Obesity and cognitive decline in adults

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OBESITY AND COGNITIVE DECLINE IN ADULTS: EFFECT OF METHODOLOGICAL CHOICES AND CONFOUNDING BY AGE IN A LONGITUDINAL STUDY

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Abstract: *Background and Objectives:* Obesity has been associated with increased risk of cognitive impairment or dementia, but recent findings are contradictory, possibly due to methodological differences. The present study tries to clarify these inconsistencies by following the cognitive trajectories of individuals with obesity over 12 years and studying the effect of obesity status (obesity at baseline versus incident obesity at follow-up), chronicity, definition, potential confounding (e.g. age, cardiovascular factors), and non-linear associations. *Design:* Longitudinal study with 12 years follow-up. *Setting:* Community based. *Participants:* 1,807 cognitively healthy individuals (aged 24-83) from the Maastricht Aging Study (1992-2004). *Measurements:* Memory, executive function and processing speed were assessed at baseline and at 6- and 12-year follow-up. Obesity was defined as having a body mass index (BMI) of ≥ 30.0 kg/m^2 or waist circumference (WC) of > 102 cm for men and > 88 cm for women. *Results:* At baseline, 545 persons were obese (BMI: 329 (18%); WC: 494 (27%); both: 278 (15%). They showed faster decline in memory, executive function, and processing speed. Chronic obese showed less widespread impairment than those who regained normal weight. Associations across cognitive domains were weaker for obesity defined by BMI than for WC. At follow-up, 190 developed obesity, and they performed worse on executive function at baseline, but showed less decline compared with participants with normal weight. Yet, age-stratification and post-hoc analyses showed that most of these associations were confounded by age. *Conclusions:* This study shows that the association between obesity and cognitive decline was confounded by the effect of age on rate of decline. Future studies should take this into account.

Key words: Cognition, cohort studies, confounding, dementia, obesity.

Introduction

The incidence of dementia is steadily increasing with 4.6 million new cases of dementia every year (1). In the absence of a treatment for dementia, identification of modifiable dementia risk factors is important to implement risk management strategies (2). Simultaneously, global age-standardized prevalence of obesity doubled from 6.4% in 1980 to 12% in 2008, with the highest absolute numbers found in women and industrialized countries (3-6), while the relative increase is largest for low- and middle-income countries (1).

Midlife obesity has been associated with a faster cognitive decline and a 60% increased risk of dementia (3, 5). However, results of prospective studies are inconsistent (7). Four recent studies found no evidence that midlife obesity increases dementia risk (8-11), or suggested that it might even be a protective factor, while underweight individuals might be at risk (11). Discrepancies in findings partly reflect differences in the measurement of obesity, residual confounding, demography and age at obesity assessment or duration. To date, few studies have investigated the age-dependent effects of obesity on cognitive change. Next, it is unclear whether this association might be mediated by obesity-related comorbidities such as hyperlipidemia, hypertension or type 2 diabetes (12, 13).

Therefore, the current study investigates the influence of a range of methodological choices in the analysis of the association between obesity and cognitive decline. More specifically, the studies assesses 1) the association between baseline and incident obesity and cognitive decline; 2) whether this association is independent of age and other important covariates (e.g. cardiovascular risk factors); 3) the effect of chronic obesity on cognition; 4) the impact of obesity measure (body mass index (BMI) versus waist circumference (WC)); and 5) the effect of accounting for both linear and non-linear associations between body weight and cognitive decline.

Methods

Participants

The Maastricht Aging Study (MAAS) is a prospective cohort study examining the determinants of cognitive aging (14). A total of 10,801 patients without major neurological conditions or psychiatric disorders were sampled from Registration Network Family Practices, a collaborative network of general practices in the south of the Netherlands (15), and were invited to participate in MAAS. The Registration Network Family Practices represents the general population with respect to demographic characteristics (14). Exclusion criteria were medical conditions that may interfere with normal cognitive function: (e.g. coma, epilepsy, dementia). All eligible participants were screened in a semi-structured interview by telephone for medical conditions that were not documented

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in the Registration Network Family Practices database such as history of transient ischemic attacks or brain surgery. For inclusion in MAAS, a sub-sample of 1823 individuals was drawn from the Registration Network Family Practices sampling frame stratified for age (12 discrete age groups from 24 to 81 years), sex, and level of occupational achievement (low/high) to have balanced groups in each stratum. At baseline (1993-1996), these participants underwent a comprehensive assessment of medical status, lifestyle, and anthropomorphic and neurocognitive measures, which were repeated 6 and 12 years after baseline. See Appendix 1 for the flowchart of the study design.

Measures

Obesity

Obesity was defined by both BMI and WC. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). The cut-off point for obesity (BMI ≥ 30.00 kg/m^2) was used according to World Health Organization guidelines (16). WC provides an indication of abdominal fat, and obesity is defined by a WC of > 102 cm (or > 41 inches) in men and > 88 cm (or > 36 inches) in women (16). Weight, height and WC were measured with a medical scale, stadiometer and tape measure, respectively. Participants were defined as obese based on BMI (measured at baseline, 6- and 12-year follow-up), WC (measured at baseline and 6-year follow-up) or both.

Cognitive decline

Neuropsychological tests were administered by psychologists and trained test assistants at baseline and the 6- and 12-year follow-up measurements. The Visual Verbal Learning Test was used to assess verbal memory (17). In this test, fifteen non-related monosyllabic words are presented in five consecutive trials on a computer screen, followed by an immediate (after each trial) and delayed (twenty minutes after last trial) recall phase. In the present study, the delayed recall was used. The Concept Shifting Test was used to measure executive function (18). In three trials, the participant has to cross out as fast as possible sixteen digits in ascending order (part A), sixteen letters in alphabetic order (part B), and finally eight digits and eight letters in alternating order (part C). The shifting score is calculated by subtracting the average time needed to complete part A and B from the time needed to complete part C. The Letter Digit Substitution Test was used to assess information processing speed (19). Using a reference key, the participant has ninety seconds to match specific letters to given numbers as quickly as possible.

Covariates

Age, sex, and educational level (low, middle and high) were included as demographic covariates. Blood pressure was measured three times at five-minute intervals on the left arm using an automatic sphygmomanometer (Critikon Dinamap 8100). Hypertension was defined as a systolic blood pressure of ≥ 140 mmHG or a diastolic blood pressure of ≥ 90 mmHG averaged over the three measurements, or self-reported antihypertensive medication intake (20). Presence of type 2 diabetes was based on a self-reported diagnosis by a physician or use of anti-diabetic medication at or after 40 years of age. Depressive symptoms were assessed using the 16-item depression subscale of the revised Symptom Checklist-90 (21). Other variables included self-report of cardiovascular disease (e.g. myocardial infarction, angina pectoris), present or past history of smoking (yes/no), and alcohol abuse (according to World Health Organization guidelines) (22).

Statistical analyses

Differences between obese and non-obese participants were analyzed using independent samples t-test and χ^2-tests. Two data transformations were used for the skewed distributions of the Visual Verbal Learning Test (square root transformation) and the Concept Shifting Test (logarithmic transformation). Random effects models tested the association between obesity and change in cognition over time. We used two inverse probability weights to reduce selection bias: 1) an attrition weight to correct for bias due to selective attrition (e.g. inclusion of individuals with missing follow-up data); and 2) a sampling weight to weight back the estimates to the population from which the MAAS sample was drawn (Registration Network Family Practices database). The attrition weight was constructed using a probit regression on being lost to follow-up at the 6 or 12 year assessment using baseline values for age, gender, education, delayed recall score, depressive symptoms, BMI, alcohol intake, smoking status, and presence of hypertension, cardiovascular disease or diabetes as predictors. The sampling weight was based on a probit regression on the likelihood of being sampled into MAAS from the Registration Network Family Practices sampling frame using age, gender and level of occupational achievement as predictors. The inverse of the probability was used in the analyses, so that participants who were less likely to be sampled or to have follow-up scores were given more weight in the analyses.

The models included a random intercept and random slope with an unstructured correlation matrix, as suggested by likelihood ratio tests. Interaction terms between obesity and a discrete time variable were included by using dummy variables for the two follow-ups (1 = baseline to 6 years; 2 = baseline to 12 years). The obesity-by-time interaction was tested using a χ^2-test with 2 degrees of freedom. First, cognition scores were adjusted for age, age^2, sex, level of education, and obesity and time, while fully-adjusted model also included baseline alcohol intake, history of smoking, and current (i.e. time-varying) hypertension, type 2 diabetes, depressive symptoms and cardiovascular disease. Analyses were stratified by sex and age group (young: < 65 years; old: ≥ 65 years). Since the results from crude models differed minimally (see Appendix 2), only the results from fully adjusted models (Model 1 in Table 2 and Table 3) are presented. Tests were two-sided with an alpha-

Table 1
Baseline characteristics of the study sample by obesity status at baseline and follow-up

	Baseline obesity			Incident obesity		
Variables[a]	**Yes, n = 545**	**No, n = 1,262**	**P-value**	**Yes, n = 190**	**No, n = 834**	**P-value**
Age, mean (SD)	58.0 (15.0)	48.9 (16.2)	< 0.001	49.0 (15.5)	46.7 (14.9)	0.060
Male, n (%)	227 (41.7)	680 (53.9)	< 0.001	79 (41.6)	479 (57.4)	< 0.001
Educational level, n (%)						
Low	263 (48.4)	397 (31.5)	< 0.001	69 (36.3)	229 (27.5)	0.049
Middle	201 (37.0)	536 (42.5)		73 (38.4)	376 (45.1)	
High	80 (14.7)	328 (26.0)		48 (25.3)	229 (27.5)	
BMI, mean (SD)	31.2 (3.9)	24.9 (2.5)	< 0.001	28.7 (2.4)	24.8 (2.4)	< 0.001
Waist circumference, mean (SD)	101.3 (9.1)	84.6 (9.6)	< 0.001	98.2 (7.3)	86.9 (9.1)	< 0.001
History of smoking, n (%)	346 (67.2)	791 (67.5)	0.901	107 (60.1)	518 (66.8)	0.093
Alcohol abuse, n (%)	14 (2.6)	37 (2.9)	0.669	1 (0.5)	25 (3.0)	0.051
Hypertension, n (%)	293 (53.8)	365 (28.9)	< 0.001	59 (31.1)	205 (24.6)	0.066
Type 2 diabetes, n (%)	35 (6.4)	33 (2.6)	< 0.001	4 (2.1)	16 (1.9)	0.867
Cardiovascular disease, n (%)	83 (15.2)	111 (8.8)	< 0.001	14 (7.4)	49 (5.9)	0.440
Depression score, mean (SD)	21.3 (6.8)	20.5 (6.1)	0.010	20.7 (5.7)	20.2 (5.8)	0.313

a. Numbers of participants are expressed as percentages. Figures may not sum to 100% because of rounding errors; Abbreviations: BMI, Body Mass Index; SD, standard deviation.

level of 0.05 and were done in Stata 13.1 (StataCorp, TX).

Results

Baseline characteristics are summarized in Table 1. Sixteen out of 1,823 participants were excluded due to missing obesity data (n=7) or because they were underweight (n=9). Of the remaining 1,807 participants, 545 (30%) persons were obese (BMI: n=329 (18%); WC: n=494 (27%); both: n=278 (15%). They were on average older, more often female, and had lower education, higher depression scores, and a history of hypertension, type 2 diabetes, and cardiovascular disease than non-obese participants. Of the 1,262 participants without baseline obesity, 238 participants were excluded due to missing obesity data at follow-up. Of the remaining 1,024 participants, 190 (19%) persons had incident obesity at 6- or 12-year follow-up. They were more often women and had a lower educational level.

Step 1: Baseline obesity and cognitive decline

Baseline cognition in participants with obesity did not differ from non-obese participants, but the former declined faster in all three cognitive domains (Model 1 in Table 2). Comparing slopes across time showed that this was dictated by an accelerated decline from 6- to 12-year follow-up (memory: χ^2=5.03; df=1; p=0.025; executive function: χ^2=5.80; df=1; p=0.016; processing speed χ^2=11.82; df=1; p=0.001). In women, but not in men, obesity was associated with a faster decline in all domains (See Appendix 3).

Step 2: Effect of age and age-related decline

In persons aged < 65 years at baseline, obesity was significantly associated with a faster decline in processing speed, but not in memory or executive function. Baseline obesity did not predict cognitive decline later in life (≥ 65 years) (see Appendix 4). To further explore the effect of age, we adjusted for age-related variation in rate of cognitive decline by including an age-by-time interaction term in above analyses (Figure 1; Model 2 in Table 2). As expected, being older was associated with a faster decline in all three cognitive domains, yet the association between obesity and cognitive decline became non-significant, suggesting that the association of obesity and cognitive decline was due to the fact that obese individuals tended to be older. The difference in effect estimates between Model 1 and Model 2 (see Table 2) was substantial. For memory this led to 78% decrease in the estimate, and for executive function and processing speed to a decrease of 70% and 91%, respectively. The same phenomenon was found in women.

Step 3: Incident obesity and cognitive decline

Table 3 summarizes the results for the comparisons between participants with incident obesity (n=190) and those with normal weight (n=834). For executive function, but not for memory and processing speed, the former group performed worse at baseline but showed less decline during the study period in comparison with healthy subjects (Model 1 in Table 3). Sex-stratified analyses showed no significant differences between males and females.

Step 4: Effect of age and age-related decline

In persons aged <65 years, incident obesity was not associated with memory or processing speed. For executive function, persons with incident obesity had lower scores at baseline but showed less decline during the study period compared with healthy participants. Obesity did not predict cognitive decline later in life (≥ 65 years) (Appendix 4).

Table 2
Change in cognitive function over time in participants with baseline obesity (n = 545) and those without (n = 1,262)

	Time							
	Baseline		Rate of decline from baseline to 6-year follow-up		Rate of decline from baseline to 12-year follow-up			
Parameter	Difference	95%CI	Difference	95%CI	Difference	95%CI	Obesity x Time χ^2, 2 degrees of freedom	P-value
Memory								
Model 1[a]	0.21	-5.13 to 5.55	-3.83	-9.79 to 2.13	-12.42	-20.26 to -4.58	9.64	0.008
Young[c]	-3.24	-9.92 to 3.45	-1.25	-8.39 to 5.90	-4.21	-12.56 to 4.14	1.00	0.606
Old[d]	0.78	-7.80 to 9.36	-1.48	-12.81 to 9.86	-7.33	-27.91 to 13.25	0.49	0.783
Model 2[b]	-1.80	-7.15 to 3.55	-0.68	-7.01 to 5.65	-2.71	-10.64 to 5.23	0.47	0.793
Executive function								
Model 1	-0.06	-0.16 to 0.05	-0.01	-0.14 to 0.13	0.19	0.02 to 0.36	6.30	0.043
Young	-0.06	-0.18 to 0.06	0.00	-0.15 to 0.14	0.10	-0.09 to 0.28	1.27	0.529
Old	0.01	-0.19 to 0.21	-0.11	-0.38 to 0.17	0.27	-0.17 to 0.70	2.70	0.259
Model 2	-0.02	-0.13 to 0.09	-0.04	-0.18 to 0.10	0.06	-0.12 to 0.23	1.29	0.524
Processing speed								
Model 1	1.14	0.19 to 2.09	-1.24	-2.07 to -0.41	-2.94	-4.15 to -1.72	22.35	< 0.001
Young	1.13	-0.01 to 2.27	-0.76	-1.55 to 0.03	-1.68	-2.60 to -0.76	12.72	0.002
Old	0.31	-1.32 to 1.93	0.08	-1.62 to 1.78	0.64	-2.74 to 4.03	0.16	0.925
Model 2	0.66	-0.29 to 1.61	-0.23	-1.03 to 0.56	-0.26	-1.31 to 0.80	0.37	0.833

a. Model 1 (fully-adjusted): obesity, time, obesity x time, sex, age, age^2, education, baseline smoking, baseline alcohol use, hypertension, type 2 diabetes, depressive symptoms, and cardiovascular disease; b. Model 2: Model 1 + age x time; c. Young: < 65 years; d. Old: ≥ 65 years; Abbreviation: CI, confidence interval.

Adjusting for the potential confounding effect of age on rate of decline in the total sample did not change results: incident obese individuals had worse baseline scores but a less steep decline than non-obese participants (Model 2 in Table 3 and Appendix 5). The difference in effect estimates between Model 1 and Model 2 (see Table 3) was considerable. For memory, the estimate was decreased by 26%, and for executive function and processing speed this decrease was 10% and 70%, respectively.

Step 5: Predictive value of BMI versus WC

In order to compare the predictive value of BMI and WC, additional analyses for baseline obesity were conducted. Obesity according to BMI predicted a faster decline in processing speed (memory: χ^2=3.77; df=2; p=0.152; executive function: χ^2=2.97; df=2; p=0.226; processing speed χ^2=10.41; df=2; p=0.006). Obesity based on WC was associated with a faster decline in all three cognitive domains (memory: χ^2=9.88; df=2; p=0.007; executive function: χ^2=6.30; df=2; p=0.043; processing speed χ^2=20.14; df=2; p<0.001). Again, after adding the age-by-time interaction term, the effect of obesity on cognitive decline was no longer significant for both measures.

Step 6: Effect of chronic obesity

To investigate the effects of being obese over a short or a longer period of time we compared persons who were not obese during the study period with two groups: (1) persons who were obese at baseline but not at follow-up (n=74); and (2) persons who were obese both at baseline and follow-up (n=342). Individual who were obese only at follow-up (incident obesity) were excluded from this analysis. Compared to non-obese participants, the first group showed a decline in all three cognitive domains, whereas the second group showed decline in memory and processing speed, but not executive function. Again, after adding the age-by-time interaction to the model the associations were no longer significant.

Step 7: Testing for non-linear associations between baseline BMI and cognition

Finally, we tested for the presence of linear and quadratic (U-shaped) associations between baseline BMI and cognition, re-entering the nine participants with a BMI < 18.5. There was no association for executive function (quadratic: χ^2=0.56; df=2; p=0.755; linear: χ^2=0.80; df=2; p=0.670). For memory, a quadratic next to a linear association was observed (quadratic: χ^2=13.97; df=2; p=0.001; linear: χ^2=16.17; df=2; p<0.001). For processing speed, we only observed a significant linear relation (quadratic: χ^2=4.65; df=2; p=0.098; linear: χ^2=7.92; df=2; p=0.019). After adding the age-by-time interaction term, the associations for memory were still present. Figure 2 shows the rate of change over twelve year as a function of baseline BMI. The graph suggests a very modest linear decline from the lowest observed baseline BMI of 17 to BMI of 30, followed by a J-shaped trajectory with increasing BMI. Sensitivity analyses suggested that these effects were driven by a very small number of subjects in the lower and upper extremes of

Table 3
Change in cognitive function over time in participants with incident obesity (n = 190) and those without (n = 834)

	Time							
	Baseline		Rate of decline from baseline to 6-year follow-up		Rate of decline from baseline to 12-year follow-up			
Parameter	**Difference**	**95%CI**	**Difference**	**95%CI**	**Difference**	**95%CI**	**Obesity x Time χ^2, 2 degrees of freedom**	**P-value**
Memory								
Model 1[a]	1.04	-6.90 to 8.97	-3.34	-11.80 to 5.12	-6.63	-17.21 tot 3.95	1.51	0.469
Young[c]	-2.55	-11.28 to 6.19	0.13	-9.49 to 9.76	-1.90	-12.34 to 8.54	0.20	0.903
Old[d]	12.17	-5.08 to 29.43	-12.58	-28.62 to 3.47	-8.23	-38.33 to 21.88	2.44	0.295
Model 2[b]	0.68	-7.14 to 8.50	-2.92	-11.20 to 5.36	-4.91	-14.98 to 5.16	0.95	0.621
Executive function								
Model 1	0.19	0.05 to 0.34	-0.21	-0.37 to -0.04	-0.20	-0.39 to -0.02	6.76	0.034
Young	0.22	0.06 to 0.38	-0.17	-0.34 to 0.00	-0.24	-0.43 to -0.05	6.44	0.040
Old	0.09	-0.32 to 0.50	-0.35	-0.79 to 0.10	-0.06	-0.60 to 0.47	2.34	0.310
Model 2	0.20	0.05 to 0.35	-0.21	-0.38 to -0.04	-0.22	-0.41 to -0.04	7.40	0.025
Processing speed								
Model 1	0.07	-1.29 to 1.42	-0.51	-1.43 to 0.41	-0.59	-1.81 to 0.63	1.37	0.504
Young	-0.57	-2.01 to 0.88	-0.72	-1.72 to 0.29	-0.54	-1.65 to 0.57	2.00	0.368
Old	2.24	-0.90 to 5.38	0.87	-1.05 to 2.80	2.61	-0.88 to 6.11	2.30	0.317
Model 2	-0.04	-1.37 to 1.29	-0.37	-1.27 to 0.53	-0.18	-1.22 to 0.86	0.67	0.714

a. Model 1 (fully-adjusted): obesity, time, obesity x time, sex, age, age2, education, baseline smoking, baseline alcohol use, hypertension, type 2 diabetes, depressive symptoms, and cardiovascular disease; b. Model 2: Model 1 + age x time; c. Young: < 65 years; d. Old: ≥ 65 years; Abbreviation: CI, confidence interval.

BMI with the severely obese group (BMI ≥ 40; n=5) showing a significant improvement in memory over the 12-year follow-up in comparison with the healthy weight group (p<0.001). They were older, more often women and had a lower educational level. In addition, they all showed a decrease in bodyweight during the study period. Persons with a BMI between 25 and 35 showed the smallest improvement in memory. When participants with a baseline BMI ≥ 40 were excluded, no significant linear (p=0.129) or quadratic (p=0.192) effects of BMI on rate of change were observed. One participant had a remarkably high baseline BMI value (> 50) and also performed poor on all cognitive tests, but exclusion of this participant in sensitivity analyses showed no substantial influence on the analyses.

Discussion

The present study investigated the association between baseline and incident obesity and cognitive decline over a 12-year follow-up period and potential differences in outcome that are due to methodological choices. Overall, results suggest that age and differences in rate of decline across the adult age range confounded the association between obesity and cognitive decline in this sample.

Initial results were largely congruent with previous reports: baseline (i.e. prevalent) obesity was associated with decline in memory, executive function, and processing speed independently of other cardiovascular risk factors, and more evidently in midlife (< 65 years at baseline). Persons who developed obesity during the study period (incident obesity) seemed to perform worse on executive function at baseline but showed less decline during the study period in comparison with healthy subjects. In addition, WC as a measure of obesity showed stronger and more widespread association with cognitive decline than BMI. However, age-stratification nullified most of the associations. Additional analyses clarified that being older was associated with being obese at baseline or follow-up and a faster cognitive decline. Adjusting for these age-dependent differences in cognitive decline (in models that already adjusted the slope for obesity-related cognitive decline for linear and squared age effects), the associations of obesity and decline were no longer significant. An isolated effect was observed in the form of a curvilinear association between BMI and 12-year change in memory. Initial decline in memory from a healthy bodyweight (BMI from 18.5 to 25) to obesity (BMI ≥ 30) was followed by memory improvement, but the association was driven by a very small number (n=5) of severely obese persons. It was remarkably that all these persons show a decrease in bodyweight during the study period. Possibly, underlying lifestyle changes are responsible for weight loss and improvement in memory. Unfortunately, we were unable to explore this further.

Figure 1

Cognitive trajectories of persons with baseline obesity (dotted line) and those without baseline obesity (solid line). Adjusted for sex, age, age^2, education, obesity x time, age x time, baseline smoking, baseline alcohol use, hypertension, type 2 diabetes, depressive symptoms, and cardiovascular disease (Model 2). For memory and processing speed, a higher score indicates better performance. For executive function, a lower score indicates better performance. Predicted mean scores are estimated marginal means of time by obesity status (obesity or no obesity) with all covariates fixed at their means

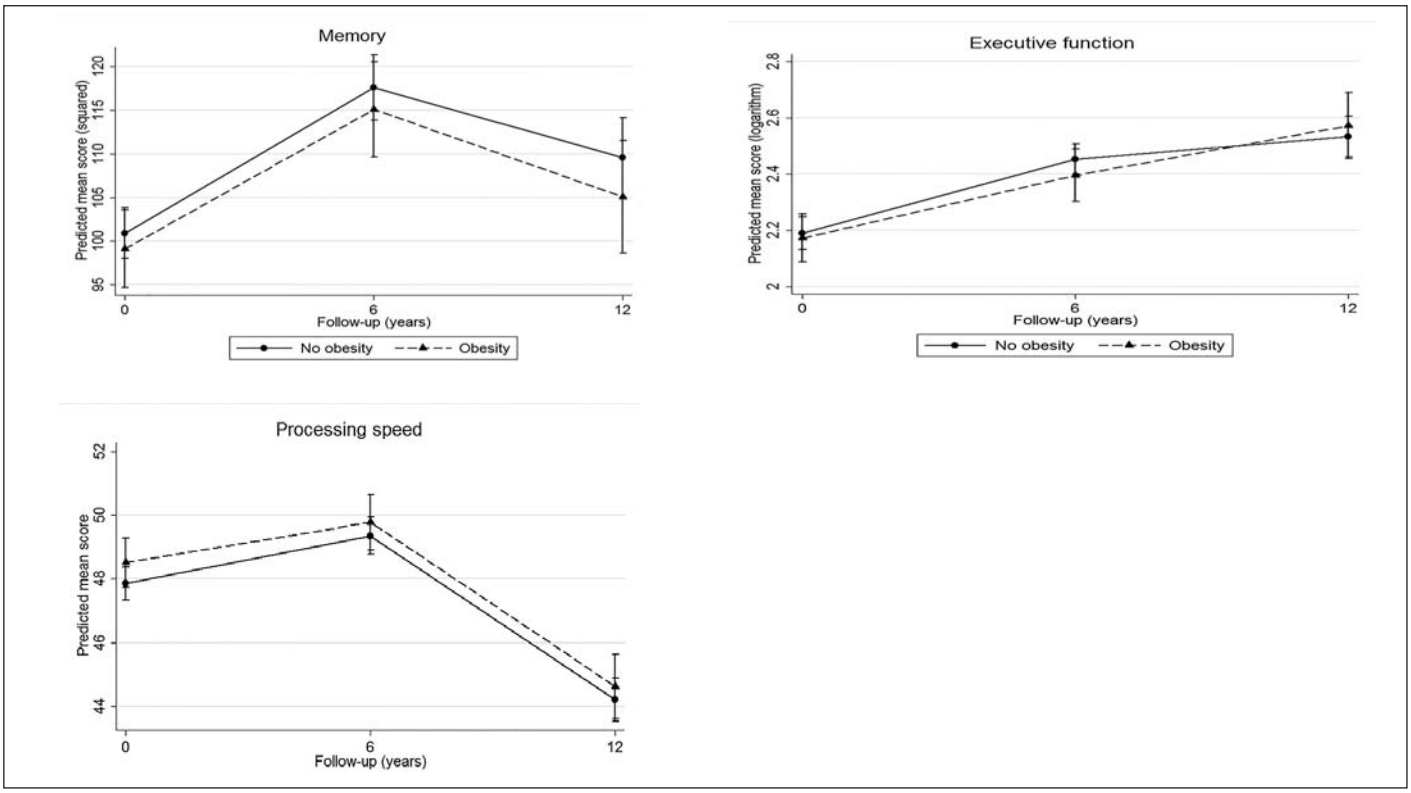
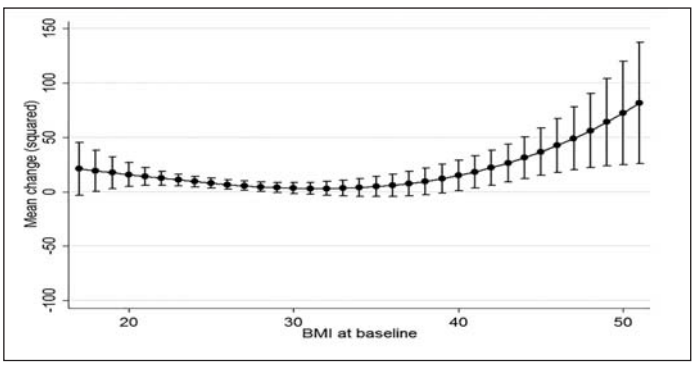


Figure 2

Change in memory performance from baseline to 12-year follow-up. Adjusted for sex, age, age^2, education, Body Mass Index and time, Body Mass Index^2 x time, age x time, baseline smoking, baseline alcohol use, hypertension, type 2 diabetes, depressive symptoms, and cardiovascular disease (Model 2)



Several studies investigated the association between obesity and cognition or dementia risk longitudinally (7, 23). The general notion is that of lower cognitive functioning and an increased risk of dementia in obese subjects, but the found associations are in fact rather inconclusive (7, 23). Out of 14 studies published between October 2009 and December 2012, 7 showed an increased risk for cognitive impairment or dementia, while 2 showed a decreased risk and 5 showed no significant association (7). What is more, four recent studies found that obese persons have a lower dementia risk than people with a healthy weight (8-11). Results might be inconclusive due to methodological differences (e.g. follow-up duration, number of participant, measure of cognition/dementia, measure of obesity, obesity cut-offs). In the present study, the associations varied considerably as a function of age-range and sex of the cohort, and the choice of how to measure obesity. In addition, similar prospective studies like the present one found significant associations between midlife overweight/obesity and cognitive functioning in late-life, but they did not adjust for the confounding effect of age on rate of cognitive decline (24-26). A biological plausible mechanism that links obesity to cognitive impairment still is unknown, even though various pathways have been identified that could play a role in this complex relation. First, obesity is associated with neuroendocrine disturbances, increased presence of adipokines, enhanced pro-inflammatory markers, and hormonal abnormalities, which have deleterious effects on cognition-related brain structures (27, 28) by leading to cerebral atrophy, white matter abnormalities,

and damage to the blood-brain barrier (25, 28-31). Second, obesity is linked to several cardiovascular diseases and diabetes, which, in turn, are associated with an increased risk of cognitive impairment (7, 30, 32), and obesity and metabolic abnormalities might have cumulative effects on cognitive decline (33). Third, there appears to be a bidirectional relation between obesity and cognition: obese persons have an increased risk of developing cognitive impairment (7, 23), while individuals with low cognitive capacities earlier in life have an increased risk of becoming obese later (reverse causality) (34). Obviously, more prospective studies on obesity-related brain changes and their correlations with cognitive decline are needed. Given the present results, such studies should look at both low and high BMI, or both under- and overweight, while carefully studying potential age-related effects.

The strengths of our study include the large sample size across the whole adult age range, the prospective design, serial assessments of obesity and cognitive functioning with a comprehensive neuropsychological test battery, and the availability of relevant covariates. Yet, a number of limitations should be mentioned. First, older participants with multiple comorbidities were more likely to drop out of the study. This could have resulted in an underestimation of the association between obesity and cognition in general, and in individuals aged ≥ 65 years in particular. This is an unfortunate but common phenomenon in aging studies. By choosing random effects models that included covariates related to attrition and using additional attrition weights, we aimed to reduce selection bias. Second, as no information on cholesterol, physical activity, diet, medicine intake and illegal substance abuse was available in MAAS, we were not able to control for these factors. For instance, some studies suggest that dietary factors influence cognitive abilities and that dietary patterns might partly explain the relationship between obesity and lower cognitive functioning (35, 36). Additionally, future public health policies should focus on healthy diet through nutritional education to reduce the increasing prevalence of obesity (37). Third, some of the covariates were assessed by self-report, which may have led to non-differential misclassification. Fourth, due to the non-experimental design of this study we are not able to make causal statements about the relationship between obesity and cognitive decline. The purpose of our explorative analyses was to investigate the influence of a range of methodological choices. For that reason, we did not correct for multiple testing, since this would reduce the chance to find an effect. Fifth, due to insufficient power we were not able to investigate the possible association between underweight (n= 9) and cognitive change. A recent retrospective study found that people who are underweight had an increased risk of dementia (11). This is partly consistent with our finding of a quadratic association between BMI and decline in memory.

This study indicates that the association between obesity and cognitive decline is not at all straightforward and may be highly dependent on methodological choices made during study design and data analysis. In MAAS, a strong confounding effect of age on rate of decline was present. Adjusting for age-differences in cognitive test scores per wave (i.e. not including a term for the interaction with time in linear mixed models) could not control for this. Future studies need to take this into account. Albeit less of an issue if dementia or other binary outcomes are studied, it might be favorable to use age as the time axis to control more rigorously for ageing effects in time-to-event or incidence rates. Also, more studies are needed that investigate biological plausible pathways as well as the complex association between obesity (and BMI and WC) and cognition, leaving room for non-linear relationships and mediating and moderating factors, in order to inform about the probability of obesity being a causal risk factor for decline.

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Author contributions: SK had the idea for the study. SK and KD analyzed and interpreted the data. KD wrote and revised the report. MVB, FV, and SK critically reviewed the report for important intellectual content. All authors contributed to and have approved the final manuscript.

Conflict of Interest: No author of the paper has any competing interests with this study.

Ethical standards: The study protocol of MAAS has been approved by the local ethics committee of Maastricht University Medical Centre. Before participating in the study, all persons were provided with oral and written information. Written informed consent was obtained from all participants at the start of the baseline assessment. Confidentiality of data is guaranteed by using a unique research ID number for each respondent, which enables to identify individuals without using their names. Only the data manager has access to the record that links the ID number with the name of the participant.

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