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Decline in Weight and Incident Mild Cognitive Impairment: Mayo Clinic Study of Aging

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Abstract

IMPORTANCE—Unintentional weight loss has been associated with risk of dementia. Since mild cognitive impairment (MCI) is a prodromal stage for dementia, we sought to evaluate whether changes in weight and body mass index (BMI) may predict incident MCI.

OBJECTIVE—To investigate the association of change in weight and BMI with risk of MCI.

DESIGN, SETTING, AND PARTICIPANTS—A population-based, prospective study of participants aged 70 years and older from the Mayo Clinic Study of Aging. Maximum weight and height in midlife (aged 40 to 65 years old) were retrospectively ascertained from the medical records of participants using a medical records linkage system.

MAIN OUTCOMES MEASURES—Participants were evaluated for cognitive outcomes of normal cognition, MCI, or dementia at baseline and prospectively assessed for incident events at

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each 15-month evaluation. The association of rate of change in weight and body mass index with risk of MCI was investigated using proportional hazards models.

RESULTS—Over a mean follow-up of 4.4 years, 524 of 1895 cognitively normal participants developed incident MCI. The mean (standard deviation) rate of weight change per decade from midlife to study entry was greater for individuals who developed incident MCI vs. those who remained cognitively normal (−2.0 (5.1) vs. −1.2 (4.9) kg; $p = 0.006$). A greater decline in weight per decade was associated with an increased risk of incident MCI (hazard ratio [HR] 95% confidence interval [CI], 1.04 [1.02, 1.06], $p < 0.001$) after adjusting for sex, education and apolipoprotein E (APOE) $\epsilon 4$ allele. A weight loss of 5 kg/decade corresponds to a 24% increase in risk of MCI (HR=1.24). Higher decline in BMI per decade was also associated with incident MCI (HR, 1.08, 95% CI = [1.03, 1.13], $p = 0.003$).

CONCLUSIONS AND RELEVANCE—These findings suggest that declining weight from midlife to late-life is a marker for MCI and may help identify persons at increased risk for MCI.

Keywords

Mild cognitive impairment; weight; body mass index; prospective; cohort study; population based

Introduction

Mild cognitive impairment (MCI) is a prodromal stage of dementia that provides opportunity to study risk factors for and to identify persons at increased risk for dementia. Approximately 5 to 15% of persons with MCI will progress to dementia per year.^{1,2} Therefore, the delay or prevention of MCI could also reduce the public health impact of dementia. Several modifiable risk factors are associated with an increased risk of MCI, including education, vascular risk factors and related outcomes.¹

Changes in body mass index (BMI) and weight are also associated with increased risk of dementia, but overall the findings of different studies have been inconclusive. Some studies have reported associations of lower late life BMI, declining weight or faster decline in BMI in late life with increased risk of dementia;^{3–7} others suggest that overweight at older ages,⁸ central obesity in midlife⁹ or higher midlife BMI^{10,11} increase the risk of dementia and Alzheimer Disease (AD). In contrast, one study found that being underweight in midlife may increase the risk of dementia in late life. Another study also observed an association between low BMI in midlife and increased dementia deaths in late life. Furthermore, other investigators have reported that obesity in midlife is associated with decreased risk of cognitive decline and dementias¹² or have not observed a predictive role of high late life BMI for cognitive decline.¹³ The association of BMI with MCI is even less certain. Few investigators have observed a decline in BMI prior to a diagnosis of MCI.^{14,15} The association of declining weight and BMI with MCI may have implications for preventive strategies for MCI. The objective of this study was to examine associations of longitudinal changes in weight and BMI with incident MCI among Mayo Clinic Study of Aging (MCSA).

Methods

Study Participants

The study design and methodology are published and are only briefly described here.^{16–18} Participants were enrolled in the population-based MCSA established in Olmsted County, Minnesota. At initiation of the study, a sampling frame of Olmsted County residents who were 70 to 89 years old on October 1, 2004 (total population = 9,953) was constructed using the medical records-linkage system of the Rochester Epidemiology Project.¹⁶ Participants were randomly selected from this sampling frame and eligible subjects (without dementia or in hospice care) were recruited to the study. Recruitment is ongoing to maintain the sample size, and participants are seen every 15 months. The current study includes participants who were cognitively normal at the baseline evaluation, had at least one follow-up evaluation, and had data on maximum weight and height in midlife (aged 40 to 65 years old; mean, 58.6).

Approval of Study Protocols, and Participant Consent

The study was approved by the Institutional Review Boards of the Mayo Clinic and the Olmsted Medical Center. Written informed consent was obtained from each participant prior to the participation.

Participant Evaluation

Participants were evaluated by a nurse or a study coordinator who assessed their memory, and administered the Clinical Dementia Rating scale,¹⁹ and Functional Activities Questionnaire²⁰ to the participant's informant. Each participant underwent neuropsychological testing using 9 tests to assess performance in four cognitive domains: memory, executive function, language, and visuospatial skills.^{17,18,21,22} Participants also had a neurological evaluation by a physician.

Identification of MCI/Dementia

The nurse or the study coordinator, the physician who evaluated the participant, and a neuropsychologist reviewed all data collected for each participant. A diagnosis of MCI, dementia or normal cognition was made by consensus.¹⁷ Participants were classified as cognitively normal if they performed in the normative range and did not meet criteria for MCI²³ or for dementia.²⁴ Incident MCI cases were classified as amnesic (aMCI) if the memory domain was impaired or nonamnesic (naMCI) if the memory domain was not impaired.²⁵

Assessment of Weight, Height, and BMI at Baseline and Follow-Up Evaluations

Weight and height were measured at each evaluation, and body mass index (BMI) was computed (as weight in kilograms/height in meters; kg/m²). The maximum weight and height in midlife (mean age, 58.6 years old) were ascertained from the medical record of each participant by trained nurse abstractors using the medical records linkage system of the Rochester Epidemiology Project.

Assortment of Other Covariates

Demographical variables including age, sex, and education were obtained at the baseline visit for each participant. A history of type 2 diabetes mellitus, hypertension, coronary heart disease, and stroke were abstracted from the medical records at baseline and during follow-up. Depressive symptoms were assessed with the Beck Depression Inventory (BDI). History of cigarette smoking (never, former, current) and diagnosed alcohol problems were assessed from self-report. Current medications were assessed from the medication bottles at each evaluation. Apolipoprotein E (APOE) $\epsilon 4$ allele genotyping was performed at baseline evaluation.

Statistical Analysis

All cognitively normal individuals at baseline were considered at risk for incident MCI. MCI onset was assigned at the midpoint between the last assessment as cognitively normal and the first-ever assessment as MCI. Persons who developed dementia without an intervening MCI diagnosis were presumed to have had an undetected MCI phase. We computed the follow-up duration from baseline to MCI onset for incident cases and through the date of the last follow-up for participants who remained cognitively normal. Subjects who refused participation, could not be contacted, or died during follow-up were censored at their last evaluation.

We computed the rate of weight change (kg/decade) from the maximum weight in midlife through follow-up, including late life weights as a time-dependent variable. We investigated the association of weight change with incident MCI using Cox proportional hazards model and reported hazard ratios (HR) and 95% confidence intervals (CI); in separate models we included maximum weight in midlife or late life weights. We examined confounding by APOE $\epsilon 4$ allele, diabetes mellitus, hypertension, stroke, and cigarette smoking with each variable added separately, and effect modification by age, sex, and APOE $\epsilon 4$ allele by including interaction terms of these covariates with rate of weight change.

Multivariable models included: Model 1: sex (where applicable), education and APOE $\epsilon 4$ genotype ($\epsilon 4$ carrier vs non-carrier); Model 2: included model 1 variables and potential confounders: alcohol problem (yes vs. no), depressive symptoms (BDI score ≥ 16), use of statins, diabetes mellitus, hypertension, coronary heart disease, cigarette smoking (never vs. former or current) and stroke.

We also examined the effect of including height in the models. In a separate model, we included both maximum weight in midlife and late life weights, but not weight change, in the same model and examined the associations with MCI. We repeated the analyses using rate of change in BMI (unit/decade). All hypothesis testing was conducted assuming an $\alpha = 0.05$ significance level and a two-sided alternative hypothesis. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

The characteristics of the 1,895 cognitively normal participants at baseline (50.3% men, mean age 78.5 years) are summarized by sex in Table 1. Men had a higher frequency of

former or current smoking (61.2% vs. 36.0%, $p < 0.001$), diabetes mellitus (20.4% vs. 14.3%, $p = 0.001$), and coronary artery disease (49.2% vs. 29.1%, $p < 0.001$) than women. Women had a non-significantly greater mean (standard deviation [SD]) rate of weight change per decade from midlife to study entry compared to men, but a lower maximum weight and lower BMI in midlife compared to men.

Over a mean 4.4 years (SD, 2.4) of follow-up, 524 participants developed incident MCI (Table 2). Participants who developed incident MCI were older, more likely to be carriers of APOE $\epsilon 4$ allele, and to have diabetes mellitus, hypertension, stroke, and coronary artery disease compared to participants who remained cognitively normal. The mean (SD) weight change was greater for participants who developed incident MCI vs. those who remained cognitively normal (-2.0 [5.1] vs. -1.2 [4.9] kg; $p = 0.006$). The decline in weight was greater in men who developed incident MCI vs. men who did not (-2.1 [5.3] vs. -1.0 [4.6] kg; $p = 0.019$), but was similar for women who developed incident MCI vs. women who did not (-1.9 [4.8] vs. -1.5 [5.3]; $p = 0.115$).

A decline in weight from midlife was associated with an increased risk of incident MCI after adjustment for sex, education and APOE $\epsilon 4$ allele (Table 3, Model 1). Based on our proportional hazards models, a weight loss of 5 kg/decade corresponds to a 24% increase in risk of MCI (HR=1.24). Table 3 also describes the effects of adjusting for maximum midlife weight, weights in late life, separately or simultaneously in models with or without weight change.

When maximum midlife weight and late life weights were included in the same model as weight change, neither was significantly associated with MCI, but weight change remained significantly associated with MCI. However, when both maximum midlife weight and late life weights, but not weight change, were included in the same model, higher maximum midlife weight and low late life weight were associated with an increased risk of MCI. Consistent with results for weight change, a greater decline in BMI per decade (i.e. unit decrease) was associated with an increased risk of MCI (HR = 1.08 [1.03, 1.13], $p = 0.003$), but the model fit was better using weight change.

When we simultaneously adjusted for potential confounders, the associations of weight change with MCI persisted (Table 3, Model 2). However, simultaneously adjusting for these variables in a multivariable model with weight change could result in over-controlling since these conditions are in the causal pathway from obesity to cognitive impairment.

There was no significant interaction of sex with weight change, however, given the higher risk of MCI in men vs. women in our cohort, we have reported results by sex (Table 3). The effect sizes were greater in men than in women. There was a significant interaction between age and maximum midlife weight in regard to MCI risk (p for interaction = 0.019). The associations of a 5-kg difference in maximum midlife weight with MCI were stronger for persons older at baseline: 70–74 years: (HR = 1.05 [1.01, 1.10], $p = 0.028$); 75–79 years: (HR = 1.07 [1.03, 1.12], $p = 0.001$); 80–84 years: (HR = 1.08 [1.04, 1.12], $p < 0.001$); 85 years and older: (HR = 1.09 [1.04, 1.14], $p < 0.001$). There was no interaction of vascular risk factors with weight change (data are not presented).

Figure 1 illustrates inter-relationships of midlife weight, weight change and MCI risk. There is no association of midlife weight with MCI after weight change is taken into account. The figure demonstrates that the slopes for the four quartiles of midlife weight do not significantly differ. For persons in the upper midlife weight quartile (Q4), the risk of MCI (hazard ratio [HR], 95% confidence interval) increased by 39% (HR, 1.39 [1.02, 1.82]) for a weight change of -10kg/decade . For persons in the lowest quartile (Q1), the risk of MCI increased by 78% (HR, 1.78 [0.99, 3.21]) for a decline of -10kg/decade . The corresponding increases in risk of MCI per -10 kg/decade were 69% (1.69 [1.04, 2.74]) for the second quartile and 61% (1.61 [1.08, 2.38]) for the third quartile. Thus, there is no significant interaction between midlife weight and weight change in determining in the risk of MCI ($p = 0.80$). Similarly, there was no significant difference in the intercepts of the 4 lines based on the general test comparing the four groups ($p = 0.47$); i.e. after taking into account the rate of weight change, there was no significant contribution of midlife weight to incident MCI. The specific test directly comparing the slopes in the upper and lower quartiles was not significant ($p = 0.43$). When we studied the association of weight change with MCI subtypes separately, weight change was significantly associated with aMCI not with naMCI (Table 4), suggesting that decline in weight may involve AD-related mechanisms.

Discussion

The results of this population-based elderly cohort demonstrate that a higher weight loss from midlife to late life and decline in weights in late life, are markers of risk for MCI. Greater rate of decline in weight or in BMI from midlife to late life increased risk of MCI. After taking into account rate of weight change, midlife and late life weights do not contribute to risk of MCI. However, without accounting for rate of change in weight, a higher maximum weight in midlife is associated with an increased risk of MCI, whereas a decline in weight in late life is associated with an increased risk of MCI.

The association of greater weight loss with MCI suggests that weight loss may be a marker for risk of MCI. While weight loss may not be causally related to MCI, we hypothesize that weight loss may represent a prodromal stage or an early manifestation of MCI. Consistent with this, there was no interaction of weight loss with midlife weight; even among persons who were of normal weight in midlife, a greater weight loss was associated with an increased risk of MCI in late life.

An important strength of our study is the ability to assess maximum midlife weight from the medical records of participants and from direct measurements in late life. From these measures, we demonstrated that age at which weight is assessed is important when investigating the association of weight with risk of MCI. Specifically, when we simultaneously considered maximum midlife and late life weight in the same model, higher maximum midlife weight and weight loss in late life were both associated with incident MCI. However, our findings suggest that, weight loss is the key weight-related marker of incident MCI in the elderly. The association of weight loss with incident MCI was stronger than estimates for maximum midlife weight or for low weights in late life when these latter variables were simultaneously considered.

Our findings for MCI are consistent with the findings of other prospective studies that correlated weight loss with the increased risk of dementia. In a study of controls for a dementia cohort, greater weight loss preceded the diagnosis of AD dementia.²⁶ In a community-dwelling elderly cohort, men and women who developed probable or possible AD dementia had a significant weight loss preceding the diagnosis compared to persons who remained cognitively normal.²⁷ In a small study of MCI participants, a low initial BMI and weight loss during follow-up were associated with a significantly greater risk of developing dementia. In a population-based cohort, higher midlife BMI was related to higher risk of dementia and AD dementia, independent of obesity-related risk factors and co-morbidities.²⁸ In an elderly African-American cohort, participants who developed MCI had a greater rate of weight loss showed by repeated BMI measures compared to elderly who remained cognitively normal.¹⁵ Similarly, in a case-control study in Olmsted County, weight loss was associated with a greater risk of dementia in women, but not in men.²⁹ In the prospective Honolulu Aging Study, weight loss preceded onset of dementia in a cohort of men followed over a 26-year follow-up.^{7,26,29}

Contrary to our findings, higher BMI in both midlife and late life was associated with decreased risk of dementia in a large population-based retrospective study.¹² Potential issues that may account for their findings¹² include lack of clarity on age at assessment of weight and BMI and onset of dementia. These may have implications on their findings if there is a mix of timings of age of weight assessment and BMI, with the majority being assessed at older ages. In another large population-based prospective study, being overweight or obese in midlife was not associated with increasing risk of dementia.³⁰

Weight loss prior to MCI or dementia may be a component of the prodementia syndrome rather than a causal relationship. If weight loss is a prodromal dementia stage, we would expect the association between weight loss and MCI to be similar across midlife weight classes. Indeed, the associations between weight loss and MCI did not differ across midlife weight quartiles, suggesting that the hypothesis of weight loss as a prodromal prodementia stage is likely.

The association of weight loss with cognitive impairment may involve direct causal mechanisms, may be due to reverse causality, or to a shared etiology. In regard to causal mechanisms, weight loss prior to cognitive impairment may be related to what has been termed 'anorexia of aging'. While the direct cause of this anorexia is not clear, we speculate that dysfunctional production of certain hormones (cholecystokinin, leptin, cytokines, dynorphin, neuropeptide Y, serotonin) on dietary intakes and energy metabolism may lead to reduced dietary intakes that impact MCI risk. In regard to reverse causality, neuropsychiatric symptoms such as depression and apathy that are prodromal and predictors of MCI and dementia, may contribute to decreased appetite and weight loss prior to the diagnosis of these conditions.³¹⁻³³ Finally, in regard to a shared etiology, protein deposits including Lewy bodies, tau or amyloid have been identified in the olfactory bulb and central olfactory pathways prior to the onset of dementia, and olfactory dysfunction is a marker for cognitive impairment and dementia.³⁴⁻³⁸ Thus, impairment in smell with related changes in taste, may contribute to decreased appetite, reduced dietary intake, and the weight loss observed with MCI, AD dementia and other neurodegenerative conditions.

The association of high midlife weight with MCI may involve effects of obesity on the brain through cerebrovascular disease and metabolic abnormalities (e.g. glucose metabolism, insulin signaling).³⁹ Obesity-related brain pathology likely includes hypoperfusion,⁴⁰ neuronal injury and death,⁴⁰ brain atrophy,⁴¹ cerebrovascular dysfunction,⁴⁰ increased levels of amyloid-beta precursor protein,⁴² increased tau expression,⁴³ blood-brain barrier dysfunction,⁴⁴ systemic^{45,46} and central⁴⁷ inflammation-related pathologies, and dysfunction of microglia and astrocytes.^{48,49}

A potential limitation of this study is that it is not possible to determine whether weight loss was intentional or unintentional. Given the consistency of the association of weight loss with incident MCI across all midlife weight quartiles, it is most likely unintentional weight loss. Despite the limited ethnic diversity of the study cohort, the findings are consistent with findings from an African-American cohort.¹⁵

Additional strengths of our study include the large cohort and population-based design. Participants were clinically assessed for risk of MCI or dementia. Furthermore, information on clinical conditions was abstracted from the medical record than from self-report.

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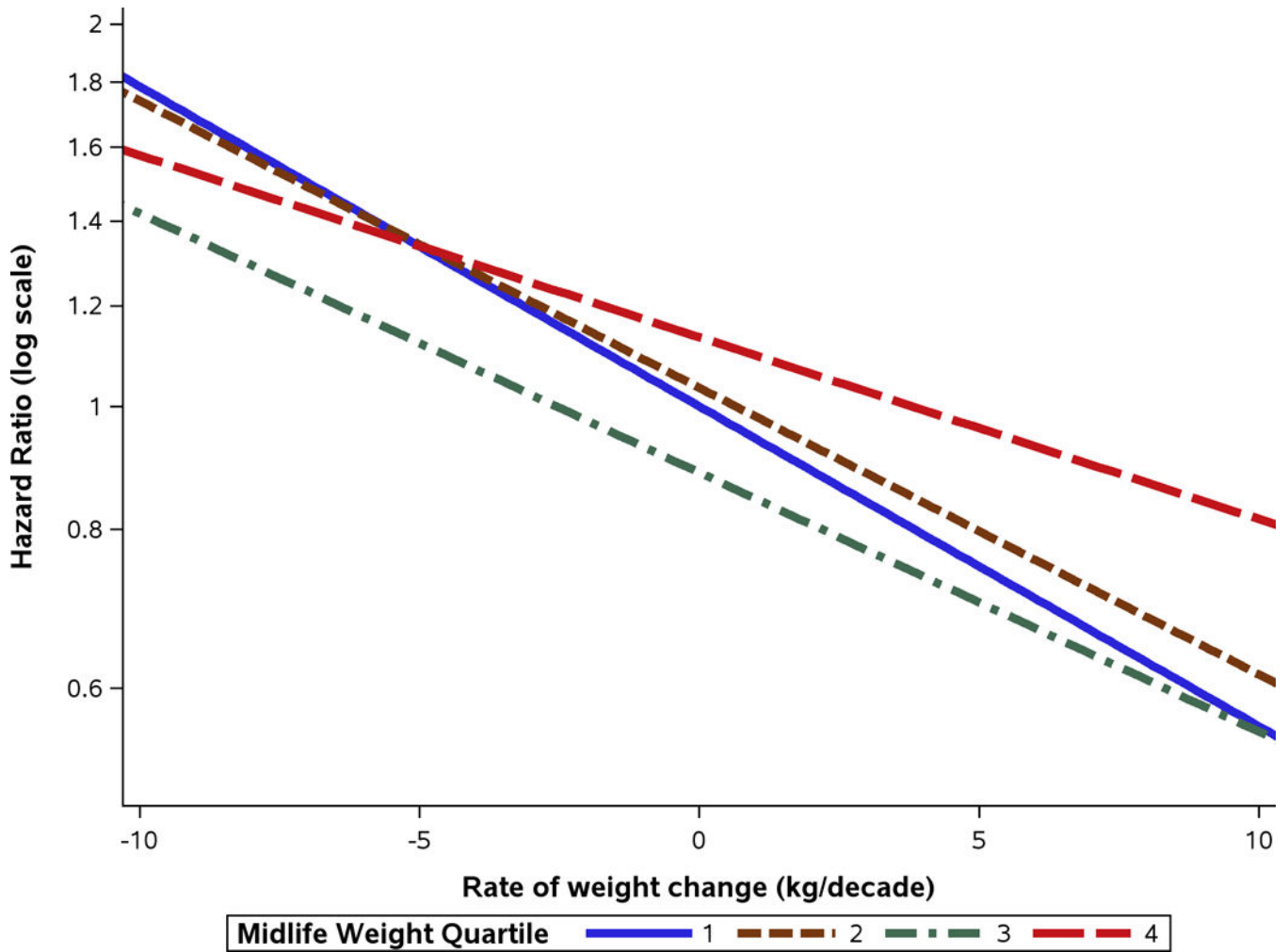


Figure 1.

Hazard ratios for midlife weight quartiles (Q1, Q2, Q3, Q4) by the rate of weight change per decade. The estimates are based on a model adjusted for sex, years of education, APOE $\epsilon 4$ allele and weight at study entry, with age as the timescale. The mean (SD) maximum weights in midlife were: 62.03 (5.08) kg for Q1; 75.94 (3.58) kg for Q2; 86.79 (2.86) kg for Q3; and 103.68 (11.83) kg for Q4. The observed median (5th and 95th percentile) rates of weight change (kg/decade) from midlife to study entry for the four weight quartiles were: 1st quartile, -0.36 (-6.50, 5.20); 2nd quartile, -1.02 (-8.24, 5.17); 3rd quartile, -1.68 (-9.37, 6.04); and 4th quartile, -2.26 (-14.44, 7.74) kg/decade. We provided the 5th and 95th percentiles to give a broader sense of the distribution of weight change for each midlife weight quartile.

Table 1

Summary of Participants' Characteristics by Sex

Characteristics	All (N = 1895)	Men (N = 954)	Women (N = 941)	<i>p</i>
Age, mean (SD) ^a	78.5 (5.1)	78.2 (4.9)	78.9 (5.4)	0.016
Men, n (%)	954 (50.3)	---	---	---
Education (years), mean (SD)	14.0 (2.9)	14.3 (3.2)	13.7 (2.4)	<0.001
Ever Smoking, n (%)	923 (48.7)	584 (61.2)	339 (36.0)	<0.001
APOE ε4 allele carrier ^b n (%)	489 (25.9)	246 (25.8)	243 (26.0)	0.94
Follow-Up (years), mean (SD)	4.4 (2.4)	4.3 (2.5)	4.5 (2.4)	0.05
Midlife Weight to Study Entry (years), mean (SD)	19.9 (8.6)	20.1 (8.6)	19.7 (8.6)	0.16
Body Mass Index (kg/m ²), mean (SD)				
Maximum Midlife ^c (ages 40–65)	28.3 (4.9)	28.7 (4.2)	27.9 (5.6)	<0.001
Late life ^d (study entry)	27.9 (5.0)	28.2 (4.4)	27.6 (5.5)	<0.001
Weight (Kg), mean (SD)				
Maximum Midlife ^e (ages 40–65)	82.0 (16.7)	89.9 (14.1)	74.1 (15.3)	<0.001
Late life ^f	79.3 (17.0)	87.4 (14.9)	71.0 (15.0)	<0.001
Rate of Weight Change ^g , mean (SD) ^h	-1.4 (5.0)	-1.3 (4.8)	-1.6 (5.1)	0.87
Clinical conditions				
Diabetes Mellitus (type 2), n (%)	330 (17.4)	195 (20.4)	135 (14.3)	<0.001
Hypertension, n (%)	1460 (77.0)	742 (77.8)	718 (76.3)	0.45
Coronary Artery Disease, n (%)	743 (39.2)	469 (49.2)	274 (29.1)	<0.001
Stroke, n (%)	80 (4.2)	43 (4.5)	37 (3.9)	0.53
Incident Mild Cognitive Impairment, n (%)	524 (27.7)	255 (26.7)	269 (28.6)	0.37

^aStandard Deviation.

^bNumber of participants with missing data from: "All" is 6; "Men" is 1; "Women" is 5.

^cNumber of participants with missing data from: "All" is 1; "Men" is 1; "Women" is 0.

^dNumber of participants with missing data from: "All" is 28; "Men" is 11; "Women" is 17.

^eNumber of participants with missing data from: "All" is 1; "Men" is 1; "Women" is 0.

^fNumber of participants with missing data from: "All" is 25; "Men" is 9; "Women" is 16.

^gFrom maximum midlife weight to study entry (kg/decade).

^hNumber of participants with missing data from: "All" is 26; "Men" is 10; "Women" is 16.

Table 2

Summary of Participants' Characteristics by Incident MCI

Characteristics	With Incident MCI (N = 524)	Without MCI (N = 1371)	<i>p</i>
Age, mean (SD) ^a	80.7 (5.2)	77.7 (4.9)	<0.001
Men, n (%)	255 (48.7)	699 (51.0)	0.37
Education (years), mean (SD)	13.4 (3.0)	14.2 (2.8)	<0.001
Ever Smoking, n (%)	243 (46.4)	680 (49.6)	0.21
APOE ε4 allele carrier ^b , n (%)	164 (31.4)	325 (23.8)	<0.001
Duration of Follow-Up (years), mean (SD)	2.8 (1.9)	5.1 (2.3)	<0.001
Time from Midlife Weight to Study Entry (years), mean (SD)	22.1 (8.5)	19.1 (8.5)	<0.001
Body Mass Index (kg/m ²), mean (SD)			
Maximum Midlife ^c (ages 40–65)	28.3 (5.0)	28.3 (4.9)	0.93
Late life ^d (study entry)	27.7 (5.2)	27.9 (5.0)	0.30
Weight (Kg), mean (SD)			
Maximum midlife ^e	81.4 (17.1)	82.3 (16.6)	0.24
Late life ^f	77.7 (17.0)	79.9 (17.0)	0.009
Rate of Weight Change ^g , mean (SD) ^h	−2.0 (5.1)	−1.2 (4.9)	0.006
Clinical conditions			
Diabetes Mellitus (type 2), n (%)	115 (21.9)	215 (15.7)	0.001
Hypertension, n (%)	430 (82.1)	1030 (75.1)	0.001
Coronary Artery Disease, n (%)	229 (43.7)	514 (37.5)	0.013
Stroke, n (%)	28 (5.3)	52 (3.8)	0.13

^aStandard Deviation.

^bNumber of participants with missing data from: "All" is 6; "With Incident MCI" is 2; "Without MCI" is 4.

^cNumber of participants with missing data from: "All" is 1; "With Incident MCI" is 0; "Without MCI" is 1.

^dNumber of participants with missing data from: "All" is 28; "With Incident MCI" is 10; "Without MCI" is 18.

^eNumber of participants with missing data from: "All" is 1; "With Incident MCI" is 0; "Without MCI" is 1.

^fNumber of participants with missing data from: "All" is 25; "With Incident MCI" is 10; "Without MCI" is 15.

^gFrom maximum midlife weight to study entry (kg/decade)..

^hNumber of participants with missing data from: "All" is 26; "With Incident MCI" is 10; "Without MCI" is 16.

Table 3

Association of Weight Measures with Incident MCI overall and by Sex

Weight-related variables ^a	Model 1 ^b		Model 2 ^b	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
All				
Wt Change/Decade ^c	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
Wt Change/Decade ^c	1.05 (1.03, 1.07)	<0.001	1.05 (1.02, 1.06)	<0.001
Max midlife wt, kg	1.00 (0.99, 1.00)	0.46	1.00 (0.99, 1.00)	0.22
Wt Change/Decade ^c	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
Late life wt, kg	1.00 (0.99, 1.01)	0.75	1.00 (0.99, 1.00)	0.33
BMI Change/Decade ^d	1.08 (1.03, 1.13)	0.003	1.06 (1.01, 1.12)	0.014
Max midlife wt, kg	1.01 (1.01, 1.02)	<0.001	1.01 (1.00, 1.02)	0.008
Late life wt, kg	0.98 (0.98, 0.99)	<0.001	0.98 (0.98, 0.99)	<0.001
Men				
Wt Change/Decade ^c	1.05 (1.02, 1.08)	<0.001	1.04 (1.02, 1.07)	0.002
Wt Change/Decade ^c	1.05 (1.02, 1.08)	0.001	1.04 (1.01, 1.07)	0.004
Max midlife wt, kg	1.00 (0.99, 1.01)	0.85	1.00 (0.99, 1.01)	0.93
Wt Change/Decade ^c	1.05 (1.02, 1.08)	<0.001	1.04 (1.02, 1.07)	0.002
Late life wt, kg	1.00 (0.99, 1.01)	0.53	1.00 (0.99, 1.01)	0.65
BMI Change/Decade ^d	1.08 (1.01, 1.16)	0.025	1.07 (1.00, 1.15)	0.06
Max midlife wt, kg	1.02 (1.00, 1.03)	0.010	1.02 (1.00, 1.03)	0.036
Late life wt, kg	0.98 (0.97, 1.00)	0.026	0.99 (0.97, 1.00)	0.05
Women				
Wt Change/Decade ^c	1.04 (1.01, 1.07)	0.002	1.03 (1.01, 1.06)	0.008
Wt Change/Decade ^c	1.05 (1.02, 1.08)	0.002	1.05 (1.02, 1.08)	0.002
Max midlife wt, kg	1.00 (0.99, 1.00)	0.27	0.99 (0.98, 1.00)	0.09
Wt Change/Decade ^c	1.04 (1.01, 1.06)	0.007	1.03 (1.00, 1.06)	0.035
Late life wt, kg	1.00 (0.99, 1.00)	0.30	0.99 (0.98, 1.00)	0.07
BMI Change/Decade ^d	1.07 (1.00, 1.14)	0.044	1.06 (0.99, 1.13)	0.09
Max midlife wt, kg	1.01 (1.00, 1.02)	0.023	1.01 (1.00, 1.02)	0.07
Late life wt, kg	0.98 (0.97, 0.99)	0.005	0.98 (0.97, 0.99)	0.002

HR, hazard ratio; CI, confidence interval; wt, weight; max, maximum; late life wt, weights during study as a time dependent variable.

^aWeight-related variables included simultaneously within the models.^bModel 1: Adjusted for sex (where applicable), education and APOE ε4 genotype (ε4 carrier vs non-carrier); Model 2: included model 1 variables and potential confounders: history of diagnosed alcohol problem (yes vs. no), depressive symptoms (BDI score ≥ 16), use of statins, diabetes mellitus, hypertension, coronary heart disease, cigarette smoking (never vs. former or current) and stroke. 6 participants in model 1 and 20 participants in model 2 with missing data were not included for rate of weight change from max midlife weight per decade through late life; max midlife wt; and late life wt. 34 participants in model 1 and 48 participants in model 2 with missing data were not included for rate of BMI change from max midlife BMI per decade through late life.

^cRate of weight change from maximum midlife weight through late life, kg per decade.

^dRate of BMI change from maximum midlife BMI per decade through late life, kg/m² per decade.

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Table 4

Association of Weight Measures with Incident MCI Subtypes^a

Weight-related variables ^b	Model 1 ^c			Model 2 ^d		
	aMCI HR (95% CI)	<i>p</i>	naMCI HR (95% CI)	<i>p</i>	aMCI HR (95% CI)	naMCI HR (95% CI)
Wt Change/Decade^e	1.05 (1.02, 1.07)	<0.001	1.00 (0.96, 1.04)	1.00	1.04 (1.02, 1.06)	0.99 (0.96, 1.04)
BMI Change/Decade^f	1.09 (1.03, 1.16)	0.002	1.02 (0.92, 1.13)	0.747	1.07 (1.01, 1.13)	1.01 (0.91, 1.12)
Max midlife wt, kg	1.01 (1.00, 1.02)	0.006	1.00 (0.98, 1.02)	0.78	1.01 (1.00, 1.02)	0.99 (0.97, 1.01)
Late life wt, kg	0.98 (0.97, 0.99)	0.002	1.00 (0.98, 1.02)	0.95	0.98 (0.97, 0.99)	1.00 (0.98, 1.02)

HR, hazard ratio; CI, confidence interval; Wt, weight; max, maximum; late life wt, weights during study as a time dependent variable.

^aThe number of incident aMCI cases was 366 and the number of incident naMCI cases was 120 in our study. The remaining 38 incident MCI cases could not be characterized in regard to MCI subtype, i.e. they progressed from cognitively normal directly to dementia.

^bWeight variables included simultaneously within the models.

^cModel 1: sex (where applicable), education and APOE ε4 genotype (ε4 carrier vs non-carrier). 2 participants with missing data were not included in model 1 for aMCI for rate of weight change from max midlife weight per decade through late life; rate of BMI change from max midlife BMI per decade through late life; max midlife wt; and late life wt. 2 participants with missing data were not included in model 1 for naMCI for rate of weight change from max midlife weight per decade through late life; max midlife wt; and late life wt. 4 participants with missing data were not included in model 1 for naMCI for rate of BMI change from max midlife BMI per decade through late life.

^dModel 2: included model 1 variables and potential confounders: alcohol problem (yes vs. no), depressive symptoms (BDI score 16), use of statins, diabetes mellitus, hypertension, coronary heart disease, cigarette smoking (never vs. former or current) and stroke. 12 participants with missing data were not included in model 2 for aMCI for rate of weight change from max midlife weight per decade through late life; rate of BMI change from max midlife BMI per decade through late life; max midlife wt; and late life wt. 5 participants with missing data were not included in model 2 for naMCI for rate of weight change from max midlife weight per decade through late life; max midlife wt; and late life wt. 7 participants with missing data were not included in model 2 for naMCI for rate of BMI change from max midlife BMI per decade through late life.

^eRate of weight change from maximum midlife weight through late life, kg per decade.

^fRate of BMI change from maximum midlife BMI through late life, kg/m² per decade.