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Obesity

Prospective Association between Body Mass Index at Midlife and Healthy Aging Among French Adults

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Objective: To assess the association between midlife body mass index (BMI) and healthy aging (HA) in the French SU.VI.MAX cohort.

Methods: HA was assessed in 2007 to 2009 among 2,733 individuals, aged 45 to 60 years and free of diabetes, cardiovascular disease and cancer at baseline (1994-1995). HA was defined as not developing any major chronic disease, good physical and cognitive functioning, no limitations in instrumental activities of daily living, no depressive symptoms, no health-related limitations in social life, good overall self-perceived health, and no function-limiting pain. Associations between anthropometric indicators (measured in 1995-1996) and HA were assessed using robust-error-variance Poisson regression.

Results: After adjustment for potential confounders, BMI (continuous) was negatively associated with HA: relative risk (RR) = 0.97 (95% confidence interval = 0.96-0.99). Moreover, the detrimental role of obesity ($RR_{obesity\ vs.\ normal\ weight} = 0.67$ [0.51-0.88]) was substantially stronger than that of overweight ($RR_{overweight\ vs.\ normal\ weight} = 0.91$ [0.81-1.01]). Furthermore, while metabolically healthy individuals with overweight had a similar HA probability as metabolically healthy individuals with normal weight, metabolically unhealthy overweight individuals had a substantially lowered HA probability.

Conclusions: This study provides novel evidence that an elevated BMI at midlife may jeopardize the preservation of health during aging. Our results also highlight the importance of maintaining a healthy metabolic profile during midlife.

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Introduction

There has been a dramatic increase in the proportion of individuals with obesity in the world over the past few decades. According to estimations of the World Health Organization, in 2014, more than 600 million adults presented obesity (1). In France, in the same year, the overall estimated prevalence of obesity was 17% (2). Because obesity is known as a major risk factor for noncommunicable diseases, the increasing prevalence of obesity is related to an important burden of various age-related chronic diseases (3). There is plentiful scientific evidence on the association of anthropometric measures with specific diseases or health conditions, notably type 2 diabetes mellitus (4), cardiovascular disease (5), several types of cancer (6), and dementia or other cognition-related health outcomes (7). The association of central obesity with dyslipidemia, altered glucose metabolism, and elevated blood pressure has notably led to the creation of the well-known "metabolic syndrome" concept (4). A

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Author contributions: SH, PG, and EKG designed the study (development of the concept, design, and protocol of the SU.VI.MAX/SU.VI.MAX 2 studies and coordination of data collection); IR and KEA performed the statistical analysis and wrote the article; EKG and KEA provided methodological guidance; IR, MA, KEA, VAA, SH, PG, and EKG were involved in interpreting the results and editing the manuscript for important intellectual content; EKG, KEA, and IR had primary responsibility for the final content. All the authors read and approved the final manuscript.

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French national representative study conducted from 2006 to 2007 (8) estimated that 21.1% of the adult population corresponds to the criteria of the metabolic syndrome that were laid down in the Joint Interim Statement (JIS) (4).

Moreover, it has been estimated that 31% of the French population will be 60 years or older by 2035 (9). Given these drastic demographic changes, the development of prevention strategies aimed at limiting and delaying age-related health decline is of high importance. Because the aging process affects a large variety of the body's functions and organ systems, multidimensional concepts of overall healthy aging have emerged (10). Such concepts are complementary to the investigation of particular diseases or bodily functions. While the study of isolated health aspects allows for the elucidation of specific elements of disease etiology and pathophysiology, multidimensional concepts of health during aging allow for a much broader point of view—and for the investigation of whether specific environmental factors favor an overall better state of health during aging. For the design of public health strategies, it is important to both evaluate the impact of modifiable factors on specific diseases and to obtain an idea of their relation to the general state of health of aging individuals. Moreover, the use of healthy aging concepts that include both components with a biomedical focus and components with a psychosocial focus enhances the promotion of a holistic consideration of the aging process. This has been suggested as important for the development of "people-centered" prevention strategies, as both dimensions are crucial for the well-being of aging individuals (11).

The majority of healthy aging concepts are based on the definition suggested by Rowe and Kahn that characterizes healthy aging (or "successful aging") as being at low risk of disease or disability, combined with the presence of high levels of cognitive and physical functioning and an active engagement with life (12). However, a variety of different definitions have been published, showing important differences with respect to the choice of the included healthy aging components and the indicators used to measure those dimensions (10). The definition used in this article follows the general outline of the concept from Rowe and Kahn, while putting an additional emphasis on mental health and perceived health, in line with suggestions from Cosco et al. (10). Moreover, the dimension "active engagement with life" was approximated by the absence of important health-related limitations of social functioning, as no other data related to an active engagement with life were available.

Current evidence indicates that individuals within the normal body mass index (BMI) range have the potential for better survival and health compared with individuals with overweight or obesity. Specifically, the available prospective observational studies suggest that elevated BMI or an increased body fat percentage plays a detrimental role with respect to healthy aging (13-19). However, studies that have investigated the relationship between anthropometric measures at midlife and healthy aging based on multidimensional concepts are scant (13,15,17).

Consequently, in the current study, our primary objective was to investigate the association of BMI and BMI group status (normal, presenting overweight, or presenting obesity) at midlife with multidimensional concepts of healthy aging, in a sample of French adults.

As a secondary objective, we aimed to test the hypothesis that individuals with obesity who do not display associated metabolic disorders have a lower risk of worse overall health (20). This hypothesis has been critically discussed in the literature, as findings from observational studies indicate that "metabolically healthy obesity" may only be a transient physiological state that tends to eventually evolve into obesity associated with manifest metabolic dysfunction (21). In previous studies, the risk of developing diabetes or cardiovascular disease was found to be substantially increased even among metabolically healthy individuals with obesity (as compared to metabolically healthy normal-weight individuals), while metabolically unhealthy individuals with obesity appeared to be at a particularly high risk (22,23). Hence, while we did not hypothesize that metabolically healthy individuals with obesity would present a similar probability to age healthily as metabolically healthy normal-weight individuals, we aimed to specifically investigate healthy aging status in participants with different combinations of BMI group status and metabolic health status (while using metabolically healthy normal-weight participants as the reference group).

Methods

Study population

The Supplementation with Vitamins and Mineral Antioxidants (SU.VI.MAX) study (1994-2002) was a randomized, double-blinded, placebo-controlled trial testing the effect of daily supplementation with antioxidant vitamins and minerals at nutritional doses on the incidence of cancer, cardiovascular disease, and overall mortality in 12,741 individuals (24). A postsupplementation observational study, the SU.VI.MAX 2 study, was conducted in 2007 to 2009 among 6,850 subjects who agreed to participate.

The SU.VI.MAX and SU.VI.MAX 2 studies were conducted in accordance with the Declaration of Helsinki and were approved by the ethics committee for studies with human subjects of the Paris-Cochin Hospital (CCPPRB no. 706 and no. 2364, respectively) and the Commission Nationale de l'Informatique et des Libertés (CNIL no. 334641 and no. 907094, respectively). All participants provided written informed consent. The SU.VI.MAX trial was registered at www.clinicaltrials.gov/ct2/show/NCT00272428.

Our study sample consisted of 2,733 participants in the SU.VI.MAX study who were 45 to 60 years old at inclusion and free from major chronic diseases at baseline, with available data on baseline BMI, baseline metabolic health status (defined below), baseline covariables, and healthy aging status at follow-up (Figure 1). Of note, data on healthy aging status was only assessed among participants of the SU.VI.MAX 2 study (and this assessment was incomplete for some participants).

Data on healthy aging status

The main outcome measure of our study was healthy aging, defined using a multidimensional concept including the following eight criteria (25): absence of incident cancer, cardiovascular disease, or type 2 diabetes during follow-up; good cognitive functioning; good physical functioning; absence of limitations in instrumental activities of daily living; absence of depressive symptomatology; absence of health-related limitations in social life; good overall self-perceived health; and absence of function-limiting pain. Healthy aging status was defined as a dichotomous outcome variable (yes/no), and participants were defined as healthy agers if all eight components were

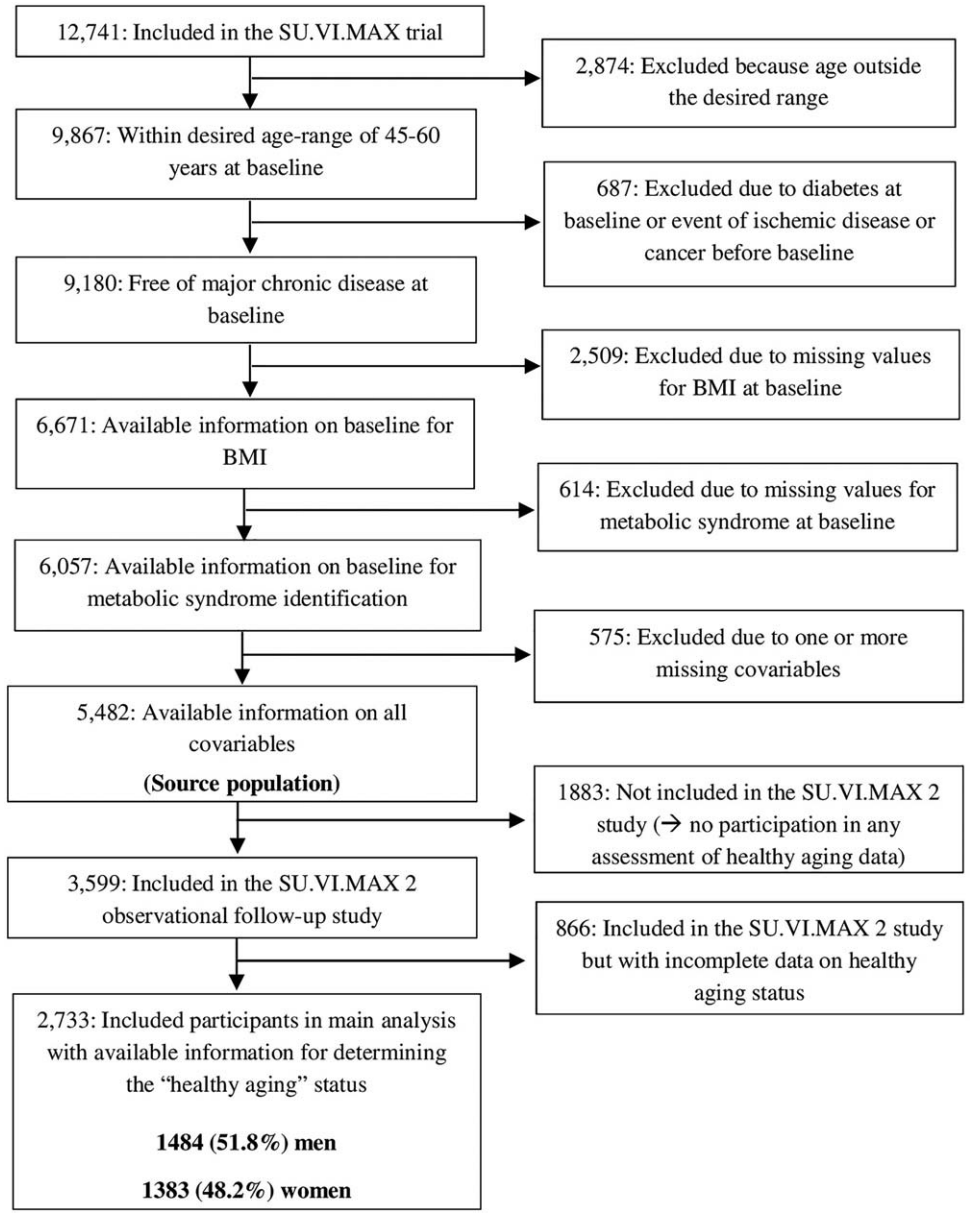

Figure 1 Selection of participants from the SU.VI.MAX (SUpplémentation en VItamines et Minéraux AntioXydants) and SU.VI.MAX 2 studies, France, 1994-2009.

met. Healthy aging status was determined between 2007 and 2009, after an average follow-up period of 13 years. More details have been published elsewhere (25) and are summarized in Table 1.

Anthropometric and metabolic data (1994-1996)

Weight was measured to the nearest 0.5 kg using an electronic scale (Seca, Hamburg, Germany), with participants wearing indoor clothing and no shoes. Height was measured to the nearest 0.5 cm with a wall-mounted stadiometer under the same conditions. Blood pressure measurements were recorded using a standard mercury sphygmomanometer.

Baseline fasting blood glucose, serum triglycerides, serum total cholesterol, and serum apolipoprotein B were measured as previously described (26). Planella's equation and the Friedewald formula were used to calculate high-density lipoprotein cholesterol concentrations from total cholesterol and apolipoprotein B (26).

Definition of metabolic health status

We defined metabolic health status using a modified version of the "metabolic syndrome" concept (27). A participant was considered to have impaired metabolic health if he or she corresponded to two or more of the following criteria: triglycerides $\geq$ 1.7 mmol/L or lipid-

TABLE 1 Healthy aging—definition developed for the SU.VI.MAX study[a]

	Definition (overall healthy aging = all criteria are met)	Percent of the total study sample who did not meet the respective criterion	Percent of those defined as "healthy aging = no" who did not meet the respective criterion
Good physical functioning	SPPB ≥ 11/12	27.2	43.3
Good cognitive functioning	MMSE ≥ 27/30, RI-48 ≥ 19/48, and DK-TMT ≥ 5.5	19.9	31.6
No limitations in IADL	<1 limitation	7.4	11.7
No incident major chronic disease	No incident cancer (i.e., cancer of any kind, except for basal cell carcinoma), cardiovascular disease, or diabetes during follow-up	15.6	24.7
No health-related limitations in social life	SF-36 responses: 1-2 to item 6 and 3-5 to item 10	9.6	15.2
Good overall self-perceived health	SF-36 responses: 1-3 to item 1	5.6	8.9
No depressive symptoms	CES-D < 16/60	16.4	26.1
No function-limiting pain	SF-36 responses: 1-3 to item 7 or 1-2 to item 8	12.0	19.1

[a]Adapted from another article on healthy aging in the SU.VI.MAX study (25).
CES-D, Center for Epidemiologic Studies Depression Scale (a validated, self-administered questionnaire assessing depressive symptomatology); DK-TMT, Delis-Kaplan Trail-making test (a validated test assessing mental flexibility); IADL, instrumental activities of daily living (a validated self-administered questionnaire assessing independence in activities such as shopping or cooking); MMSE, Mini Mental State Examination (a validated test of overall cognitive functioning); RI-48, rappel indicé-48 items (a validated test of episodic memory); SF-36, Medical Outcome Study Short Form-36 (a validated, self-administered questionnaire assessing various dimensions of health-related quality of life); SPPB, Short Physical Performance Battery (a validated test battery assessing lower extremity function).

lowering drugs; systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥85 mm Hg, or use of antihypertensive drugs; glucose ≥ 5.6 mmol/L or use of antidiabetic medication; and high-density lipoprotein cholesterol < 1.03 mmol/L for men and <1.29 mmol/L for women.

Baseline covariates

Self-administered questionnaires were completed at recruitment (1994-1996), including information on gender, date of birth, educational level (primary/secondary/university or equivalent), occupation (homemaker/manual worker/office employee/intellectual profession or managerial staff), family situation (living alone/cohabiting), smoking status (nonsmoker/former smoker/current smoker), alcohol consumption (in grams per day), and physical activity level (irregular or none/<1 hour per day/≥1 hour per day).

Descriptive statistics

Based on the source population, excluded and included participants were compared using Mann-Whitney U tests and χ^2 tests. Baseline characteristics of the included participants were compared across BMI categories (normal weight: < 25, individual with overweight [excluding obesity]: ≥ 25.0-30, and individual with obesity: ≥ 30.0 kg/m^2) using linear contrast and Cochran-Mantel-Haenszel trend tests.

Main statistical analyses

Estimating odds ratios as proxies for relative risks (RRs) is only valid under the "rare (<10%) disease assumption." Because this assumption was not met for our outcome variable (healthy aging), we used Poisson regression with robust error variance to directly estimate the RRs (28). BMI was included either in its continuous form or as a three-category variable according to the thresholds mentioned above. Three models were fit. The first was unadjusted; the second was adjusted for baseline age, gender, education, occupation, living arrangement, and antioxidant supplementation; and the third model (main model) was further adjusted for baseline tobacco status, alcohol consumption, and physical activity.

In addition to these analyses, which assessed multidimensional healthy aging as a composite variable, we also conducted analyses in which we considered each component as a separate outcome.

Analyses on the combined role of overweight/obesity and metabolic health

We carried out an additional analysis to investigate the combined role of BMI group status and metabolic health status at baseline. The participants were divided into six groups as follows: metabolically normal with normal weight, metabolically abnormal with normal weight, metabolically normal with overweight, metabolically abnormal with overweight, metabolically normal with obesity, and metabolically abnormal with obesity. *P* values for interaction between BMI and metabolic health status in the fully adjusted models were 0.047 when using continuous BMI, 0.82 when using BMI group, and 0.41 when using a binary variable BMI <25 versus ≥ 25 (providing more statistical power than BMI group, given the small size of the group with obesity). Because our objective to study the combined role of overweight/obesity was hypothesis-driven, we judged it as legitimate to conduct these analyses despite the lack of statistical significance for some of the interaction tests.

TABLE 2 Sample characteristics at baseline, SU.VI.MAX 2 study, 2007-2009, $N = 2,733$[a]

	BMI < 25 (normal weight)[b]	BMI 25-29.9 (overweight)	BMI ≥ 30 (obesity)	*P* value[c]
n (%)	1698 (62.1)	865 (31.7)	170 (6.2)	
Age (y), mean (SD)	51.6 (4.6)	52.6 (4.5)	52.4 (4.7)	0.02
Gender (male), *n* (%)	699 (41.2)	613 (70.9)	90 (52.9)	<0.001
Metabolically unhealthy, *n* (%)[d]	425 (25.0)	454 (52.5)	116 (68.2)	<0.001
Educational level, *n* (%)				0.002
Primary education only	328 (19.3)	215 (24.9)	37 (21.8)	
Secondary education	674 (39.7)	336 (38.8)	76 (44.7)	
University level	696 (41.0)	314 (36.3)	57 (33.5)	
Occupational status, *n* (%)				0.02
Homemaker	156 (9.2)	39 (4.5)	11 (6.5)	
Manual worker	80 (4.7)	57 (6.6)	14 (8.2)	
Office employee	966 (56.9)	488 (56.4)	92 (54.1)	
Intellectual profession[e]	496 (29.2)	281 (32.5)	53 (31.2)	
Smoking status, *n* (%)				<0.001
Nonsmoker	952 (56.1)	372 (43.0)	79 (46.5)	
Former smoker	571 (33.6)	405 (46.8)	71 (41.8)	
Current smoker	175 (10.3)	88 (10.2)	20 (11.8)	
Living arrangement, *n* (%)				0.07
Living alone	254 (15.0)	106 (12.3)	21 (12.4)	
Married/cohabiting	1444 (85.0)	759 (87.7)	149 (87.6)	
Physical activity level, *n* (%)				0.02
Irregular or none	374 (22.0)	200 (23.1)	55 (32.4)	
<1 h/d	539 (31.7)	261 (30.2)	54 (31.8)	
≥1 h/d	785 (46.2)	404 (46.7)	61 (35.9)	
Antioxidant supplementation, *n* (%)	897 (52.8)	467 (54.0)	87 (51.2)	0.94
Alcohol consumption (g/d), mean (SD)	14.1 (15.5)	21.6 (19.5)	18.7 (20.1)	<0.001

[a]Values are mean (SD) or *n* (%) as appropriate.
[b]This includes 52 moderately underweight individuals (16.1-18.5 kg/m^2), representing 2.8% of participants in the subsample of BMI < 25 kg/m^2.
[c]*P* values for trend are based on linear contrast tests (continuous variables) and Cochran-Mantel-Haenszel tests (categorical variables).
[d]Being metabolically unhealthy was defined by corresponding to >1 of the following criteria: blood triglycerides ≥ 1.7 mmol/L or lipid-lowering drugs; systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, or use of antihypertensive drugs; blood glucose ≥ 5.6 mmol/L or use of antidiabetic medication; blood high-density lipoprotein cholesterol < 1.03 mmol/L for men and <1.29 mmol/L for women.
[e]Or managerial staff.

Supplementary analyses

To test a more refined outcome than our binary multidimensional healthy aging concept, we also modelled the number of criteria for which a participant was classified as unhealthy, using multinomial logistic regression. Participants were separated into four groups according to the observed count of unsatisfied components (0—reference group; 1-2; 3-5; and 6-7).

Sensitivity analyses

Finally, we used the inverse probability weighting method (29) to test the robustness of our findings to potential bias related to missing values on healthy aging status. Among the 5,482 participants with available data on our exposure variables and on covariables, we calculated probabilities of inclusion into our analysis using logistic regression. The inverse of these probabilities, multiplied by the proportion of included subjects, were then used as weights (29).

All analyses were performed using SAS version 9.4 (SAS Institute Cary, North Carolina, USA).

Results

Compared with excluded participants, their included counterparts were younger, had a lower BMI, were less frequently metabolically unhealthy, had a higher educational level, were less often smokers, were more physically active, and were more often part of the antioxidant supplementation group of the initial SU.VI.MAX trial (Supporting Information Table S1).

The mean age of our study sample was 52.0 years, the prevalence of obesity was 6.2%, and 36.4% of participants were defined as metabolically unhealthy (Supporting Information Table S1). The mean follow-up time was 13.5 years, and 37.1% of participants satisfied all criteria of our healthy aging definition. Table 2 presents sample

TABLE 3 Relative risk[a] estimates (95% CI) for the association between BMI at baseline and HA, SU.VI.MAX 2 study, 2007-2009, *N* = 2,733

	Normal weight	Overweight	Obesity[e]	BMI (continuous)	*P* value (continuous)
Model 1[b]	1.00 (ref)	0.89 (0.80-1.00)	0.63 (0.48-0.82)	0.97 (0.96-0.98)	<0.0001
Model 2[c]	1.00 (ref)	0.90 (0.81-1.00)	0.64 (0.49-0.84)	0.97 (0.95-0.99)	0.0001
Model 3[d]	1.00 (ref)	0.91 (0.81-1.01)	0.67 (0.51-0.88)	0.97 (0.96-0.99)	0.0005

[a]Relative risk estimates were obtained from Poisson regression with robust error variance.
[b]Model 1 is the unadjusted univariate model between BMI at baseline and HA.
[c]Model 2 is model 1 further adjusted for age, gender, education, occupation, living arrangement and antioxidant supplementation.
[d]Model 3 is model 2 further adjusted for tobacco status, alcohol consumption, and physical activity.
[e]All *P* values were significant for the group of participants with obesity.
CI, confidence interval; HA, healthy aging.

TABLE 4 Relative risk estimates (95% CI) for the association between BMI and HA components, SU.VI.MAX 2 study, 2007-2009, *N* = 2,733

HA component[a,b]	Normal weight	Overweight	Obesity	BMI (continuous)	*P* value (continuous)
Chronic diseases	1.00 (ref)	0.93 (0.90-0.97)	0.75 (0.67-0.83)	0.98 (0.98-0.99)	<.0001
Cognitive functioning	1.00 (ref)	1.03 (0.98-1.07)	1.02 (0.95-1.10)	1.00 (1.00-1.01)	0.33
Physical functioning	1.00 (ref)	0.91 (0.87-0.96)	0.77 (0.67-0.88)	0.98 (0.97-0.99)	<.0001
Self-perceived health	1.00 (ref)	0.98 (0.96-1.00)	0.91 (0.86-0.97)	0.99 (0.99-1.00)	0.003
Limitations in activities	1.00 (ref)	0.98 (0.96-1.01)	0.93 (0.87-0.98)	0.99 (0.99-1.00)	0.006
Depressive symptoms	1.00 (ref)	1.00 (0.97-1.04)	1.02 (0.95-1.09)	1.00 (1.00-1.01)	0.21
Limitations in social life	1.00 (ref)	1.00 (0.97-1.02)	0.97 (0.92-1.03)	1.00 (1.00-1.00)	0.80
Function-limiting pain	1.00 (ref)	0.95 (0.92-0.98)	0.85 (0.78-0.92)	0.99 (0.98-0.99)	<.0001

[a]Relative risk estimates are obtained from the Poisson regression with robust error variance.
[b]Main model adjusted for age, gender, education, occupation, living arrangement, antioxidant supplementation, tobacco status, alcohol consumption, and physical activity.
CI, confidence interval; HA, healthy aging.

characteristics at baseline, presented across BMI categories. Compared to the normal-weight group, those in the obesity group were older, more often men, more often metabolically unhealthy, less educated, and more often manual workers and smokers, and they were less physically active and consumed more alcohol.

The results of our main analyses are presented in Tables (3 and 4). As shown in Table 3, a negative association between BMI (modeled as a continuous and as a categorical variable) and healthy aging was observed in the main model (model 3), with a 33% reduction of the probability of healthy aging among individuals with obesity as

TABLE 5 Association between corpulence and HA, stratified by metabolic health status at baseline, SU.VI.MAX 2 study, 2007-2009, *N* = 2,733

		Unadjusted		Adjusted[b]	
	n	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Metabolically normal–NW[a]	1,273	1.00	–	1.00	–
Metabolically abnormal–NW	425	0.94 (0.81-1.08)	0.37	0.96 (0.83-1.10)	0.53
Metabolically normal–OW	411	0.93 (0.81-1.08)	0.34	0.95 (0.83-1.09)	0.46
Metabolically abnormal–OW	454	0.83 (0.72-0.97)	0.01	0.84 (0.72-0.98)	0.03
Metabolically normal–Obesity	54	0.60 (0.37-0.97)	0.04	0.70 (0.43-1.14)	0.15
Metabolically abnormal–Obesity	116	0.63 (0.45-0.86)	0.005	0.64 (0.47-0.89)	0.007

[a]Reference category.
[b]Model adjusted for age, gender, education, occupation, living arrangement, tobacco status, alcohol consumption, physical activity, and antioxidant supplementation.
RR, relative risk; CI, confidence interval; HA, healthy aging; NW, normal weight; OW, overweight.

TABLE 6 Association between BMI (continuous) at baseline and the number of unsatisfied HA components with polytomous logistic regression analysis, $N = 2,733$

Number of unsatisfied HA criteria[a]	*n*	Unadjusted		Adjusted[b]	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
0[c]	1,013	1.00	–	1.00	–
1-2	1,367	1.03 (1.01-1.06)	0.01	1.03 (1.00-1.06)	0.03
3-5	334	1.10 (1.06-1.14)	<0.0001	1.10 (1.06-1.14)	<0.0001
6-7	19	1.14 (1.01-1.28)	0.03	1.14 (1.01-1.29)	0.02

[a]Participants were categorized into four groups according to the number of unsatisfied HA components.
[b]Model adjusted for age, gender, education, occupation, living arrangement, tobacco status, alcohol consumption, physical activity, and antioxidant supplementation (main model).
[c]Reference group: participants with no unsatisfying healthy aging components.
OR, odds ratio; CI, confidence interval; HA, healthy aging.

compared to the normal-weight group. As shown in Table 4, the healthy aging components that were associated with BMI were chronic diseases, physical functioning, self-perceived health, limitations in instrumental activities of daily living, and function-limiting pain.

Table 5 presents the combined analysis of BMI groups and the metabolic health status with respect to healthy aging. In general, compared to the metabolically normal–normal-weight group, the other five groups tended to have a lower probability for healthy aging. For overweight individuals without the metabolic syndrome, this tendency was nonsignificant ($P_{\text{adjusted}} = 0.46$), whereas their counterparts with metabolic abnormalities had a reduced probability for healthy aging ($P_{\text{adjusted}} = 0.03$).

A similar observation was made with respect to metabolically healthy versus unhealthy individuals with obesity; however, the RRs observed for these two groups were quite similar. To verify whether the probability to age healthily really differed between metabolically healthy and unhealthy participants with obesity, we calculated a contrast estimate of the respective RRs. This contrast estimate was not significant ($P = 0.78$), indicating that the reduction in the probability to age healthily was similar for metabolically healthy and metabolically unhealthy individuals with obesity.

Results on the supplementary analysis investigating the association between continuous baseline BMI and the number of unsatisfied healthy aging components are presented in Table 6. Individuals with an elevated BMI had an increased risk of greater severity of non-healthy aging, as there was a positive association between BMI and the number of unsatisfied healthy aging criteria.

In the sensitivity analysis aiming to partially control for potential selection bias, we obtained essentially the same results as in our main analysis (Table 7).

Discussion

In this investigation within the French SU.VI.MAX cohort, having a higher BMI at midlife was related to a significantly lower probability of healthy aging. Moreover, when considering categories of BMI, both overweight and obesity were associated with a decreased probability of aging healthily, with the detrimental role of obesity being substantially stronger than that of overweight, as expected.

Several studies have suggested that midlife may be a crucial time window for the prevention of age-related health decline (13,17,30).

TABLE 7 Sensitivity analysis using inverse probability weighting—association between BMI at baseline and healthy aging (HA)[a]

	Normal weight	Overweight	Obesity	BMI (continuous)	*P* value (continuous)
Model 1[b]	1.00 (ref)	0.89 (0.80-0.99)	0.62 (0.47-0.82)	0.97 (0.96-0.98)	<0.0001
Model 2[c]	1.00 (ref)	0.89 (0.79-0.99)	0.63 (0.47-0.83)	0.97 (0.95-0.98)	<0.0001
Model 3[d]	1.00 (ref)	0.90 (0.81-1.01)	0.66 (0.50-0.88)	0.97 (0.96-0.99)	0.0004

[a]The reported values are relative risk estimates obtained from the Poisson regression with robust error variance.
[b]Model 1 is unadjusted, including BMI (three-class or continuous) as the exposure variable.
[c]Model 2 is model 1 further adjusted for age, gender, education, occupation, living arrangement, and antioxidant supplementation.
[d]Model 3 is model 2 further adjusted for tobacco status, alcohol consumption, and physical activity.

Several studies on the link between corpulence and either multidimensional healthy aging or longevity (13-19,31) have been published. However, the commonly used main outcome has been survival (13,14,18,19), and only four studies have specifically targeted midlife as an exposure period (13,15,17,18).

In the British Whitehall II study, both the presence of obesity and a large waist circumference (≥102/88 cm in men/women) at midlife were related to lower odds of successful aging compared to normal-weight individuals (15). Healthy aging was defined in a similar manner as in our study: being alive at the end of the follow-up and aged ≥ 60 years; absence of coronary heart disease, stroke, cancer, and diabetes during follow-up; good cardiovascular, metabolic, respiratory, physical, and cognitive functioning; and absence of mental health problems at the clinical examination. In addition, an investigation of data from nearly 6,000 Japanese-American middle-aged men showed that several health indicators and lifestyle factors at midlife, including the avoidance of overweight, were associated with an increased probability for "exceptional survival," assessed 40 years later and defined as the absence of morbidity as well as the absence of physical or cognitive impairment (13). Next, a prospective investigation of cardiovascular disease with 28 years of follow-up comprising nearly 8,000 middle-aged men of Japanese ancestry residing in Hawaii showed that not presenting obesity was one of the most consistent predictors of healthy aging (17). Finally, the Uppsala Longitudinal Study, including around 2,300 Swedish men with a follow-up of four decades, found increased BMI at midlife to play a detrimental role with respect to "independent aging," defined as surviving up to age 85 with good cognitive functioning, having independence in personal care and daily activities, and not living in an institution. Of note, no criterion on chronic diseases was included in the definition (18). Thus, overall, despite disparities in healthy aging definitions, follow-up duration, and population characteristics, the four above-cited studies consistently reported a detrimental role of obesity in the preservation of health during aging.

In our study, metabolically unhealthy overweight individuals showed a lower probability of healthy aging as compared to those who were metabolically healthy and normal weight, whereas metabolically healthy overweight individuals did not. This is in agreement with previous studies (32,33) that have found individuals with both excess body weight and an adverse metabolic profile to be particularly at risk. For example, among overweight participants of the Whitehall study, an indicator of global cognitive functioning was lower among those presenting metabolic abnormalities as compared to those who were metabolically normal.

While our analyses indicated that a healthy metabolic profile played an important role among overweight individuals, there was no indication that the probability of healthy aging differed between participants presenting obesity with versus without the metabolic syndrome. Participants with obesity had a similarly low probability of aging healthily whether they were metabolically healthy or unhealthy—although the observed RR was only significant for metabolically unhealthy individuals with obesity. This is likely explained by the restricted sample size of the group with obesity and a metabolically healthy state ($n = 54$) and, thus, a lack of statistical power.

Our results are, thus, partly in agreement with several studies that have identified an elevated risk in both metabolically healthy and metabolically unhealthy obesity phenotypes for health conditions such as diabetes (22,34), cardiovascular disease (30,34-36), and all-cause mortality (36,37). It is possible that metabolically healthy individuals with obesity make up an intermediate group in terms of chronic disease risk with respect to metabolically healthy normal-weight individuals and metabolically unhealthy individuals with obesity.

One reason that the RR estimates for metabolically healthy obesity and metabolically unhealthy obesity were quite similar in magnitude (despite differential levels of statistical significance) may be that metabolically healthy obesity is probably only a transient condition among many individuals (21). Pathophysiological pathways related to frequent comorbidities of obesity, such as diabetes and cardiovascular disease, include adipose tissue inflammation, which has been suggested to lead to insulin resistance via an increased expression of TNF-α (38). Moreover, a multitude of different mechanisms has been advanced to explain the strong association between obesity and cardiovascular disease incidence, including an increased expression of factors such as plasminogen activator inhibitor-1 and angiotensinogen by the adipose tissue (38). Mendelian randomization studies suggesting a causal implication of a higher BMI in the development of metabolic dysfunctions (39,40) have further suggested that currently metabolically healthy individuals with obesity are probably at risk of developing metabolic dysfunction in the long run.

Several limitations should be noted. First, the exclusion of individuals with missing data for healthy aging status may have led to selection bias. Although the results of our sensitivity analyses were consistent with those of our main analysis, the use of inverse probability weighting may have only partly accounted for potential selection bias. Second, some indicators of the healthy aging definition were not available at baseline, limiting the potential for causal inference. However, participants were initially middle-aged adults, free of chronic diseases, and sufficiently healthy to be involved in a long-term nutritional trial, supporting our working hypothesis that only few participants were, in reality, not at good overall health at baseline. Finally, the SU.VI.MAX cohort included motivated volunteers involved in a long-term intervention trial, which may limit the external validity of our findings.

The strengths of this study include its longitudinal design, the large sample, and the long follow-up period. The use of a wide range of indicators to define healthy aging is an additional positive feature of our study.

In conclusion, this prospective investigation of data from a large French cohort provides novel evidence that overweight and obesity at midlife may jeopardize the preservation of health during aging. Our results also highlight the importance of maintaining a healthy metabolic profile during midlife—although obesity per se appears to be an important risk factor for a reduced probability of aging healthily. O

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