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Relation between body mass index and cognitive function in healthy middle-aged men and women

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Abstract—*Objective:* To assess whether body mass index (BMI) is associated with cognitive function and cognitive decline in healthy men and women. *Methods:* In this prospective cohort study, we analyzed data from 2,223 healthy workers aged 32 to 62 years at baseline. Medical, psychosocial, and environmental data were collected in 1996 and in 2001. We tested cognitive functions at baseline and at follow-up with word-list learning (four recalls), a Digit–Symbol Substitution Test, and a selective attention test. *Results:* Cross-sectionally, a higher BMI was associated with lower cognitive scores after adjustment for age, sex, educational level, blood pressure, diabetes, and other psychosocial covariables. A higher BMI at baseline was also associated with a higher cognitive decline at follow-up, after adjustment for the above-cited confounding factors. This association was significant for word-list learning. For the changes in scores at word-list learning (delayed recall), regression coefficients were -0.008 ± 0.13, -0.09 ± 0.13, -0.17 ± 0.14, and -0.35 ± 0.14 (p for trend < 0.001) for the second, third, fourth, and fifth quintiles of BMI at baseline when compared with the first quintile. No significant association was found between changes in BMI and cognitive function. *Conclusions:* Body mass index was independently associated both with cognitive function (word-list learning and Digit–Symbol Substitution Test) and changes in word-list learning in healthy, nondemented, middle-aged men and women.

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Different links have been found between dementia and obesity. Several studies have found a weight loss associated with dementia,[1] and a longitudinal study has shown that weight loss often precedes dementia in elderly people.[2] Over longer follow-ups, associations between obesity or overweight and incidence of dementia have been shown in elderly women[3] or in middle-aged adults in the general population.[4] Still, available data are insufficient to suggest a causal link between the two diseases.

The prevalence of both dementia[5] and obesity[6,7] is increasing in epidemic proportions, and a possible implication of this association between the two diseases could be the assessment of specific strategies in dementia prevention, integrating the management of obesity in middle age. However, these relationships between obesity and dementia were documented only at an advanced stage of the two diseases (obesity and dementia), and assessing this link at a preclinical stage would be helpful to improve and adapt preventive measures.

In this study, we investigated the relationships between body mass index (BMI) and cognitive function in a population of apparently healthy men and women. We used a cross-sectional approach to determine whether BMI was associated with cognitive function even in nondemented and nonobese subjects. We also used a predictive approach to study the link between BMI and the changes in cognitive performance over time.

Methods. *Population sampling.* Details regarding the population sampling in the Vieillissement et Santé au Travail (aging and health at work; VISAT) Study have been described elsewhere.[8] Briefly, 4,258 current and former salaried workers were recruited in 1995. Among them, 3,236 subjects agreed to participate in a prospective cohort study (participation rate: 76%). Globally, the participation rates were equally distributed in each age stratum. The sample consisted of 1,660 men and 1,576 women, aged 62, 52, 42, or 32 years when selected. Participants were drawn from occupational physicians' lists of patients in three southern French regions. These lists included all of the salaried workers because, according to French employment law, all workers have a compulsory annual medical examination to assess their aptitude for working. Data were recorded during this examination. Retired workers in the 62-year-old group were specially requested to participate in the study and were screened by the occupational physician from the last company for which they had worked. Data were collected at two cross-sectional times in 1996 and 2001. All subjects participating in the study were volunteers. Authorization

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from the appropriate ethics committee was obtained. French was the first language of all participants.

The questionnaire included the following data.

Personal and medical history. In 1996 and 2001, questionnaires regarding the participants' past and present medical histories were administered by physicians. A self-administered questionnaire was also completed regarding the participants' social, family, and occupational status and lifestyles. Medical history was self-reported, and the participants had to show their medical prescriptions (if any) to the physician. Workers were categorized according to their current occupation, and retired subjects were categorized according to their last occupation. Educational level (number of years of schooling) was collected as a continuous variable and was thus considered as a categorical variable for analyses. Leisure-time physical exercise level was assessed using a four-item variable that was summarized in the following two modalities: from no activity to less than twice a week vs twice a week or more. A questionnaire was made up by a selection of items from the validated French version of the Nottingham Health Profile (NHP).[9] The 17 items corresponded to three of the six dimensions of the NHP: energy level and stamina, emotional reactions, and social isolation. The scores for each dimension ranged from 0 (no problem or absence of limitations) to 100 (all of the listed problems were present). Secondly, the participants gave an overall evaluation of their state of health on a 10-point scale ranging from "very bad" to "very good." Finally, the participants had to fill out the short version of a perceived stress scale,[10] with a total stress score ranging from 4 to 20.

Clinical measurements. The medical examinations were performed in 1996 and 2001 and included height, weight, blood pressure, and heart rate measurements. Blood pressure was measured on the right arm with a standard mercury sphygmomanometer. Measurements were rounded to the nearest 2 mm Hg. Height and weight were measured according to a standardized protocol. Weight was measured using digital scales. Height was measured on a standing position, without shoes, with a flexible nonextendable tape. BMI was calculated as follows: (weight [kg]/height [m^2]). Obesity was defined as BMI $\geq$ 30 kg/m^2.

Cognitive function. All subjects were free of medical diagnosis of dementia at baseline. Individuals' cognitive function was assessed at the two cross-sectional time points through various cognitive tests. The psychometric tests were designed to measure the efficiency of some of the basic cognitive resources considered in the literature to account for young/old differences on a wide variety of tasks. Four tests were administered in the following order: 1) word-list learning in three trials, each followed by immediate free recall; 2) the Wechsler Adult Intelligence Survey (WAIS) Digit–Symbol Substitution Subtest; 3) a selective attention test; and 4) a delayed free recall test of the material learned earlier. 1. The word-list learning test consisted of three trials, each followed by immediate free recall. This test was an adapted version of the Rey auditory verbal learning test. Performance on this type of test turned out to be a sensitive measure of age-related learning differences.[11] Given the longitudinal nature of the study, three different 16-word lists (A, B, and C) were set up so the participants were tested 5 years later using different lists enumerating different words each time. The words were two-syllable, phonetically unambiguous common nouns. 2. The next test was the WAIS Digit–Symbol Substitution Test (DSST), which is considered to be highly loaded by the information processing speed component and very sensitive to aging effects.[12,13] A recent meta-analysis of 141 studies concluded that the robustness of the age–DSST relationship led to the conviction that DSST should be used routinely as a general marker in age-comparative studies.[14] 3. The selective attention test was derived from the Sternberg test[15] and was composed of two subtests. The first one was to scan as quickly as possible a line of 58 alphabetic characters to find a target letter shown in the margin and then cross it out. This task was repeated six times. The second subtest also had six lines of 58 alphabetic characters, but this time, the memory load was greater because the target was to locate one of the four letters shown in the margin. 4. In the last test, delayed free recall, the participants had to write down all the words they could remember from the word list (1) on the provided sheet of paper.

Results regarding word-list learning tests are given as a mean number of cited words, results regarding the DSST are given as a mean score, and results regarding the selective attention test are given as a mean time spent to perform the test. This is why, in all analyses, a better performance corresponds to a higher score for word-list learning and DSST and a lower score (short time) for the selective attention test. All tests were run by senior physicians who had been adequately trained.

Data analysis. Data were analyzed for participants who had the cognitive tests both at baseline (1996) and over the follow-up (2001) and with no missing data regarding BMI and other covariates, i.e., 2,223 subjects (1,143 men and 1,080 women). Subjects were categorized according to quintiles of BMI at baseline. Paired t test and χ^2 test were used to compare the samples' characteristics between baseline and follow-up. All continuous variables had a normal distribution. Homogeneity of variances was tested by using the Bartlett test. One-way analysis of variance and backward linear multivariate regression analyses were used to test the significance in cognitive performance between the quintiles of BMI at baseline. In the cross-sectional step, the dependent variables were the cognitive test scores. In the predictive approach, dependent variables were the changes observed in cognitive test scores between baseline and follow-up. In that approach, we also performed analyses using cognitive test changes as noncontinuous variables. We compared subjects with cognitive decline (subjects with change in scores below the 25th percentile of the distribution for word-list learning and DSST; subjects above the 75th percentile for selective attention test) with subjects with mild cognitive decline or improvement using backward stepwise logistic regression. One analysis was performed for each type of cognitive tests. The significance level for removing variables in regression analyses was $p \leq 0.10$. Tests for trend were performed for each ordinal variable in the final model, including all independent variables significantly associated with cognitive scores or cognitive changes. Statistical analyses were performed using STATA 7.0 statistical software (Stata Corporation, College Station, TX).

Results. *Characteristics of the sample and changes in BMI and cognitive scores throughout time.* The characteristics of the sample are presented in table 1. Among the participants for whom complete data were available, 291 subjects (9%) were obese at baseline (BMI $\geq$ 30 kg/m^2). Diabetes mellitus was present in 45 subjects (2.0%), hypertriglyceridemia was present in 130 subjects (5.8%), 16 subjects had a personal history of stroke (0.7%), and 37 subjects had a personal history of coronary artery disease (1.5%). Sixty-seven subjects (3%) were followed and treated for coexisting thyroid disease. BMI increased significantly between baseline and follow-up. The mean increase in BMI was 0.5 kg/m^2 in the whole sample, and this increase was correlated with age (+0.67, +0.59, +0.57, and + 0.32 kg/m^2 for subjects aged 32, 42, 52, and 62 years at baseline; p for trend = 0.01). There was a slight improvement in cognitive test score between baseline and follow-up: +0.4 words for the word-learning test, +1.6 points for the DSST, and −10 seconds for the selective attention test. The variation was associated with age (e.g., for the learning test: +0.51, +0.41, +0.34, and +0.18 words for subjects aged 32, 42, 52, and 62 years at baseline; p for trend = 0.04).

Cross-sectional associations between BMI and cognitive test performances. At baseline, cognitive performances were lower when BMI was higher, as shown by the variations of the scores across the quintiles of BMI at baseline (table 1). This cross-sectional association between BMI at baseline and cognitive scores persisted after adjustment for age, sex, educational level, physical activity, and region of residence and had a linear shape (figure). Moreover, BMI at baseline was significantly associated with cognitive test scores at follow-up for the four types of tests (univariate analyses) (table 2). Among the word-list learning tests, the delayed recall was the most significantly associated

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Table 1 Characteristics of the sample according to quintiles of BMI at baseline

	Quintile 1 (15–21.5), n = 445	Quintile 2 (21.5–23.4), n = 445	Quintile 3 (23.4–25.2), n = 444	Quintile 4 (25.2–27.7), n = 445	Quintile 5 (27.7–45), n = 444	Total, n = 2,223	p* for trend
Women (%)	340 (76.2)	266 (59.6)	175 (39.6)	132 (29.7)	169 (38.1)	1,080 (48.6)	<0.001
Age at baseline (%)							<0.001
32 years	187 (42.2)	133 (29.8)	127 (28.5)	98 (22.0)	89 (20.0)	634 (28.5)	
42 years	153 (34.3)	160 (35.9)	129 (29.2)	143 (32.1)	119 (26.8)	704 (31.7)	
52 years	73 (16.4)	110 (24.7)	123 (27.6)	123 (27.6)	161 (36.3)	589 (26.5)	
62 years	32 (7.2)	43 (9.6)	65 (14.7)	81 (18.2)	75 (16.9)	296 (13.3)	
Educational level (%)							<0.001
≤9 years	78 (17.5)	88 (19.8)	97 (21.7)	106 (23.8)	159 (35.9)	528 (23.7)	
10–12 years	74 (16.3)	84 (18.9)	82 (18.3)	79 (17.8)	91 (20.3)	409 (18.4)	
>12 years	293 (65.8)	273 (61.4)	265 (60.0)	260 (58.4)	194 (43.8)	1,286 (57.9)	
Occupation (%)							<0.001
Craftsman, manager	35 (7.9)	37 (8.3)	71 (16.0)	63 (14.1)	38 (8.6)	244 (11.0)	
Intermediate	147 (33.0)	153 (34.4)	139 (31.3)	134 (30.1)	117 (26.4)	690 (31.0)	
White collar	177 (39.8)	169 (38.0)	137 (31.0)	142 (32.0)	146 (32.9)	771 (34.7)	
Blue collar	86 (19.3)	86 (19.3)	97 (21.7)	106 (23.8)	143 (32.1)	518 (23.3)	
BMI, kg/m^2	19.8 ± 1.2	22.5 ± 0.6	24.3 ± 0.5	26.3 ± 0.8	30.5 ± 2.8	24.7 ± 3.8	—
Changes in BMI, kg/m^2 (between baseline and follow-up)	+0.83 ± 1.5	+0.55 ± 1.4	+0.47 ± 1.5	+0.65 ± 1.7	+0.40 ± 2.2	+0.58 ± 1.7	<0.001
Systolic BP, mm Hg	121 ± 13	126 ± 15	128 ± 14	133 ± 14	136 ± 15	129 ± 15	<0.001
Diastolic BP, mm Hg	74 ± 9	76 ± 10	77 ± 10	80 ± 10	82 ± 10	77 ± 10	<0.001
Diabetes (%)	4 (0.9)	5 (1.1)	6 (1.4)	10 (2.2)	20 (4.5)	45 (2.0)	0.004
Current smoking (%)	164 (36.8)	139 (31.2)	121 (27.2)	131 (29.4)	119 (26.8)	674 (30.2)	0.005
Daily alcohol consumption (%)	74 (16.6)	122 (27.4)	144 (32.4)	158 (35.5)	142 (32.0)	640 (28.8)	<0.001
Physical activity (%)							<0.001
None to < twice a week	220 (49.4)	188 (42.2)	197 (44.4)	225 (50.6)	249 (56.1)	1,029 (46.3)	
Twice a week or more	225 (50.6)	257 (57.8)	247 (55.6)	220 (49.4)	195 (43.9)	1,194 (53.7)	
Word-list learning words							
Recall 1	6.3 ± 1.9	6.2 ± 1.9	6.0 ± 1.9	5.7 ± 1.8	5.5 ± 1.9	5.9 ± 1.9	<0.001
Recall 2	8.8 ± 2.5	8.6 ± 2.4	8.4 ± 2.4	8.0 ± 2.4	7.8 ± 2.3	8.3 ± 2.4	<0.001
Recall 3	10.6 ± 2.7	10.2 ± 2.6	10.1 ± 2.5	9.5 ± 2.6	9.2 ± 2.6	9.9 ± 2.6	<0.001
Delayed recall	8.6 ± 2.8	7.8 ± 2.8	7.8 ± 2.7	7.2 ± 2.7	6.9 ± 2.7	7.6 ± 2.8	<0.001
DSST score	55.0 ± 15.1	53.2 ± 13.8	51.3 ± 13.9	49.0 ± 13.8	47.1 ± 14.5	51.2 ± 14.5	<0.001
Selective attention, seconds	201.3 ± 90	201.9 ± 87	208.0 ± 100	219.5 ± 101	226.1 ± 100	211.4 ± 96.5	<0.001
Perceived health	8 (6–9)	8 (6–9)	7.5 (5–9)	7.5 (5–9)	7 (5–9)	7 (5–9)	0.17
Nottingham Health Profile score/100							
Energy	18.5 ± 28.9	15.4 ± 26.6	14.1 ± 26.9	14.7 ± 26.5	18.9 ± 21.4	16.3 ± 28.2	0.03
Emotional reactions	17.0 ± 18.5	14.5 ± 16.6	14.1 ± 17.6	13.4 ± 17.0	15.8 ± 18.8	15.0 ± 17.7	0.02
Social isolation	6.5 ± 14.8	5.7 ± 13.6	4.7 ± 13.4	5.8 ± 13.9	6.0 ± 14.5	5.7 ± 14.0	0.15
Perceived stress score/20	8.8 ± 2.9	8.2 ± 2.8	8.1 ± 2.9	8.2 ± 2.9	8.4 ± 3.0	8.4 ± 2.9	0.002

BMI = body mass index; BP = blood pressure; DSST = Digit–Symbol Substitution Test.

with BMI and was chosen to present the results. Similar significant effects were found for the three immediate free recalls. After adjustment for age, sex, educational level, diabetes, systolic blood pressure, and perceived health score, the relationship persisted with a significant linear trend for word-list learning and DSST. Regarding the selective attention test, there was an interaction between BMI and sex because the association was significant in women only. Higher BMI changes were associated with poorer performances on the selective attention test at follow-up.

Longitudinal associations between BMI and changes in cognitive test scores. We investigated the relationship between BMI at baseline and the changes in cognitive test scores between baseline and follow-up. Results are presented in table 3. In a univariate analysis, old age, low educational level, daily alcohol intake, physical activity, perceived health, the presence of diabetes and high systolic blood pressure were associated with a poor improvement in cognitive test scores. Male sex was also associated with a lower change in word-list learning and the DSST. Whatever the test, we found a negative association between BMI at baseline and the improvement of cognitive performance, with a statistically significant linear trend. After adjustment for age, sex, region of residence, educational level, baseline cognitive score, and other medical or psychosocial confounders (depending on the cognitive test), the negative association between BMI and the progression in cognitive performance remained significant for word-list learning. There was no interaction between BMI and gen-

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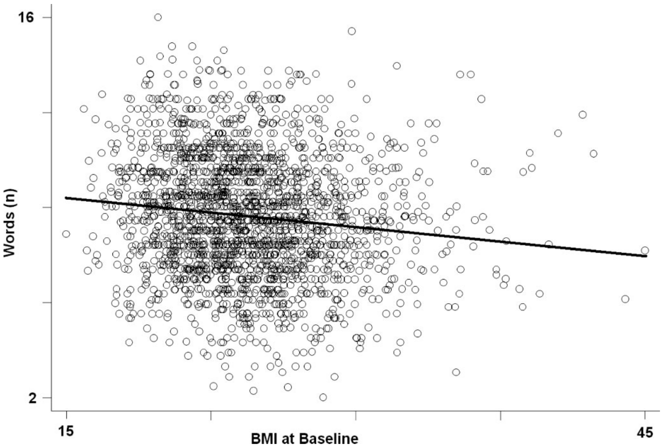

Figure. Relationship between body mass index (BMI) and score at the delayed memory recall test at baseline, after adjustment for age, sex, educational level, physical activity, and region of residence. The black continuous line is the regression line in a multiple linear regression analysis ($\beta = -0.08$ [-0.11, -0.05]). Results are presented for the delayed recall, but a similar shape is obtained from other cognitive tests.

der, whatever the test. In these multivariate models, the independent effect of systolic blood pressure stopped when BMI at baseline was introduced into the model. Consistent results were obtained when comparing subjects with high cognitive decline with those with mild cognitive decline or improvement (table 4). In that analysis, the association between BMI and decline in DSST remained significant after multivariate adjustment.

Discussion. Higher BMIs were associated with poorer cognitive performances in a linear way. This was obtained for the four types of tests, after adjustment for the main confounding factors, and in the two sets of data. Second, higher BMIs at baseline were associated with a higher cognitive decline. That relationship was significant in a multivariate analysis for word-list learning. Third, we found no association between changes in BMI and cognitive functions.

This work has provided a panel of coherent results on the relationship between BMI and cognitive function. Indeed, the relationship was assessed in the cross-sectional approach both at baseline and over the follow-up and, in the longitudinal approach, through the relationship between BMI and cognitive changes or cognitive decline.

This longitudinal data collection has provided various data and measurements such as anthropometric measurements and several psychometric tests, assessing the efficiency of different cognitive resources in a large sample of apparently healthy subjects. Therefore, we could analyze the relationships between BMI and cognitive performance with no need to select a group of obese subjects. This study was also the first one taking into account several psychosocial variables, such as perceived health or stress, which may be powerful confounders in the relationship between BMI and cognitive status. However, measurement errors are likely to be lower for height and weight than for blood pressure and psychosocial factors. This could partly explain the strength and significance of BMI in multivariate analyses.

Because baseline and follow-up cognitive scores are strongly correlated, the association between BMI at baseline and cognitive scores at follow-up should

***Table 2** Relationship between BMI and cognitive test scores at follow-up in univariate and multivariate analyses (linear regression)*

	Word-list learning, delayed recall, number of cited words, β ± SE		Digit–Symbol Substitution Test score, β ± SE		Selective attention time, β ± SE		
						Multivariate	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Men	Women
Age‡	−0.92 ± 0.05*	−0.68 ± 0.05*	−5.97 ± 0.33*	−4.37 ± 0.33*	+20.96 ± 1.67*	+20.31 ± 0.50*	+16.41 ± 2.71*
Female sex (vs male)	+0.86 ± 0.12*	+0.62 ± 0.11*	+4.35 ± 0.71*	+2.64 ± 0.64*	+0.57 ± 3.88	—	—
BMI at baseline							
1st quintile (ref)	—	—	—	—	—	—	—
2nd quintile	−0.37 ± 0.18†	−0.14 ± 0.17	−1.60 ± 1.22	−0.20 ± 0.99	−0.96 ± 5.52	−15.50 ± 10.25	1.15 ± 6.8
3rd quintile	−0.84 ± 0.18*	−0.50 ± 0.17*	−2.71 ± 1.22*	−0.53 ± 1.00	3.62 ± 5.52	−21.16 ± 9.63	4.9 ± 7.9
4th quintile	−1.22 ± 0.18*	−0.74 ± 0.17*	−6.16 ± 1.11*	−3.04 ± 1.00†	12.62 ± 5.52†	−13.99 ± 9.48	16.7 ± 7.8†
5th quintile	−1.43 ± 0.18*	−0.84 ± 0.17*	−7.90 ± 1.10*	−2.92 ± 1.00†	16.71 ± 5.52†	−14.66 ± 9.71	17.8 ± 8.6†
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.50	0.001
BMI changes, kg/m^2	+0.02 ± 0.03	—	−0.05 ± 0.21	—	−0.14 ± 1.14		—
R^2	—	0.23		0.17		0.17	0.17

In multivariate analyses, coefficients are adjusted for educational level, diabetes, systolic blood pressure, daily alcohol intake, physical activity, perceived health score, perceived stress score, and social isolation (Nottingham Health Profile). R^2 denotes the coefficient of determination.

* $p < 0.001$.
† $p < 0.05$.
‡ β for trend across age classes.

BMI = body mass index.

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Table 3 Variables associated with changes in cognitive test scores between baseline and follow-up (linear regression)

	Changes in word-list learning, delayed recall, number of cited words, β ± SE		Changes in Digit–Symbol Substitution Test score, β ± SE		Changes in selective attention time, β ± SE	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age‡	−0.45 ± 0.01*	−0.29 ± 0.04*	−0.42 ± 0.02*	−2.53 ± 0.32*	14.03 ± 1.66*	11.77 ± 1.69*
Female sex (vs male)	+0.32 ± 0.09*	+0.37 ± 0.09*	−0.35 ± 0.02*	—	+4.01 ± 3.88	—
BMI at baseline						
1st quintile (ref)	—	—	—	—	—	—
2nd quintile	−0.07 ± 0.13	−0.008 ± 0.13	−0.44 ± 0.94	0.28 ± 0.91	2.39 ± 5.21	−0.80 ± 5.11
3rd quintile	−0.19 ± 0.14	−0.09 ± 0.13	−0.43 ± 0.94	0.61 ± 0.93	5.62 ± 5.23	2.15 ± 5.27
4th quintile	−0.28 ± 0.14†	−0.17 ± 0.14	−2.37 ± 0.94†	−1.10 ± 0.94	6.60 ± 5.22	2.57 ± 5.38
5th quintile	−0.58 ± 0.14*	−0.35 ± 0.14†	−2.96 ± 0.94†	−0.92 ± 0.96	10.23 ± 5.23†	0.84 ± 5.35
p for trend	<0.001	<0.001	<0.001	0.14	<0.001	0.69
BMI changes, kg/m^2	−0.02 ± 0.02	—	−0.02 ± 0.18	—	2.5 ± 1.14	—
R^2	—	0.27	—	0.19	—	0.32

All coefficients are adjusted for cognitive test score at baseline and region of residence. In multivariate analyses, coefficients are adjusted for educational level, diabetes, systolic blood pressure, daily alcohol intake, physical activity, perceived health score, perceived stress score, and energy (Nottingham Health Profile). R^2 denotes the coefficient of determination.

* $p < 0.001$.
† $p < 0.05$.
‡ β for trend across age classes.

BMI = body mass index.

not be considered as strictly longitudinal, unlike the association between BMI and cognitive changes.

Our sample was not strictly population based, and this might be considered as a limitation to the study for the generalization of our results. However, the overall distribution by socioprofessional category was close to the distribution observed at the national level.[16] Moreover, in our sample BMI, blood pressure and the prevalence of diabetes were either similar to or lower than the prevalence found in several European studies, France included.[17,18] A potential healthy-worker effect may account for this difference because nonworking subjects younger than 62 years were not recruited. Still, this impact might be considered as minor because BMI is known to be lower in the south of France than in other countries geographically close.[19] Moreover, this potential healthy-worker effect, if it exists, would be logically responsible for a decrease in the strength of the relationship between BMI and cognitive function. This particular recruitment enabled the inclusion of apparently healthy subjects, free of severe alteration of cognitive function.

The majority of the participants were born in Caucasian countries. We were not allowed to analyze the influence of racial category because French law for biomedical research strictly forbids obtaining information on racial category or ethnic origin from patients.

Of the 3,236 persons initially included, 1,013 were not included in the analyses (lost to follow-up or missing data). Those subjects, when compared with the participants, were overall older. After adjustment for age, the significant differences were a lower

Table 4 Association between BMI at baseline and cognitive decline in univariate and multivariate analyses (logistic regression)

	Decline in word-list learning, change <25th percentile (−1 word) vs ≥25th percentile, OR (95% CI)		Decline in DSST, change <25th percentile (−4.3) vs ≥25th percentile, OR (95% CI)		Decline in selective attention score, change >75th percentile (+40 seconds) vs ≤75th percentile, OR (95% CI)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
BMI at baseline						
1st quintile (ref)	1	1	1	1	1	1
2nd quintile	0.82 (0.57–1.18)	0.78 (0.54–1.11)	1.09 (0.79–1.52)	1.01 (0.72–1.42)	0.96 (0.70–1.32)	0.85 (0.61–1.18)
3rd quintile	1.18 (0.83–1.67)	1.06 (0.74–1.52)	1.20 (0.87–1.68)	1.07 (0.76–1.50)	1.44 (1.06–1.97)	1.24 (0.90–1.71)
4th quintile	1.18 (0.83–1.67)	1.05 (0.72–1.53)	1.93 (1.40–2.67)	1.69 (1.20–2.37)	1.01 (0.73–1.39)	0.85 (0.60–1.20)
5th quintile	1.49 (1.05–2.11)	1.24 (0.84–1.80)	2.05 (1.47–2.83)	1.68 (1.18–2.37)	1.15 (0.83–1.59)	0.86 (0.60–1.22)
p for trend	0.006	0.09	<0.001	<0.001	0.35	0.48

All coefficients are adjusted for region of residence. In multivariate analyses, coefficients are adjusted for age, sex, educational level, diabetes, systolic blood pressure, daily alcohol intake, physical activity, perceived health score, perceived stress score, and energy (Nottingham Health Profile).

BMI = body mass index; OR = odds ratio; = DSST = Digit–Symbol Substitution Test.

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educational level and a higher prevalence of diabetes in these subjects, whereas cognitive scores at baseline were similar. The cross-sectional association between BMI and cognitive score at baseline was found in those subjects, as it was in the participants.

The slight improvement of cognitive test score throughout time might be somewhat surprising. This statistically but not clinically significant improvement could be explained by the relatively young age of our subjects, involving a low incidence of cognitive decline over a period of 5 years, but also by an increased familiarization with the test at follow-up. Repeated practice of cognitive tests can offset the expected time-related (aging) cognitive decline, and some studies have even reported reliable improvements in test performance at follow-up, despite the use of a different word list at each examination.[20] Improvement in cognitive performances observed when participants are repeatedly assessed with the same tests is a persistent methodologic problem inherent to longitudinal studies.

The functional significance of cognitive changes in our sample is difficult to assess because functional scales used in elderly people are not adapted to this healthy working population. We did not collect any direct index of work performance. However, slight functional changes in relation to cognitive changes cannot be excluded. For example, 25% of subjects who most declined (<25th percentile in change in DSST) thought they were unable to keep up their occupation until retirement, vs 19% in subjects who presented no decline ($p = 0.02$). Subjects who most declined stopped working a mean of 1.75 times for health reasons in the year before the second survey, vs 1.60 times for subjects who did not decline ($p = 0.01$).

We found no association between changes in BMI and cognitive performance, unlike a study recently conducted in older subjects.[21] Another study involving two groups of young adults, an obese and a nonobese group, did not demonstrate this association, after adjustment for educational level.[22] It might be due either to a lack of association between BMI changes and cognitive function early in life, or to a follow-up period too short to observe important BMI variations in our study.

Relationships between BMI and cognitive test scores have already been evidenced in a few previous studies, such as the Framingham Study.[23] In that study, obesity and hypertension were both independently associated with the scores of cognitive tests performed 4 to 6 years later, in a sample of 1,421 subjects aged 55 to 88 years. However, the study design included only one measurement of cognitive function.

The longitudinal link between BMI and cognitive changes has been reported in a recent study.[4] However, that work investigated the link between obesity (BMI $\geq$ 30 kg/m^2) and the subsequent occurrence of clinical dementia. Our study has extended this relationship to healthy subjects, even in the lowest classes of BMI, and for nonpathologic cognitive function. This relationship remained significant after taking into account the major confounding factors represented by age, sex, educational level, and quality of life. Several hypotheses accounting for this issue could be put forward.

One suggests a direct action of adiposity on neuronal tissue through neurochemical mediators produced by the adipocyte.[24] For example, several studies support the role played by leptin not only in the modulation of food intake, but also in relation to learning and memory processes. This hypothesis is confirmed by animal models of knockout-leptin mice showing morphologic and functional modifications of the hypothalamus and cognitive impairment.[25,26] In humans, another study has reported a link between obesity or overweight and temporal atrophy on CT in elderly women.[27]

Another hypothesis focuses on atherosclerosis and vascular factors involved in dementia. Cardiovascular diseases are associated with both obesity and dementia (not only vascular dementia but also Alzheimer disease).[28] Therefore, they could be both a physiopathologic explanation and a confounding factor. To eliminate the potential effect of an evolving vascular disease, analyses were performed a second time after exclusion of the 53 subjects with personal history of ischemic stroke or coronary disease. The regression coefficients remained similar and significant.

Diabetes and, more generally, insulin resistance must be included in this group of physiopathologic hypotheses because they are associated with BMI and with cognitive function in elderly subjects.[29,30] The effect could be mediated by the atherogenic action of diabetes but also by a direct action of insulin on neuronal structures.[31,32] Recently, one study demonstrated the formation of amyloid plaques in a model of insulin-resistant mice.[33] In our study, adjustment for diabetes, blood pressure, or hypertriglyceridemia did not affect the results regarding BMI, thus making insulin resistance unlikely as the only explanation for our results. However, our data were not sufficient to explore insulin resistance in our subjects in detail.

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Relation between body mass index and cognitive function in healthy middle-aged men and women

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