Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study[1–3]

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ABSTRACT

Background: The extent to which cognition in late midlife is influenced by lifetime obesity is unclear.

Objective: We examined the association between body mass index (BMI) over the adult life course and cognition in late midlife and assessed the cumulative effects of obesity and underweight.

Design: Data from the Whitehall II Study were examined. BMI at 25 y (early adulthood) was self-reported at phase 1 and was measured in early midlife (mean age = 44 y; phase 1) and in late midlife (mean age = 61 y; phase 7). Cognition ($n = 5131$) was assessed in late midlife (phase 7) by using the Mini-Mental State Examination and tests of memory and executive function, all of which were standardized to *T* scores (mean ± SD: 50 ± 10).

Results: Both underweight and obesity were associated with lower cognition in late midlife and with early adulthood, early midlife, and late midlife measures of BMI. Being obese at 2 or 3 occasions was associated with lower Mini-Mental State Examination scores and scores of memory and executive function in analyses adjusted for age, sex, and education [difference (95% CI) in mean *T* scores compared with normal-weight group: −1.51 (−2.77, −0.25), −1.27 (−2.46, −0.07), and −1.35 (−2.45, −0.24), respectively]. Participants who were underweight at ≥2 occasions from early adulthood to late midlife had lower executive function [difference (95% CI) in mean *T* score: −4.57 (−6.94, −2.20)]. A large increase in BMI from early to late midlife was associated with lower executive function.

Conclusions: Long-term obesity and long-term underweight in adulthood are associated with lower cognitive scores in late midlife. Public health messages should promote a healthy weight at all ages. *Am J Clin Nutr* 2009;89:601–7.

INTRODUCTION

The World Health Organization (WHO) reports that ≈1.6 billion adults were overweight and ≥400 million adults were obese in 2005. The epidemic of overweight and obesity is on the rise, and the respective values are projected to be 2.3 billion and >700 million, respectively, by 2015 (1). At the same time, in developed countries, the prevalence dementia is ≈1.5% at age 65 y, and more than doubles every 4 y to reach 30% at 80 y of age (2). Because the proportion of the elderly is growing rapidly, the extent to which lifetime overweight and obesity are related to old-age cognition is of substantial public health relevance.

Overweight and obesity, indicated by body mass index (BMI), calculated as weight (in kg) divided by height squared (m), have been found to be associated with a higher risk of dementia (3, 4). Prospective studies have shown that those with a higher BMI in midlife were at higher risk of cognitive impairment (5–7) and dementia (8–11) later in life, which emphasizes the importance of midlife risk factors in the development of cognitive impairment in late life (12). Furthermore, research suggests that cognition in late midlife, whether memory or executive function, is clinically relevant because individuals with mild cognitive impairment progress to clinically diagnosed dementia at an accelerated rate (13–15). It appears important to use a life-course approach to study the association between BMI and cognition (4). Some long-term prospective studies (6–11, 16–18) measured BMI in midlife, but it remains unknown when the association between BMI and late life cognition becomes apparent. The objective of the present study was to examine the associations of BMI at age 25 y and in early and late midlife with multiple domains of cognition assessed in late midlife. A second objective was to assess whether the effect of obesity on cognition accumulates over the adult life course.

SUBJECTS AND METHODS

Study population

The target population for the Whitehall II Study consisted of London-based office staff, aged 35–55 y, working in 20 civil

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service departments (19). The baseline examination (phase 1) was conducted during 1985–1988 ($n = 10{,}308$; 67% men) and involved a clinical examination and a self-administered questionnaire containing sections on demographic characteristics, health, and lifestyle factors, such as smoking habits, work characteristics, social support, and life events. Clinical examination included measures of blood pressure, body composition, biochemical variables, neuroendocrine function, and subclinical markers of cardiovascular disease. Subsequent phases of data collection have alternated between a postal questionnaire alone [phases 2 (1988–1990), 4 (1995–1996), 6 (2001), and 8 (2006)] and a postal questionnaire and a clinical examination [phases 3 (1991–1994), 5 (1997–1999), and 7 (2002–2004)]. Because of ethnic differences in BMI, we the restricted analyses to the white population of the cohort ($n = 9181$) because the other ethnic populations were not large enough (black, $n = 368$; South Asian, $n = 588$; and others, $n = 79$) to allow further analysis. The ethics committee of the University College London approved the study.

Measures of BMI

Weight at 25 y was self-reported at phase 1. Height and weight were recorded at the clinical examination in early (phase 1: mean ± SD age = 43.8 ± 5.9 y) and late midlife (phase 7: mean ± SD age = 60.8 ± 5.9 y). Weight was measured with all clothes removed except underwear with an electronic Soehnle scale with digital readout (Leifheit AS, Nassau, Germany). Height was measured with a stadiometer while the subjects stood completely erect with their heads in the Frankfort plane. These data were used to calculate BMI. Categorization of BMI was done according to WHO criteria (20): BMI $<$ 18.5, underweight; BMI = 18.5–24.99, normal weight; BMI = 25–29.99, overweight; and BMI $\geq$ 30, obese.

Measures of cognitive function

Cognition was assessed at the clinical examination at phase 7 using a battery of 5 tests, described below. The 30-item Mini-Mental State Examination (MMSE) was used to assess *global cognition* assessing aspects of orientation, registration, attention, calculation, recall, language, and praxis (21).

Short-term verbal memory was assessed with a 20-word free recall test. Participants were presented a list of 20 one- or two-syllable words at 2-s intervals and then had 2 min to recall in writing as many of the words in any order.

Executive function was assessed according to 3 measures. The AH4-I (Alice Heim 4-I) was used to assess reasoning. This test is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty (22). It tests inductive reasoning by measuring the ability of the participant to identify patterns and infer principles and rules. Participants had 10 min to complete this section. We used 2 measures of verbal fluency: phonemic and semantic fluency (23). Phonemic fluency was assessed via "s" words, and semantic fluency via "animal" words. Subjects were asked to recall in writing as many words beginning with "s" and as many animal names as they could. One minute was allowed for each test.

Covariates

The sociodemographic variables used were age, sex and education (no or lower primary school, lower secondary school, higher secondary school, university, and higher university degree). Health behaviors were self-reported at phases 1 and 7 and included smoking status (current, past, and never), units of alcohol (1 unit was equivalent to 8 g) consumed in the past week, frequency of fruit and vegetable consumption assessed on an 8-point scale (ranging from "seldom or never" to "2 or more times a day," and the sum of hours of moderate and vigorous activity per week (24).

Health measures were drawn from phases 1 and 7. The prevalence of coronary heart disease was based on clinically verified events and included myocardial infarction and definite angina (25). Stroke was assessed according to a self-reported measure of physician diagnosis. Diabetes was based on self-reports and glucose tolerance test according to WHO criteria. Serum cholesterol and blood pressure (systolic and diastolic) were measured during the clinical examination.

Statistical methods

The association of BMI at phase 1 with mortality through phase 7 was assessed by using Cox regression and that with nonparticipation in cognitive tests at phase 7 by using logistic regression. These analyses were adjusted for age, sex, and education.

Cognitive test scores were standardized to a *T* score, similar to a *z* score but centered on 50 (mean = 50) with an SD of 10 to allow comparison between tests. For each test, a one-point difference in cognitive *T* score corresponds to one-tenth of an SD difference. The executive function score was defined as the mean of reasoning, phonemic, and semantic *T* scores and was rescaled to have an SD of 10. We also explored an alternative way of evaluating executive function by using the first factor of a principal component analysis on the measures of reasoning and semantic and phonemic fluencies.

We first used multiple analysis of covariance (MANCOVA) to examine the association between BMI and cognition. The use of MANCOVA serves 2 purposes: it takes the correlation between the cognition tests into account and provides a *P* value for the overall association between BMI categories and cognition (26). This method reduces the likelihood of type I error, which is common when multiple outcomes are analyzed separately. For these analyses, we reported the overall test of significance for the association between BMI categories and cognitive function. Subsequently, an analysis of covariance (ANCOVA) was used to calculate mean differences in cognitive *T* scores across BMI categories, with the "normal weight" category as the reference for each of the 3 cognitive tests (MMSE, memory, and executive function) separately. These analyses were first carried out for BMI at 25 y, then for BMI at early midlife (phase 1), and finally for BMI at late midlife (phase 7). All analyses were adjusted for age, sex, and education. All analyses shown herein used the WHO categories for BMI (20). However, we also further examined the shape of the relation between BMI and cognition using sex-specific quartiles of BMI measures and BMI categories with a different cutoff to define underweight (BMI $<$ 20).

Then, a cumulative score of obesity was calculated by counting the number of times (at age 25 y; phases 1 and 7) a person was classified as obese, ranging from 0 to 3 times. A similar cumulative score was calculated for the underweight category. The analysis of the cumulative effects of obesity was restricted to

those who were not underweight at any of the 3 time points ($n = 4899$), and the analysis of the cumulative effects of underweight was restricted to those who were not obese at any of the 3 time points ($n = 4173$). Mean differences in cognitive T scores were calculated with a score 0 as the reference (never obese for the cumulative score for obesity and never underweight for the cumulative score for underweight). These analyses were adjusted first for age, sex, and education (model 1). Subsequently, health behaviors (model 2) were added to model 1, and then measures of health (model 3) were added to model 1. Model 4 includes all covariates. The results of these analyses using covariates at phase 1 are shown; however, we also examined the effects of using covariates at phase 7.

Finally, the association between change in BMI, from phase 1 to phase 7, and cognitive function was examined. The analysis of change compared those in the lowest decile (0-9.9th percentile) and highest decile (90.1st-100th percentile) in the distribution of change with all others. All analyses were performed by using SAS statistical software, version 9 (SAS Institute, Cary, NC).

RESULTS

Sample description and missing data

Of the 9181 white participants at phase 1 (1985–1988), 5645 participated in cognitive testing at phase 7 (2002–2004). Data on BMI, cognitive function, and all covariates were available for 5131 respondents. Compared with the 4050 participants not included in these analyses, this group was younger (60.7 y compared with 61.9 y), had a lower BMI (phase 1: 24.3 compared with 25.0), and had a healthier lifestyle (61.4% compared with 54.7% ate at least one fruit or vegetable per day; $P < 0.0001$).

To assess whether the association between BMI and cognition was underestimated because of premature mortality among the obese participants, we examined the association between BMI at phase 1 and mortality during the mean (± SD) 17.1 ± 2.2 y of follow-up until phase 7. Obese participants at phase 1 had a higher risk of dying during follow-up than did those with a normal weight (hazard ratio: 1.86; 95% CI: 1.36, 2.54). Of the survivors at phase 7 ($n = 8644$), overweight (odds ratio: 1.22; 95% CI: 1.10, 1.36) and obese (odds ratio: 1.44; 95% CI: 1.18, 1.76) participants at phase 1 were less likely to participate in cognitive tests.

Baseline characteristics of the participants included in the analysis on the association between BMI and cognition are presented in **Table 1** as a function of BMI categories at phase 1. All covariates except the marker for diet were associated with BMI. There was no evidence of an interaction between BMI and sex, education, or age (all P for each period > 0.10). Thus, the analyses were not stratified by sex or age.

Association between BMI and cognitive function

Mean differences in cognitive T scores at phase 7 across BMI categories adjusted for age, sex, and education are presented in **Table 2**. The proportion of the population that was either overweight (BMI = 25–29.99) or obese (BMI ≥ 30) increased from 13.6% at age 25 y to 63.1% at mean age 61 y at phase 7. In general, associations with cognition were stronger for BMI at phase 7 than for BMI at age 25 y. MANCOVA adjusted for age, sex, and education showed a overall association between categories of BMI at age 25 y ($P = 0.06$) at phases 1 ($P = 0.02$) and 7 ($P = 0.006$). Compared with the normal-weight participants, those who were underweight at phase 7 had a 3.52-point (95% CI: −6.83, −0.21) lower T score on the MMSE and a 3.96-point (95% CI: −6.83, −1.10) lower T score for executive function. Those who were obese at phase 7 had lower MMSE (mean difference: −0.99; −1.78, −0.21), memory (mean difference: −0.82; −1.57, −0.08), and executive function (mean difference: −0.80; −1.49, −0.12) scores than did their normal-weight counterparts.

TABLE 1
Characteristics of the study population at phase 1 by weight status (1985–1988)[1]

	Underweight	Normal weight	Overweight	Obese	P for heterogeneity
BMI (kg/m^2)	<18.5	18.5–24.99	25–29.99	≥30	—
No. of subjects (%)	62 (1.2)	3232 (63.0)	1580 (30.8)	257 (5.0)	—
Sociodemographic variables					
Age (y)	40.9 ± 4.8[2]	43.3 ± 5.8	44.8 ± 6.0	44.9 ± 5.9	<0.0001
Women [n (%)]	33 (53.2)	886 (27.4)	317 (20.1)	107 (41.6)	<0.0001
University degree or higher [n (%)]	24 (38.7)	1072 (33.2)	413 (26.1)	55 (21.4)	<0.0001
Health behaviors					
Current smoking [n (%)]	8 (12.9)	696 (21.5)	369 (23.4)	68 (26.5)	0.04
Alcohol intake (units/wk)	7.6 ± 10.7	10.7 ± 11.9	13.1 ± 13.3	12.0 ± 16.0	<0.0001
Physical activity (h/wk)	3.1 ± 3.5	4.1 ± 4.2	4.1 ± 4.1	3.2 ± 3.4	0.003
Fruit and vegetable intake [n (%)][3]	41 (66.1)	1999 (61.9)	952 (60.3)	157 (61.1)	0.63
Health measures					
CHD [n (%)]	0	18 (0.6)	10 (0.6)	2 (0.8)	—
Stroke [n (%)]	0	4 (0.1)	3 (0.2)	1 (0.4)	—
Diabetes [n (%)]	0	20 (0.6)	7 (0.4)	2 (0.8)	—
SBP (mm Hg)	118.0 ± 14.6	120.3 ± 13.3	125.0 ± 14.3	127.7 ± 15.0	<0.0001
DBP (mm Hg)	71.0 ± 9.3	74.8 ± 9.3	78.5 ± 9.7	81.4 ± 10.6	<0.0001
Cholesterol (mmol/L)	5.4 ± 1.0	5.7 ± 1.1	6.2 ± 1.1	6.3 ± 1.2	<0.0001

[1] CHD, coronary heart disease; SBP, systolic blood pressure; DBP: diastolic blood pressure.
[2] Mean ± SD (all such values).
[3] At least daily consumption.

TABLE 2
Mean differences (95% CIs) in standardized cognitive scores at phase 7 between categories of BMI ($n = 5131$)[1]

	No. of subjects (%)	MMSE	Memory	Executive function	P^2
BMI at age 25 y	—	—	—	—	0.06
<18.5 kg/m^2	199 (3.9)	−1.04 (−2.45, 0.37)	0.03 (−1.32, 1.38)	−1.19 (−2.43, 0.05)	—
18.5–24.99 kg/m^2	4236 (82.6)	Reference	Reference	Reference	—
25–29.99 kg/m^2	616 (12.0)	−0.36 (−1.20, 0.48)	−1.07 (−1.87, −0.28)[3]	−0.62 (−1.36, 0.11)	—
≥30 kg/m^2	80 (1.5)	−1.17 (−3.33, 0.99)	0.56 (−1.53, 2.65)	0.47 (−1.46, 2.39)	—
BMI at phase 1, mean age: 44 y	—	—	—	—	0.02
<18.5 kg/m^2	62 (1.2)	−1.27 (−3.75, 1.20)	−1.30 (−3.68, 1.08)	−3.89 (−6.07, −1.70)[3]	—
18.5–24.99 kg/m^2	3232 (63.0)	Reference	Reference	Reference	—
25–29.99 kg/m^2	1580 (30.8)	−0.29 (−0.89, 0.31)	−0.41 (−0.98, 0.16)	−0.20 (−0.72, 0.33)	—
≥30 kg/m^2	257 (5.0)	−0.98 (−2.25, 0.30)	−1.11 (−2.31, 0.10)	−1.45 (−2.55, −0.34)[3]	—
BMI at phase 7, mean age: 61 y	—	—	—	—	0.006
<18.5 kg/m^2	36 (0.7)	−3.52 (−6.83, −0.21)[3]	0.03 (−3.09, 3.15)	−3.96 (−6.83, −1.10)[3]	—
18.5–24.99 kg/m^2	1858 (36.2)	Reference	Reference	Reference	—
25–29.99 kg/m^2	2313 (45.1)	−0.08 (−0.68, 0.53)	−0.72 (−1.30, −0.14)[3]	−0.32 (−0.85, 0.22)	—
≥30 kg/m^2	924 (18.0)	−0.99 (−1.78, −0.21)[3]	−0.82 (−1.57, −0.08)[3]	−0.80 (−1.49, −0.12)[3]	—

[1] MMSE, Mini-Mental State Examination. The analyses were adjusted for age at phase 7 (continuous), sex, and education (6 categories).
[2] MANCOVA.
[3] $P < 0.05$.

Subsidiary analyses using sex-specific quartiles of BMI (data not shown but available on request) yielded results similar to those reported on the basis of the WHO categories for BMI, and the lowest and highest quartiles were associated with lower cognitive scores on MMSE and executive function and the 2 highest quartiles were associated with lower memory. To avoid low numbers in underweight participants, we also reanalyzed the data using a cutoff of 20 to define underweight. These results were similar, albeit somewhat attenuated compared with those reported in Table 2.

There was no interaction between the BMI measures at the 3 time periods (all $P > 0.17$), which allowed us to examine the cumulative effects of obesity (**Table 3**) and of underweight (**Table 4**) on cognition. Because few people were obese at all 3 time points ($n = 49$), we regrouped those with cumulative scores of 2 and 3 on obesity in the same category. The same was done for the cumulative score of underweight. In analyses adjusted for age, sex, and education (model 1), cumulative obesity at 2–3 time points was associated with lower mean MMSE, memory, and executive function scores. After further adjustment for health behaviors and health measures (model 4) at phase 1, this association remained for the MMSE score (P for trend = 0.004) with some evidence for a trend also for executive function ($P = 0.04$). With adjustment for all covariates measured at phase 7 (data not shown), the association with executive function was substantially attenuated but that with MMSE remained such that those who were obese on 2–3 occasions had lower scores (mean difference: −1.34; 95% CI: −2.63, −0.05; P for trend = 0.01).

Results of the analysis of the cumulative effects of being underweight are shown in Table 4. Model 1 suggests a trend for the cumulative effect of underweight on MMSE score ($P = 0.02$) and on executive function ($P = 0.0006$) but not on memory ($P = 0.95$). Adjustment for health behaviors and health measures at phase 1, separately (models 2 and 3) and combined (model 4), did not substantially change the results (P for trend 0.02 for MMSE and 0.0009 for executive function). The results were also robust to adjustments for health behaviors and health measures at phase 7 (data not shown; P for trend = 0.03 for MMSE and 0.001 for executive function in an analysis corresponding to model 4).

We also examined the association between change in BMI from phase 1 to phase 7 and cognition. Those in the lowest 10th percentile of change, corresponding to a decrease in BMI (10th percentile: −0.32 in men and −0.53 in women), had, on average, lower executive function scores (mean difference: −0.64; 95% CI: −1.44, 0.16) than the reference group (10th to 90th percentile of change in BMI), but the association was not significant. Those in the 90th to 100th percentile of change, corresponding to an increase in BMI (90th percentile: 4.90 in men and 6.67 in women), had, on average, lower executive function scores (mean difference: −1.31; −2.11, −0.51). After adjustment for health behaviors and health measures at phase 1 and at phase 7, the association with increases in BMI in the 90th–100th percentile remained statistically significant. No association was found with MMSE score and memory.

DISCUSSION

This study suggests that both long-term obesity and long-term underweight are associated with lower cognitive performance in late midlife. Whereas obesity was related to poorer MMSE scores and executive function, underweight was associated with lower MMSE scores and executive function. A major increase in BMI predicted lower performance on executive function tests. These results emphasize the importance of measuring BMI over the life course to estimate the relation between body weight and cognition at older ages.

In the few previous studies conducted in middle-aged populations, a higher BMI in midlife was found to be associated with lower cognitive scores in multiple domains both in cross-sectional (5) and longitudinal (5, 7) analyses. To our knowledge, despite several prospective studies (6–11, 16–18), none examined long-term and cumulative effects of BMI from early adulthood to late midlife. Our results suggest that the effect of obesity on cognition accumulates over the adult life course, examined over a mean duration of 36 y.

TABLE 3
Mean differences (95% CIs) in standardized cognitive scores at phase 7 as a function of the cumulative score of obesity ($n = 4899$)[1]

Cumulative score of obesity[2]	No. of subjects (%)	MMSE	Memory	Executive function
Model 1[3]				
0	3948 (80.6)	Reference	Reference	Reference
1	697 (14.2)	−0.74 (−1.53, 0.05)	−0.08 (−0.84, 0.68)	−0.37 (−1.07, 0.34)
2–3	254 (5.2)	−1.51 (−2.77, −0.25)[4]	−1.27 (−2.46, −0.07)[4]	−1.35 (−2.45, −0.24)[4]
P for trend		0.005	0.09	0.02
Model 2[5]				
0	3948 (80.6)	Reference	Reference	Reference
1	697 (14.2)	−0.78 (−1.57, 0.02)	−0.11 (−0.87, 0.65)	−0.44 (−1.14, 0.25)
2–3	254 (5.2)	−1.51 (−2.78, −0.24)[4]	−1.22 (−2.42, −0.02)[4]	−1.33 (−2.43, −0.23)[4]
P for trend		0.004	0.09	0.01
Model 3[6]				
0	3948 (80.6)	Reference	Reference	Reference
1	697 (14.2)	−0.76 (−1.55, 0.04)	−0.07 (−0.83, 0.69)	−0.28 (−0.99, 0.42)
2–3	254 (5.2)	−1.58 (−2.86, −0.31)[4]	−1.23 (−2.43, −0.02)[4]	−1.16 (−2.28, −0.04)[4]
P for trend		0.004	0.11	0.04
Model 4[7]				
0	3948 (80.6)	Reference	Reference	Reference
1	697 (14.2)	−0.78 (−1.57, 0.02)	−0.09 (−0.85, 0.68)	−0.34 (−1.04, 0.36)
2–3	254 (5.2)	−1.56 (−2.84, −0.28)[4]	−1.16 (−2.37, 0.05)	−1.09 (−2.20, 0.02)
P for trend		0.004	0.12	0.04

[1] MMSE, Mini-Mental State Examination.

[2] Number of times a person was classified as obese in the 3 assessments; restricted to those who were never underweight at the 3 time points.

[3] Model 1: analyses adjusted for age at phase 7 (continuous), sex, and education (6 categories).

[4] $P < 0.05$.

[5] Model 2: model 1 + health behaviors at phase 1 [continuous measures of alcohol intake units, an 8-point scale of consumption of fruit and vegetables and hours of moderate and vigorous physical activity, and categories of smoking status (current, past, and never)].

[6] Model 3: model 1 + health measures at phase 1 [continuous measures of cholesterol, systolic and diastolic blood pressure, and dichotomous measures of cardiovascular disease (diabetes, coronary heart disease, and stroke)].

[7] Model 4: model 1 + health behaviors at phase 1 + health measures at phase 1.

Vascular disease is likely to underlie the association between obesity and cognition because obesity is a risk factor for vascular disease (27), which, in turn, is related to a higher risk of cognitive impairment (12). Adjustment for cardiovascular disease risk factors and diseases in early midlife (phase 1) did not substantially change the associations found in our study or in most previous studies (5, 9–11, 28, 29). However, adjustment for late midlife risk factors (phase 7) had more of an effect. With both adjustments, the association between cumulative obesity and executive function was substantially attenuated after adjustment for cardiovascular disease risk factors (health behaviors, blood pressure, and cholesterol). This suggests that vascular disease explains a large part of the association between obesity and executive function. Other hypotheses on the underlying mechanisms concern the secretions of adipose tissue, such as hormones, cytokines, and growth factors that can cross the blood-brain barrier and affect brain health (4).

Our findings on the association between underweight and cognition in late midlife are novel. This association was seen with the use of BMI measurements both at early and late midlife. The risk of poor cognition increased with increasing underweight in a dose-response manner. There is some evidence that underweight persons in midlife are more likely to develop dementia later in life (10, 11). Our results and those of previous studies suggest that persistent underweight is a risk factor for poorer executive function, because this association was robust to adjustments for all covariates.

Although prospective studies have found that those with higher BMI in midlife were at higher risk of cognitive impairment (5–7, 30) and dementia (8–11, 29, 31), research conducted in elderly persons indicates that a lower BMI is associated with worse cognition (32) and a higher risk of dementia (29, 33, 34). In the elderly, the association between underweight and cognitive function is likely to be the result of preclinical dementia (4). Our results on cross-sectional associations between underweight and cognition in late midlife are consistent with this hypothesis. However, we also show a cumulative effect of underweight over time on cognition, which suggests the existence of other mechanisms. Underweight could be a result of poor health (35); a further possibility is that underweight persons experience a dysregulation in hormone secretion corresponding to that in anorexia, which results in cognitive disorders (4). Further investigation of the mechanisms underlying the cumulative effects of underweight on later cognition would be an important topic for future research.

In studies of cognitive function, different domains of cognition have been found to be associated with BMI: composite scores of cognition (6, 28, 36), memory (5, 37), vocabulary (28), speed processing (28), and reasoning (28, 38). Some studies found no association using the MMSE (32), measures of memory (28), and verbal fluency (28). Increased BMI was also associated with

TABLE 4
Mean differences (95% CIs) in standardized cognitive scores at phase 7 as a function of the cumulative score of underweight ($n = 4173$)[1]

Cumulative score of underweight[2]	No. of subjects (%)	MMSE	Memory	Executive function
Model 1[3]				
0	3948 (94.6)	Reference	Reference	Reference
1	173 (14.2)	−1.10 (−2.60, 0.40)	0.44 (−1.00, 1.88)	−0.70 (−2.02, 0.62)
2–3	52 (1.2)	−2.51 (−5.23, 0.21)	−0.81 (−3.40, 1.78)	−4.57 (−6.94, −2.20)[4]
P for trend	—	0.02	0.95	0.0006
Model 2[5]				
0	3948 (94.6)	Reference	Reference	Reference
1	173 (14.2)	−1.10 (−2.60, 0.40)	0.36 (−1.08, 1.80)	−0.68 (−1.99, 0.63)
2–3	52 (1.2)	−2.47 (−5.20, 0.25)	−0.73 (−3.32, 1.86)	−4.36 (−6.72, −2.00)[4]
P for trend	—	0.02	0.93	0.0009
Model 3[6]				
0	3948 (94.6)	Reference	Reference	Reference
1	173 (14.2)	−1.13 (−2.63, 0.37)	0.42 (−1.02, 1.86)	−0.67 (−1.99, 0.65)
2–3	52 (1.2)	−2.58 (−5.30, 0.14)	−0.87 (−3.46, 1.72)	−4.61 (−6.97, −2.24)[4]
P for trend	—	0.02	0.91	0.0006
Model 4[7]				
0	3948 (94.6)	Reference	Reference	Reference
1	173 (14.2)	−1.14 (−2.64, 0.36)	0.34 (−1.10, 1.79)	−0.66 (−1.97, 0.65)
2–3	52 (1.2)	−2.55 (−5.27, 0.18)	−0.80 (−3.39, 1.79)	−4.39 (−6.75, −2.05)[4]
P for trend	—	0.02	0.89	0.0009

[1] MMSE, Mini-Mental State Examination.
[2] Number of times a person was classified as underweight in the 3 assessments; restricted to those who were never obese at the 3 time points.
[3] Model 1: analyses adjusted for age at phase 7 (continuous), sex, and education (6 categories).
[4] $P < 0.05$.
[5] Model 2: model 1 + health behaviors at phase 1 [continuous measures of alcohol intake units, an 8-point scale of consumption of fruit and vegetables and hours of moderate and vigorous physical activity, and categories of smoking status (current, past, and never)].
[6] Model 3: model 1 + health measures at phase 1 [continuous measures of cholesterol, systolic and diastolic blood pressure, and dichotomous measures of cardiovascular disease (diabetes, coronary heart disease, and stroke)].
[7] Model 4: model 1 + health behaviors at phase 1 + health measures at phase 1.

poorer selective attention in midlife (5); these results were comparable with ours in terms of the population studied, which showed associations with executive function. The MMSE, a test of general cognitive status used to screen for dementia at older ages, also showed robust associations with BMI in our data. Executive function, an umbrella term for various complex cognitive processes involved in achieving a particular goal (39), has been shown to be particularly affected in vascular dementia (40). In our study, executive function was assessed by using measures of reasoning and verbal fluency because these tasks require the combination of different cognitive abilities, such as reasoning, attention, and speed of information processing (22, 23). Obesity is an important risk factor for vascular disease (27) and can influence executive function via the vascular pathway. In support of this hypothesis, adjustment for cardiovascular diseases risk factors decreased the effect size of the association between cumulative obesity and executive function. In contrast, our results provide less consistent evidence for memory as one of the specific cognitive domains influenced by BMI. This lack of association between cardiovascular risk factors (hypertension, cholesterol, and BMI) and memory was also reported previously (6, 41–43).

The strengths of this study included a detailed prospective assessment of BMI over the adult life course, control for a number of potential confounding and mediating factors, and sufficient numbers of participants to examine the effects of underweight. Sensitivity analyses with different categorizations of BMI were also undertaken to check the robustness of the reported associations. There is clear evidence of poor cognition for persons in the underweight and the overweight and obese categories, which suggests an inverse V-shaped association between BMI and cognition. At least 5 limitations of this study are noteworthy. First, although the sample covered a wide socioeconomic range (annual full-time salaries ranging from £4995 to £150,000), data are from white-collar civil servants and cannot be assumed to represent the general population. Second, during the follow-up, 44% of the baseline population was lost and there was a higher risk of death and nonparticipation among obese participants. The participants included in the analyses were healthier, which suggests that the association between obesity and cognition, even in midlife, could be underestimated in this study. Third, weight at 25 y was self-reported at phase 1 and may have been influenced by recall bias, particularly among overweight individuals, who have been shown to underestimate their weight (44). Waist circumference has been suggested to be a better indicator of adiposity than is BMI (45), but longitudinal data on waist circumference were not available in our cohort to test this hypothesis. Finally, we cannot rule out the possibility that the association between BMI and cognition is independent

of confounders such as physical activity and diet, which were self-reported.

In conclusion, we found persistent BMI and persistent underweight over the adult life course to be associated with poor cognition in late midlife. Executive function was identified as being one of the key specific cognitive domains to be associated with BMI. Public health messages should promote a healthy weight at all ages.

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