



Body mass index and cognitive function: the potential for reverse causation

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1 **Body mass index and cognitive function: the potential for reverse causation**

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9

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1 **Abstract**

2 **Background/Objective:** Higher late life body mass index (BMI) is unrelated to or even predicts
3 lower risk of dementia in late-life, a phenomenon that may be explained by reverse causation due
4 to weight loss during pre-clinical phases of dementia. We aim to investigate the association of
5 baseline BMI and changes in BMI with dementia in a large prospective cohort, and to examine
6 whether weight loss predicts cognitive function.

7 **Methods:** Using a national cohort of adults average age 58 at baseline in 1994 (n=7,029), we
8 investigated the associations between baseline BMI in 1994 and memory scores from 2000 to
9 2010. We also examined the association of BMI change from 1994 to 1998 with memory scores
10 from 2000 to 2010. Lastly, to investigate reverse causation, we examined whether memory
11 scores in 1996 predicted BMI trajectories from 2000 to 2010.

12 **Results:** Baseline overweight predicted better memory scores 6 to 16 years later ($\beta=0.012$,
13 $95\%CI=0.001; 0.023$). Decline in BMI predicted lower memory scores over the subsequent 12
14 years ($\beta= -0.026$, $95\%CI= -0.041; -0.011$). Lower memory scores at mean age 60 in 1996
15 predicted faster annual rate of BMI decline during follow-up ($\beta= -0.158 \text{ kg/m}^2$ per year, 95%
16 $CI= -0.223;-0.094$).

17 **Conclusion:** Consistent with reverse causation, greater decline in BMI over the first four years
18 of the study was associated with lower memory scores over the next decade and lower memory
19 scores was associated with a decline in BMI. These findings suggest that pre-clinical dementia
20 predicts weight loss for people as early as their late 50s.

1

2 **Introduction**

3 Increasing evidence suggests that adiposity increases risk of dementia, particularly Alzheimer’s
4 disease (AD).¹ The potential underlying mechanisms linking higher BMI to dementia may
5 include direct effects of adiposity (hyperinsulinemia, advanced glycosylation end products,
6 adipokines and cytokines), as well as indirect effects (increases in the prevalence of other
7 vascular risk factors and related cerebrovascular disease).² An influential meta-analysis
8 concluded that being underweight, overweight or obese in midlife predicted higher risk of
9 dementia, with much of the evidence resting on a single sample aged 40-45 at body mass index
10 (BMI) assessment.^{1,3,4} On the other hand, results from studies examining late-life BMI and
11 dementia risk are mixed, with many studies reporting no associations of overweight or obesity
12 with dementia or even reporting that individuals with higher BMI had lower risk of dementia.^{1,5,}
13 ⁶ These unexpected findings may be explained by reverse causation. Since dementia has a long
14 preclinical phase, weight loss may begin years before the onset of clinical cognitive symptoms.⁷
15 Therefore, the null or protective association of adiposity and dementia risk in late-life may be
16 due to weight loss directly related to the developing cognitive impairment or secondary to
17 incipient neuropathological changes that produce both cognitive impairment and weight loss.⁸

18 Prior research leaves critical questions unanswered. First, the boundary between “midlife” and
19 “late-life” is unclear. If the weak association between higher BMI and dementia reflects the early
20 consequences of dementia, it is important to know when in the life-course, and how many years
21 prior to detectable cognitive impairments, BMI begins to reflect the influence of incipient
22 dementia. Currently, we have evidence that elevated BMI at ages 40-50 predicts later dementia^{3,}
23 ^{4,9-13}, but elevated BMI at ages 65+ does not.¹⁴⁻¹⁶ There is almost no evidence on whether the

1 association between elevated BMI and later dementia risk persists among individuals in their 50s
2 and early 60s. Second, under the reverse causation hypothesis, decline in BMI should predict
3 future dementia risk. Prior studies support this association among older adults (65 years and
4 older),¹⁷⁻²² but no studies have examined change in BMI and future dementia risk among middle
5 aged individuals. Finally, the reverse causation hypothesis also implies that cognitive
6 assessments indicating higher probability of incipient dementia should predict future BMI
7 decline, but no study to date has examined this association.

8 To address these gaps, we investigated the association of baseline BMI and change in BMI with
9 future memory scores as well as whether baseline memory scores predict subsequent BMI
10 trajectories in 7,029 Health and Retirement Study (HRS) participants who were average age 58
11 years at baseline.

12

13 **Methods**

14 *Participants*

15 HRS is a national cohort of Americans born between 1931 and 1941 and their spouses.

16 Participants were enrolled in 1992 and they have been interviewed biennially through 2010.

17 Retention rates were above 80%. Detailed information about HRS can be found elsewhere.²³

18 HRS was approved by the University of Michigan Health Sciences Human Subjects Committee
19 and this analysis was determined exempt by the Harvard School of Public Health Office of
20 Human Research Administration.

21 For this study, 1994 was considered baseline since most of the information for exposure and
22 covariates were available at this time. We considered 2000 as the first cognitive measure to allow

1 an interval between BMI and cognitive evaluation. We included individuals born 1935 or earlier,
2 alive in 2000, and with complete data for BMI and covariates at baseline. We excluded
3 Hispanics (n=744) because of evidence that the cognitive measures were not valid in this
4 subgroup.²⁴ We also excluded participants with BMI<18.5 kg/m² at baseline (n=91) to avoid
5 unmeasured confounding associated with baseline severe disease leading to very low BMI.

6 ***BMI measurements***

7 The main exposure was BMI in 1994, calculated by dividing self-reported weight in kilograms
8 by the square of the self-reported height in meters. BMI was categorized in 4 groups: 18.5-<20,
9 20-<25 (reference group), 25-<30, and ≥ 30 kg/m².²⁵ We performed additional analyses
10 considering BMI as a continuous variable, categorized in quartiles, quintiles, including additional
11 categories for obesity²⁵, and categorizing BMI at every 2 points.

12 At up to two interview waves occurring between 2004 and 2010, 10,445 participants had their
13 weight and height measured without shoes and heavy clothing during a home interview. We
14 applied the Bland and Altman method to evaluate agreement between measured and self-reported
15 BMI, considering repeated measures in the same individual.²⁶ Briefly, we plotted the difference
16 between the two measures (y axis) against their mean (x axis). The difference between measured
17 and self-reported BMI was 1.55 kg/m² (95% CI=1.51 to 1.59). The lower limit of agreement for
18 the difference between measured and self-reported BMI was -2.88 (95% CI=-2.96; -2.80) and
19 upper limit was 5.98 (95% CI=5.90; 6.06) (Supplementary Figure 1A). Using Spearman
20 correlations, we found a high correlation between self-reported and measured BMI (r=0.921;
21 p \leq 0.0001).

1 We examined BMI change by subtracting BMI in 1998 from BMI in 1994. To minimize the
2 influence of outliers, BMI change values were truncated at the 1st and 99th percentiles. For our
3 main analyses, we analyzed BMI change as a continuous variable with a quadratic term and also
4 categorized it in quintiles. In addition, we considered the effect of changes in BMI category on
5 cognitive measures, to account for both baseline BMI group and BMI change.²⁷⁻²⁹ For this
6 analysis, participants were classified into 11 groups, cross-classifying change and baseline
7 category: 4 groups whose BMI category did not change (no change from baseline BMI=18.5-
8 <20, 20-<25, 25-<30, or ≥ 30 kg/m²), 4 groups whose BMI category increased (increase from
9 baseline BMI=18.5-<20, 20-<25 kg, 25-<30, or ≥ 30), and 3 groups whose BMI category
10 declined (decrease from baseline BMI=20-<25 kg/m², 25-<30 kg/m², or ≥ 30). For example, if a
11 participant had a BMI of 26 kg/m² in 1994 and a BMI of 21 kg/m² in 1998, he or she was
12 included in the group “decrease from baseline BMI=25-<30”.

13 The agreement between measured and self-reported change in BMI from 2006 to 2010 was
14 investigated in 3,557 participants, using the Bland-Altman plot. The difference between
15 measured and self-reported BMI change was 1.59 (95% CI=1.41 to 1.51), and the lower limit of
16 agreement was -1.72 (95% CI=-1.77; -1.67) and the upper limit was 4.64 (95% CI=4.59; 4.69)
17 (Supplementary Figure 2A). The correlation between self-reported and measured BMI change
18 was moderate ($r=0.656$; $p<0.0001$).

19 In addition, since participants with impaired cognition could report BMI wrongly, we applied the
20 Bland and Altman method to compare measured and self-reported BMI in those in the lowest
21 quantile for the 10-word delayed recall test in 2004. The results were similar to the whole sample
22 for baseline BMI [difference= 1.55 (95% CI=1.51 to 1.59), lower limit of agreement= -2.97
23 (95% CI=-3.05; -2.89), upper limit= 6.07 (95% CI=5.99; 6.15)] and BMI change

1 [difference=1.37 (95% CI=1.26 to 1.48), lower limit of agreement= -1.80 (95% CI= -1.91; -
2 1.69), upper limit= 4.54 (95% CI=4.43; 4.65)] (Supplementary Figures 1B and 2B).

3 *Cognitive measures*

4 Participants completed cognitive function evaluations biennially from 2000 to 2010. Cognitive
5 function was evaluated using a 10-word immediate and delayed recall and the Telephone
6 Interview for Cognitive Status (TICS).³⁰ When a participant was too impaired to complete the
7 interview (approximately 10% at each wave), a proxy informant, typically a spouse (70%),
8 reported on the participant's cognitive function using the Informant Questionnaire on Cognitive
9 Decline in the Elderly (IQCODE).³¹ Composite dementia probabilities and memory scores were
10 calculated by combining direct and proxy cognitive assessments.²⁴ Briefly, the dementia
11 probability score and composite memory score algorithms were developed in a subsample of
12 HRS participants (n=856) who underwent full neuropsychological examinations (CERAD Word
13 Listing learning, delayed recall and recognition and/or Wechsler Memory Scale –Logical
14 Memory) as part of the Aging, Demographics, and Memory Study (ADAMS).³² The dementia
15 probability score algorithm was derived based on a logistic regression model using the cognitive
16 measures available for the full HRS cohort (immediate and delayed recall, TICS or IQCODE) to
17 predict DSM IV-based dementia diagnosis for all ADAMS participants (C-statistic=94.3%).
18 The memory score algorithm was developed using linear regression models to calibrate the
19 cognitive measures available for the full HRS cohort to predict a composite memory Z-score
20 assessed in ADAMS ($r^2=0.61$). These algorithms were applied to the direct or proxy cognitive
21 assessments completed to estimate dementia probability and memory scores for all participants at
22 each wave.²⁴

23 *Covariates*

1 An extensive set of confounders for the association of BMI and cognitive outcomes were
2 evaluated in 1994 and included: age, sex, race, years of education, place of birth (Southern, non-
3 Southern, or outside US), marital status (married vs. non-married), engagement in the labor force
4 (working, retired, or not engaged), annual income per capita, wealth per capita, physical activity
5 (frequency of vigorous activity, such as heavy housework, aerobics, running, swimming, and
6 bicycling, in the past 12 months categorized as 0, <3, or ≥ 3 times/week), alcohol use (ever
7 consumed any alcohol), current smoking, self-reported health ('excellent', 'very good', 'good'
8 vs. 'fair', 'poor'), basic (ADLs) and instrumental activities of daily living (IADLs), depressive
9 symptoms, and self-report of ever having a physician diagnosis of hypertension, diabetes, stroke,
10 heart disease, and cancer. Income and wealth per household member were highly skewed;
11 therefore natural log transformations were used. ADLs included the ability to bathe, dress, eat,
12 transfer, and walk without help. IADLs included the ability to use the phone, manage money,
13 take medications, shop for groceries, and prepare hot meals. For ADLs and IADLs, participants
14 were considered to have some impairment if they were unable to perform ≥ 1 of these activities.
15 Depressive symptoms were evaluated with a modified 8-item Centers for Epidemiologic Studies-
16 Depression (CES-D) scale.³³ Depressive symptoms were considered present if the respondent
17 reported ≥ 3 symptoms in the last week.³⁴

18 ***Statistical analysis***

19 *Effect of baseline BMI on cognitive measures*

20 Study population characteristics were compared by baseline BMI categories using one-way
21 ANOVA for continuous variables and chi square tests for categorical variables. To estimate the
22 effect of BMI on cognitive function, we used generalized linear models (GLM) with robust
23 variance to account for repeated measures in the same individual. To estimate the effect of BMI

1 category on future dementia probability, we used a logit link in the GLM; therefore, the
2 exponentiated regression coefficients correspond to odds ratios for dementia probability. For
3 memory scores, we used an identity link in the GLM, so regression coefficients correspond to
4 differences in mean memory score at each time point. Though we considered the possibility of
5 non-linear changes in cognitive measures over time, effects appeared approximately linear for
6 both outcomes on graphical inspection, so our main models specify time as linear.

7 We adjusted for an extensive set of confounders in our primary analyses. In sensitivity analysis,
8 we excluded confounders that may also serve as mediators and adjusted only for age, sex, race,
9 schooling, Southern birth, engagement in the labor force, marital status, income, and wealth.

10 Selection bias due to loss to follow-up and mortality is a concern in longitudinal studies of
11 cognition because cognitive impairment is an important predictor of study participation and
12 survival. To account for possible selection bias, we conducted sensitivity analyses with time-
13 updated inverse probability weighting (IPW).³⁵ We calculated two weights with logistic
14 regression: inverse probability of (1) survival at each wave (conditional on surviving up to and
15 participating in the previous wave) and (2) participation at each wave among those who survived
16 and previously participated.³⁶ To stabilize the weights, models for the numerators of the weights
17 included the following baseline variables: age, sex, race, schooling, BMI, marital status, and
18 dummy variables for each wave of follow-up. The denominators for the weights included the
19 extended set of covariates, BMI category, and dementia probability/memory score in the wave
20 prior to the outcome assessment, and dummy variables for each wave of follow-up. The survival
21 and participation weights were truncated at the 99th percentile to minimize the influence of
22 outliers. We multiplied the weights for survival and participation to create a weight for each
23 observation and applied them in the GLM for dementia probability and memory scores.

1 *Effect of BMI change on cognitive measures*

2 We examined effects of BMI change quintiles and categories from 1994 to 1998 on dementia
3 probability and memory score trajectories from 2000 to 2010. Participants (n=6,690) were on
4 average 58.1 years old (SD=4.3) in 1994 and 74.1 (SD=4.3) in 2010. For these analyses, n=339
5 participants were excluded because they did not have a BMI measure in 1998. We used a logit
6 link for dementia probability and an identity link for memory scores in the GLMs, adjusted for
7 the extended set of covariates.

8 *Effect of cognitive measures on BMI trajectories*

9 To further investigate the possibility of reverse causation, we examined the effects of dementia
10 probability and memory score quartiles in 1996 on BMI trajectories from 2000 to 2010, using
11 GLM adjusted for the comprehensive set of covariates. As a sensitivity analysis, we used age as
12 the time-dimension and considered models with quadratic terms for time dimensions.

13 All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). We present 95%
14 confidence intervals (CIs) with two-sided p-values.

15
16 **Results**

17 From the 9,285 HRS participants enrolled, 7,029 met the criteria for this study (Supplementary
18 Figure 3). Participants in the analysis sample were older, more likely to be female, and had better
19 overall health compared to those not included (Supplementary Table 1). The 339 participants
20 who were excluded from the BMI change analysis had higher dementia probabilities, higher
21 BMI, lower measures of socioeconomic and health status (Supplementary Table 2). At baseline,
22 the mean age was 58.1 years (SD=4.4) (range: 50-94 years), 44.5% were male, and mean BMI
23 was 27.2 kg/m² (SD=5.0) (range: 18.5-60.1 kg/m²). Table 1 displays study population

1 characteristics according BMI categories. Overall, the probability of dementia was very low at
2 the first cognitive assessment in 2000 and remained low during most of the follow-up. Memory
3 scores declined during this period (Figure 1). The mean number of cognitive assessments per
4 participant was 4.22 (SD=1.82).

5 *Association of baseline BMI with cognitive measures over follow-up*

6 In models adjusted for the extensive set of covariates, obesity ($BMI > 30 \text{ kg/m}^2$) was not
7 significantly associated with memory scores, but overweight ($BMI 20 - < 25 \text{ kg/m}^2$) predicted
8 higher memory scores ($\beta = 0.012$, 95% CI = 0.001; 0.023, $p = 0.04$) compared to BMI 20 - < 25
9 kg/m^2 . However, this result was not significant when we excluded possible mediators from the
10 covariate list (Table 2).

11 We investigated factors related to survival and dropout in our study. Higher memory scores
12 (OR=1.81, 95% CI=1.50; 2.19), being married (OR=1.53, 95% CI=1.31; 1.78), reporting health
13 as 'excellent, very good, or good' (OR=1.23, 95%CI=1.05-1.44), alcohol use (OR=1.21,
14 95%CI=1.05; 1.41), and being physically active (OR=2.07, OR=1.71; 2.49) were related to better
15 survival. On the other hand, older age (OR=0.89, 95%CI=0.88-0.91), underweight (OR=0.54,
16 95%CI=0.40; 0.72), male sex (OR=0.83, 95%CI=0.71; 0.94), impairment in basic (OR=0.61,
17 95%CI=0.52;0.73) and instrumental activities of daily life (OR=0.71, 95%CI=0.57; 0.89), heart
18 disease (OR=0.74, 95%CI=0.64-0.86), lung disease (OR=0.61, 95%CI=0.52; 0.73), cancer
19 (OR=0.35, 95%CI=0.30; 0.40), diabetes (OR=0.57, 95%CI=0.49; 0.67), hypertension (OR=0.75,
20 95% CI=0.65; 0.87), stroke (OR=0.81. 95%CI=0.67; 0.99), and smoking (OR=0.70, 95%CI=
21 0.59; 0.84) were independently related to shorter survival. Regarding dropout, older age
22 (OR=0.91, 95%CI=0.90; 0.93), higher education (OR=0.97, 95%CI=0.94; 0.99), hypertension

1 (OR=0.75, 95%CI=0.64; 0.87), and reporting health as ‘excellent, very good, or good’
2 (OR=0.73, 95%CI=0.59; 0.89) predicted higher dropout. Higher memory scores (OR=1.85,
3 95%CI=1.44; 2.38), male sex (OR=1.78, 95%CI=1.50; 2.10), and being physically active
4 (OR=1.27, 95%CI=1.08; 1.49) predicted lower dropout. Since the outcome, some covariates, and
5 in some situations even the exposure were related to survival and dropout, the use of IPW was
6 justified. When we applied IPW to address selection bias, neither overweight nor obesity
7 predicted memory scores, and the point estimates for the coefficients were slightly positive
8 (Table 2).

9 In sensitivity analyses, we found a small positive association between continuous BMI with a
10 quadratic term and memory scores. When we categorized BMI into quartiles, quintiles, and
11 additional categories, we found suggestive evidence that BMI in the overweight range was
12 associated with higher memory scores (Supplementary Table 3).

13 *Association of BMI change with cognitive measures*

14 Declines in BMI from 1994 to 1998 predicted lower memory scores from 2000 to 2010 [β for 1st
15 quintile (< -0.8 kg/m²) vs. 3rd quintile (0 to 0.7 kg/m²) = -0.026, 95%CI= -0.041; -0.011,
16 p=0.0008]. In addition, BMI change, analyzed as a continuous variable with a quadratic term,
17 was associated with memory scores (BMI change: $\beta=0.005$, 95%CI=0.002; 0.009, p=0.0005;
18 BMI change*BMI change: $\beta= -0.002$, 95%CI= -0.003; -0.001, p=0.0007). When we examined
19 change in BMI category stratified by baseline BMI, we found lower memory scores among
20 participants who were overweight (BMI=25-<30 kg/m²) in 1994 and lost weight by 1998
21 compared to participants who were normal weight (BMI=18.5-<25 kg/m²) in both 1994 and
22 1998 ($\beta= -0.039$, 95%CI= -0.068; -0.010, p=0.008). On the other hand, participants who
23 remained overweight (BMI=25-<30 kg/m² in both 1994 and 1998) had better memory scores

1 than those who had normal BMI at both time points ($\beta= 0.014$, 95% CI=0.001; 0.026, $p=0.03$)
2 (Table 3).

3 *Association of cognitive measures with BMI trajectories*

4 Compared to participants with the higher memory scores in 1996, participants with lowest scores
5 averaged significant declines in BMI from 2000 to 2010 [2nd quartile: $\beta=-0.028$ kg/m²/year
6 (95%CI=-0.082; -0.027); 3rd quartile: $\beta=-0.063$ kg/m²/year (95%CI=-0.117; -0.010); 4th quartile:
7 $\beta=-0.158$ kg/m²/year (95%CI=-0.223;-0.094); $p<0.0001$] (Figure 2).

8 *Sensitivity analyses*

9 Similar results were found when we considered dementia probability as the outcome for baseline
10 BMI and BMI change, and the effects of dementia probabilities on BMI trajectories.
11 (Supplementary Tables 4-6)

12

13 **Discussion**

14 In this large, diverse cohort, we find several lines of evidence that pre-clinical dementia may
15 cause BMI declines in cognitively normal individuals in their late 50s. Overweight at mean age
16 of 58 years predicted higher memory scores through mean age of 74 years. Depending on the
17 categorizations of BMI, higher memory scores prevailed for individuals in the overweight and
18 obese ranges. Declines in BMI over four years predicted lower memory scores over the next
19 decade, especially among individuals who were initially overweight. Finally, participants with
20 lower memory scores at baseline averaged faster declines in BMI during the follow-up. Current
21 research in the dementia field aims to identify individuals who are at the preclinical or early

1 stages of dementia, either for the purposes of early intervention trials or to evaluate etiologic risk
2 factors prior to the influence of dementia. For these purposes, being able to show that even
3 individuals in their 50s were already manifesting physiologic changes that are likely
4 consequences of dementia is important. Another relevant use of this research is to understand the
5 time course from the first pathologic changes to diagnosis, identifying the delay before onset of
6 dementia.

7 Prior findings on the relationship between late-life BMI and dementia risk are mixed. While
8 retrospectively reported obesity at age 50 was associated with increased risk of dementia in the
9 Cardiovascular Health Study, when BMI was measured at age 65 years or older, underweight
10 participants (BMI <20 kg/m²) had a higher risk of dementia, overweight participants had a
11 similar risk, and obese participants had a lower risk compared to normal weight participants.³⁷
12 In a male elderly cohort (age range: 65-84 years), being overweight was protective against
13 dementia, and obesity was not associated with risk of dementia.¹⁶ In studies treating late-life
14 BMI as a continuous variable, higher BMI is associated with either lower¹⁴ or no¹⁵ risk of
15 dementia. These findings are in stark contrast to the association between obesity in midlife and
16 increased risk of dementia in late life. The reversal of the association between BMI and dementia
17 in late-life is sometimes referred to as the obesity paradox.³⁸

18 Although prior studies suggested that elderly individuals who experienced BMI declines are at
19 higher dementia risk,^{17-21, 39} the average baseline age in our cohort is roughly 10 years younger
20 than prior research. Our results indicate that pre-clinical dementia may influence BMI, via
21 behavioral or physiologic mechanisms, for people in their late 50s, which is surprisingly early
22 considering previous studies and typical age at diagnosis of dementia. Dementia is relatively rare
23 among people in their 60s: the prevalence of dementia is estimated to be <2% among adults age

1 60-69 year in the United States .⁴⁰ However, the preclinical phase of dementia is believed to last
2 many years, and our finding may suggests that weight loss caused by incipient dementia begins
3 many years prior to onset of dementia.^{41, 42}

4 In fact, weight loss may be a prodrome of dementia and is probably related to neuropsychiatric
5 symptoms that are common in very early phases of the disease, like apathy and loss of
6 initiative.⁴³ Moreover, the presence of neuropathological lesions were found in the olfactory bulb
7 in early stages of neurofibrillary tangle deposition (Braak's stage 0 or 1) in 15 controls and 15
8 patients with AD.⁴⁴ As a result, reduced olfaction may contribute to decreased intake of food, as
9 it becomes less tasty. Apathy, reduced initiative and olfaction contribute to reduced food intake
10 mediated by decreased motivation to prepare meals, increased probability of missing meals, and
11 decreased interest in food. Other possible explanations for weight loss in preclinical dementia
12 may include dysfunction in the limbic system and hypothalamus⁴⁵ and altered automaticity in
13 swallowing and chewing.⁴⁶

14 Although survival bias, prior to or during the study period, is another possible explanation for
15 the protective association between obesity and cognition in studies of older adults, we think it is
16 unlikely to account for our findings. Survival bias prior to the start of studies of older adults may
17 occur if individuals who were overweight and obese in midlife die before enrolling in the study,
18 which could result in selection of healthy overweight and obese with better cognition than the
19 normal weight participants in our study. Approximately 23% of the 1930 US birth cohort died
20 between ages 20 and 55, and thus the pattern of selection would have to be exceptionally strong
21 to introduce substantial bias.⁴⁷ Selection bias during the study may occur if differential loss to
22 follow-up is not considered, since healthier overweight and obese could be preferentially
23 retained. One of the strengths of our study was the use of IPW to account for selective attrition.

1 The results of IPW models were similar to the findings from our main analysis but IPW accounts
2 only for post-enrollment attrition and depends on the assumption that there are no unmeasured
3 common causes of the cognitive measures and survival and dropout.

4 Other strengths of our study include: (1) the large sample size; (2) sensitivity analyses of
5 alternative functional forms of BMI at baseline (different categories and as a continuous
6 variable); (3) adjustment for confounders, considering the exclusion of possible mediators; (4)
7 the use of GLM with robust variance, and (5) extensive sensitivity analyses that showed the
8 robustness of our results. On the other hand, our study must be interpreted with some limitations
9 in mind. Although the agreement of self-reported and measured baseline BMI and BMI change
10 can be considered satisfactory, some measurement error occurred. This error may have
11 attenuated the true associations. Moreover, we could not investigate the effects of other measures
12 of abdominal obesity, like waist circumference and waist-to-hip ratio, to confirm our
13 conclusions. In addition, some of our findings must be interpreted with caution due to borderline
14 associations in the context of multiple testing (e.g. the association between baseline overweight
15 and memory scores, and the improvement in memory scores in overweight with stable BMI
16 category). Regarding the study outcomes, although memory scores and dementia probabilities
17 were calculated based on the participant's or proxy's cognitive evaluation, combining these
18 evaluations was important to keep participants with higher dementia risk in the sample. Finally,
19 the memory scores may have some ambiguity regarding domain specificity, since they had a
20 moderate r^2 value with the ADAMS memory composite. This may be due to the fact that
21 multiple aspects of memory were evaluated in the ADAMS subsample, whereas the assessment
22 we used to develop the memory scores included only immediate and delayed word list recall plus
23 the proxy assessment. None of these limitations could explain our key results: BMI in late

1 middle age was not associated with worse subsequent cognition; weight loss in late middle age
2 did not predict better subsequent cognition and for some groups predicted worse cognitive
3 outcomes; and lower cognition in late middle age predicted subsequent weight loss.
4 These results in combination support the reverse causation explanation for the obesity paradox in
5 dementia in late life. Surprisingly, the effects of preclinical dementia on BMI may start decades
6 before average age of dementia diagnosis, since we detected evidence of this process in a sample
7 with a mean age of 58 years.

8

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10

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17

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2 **Figure legends**

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5 Figure 1. Trajectories of dementia probabilities (A) and memory scores (B) from 2000 to 2010
6 according to BMI category in 1994.

7

8

9 Figure 2. Predicted BMI trajectories according to memory scores quartiles. First quartile was the
10 reference group and included participants with lowest memory scores.

11