50 kgs to gain of 27.50 kgs). Compared to women who had MCI/dementia at the Year 20 visit, women who were cognitively normal at Year 20 had less weight loss from baseline to the Year 20 visit (-4.44 kgs [SD=8.39 kgs] vs -6.80 kgs [SD=9.65 kgs]; $p<0.0001$), which translated into a less steep slope of weight loss (-0.20 kgs/year [SD=0.41] vs -0.31 kgs/year [SD=0.47]; $p<0.0001$). In unadjusted models, each 0.5 kg/year decrease in weight (10 kg loss over 20 years) resulted in a 35% increase in odds of developing MCI/dementia (OR=1.35 [95% CI: 1.19, 1.54]; Table 2). These estimates were similar after adjustment for age, education, and clinic (30% increase in odds of developing MCI/dementia for each 0.5 kg/year weight loss (OR=1.30 [95% CI: 1.14, 1.49])). Although estimates were attenuated after full adjustment, women still had a significant, 17% increase in odds of developing MCI/dementia for each 0.5 kg/year weight loss (OR=1.17 [95% CI: 1.02, 1.35]).

When we examined slope of weight change categories and MCI or dementia at Year 20, we found associations similar to the continuous models. Women who had moderate negative slopes of weight loss had more than a two-fold (OR=2.25 [95% CI: 1.57, 3.24]) greater unadjusted odds of developing MCI or dementia at the Year 20 exam compared to those with positive slopes. The estimate was similar after adjustment for age, education, and clinic (OR=2.02 [95% CI: 1.39, 2.93]) but was attenuated after adjustment for walking speed and depressive symptoms (OR=1.46 [95% CI: 0.98, 2.17]).

The presence of an abrupt, unrecovered weight decline was not associated with development of MCI or dementia in unadjusted models (OR=0.87 [95% CI: 0.68, 1.13]) or adjusted models (OR=0.82 [95% CI: 0.63, 1.07] and OR=0.78 [95% CI: 0.59, 1.03] in age/education/clinic-adjusted and fully adjusted models, respectively).

Women who were cognitively normal at Year 20 also had less variability around their weight trajectory compared to women who developed MCI/dementia (RMSPE mean 2.78 [SD=1.71] compared to 3.09 [SD=1.92]; $p=0.003$). In unadjusted models, there was a 10% greater odds of developing MCI/dementia for each 1% average deviation from predicted weight curve (OR=1.10 [95% CI: 1.03, 1.17]). The estimate remained similar after adjustment for age, education, and clinic (OR=1.11 [95% CI: 1.04, 1.18]) but was attenuated after further adjustment for walking speed and depression (OR=1.06 [95% CI: 0.99, 1.14]).

Weight characteristics included simultaneously—Higher rate of weight loss and greater weight variability were both determined to be significant, independent predictors of MCI/dementia. Table 3 shows the likelihood of MCI/dementia when these are examined simultaneously in unadjusted and adjusted models. In unadjusted models, each 0.5 kg per year decrease in weight was associated with a 32% increase in odds (OR=1.32 [95% CI: 1.16, 1.51]) of developing MCI/dementia, and each 1% average deviation from predicted weight curves was associated with an 8% increase in odds (OR=1.08 [95% CI: 1.01, 1.15]) of developing MCI or dementia. Estimates were similar after adjustment for age, education, and clinic (OR=1.27 [95% CI: 1.11, 1.45] and OR=1.09 [95% CI: 1.02, 1.16] for slope and variability, respectively) but were attenuated after further adjustment for walking speed and depression (OR=1.16 [95% CI: 1.00, 1.33] and OR=1.05 [95% CI: 0.98, 1.13] for slope and variability, respectively).

Individual cognitive tests—We examined the association between weight trajectory variables and individual cognitive test performance at Year 20. In age/education/clinic-adjusted “base” models, we found that women with greater weight loss over 20 years (as measured by either slope of weight change or total weight change) had poorer cognitive performance on MMSE, 3MS, Trails B, CVLT-I, CVLT-D, Verbal Fluency and Category Fluency ($p<0.05$ for all; data not shown). When adjusted for walking speed and depression, only CVLT-I remained significantly associated with absolute weight change ($p=0.002$), and CVLT-I and CVLT-D remained significantly associated with rate of weight loss (p 's=0.001 and 0.03, respectively; Table 4). Digit Span Forward and Backward were not associated with weight change over time in any models (total weight change adjusted p 's=0.33, and 0.55, respectively; slope of weight change adjusted p 's=0.19, and 0.85, respectively; Table 4). Abrupt weight decline was not associated with performance on any cognitive test.

Greater weight variability was associated with poorer performance on several cognitive tests. In age/education/clinic-adjusted models, women with greater weight variability as measured by RMSPE had poorer performance on MMSE, 3MS, Trails B, CVLT-I, CVLT-D, Verbal Fluency, and Category Fluency ($p<0.05$ for all; data not shown). The association remained significant in models adjusted for walking speed and depression for 3MS ($p=0.05$), Verbal Fluency ($p=0.03$), and and Category Fluency ($p=0.03$). There was no association between weight variability and Digit Span Forward or Backward in any of these models (p 's=0.64 and 0.31, respectively; Table 4).

DISCUSSION

Among older women (ages 83–102) in the SOF cohort with measured weights over 20 years, greater than average weight loss over time (approximately >0.5 kg/year) was associated with development of MCI/dementia. Although weight variability was associated with development of MCI/dementia, rate of weight loss was a more important predictor than variability. An abrupt decline in weight was not associated with development of MCI/dementia.

This study offers a unique perspective into how women's weight trajectories in the 20 years leading up to ages 83–102 are associated with cognitive function. Previous research that followed older persons for shorter periods (3–12 years) found that weight loss was associated with development of dementia.^{1–12} However, cognitive decline has been shown to precede dementia diagnosis by up to 9 years.⁴⁵ Therefore, it was possible in these shorter studies that preclinical cognitive decline was causing weight loss. Our study, with its 20 years of follow-up, is less likely to be subject to this bias and suggests that losing weight in later decades is associated with greater likelihood of cognitive decline.

We also examined the association between weight trajectory variables and performance on individual cognitive tests. We found that women with more weight loss had poorer verbal memory and verbal fluency at Year 20 compared to those with less weight loss. The Women's Health Initiative Study of Cognitive Aging (WHISCA) study also found that women who lost weight performed more poorly on verbal fluency at follow-up compared to those who had more stable weight; however, they did not find the difference in verbal memory that we observed, perhaps because women in the WHISCA study were younger.⁴⁶ Although both weight loss and weight variability were associated with overall mental status, the association was attenuated with adjustment for walking speed and depression. There was no association between weight trajectory variables and tests of executive function and working memory, which was similar to the findings in WHISCA.

As far as we know, we are the first to examine weight variability in relation to cognitive function. Previous studies examining the association between weight cycling with mortality and physical function have shown conflicting results.^{47–49} These studies differ from the current work by relying on subjective weight history^{48,49} or following measured weights for only 7 years.⁴⁷ Based on work from the Cardiovascular Health Study showing that variations in measured weight were associated with future physical limitations and mortality in older adults,⁴⁷ we hypothesized that greater weight variability would be associated with accelerated cognitive aging. We hypothesized that variability in weight may reflect difficulties in maintaining homeostasis possibly secondarily to cognitive decline with aging. Although we found that greater weight variability was associated with a higher likelihood of MCI/dementia in univariable models, it was not as strong of a predictor as rate of weight loss when considered together.

As people age, they are at risk of weight loss because of changes in taste and smell, impaired digestion, and malabsorption/poor usage of nutrients due to chronic diseases or drug-nutrient interactions. In addition, social-environmental factors (e.g. solitude, institutionalization),

psychological factors (e.g. depression), or a limited level of independence (e.g. difficulty in purchasing and preparing foods) can lead to weight loss.⁵⁰ Weight loss and the associated alterations in adipose tissue function and structure could negatively affect brain health. For example, persons with adiposopathy^{51,52} or excessive hypertrophy of adipocytes have dysregulated paracrine and endocrine adipose tissue that contributes to the syndrome of weight loss, sarcopenia, frailty, and impaired cognitive function. Adipokines may play an important role in this association.^{4,53} Leptin has been called a potential cognitive enhancer/protector because higher levels have been associated with improved hypothalamic and hippocampal function,⁵⁴ slower preclinical cognitive decline,^{55,56} and reduced incidence of dementia and AD.⁵⁷ In the hippocampus, leptin facilitates presynaptic and postsynaptic transmitter release and sensitivity, affecting learning and memory.⁵⁴ Experimental models suggest that leptin may either directly or indirectly, through its effect on lipid metabolism, help decrease AD pathology.⁵⁸

Alternatively, both impaired cognition and decreased weight could result from age-related degenerative processes in the brain or other comorbidities. Low BMI is correlated with cerebral atrophy in dementia patients.⁵⁹ Atrophy of the mesial temporal cortex, which is involved in feeding behavior and memory, is preferentially involved in AD.⁵⁹ Weight loss with aging could potentially accelerate brain atrophy, as occurs during anorexia nervosa in younger adults.^{59–61} As the deficits seen with anorexia nervosa may not fully reverse after weight recovery⁶² and leptin's effects on the brain could be cumulative, weight variability with its repeated episodes of weight loss could negatively affect the brain.

Our findings were attenuated after adjustment for walking speed and depressive symptoms, both of which are associated with cognition and weight.^{63–66} This may be due to episodes of illness that lead to lower walking speed and/or bouts of depression, both of which might affect weight trajectory and cognitive function. Given that we tested many other potential covariates, with only walking speed and depressive symptoms influencing the weight loss/variability and cognitive function relationship, our results suggest that walking speed and depression should be measured and examined during studies on the association between weight and cognition.

We did not find that an abrupt decline in weight was associated with poorer cognitive function. Although previous studies have not specifically looked at abrupt, unrecovered weight loss, several studies have noted that weight decreases in the years preceding dementia diagnosis.^{2,67} Our study differed in that our population consisted of exceptionally older women who had survived into their 80s, 90s and beyond. In addition, we examined weight trajectories starting after age 65, while previous studies followed subjects from midlife (50s).^{2,67,68}

Our study had several strengths. We studied a large cohort of women with multiple weight measurements over 20 years. The mean age of our population at study's end was 88 (range 83–102), so our observation period covered the period when risk of cognitive decline is greatest.⁶⁹ Women were recruited irrespective of BMD status and measurements were rigorous,¹⁵ including detailed cognitive evaluation at the Year 20 examination. However, our study had some limitations. We relied on participants' self-reports of medical conditions and

functional limitations. Women must have been observed for 20 years to be measured for weight change and Year 20 cognitive function, so only survivors were included in analyses, potentially leading to survival bias. We did not have sufficient data on voluntary weight loss to be able to distinguish between intentional and unintentional weight loss, which are very different. We did not measure cognitive function at baseline, so we cannot exclude that early, preclinical cognitive decline resulted in greater weight loss over time in those who developed MCI/dementia. Finally, our study sample comprised Caucasian women; thus, our findings may not be generalizable to men or other racial/ethnic groups.

Conclusions

Women who survived into their 80s and 90s with normal cognitive function had more stable weight in the prior 20 years. Although the association seen with weight loss is smaller than that associated with traditional risk factors such as age⁶⁹ and education,³⁰ it could be of importance given the high prevalence of cognitive decline and dementia with aging, and because weight is a potentially modifiable risk factor in older age. Future research should target nutritional status, social-environmental factors, and/or adipose tissue function and structure as methods for preserving cognitive function into old age.

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Conflict of Interest Checklist

Elements of Financial/Personal Conflicts	ESL		JR		KP		KY	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x		x		x
Grants/Funds	x			x		x		x
Honoraria		x		x		x		x
Speaker Forum		x		x		x		x
Consultant		x		x		x		x
Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
Board Member		x		x		x		x
Patents		x		x		x		x
Personal Relationship		x		x		x		x

Elements of Financial/Personal Conflicts	KE		JC		PC		SC	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x		x		x
Grants/Funds		x		x		x		x
Honoraria		x		x		x		x
Speaker Forum		x		x		x		x
Consultant		x		x		x		x
Stocks		x		x		x		x
Royalties		x		x		x		x
Expert Testimony		x		x		x		x
Board Member		x		x		x		x
Patents		x		x		x		x
Personal Relationship		x		x		x		x

Elements of Financial/Personal Conflicts	TH	
	Yes	No
Employment or Affiliation		x
Grants/Funds		x
Honoraria		x
Speaker Forum		x
Consultant		x
Stocks		x
Royalties		x
Expert Testimony		x
Board Member		x
Patents		x
Personal Relationship		x

For “yes”, provide a brief explanation: Dr. LeBlanc’s institute has received research funding from Amgen, Astrazeneca, and Bristol Meyers Squibb for unrelated projects on which she was investigator.

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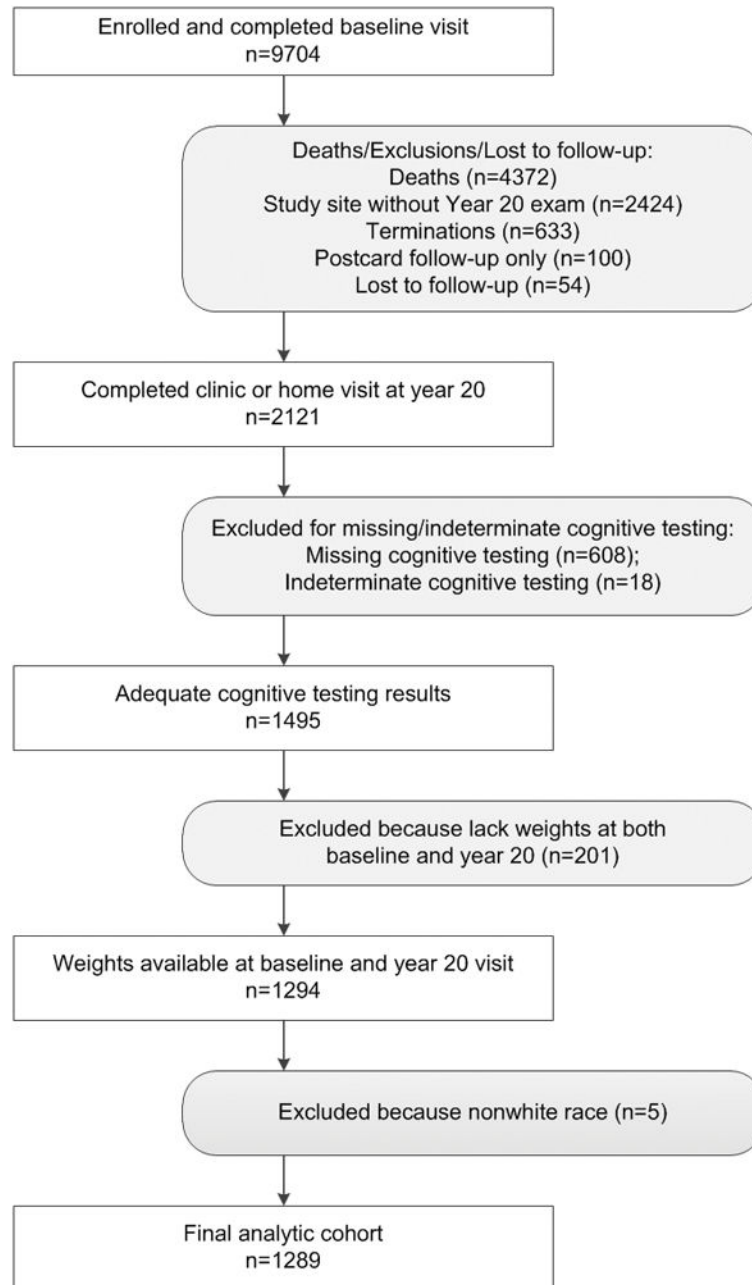


Figure 1.
Consort diagram

Table 1

Overall Characteristics

	Normal at Year 20	MCI/dementia at Year 20	p-value
N	775	514	
Baseline age, yrs (mean, se)	67.87 (0.09)	68.89 (0.14)	<.0001
Education, =>12 yrs (n, %)	687 (88.65)	413 (80.35)	<.0001
Baseline BMI, kg/m2 (mean, se)	26.57 (0.15)	26.9 (0.20)	0.18
Baseline height, cms (mean, se)	160.5 (0.21)	160.0 (0.25)	0.09
Baseline estrogen use, ever (n, %)	386 (50.26)	230 (45.36)	0.09
Year 20 weight, kgs (mean, se)	63.76 (0.41)	61.72 (0.52)	0.002
Year 20 walking speed, m/sec (mean, se)	0.75 (0.01)	0.57 (0.01)	<.0001
Year 20 comorbidity score ^a (n, %)			0.57
1	236 (30.45)	165 (32.29)	
2 or more	132 (17.03)	93 (18.20)	
Year 16 visual acuity, poor (n, %)	105 (15.46)	80 (19.95)	0.06
Year 20 ever smoker (n, %)	248 (32.00)	180 (35.02)	0.26
Year 20 alcohol use (n, %)			<.0001
<3 days/ week	236 (30.49)	122 (23.87)	
3–7 days/ week	98 (12.66)	39 (7.63)	
Year 20 self-reported health, good/excellent (n, %)	622 (80.26)	396 (77.65)	0.26
Year 20 walks for exercise (n, %)	340 (44.91)	204 (40.88)	0.16
Year 20 depression ^b (n, %)	53 (6.86)	91 (18.42)	<.0001
Weight change baseline to Year 20, kgs (mean, se)	−4.44 (0.30)	−6.80 (0.43)	<.0001
Slope of weight change from baseline to year 20, kg/year (mean, se)	−0.20 (0.01)	−0.31 (0.02)	<.0001
Weight variability, RMSPE ^c (mean, se)	2.78 (0.06)	3.09 (0.08)	0.003
Weight decline (n, %) ^d	218 (28.13)	131 (25.49)	0.30

Abbreviation: se refers to standard error

^aComorbidity index was calculated using the sum (0–7) of seven possible self-reported medical conditions, including ever having a stroke, diabetes, COPD, Parkinson's disease, heart attack/angioplasty, congestive heart failure, or peripheral vascular disease.

^bDepressive symptoms were assessed with the 15-item Geriatric Depression Scale (GDS). Those with scores ≥ 6 were considered to have depression.

^cVariability of weight calculated using the root mean square percentage error (RMSPE) of the estimated linear and quadratic weight curves for each woman.

^dN, % refers to the number and percentage of women with an unrecovered abrupt decline in weight based on whether the weight trajectory fit a quadratic equation with a relative maximum and weight loss continued to the end of weight trajectory.

Table 2
Odds of Developing Dementia or MCI According to Individual Characteristics of Weight Trajectory

Weight Measure ^a	Unadjusted OR (95% CI)	Age, education, clinic adjusted OR (95% CI)	Fully adjusted ^b OR (95% CI)
Change in weight from baseline to Year 20			
Per 10 kg decrease in weight	1.35 (1.19, 1.53)	1.30 (1.14, 1.47)	1.18 (1.03, 1.35)
Slope of weight change from baseline to Year 20			
Per 0.5 kg/year decrease in weight	1.35 (1.19, 1.54)	1.30 (1.14, 1.49)	1.17 (1.02, 1.35)
Slope of weight change category^c			
Positive slope	1.0(ref)	1.0(ref)	1.0(ref)
Minimal negative slope	1.33 (1.02, 1.72)	1.22 (0.93, 1.59)	1.09 (0.82, 1.44)
Moderate negative slope	2.25 (1.57, 3.24)	2.02 (1.39, 2.93)	1.46 (0.98, 2.17)
Abrupt weight decline^d			
No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.87 (0.68, 1.13)	0.82 (0.63, 1.07)	0.78 (0.59, 1.03)
Weight variability (RMSPE)^e Per \approx 1% average deviation from predicted curve	1.10 (1.03, 1.17)	1.11 (1.04, 1.18)	1.06 (0.99, 1.14)
Weight variability (RMSPE) quartile^e			
Q1	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q2	1.12 (0.81, 1.54)	1.15 (0.83, 1.60)	1.24 (0.87, 1.75)
Q3	1.29 (0.94, 1.77)	1.33 (0.96, 1.84)	1.16 (0.82, 1.63)
Q4	1.51 (1.10, 2.07)	1.60 (1.15, 2.21)	1.33 (0.94, 1.88)

^aEach model includes only the weight measure of interest and the non-weight covariates.

^bIncludes age, education, clinic, depression, and walking speed (quartiles).

^cCategories are relative to overall population slope (0.44 kg per year decrease in weight); positive slope (slope \geq 0) indicates weight gain; minimal negative slope indicates rate of weight loss the same as or slightly greater (within 1 SD) than the population rate (1 SD \leq slope $<$ 0); moderate negative slope indicates rate of weight loss greater than the SD for the population rate (slope $<$ 1 SD).

^dPresence of an unrecovered abrupt decline in weight based on whether the weight trajectory fit a quadratic equation with a relative maximum and weight loss continued to the end of weight trajectory (yes/no).

^eVariability of weight calculated using the root mean square percentage error (RMSPE) of the estimated linear and quadratic weight curves for each woman.

Table 3

Odds of Developing Dementia or MCI When Weight Trajectory Characteristics Examined Simultaneously

Weight Measure ^a	Unadjusted score (95% CI)	Age, education, clinic adjusted OR (95% CI)	Fully adjusted ^b OR (95% CI)
Slope of weight change from baseline to Year 20			
Per 0.5 kg/year decrease in weight	1.32 (1.16, 1.51)	1.27 (1.11, 1.45)	1.16 (1.0, 1.33)
Weight variability (RMSPE) ^c			
Per ≈1% average deviation from predicted curve	1.08 (1.01, 1.15)	1.09 (1.02, 1.16)	1.05 (0.98, 1.13)

^aModels include both weight measures simultaneously.

^bIncludes age, education, clinic, depression, and walking speed (quartiles).

^cVariability of weight calculated using the root mean square percentage error (RMSPE) of the estimated linear and quadratic weight curves for each woman.

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Table 4

Cognitive Function According to Individual Characteristics of Weight Trajectory in Fully Adjusted Models

Weight change characteristic ^{a,b}	MMSE		3MS		Trails B		CVLTI		CVLT-D		Verbal Fluency		Category Fluency		Digit span Forward		Digit Span Backward	
	Mean ^c (95% CI)		Mean ^c (95% CI)		Mean ^c (95% CI)		Mean ^c (95% CI)		Mean ^c (95% CI)		Mean ^c (95% CI)		Mean ^c (95% CI)		Mean ^c (95% CI)		Mean ^c (95% CI)	
Weight change baseline to year 20^d																		
No weight loss	22.06 (21.51, 22.62)		85.42 (84.08, 86.78)		174.57 (161.74, 188.42)		22.78 (22.07, 23.49)		4.76 (4.39, 5.12)		9.83 (9.28, 10.38)		10.22 (9.75, 10.70)		7.05 (6.75, 7.34)		5.02 (4.74, 5.29)	
Minimal weight loss	21.77 (21.33, 22.21)		84.89 (83.81, 85.98)		180.89 (169.59, 192.95)		22.42 (21.85, 23.0)		4.96 (4.66, 5.25)		9.89 (9.45, 10.34)		10.12 (9.73, 10.50)		7.11 (6.87, 7.35)		5.14 (4.92, 5.36)	
Moderate Weight loss	21.51 (20.85, 21.19)		84.37 (82.73, 86.05)		190.27 (173.04, 209.21)		21.31 (20.43, 22.19)		4.28 (3.84, 4.73)		9.18 (8.49, 9.86)		9.83 (9.24, 10.42)		7.24 (6.88, 7.61)		5.13 (4.79, 5.47)	
Adjusted P value for trend	0.14		0.25		0.09		0.002		0.06		0.08		0.23		0.33		0.55	
Slope of weight change baseline to year 20^e																		
Positive slope	22.07 (21.54, 22.62)		85.55 (84.23, 86.89)		174.55 (161.96, 188.13)		22.85 (22.15, 23.55)		4.83 (4.48, 5.19)		10.0 (9.46, 10.54)		10.12 (9.65, 10.59)		7.02 (6.74, 7.31)		5.10 (4.83, 5.37)	
Minimal negative slope	21.78 (21.33, 22.23)		84.81 (83.71, 85.91)		182.64 (171.10, 194.95)		22.43 (21.85, 23.01)		4.93 (4.63, 5.23)		9.81 (9.36, 10.26)		10.14 (9.75, 10.53)		7.11 (6.87, 7.35)		5.10 (4.88, 5.33)	
Moderate negative slope	21.45 (20.79, 22.12)		84.44 (82.81, 86.10)		185.38 (168.60, 203.83)		21.23 (20.35, 22.10)		4.31 (3.87, 4.76)		9.27 (8.59, 9.95)		9.95 (9.36, 10.54)		7.28 (6.92, 7.65)		5.14 (4.80, 5.47)	
Adjusted P value for trend	0.09		0.22		0.24		0.001		0.03		0.05		0.59		0.19		0.85	
Abrupt weight decline^f																		
No	21.74 (21.32, 22.17)		84.77 (83.72, 85.84)		181.46 (170.29, 193.37)		22.31 (21.74, 22.87)		4.75 (4.46, 5.04)		9.76 (9.33, 10.20)		9.98 (9.60, 10.35)		7.16 (6.93, 7.39)		5.14 (4.92, 5.36)	
Yes	21.95 (21.42, 22.49)		85.35 (84.05, 86.67)		179.55 (166.94, 193.12)		22.44 (21.75, 23.13)		4.92 (4.57, 5.27)		9.80 (9.27, 10.33)		10.40 (9.94, 10.86)		7.01 (6.73, 7.30)		5.04 (4.77, 5.30)	
Adjusted P value for trend	0.40		0.35		0.75		0.67		0.31		0.88		0.05		0.26		0.41	
Weight variability (RMSPE) quartiles^g																		
Q1	21.92 (21.37, 22.47)		85.46 (84.12, 86.83)		173.47 (160.64, 187.33)		22.38 (21.66, 23.10)		4.94 (4.57, 5.31)		10.01 (9.45, 10.56)		10.48 (10.01, 10.96)		7.04 (6.75, 7.34)		4.96 (4.69, 5.24)	
Q2	21.93 (21.37, 22.51)		85.46 (84.07, 86.87)		182.87 (168.89, 198.00)		22.54 (21.79, 23.28)		4.76 (4.39, 5.14)		10.11 (9.54, 10.68)		10.23 (9.74, 10.73)		7.26 (6.96, 7.57)		5.28 (5.0, 5.57)	
Q3	21.89 (21.36, 22.44)		84.86 (83.55, 86.20)		178.93 (165.75, 193.16)		22.39 (21.68, 23.09)		4.80 (4.44, 5.16)		9.60 (9.06, 10.14)		9.72 (9.25, 10.18)		6.98 (6.69, 7.27)		5.01 (4.75, 5.28)	
Q4	21.47 (20.93, 22.03)		84.07 (82.72, 85.44)		189.32 (174.94, 204.89)		22.10 (21.37, 22.83)		4.70 (4.33, 5.08)		9.44 (8.87, 10.0)		10.04 (9.55, 10.53)		7.22 (6.92, 7.52)		5.22 (4.94, 5.50)	
Adjusted P value for trend	0.17		.05		0.07		0.44		0.31		0.03		0.03		0.64		0.31	

^a Each model includes the single weight measure of interest and the non-weight covariates of age, education, clinic, depression, and walking speed (quartiles).

^b Sample size for analyses varied based on completion of cognitive tests and covariate assessment: MMSE (n=1267), 3MS (n=1267), Trails B (n=1035), CVLT – Immediate recall (n=1246), CVLT – Delayed recall (n=1246), Verbal fluency (n=1246), Digit span – forward (n=1259), Digit span – backward (n=1254)

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^cMeans are adjusted.

^dCategories are relative to population change SD (8.99 kg); no weight loss signifies weight change ≥ 0 ; minimal weight loss indicates weight change was ≤ -1 SD but > -0 ; moderate weight loss indicates weight change was > -1 SD.

^eCategories are relative to overall population slope (0.44 kg per year decrease in weight); positive slope (slope ≥ 0) indicates weight gain; minimal negative slope indicates rate of weight loss the same as or slightly greater (within 1 SD) than the population rate (1 SD \leq slope < 0); moderate negative slope indicates rate of weight loss greater than the SD for the population rate (slope < -1 SD).

^fPresence of an unrecovered abrupt decline in weight determined from whether the weight trajectory fit a quadratic equation with a relative maximum and weight loss continued to the end of the weight trajectory (yes/no).

^gVariability of weight calculated using the root mean square percentage error (RMSPE) of the estimated linear and quadratic weight curves for each woman.