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An association study between epicardial fat thickness and cognitive impairment in the elderly

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Mazzoccoli G, Dagostino MP, Vinciguerra M, Ciccone F, Paroni G, Seripa D, Addante F, Montella RC, De Cosmo S, Sera F, Greco A. An association study between epicardial fat thickness and cognitive impairment in the elderly. *Am J Physiol Heart Circ Physiol* 307: H1269–H1276, 2014. First published August 29, 2014; doi:10.1152/ajpheart.00175.2014.—The amount of fat surrounding the heart, called epicardial adipose tissue (EAT), is a marker of cardiometabolic risk and correlates with the quantity of visceral adipose tissue (VAT). The amount of VAT is associated with an increased risk of cardiovascular and cerebrovascular disease and with cognitive impairment. We aimed to evaluate the association between EAT thickness as a measure of VAT and cognitive function. In 71 elderly subjects (mean age 72.7 ± 7.1 yr) we measured EAT thickness through transthoracic echocardiography, assessed the metabolic profile through evaluation of biochemical parameters, and estimated the cognitive function via the Mini Mental State Examination (MMSE). We found that greater EAT thickness was associated with lower cognitive performance evaluated by MMSE ($P < 0.01$) independently of the presence or absence of metabolic syndrome or obesity. Lower MMSE results were also associated with the presence of metabolic syndrome ($P < 0.01$), elevated HOMA index ($P < 0.01$), and high BMI values ($P < 0.01$). The results of mediation analysis confirmed that the total effect of metabolic syndrome, HOMA, and BMI on MMSE is mainly explained by an indirect effect through EAT thickness. In conclusion, increased EAT thickness assessed by transthoracic echocardiography is associated with deficient results of psychometric tests assessing cognitive performance and may consistently foresee impairment of cognition in the elderly.

epicardial fat; cardiometabolic risk; MMSE; cognitive impairment

EPICARDIAL ADIPOSE TISSUE (EAT), the fat enfolding 80% of the heart's surface, represents one-fifth of total heart weight and is an index of visceral adiposity (39). EAT physiologically supplies fatty acids to myocardium and cardiac microcirculation to face high myocardial energy requirements, assists remodeling of coronary arteries, and shelters them from the torsion induced by the arterial pulse wave and cardiac contraction (22). With respect to abdominal subcutaneous adipose tissue and other visceral adipose tissue compartments, EAT is hallmarked by smaller volume of adipocytes, minor decrease through weight loss, elevated protein content, dissimilar fatty acid profile, and high rates of fatty acid incorporation, as well as insulin-induced lipogenesis, fatty acid synthesis, or fatty acid breakdown. Other characteristics are represented by low glucose consumption rates, low lipoprotein lipase expression, and high adipokine secretion (42, 43). The amount of EAT is associated with total body adiposity, and data derived from animal studies, human autopsy series, and noninvasive instrumental evaluations showed that its thickness is correlated with age and abdominal obesity (11, 46, 35). EAT thickness is related to traits of the metabolic syndrome, and EAT is correlated with insulin resistance, especially in obese subjects, and is a valuable indicator of cardiovascular risk (19, 20).

Body mass index (BMI) is the most widespread index of adiposity used in clinical practice, but despite an apparent association between BMI and the recognized comorbidities associated with excess body fatness, obesity is a heterogeneous condition and BMI cannot always properly discriminate the risk of chronic disease at the individual level. Some obese patients, the so-called metabolically healthy obese, show minor or even no metabolic complications, while others with similar BMI values show numerous metabolic abnormalities and a prothrombotic inflammatory profile (6). Individuals with the same level of obesity on the basis of BMI calculation have different comorbidity risks, which could be more closely related to the distribution of body fat than to the absolute degree of fatness per se, and in particular to the amount of visceral and

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subcutaneous compartments (6). Although the gold standard technique to precisely assess visceral adiposity is represented by whole body magnetic resonance imaging (MRI), a strong direct correlation has been evidenced between EAT and abdominal visceral adiposity (16). Besides, several studies have confirmed the validity and reliability of a direct assessment of EAT thickness by means of transthoracic ultrasonography (21, 23). Interestingly, simple linear regression evidenced an excellent correlation between EAT assessed by transthoracic echocardiogram, waist circumference, and measurement of abdominal visceral adipose tissue by MRI, but multiple regression analysis evidenced that EAT thickness was the strongest independent variable correlated to visceral adipose tissue measured using MRI. Besides, excellent consistency was confirmed between the two methods, suggesting that transthoracic echocardiography could be an easy and reliable imaging method for prediction of visceral adipose tissue (23). Accordingly, waist circumference as well as waist-to-hip ratio, substitute estimates of visceral abdominal obesity, are markers of an adverse metabolic profile associated with high cardiovascular risk, but afford a reliable measure of subcutaneous more than visceral adipose tissue, and could be biased by great quantities of subcutaneous fat, above all in subjects with severe obesity (17, 45, 51). Human ageing features modifications of body composition provided by augmented fat percentage and decreased muscle mass, contributing to onset of insulin resistance, and representing risk factors for a range of metabolic disorders closely related to disability, morbidity, and mortality in the elderly (10). EAT and abdominal adipose tissue are a source of inflammation modulators that may play a role in coronary atherosclerosis as well as in systemic inflammation mediating vasculopathic effects (3, 7). EAT actively produces both proinflammatory cyto/chemokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, monocyte chemoattractant protein-1, and resistin, and anti-inflammatory adipokines, such as adiponectin and adrenomedullin (5). In particular, in populations of elderly subjects the distribution of adiponectin isoforms was different, in line with the presence of coronary atherosclerosis, corroborating the protective role of low-molecular-weight adiponectin during aging. Total adiponectin is abundantly produced in response to vascular inflammation to counter the atherosclerosis process; regarding the exact role of adiponectin in vascular disease probably vascular inflammation induces total adiponectin and high-molecular-weight adiponectin synthesis, and rising low-molecular-weight adiponectin levels might be a reflection of a salvage mechanism aimed at vascular protection (40).

Previous studies showed an association between epicardial fat thickness, altered vascular function, and thrombotic events (34, 36–38). As well, low-grade chronic inflammation leading to systemic vasculopathy is related to progressive cerebral deterioration and may play a role in risk for dementia (14, 41). Age-related cognitive decline is hallmarked by constant worsening of numerous fields of cognitive ability, including executive function, working and episodic memory, processing speed, and attention. These domains are reliably evaluated with psychometric tests, among which the Mini Mental State Examination (MMSE) is the most regularly utilized test by clinicians to detect dementia and assess its severity and evolution (48).

We hypothesized that higher levels of adiposity are related to lower cognitive function and that EAT thickness as a measure of visceral adipose tissue is predictive of lower cognitive function. To test this hypothesis, we evaluated the association between EAT thickness measured through transthoracic echocardiography, the metabolic profile assessed by biochemical parameters, and the presence and severity of cognitive impairment estimated by means of MMSE in elderly subjects.

METHODS

Sample size. A total sample of 71 subjects allowed to detect an effect size of 0.78 (large effect size) with an alpha level of 0.050 and a statistical power greater than 0.90.

Patients. After approval by the local Scientific and Ethical Committee, the study was carried out on consecutive voluntary outpatients, aged over 65 yr old and in apparently good health, who came to the Department of Medical Sciences, for consulting the Outpatient Clinic of the Division of Internal Medicine and the Geriatrics Unit for gastroesophageal reflux disease, peptic ulcer disease, irritable bowel syndrome, or subacute and chronic low back pain. Subjects gave written informed consent and the investigation conformed to the principles outlined in the Declaration of Helsinki. We enrolled 71 Caucasian subjects, 35 men and 36 women. Medical history was obtained from all subjects, including age, sex, personal medical history, drug use, drug abuse and addiction, smoking and alcohol consumption, and physical exercise. Exclusion criteria included arterial hypertension, infectious diseases, cancer, thoracic trauma, surgical procedures in the last 180 days, smoke, drug use, alcohol or drug addiction, hypo- or hyperthyroidism, psychiatric disorders, anemia by any cause, liver, kidney or heart failure or condition of being chronically ill and treatment with chemotherapeutic or hormonal agents.

Physical and biochemical parameters. In all enrolled subject weight in kilograms and standing height in centimeters were measured at the clinical examination by standard protocols to calculate the BMI [mass(kg)/height(m)^2]. Normal weight was defined as BMI values ranging from 18.5 to 25, overweight was defined as BMI values > 25 and < 30, and obesity was defined as BMI values ≥ 30. Blood pressure was measured via the following protocol: three measurements were taken with a random-zero sphygmomanometer, and the mean of the last two of three measurements was used. After an overnight fast a venous blood sample was drawn for the determination of plasma glucose, blood urea nitrogen, levels of serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipid parameters, such as total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and hemoglobin (Hb). Plasma glucose, blood urea nitrogen, serum creatinine, AST, ALT, total cholesterol, and triglyceride levels were measured by enzymatic methods. HDL cholesterol was measured after precipitation of the other lipoprotein fractions by dextran sulfate. Low-density lipoprotein (LDL) cholesterol was calculated indirectly using the Friedewald equation. For insulin determination we used a two-site immunoenzymometric assay (ST AIA-PACK IRI, Tosoh Bioscience, San Francisco, CA). To estimate insulin sensitivity and β-cell function, we used the homeostasis model assessment (HOMA) index (13, 33).

To cope with exclusion criteria we considered the following cut-off values for definition of arterial hypertension: systolic arterial pressure $>$ 140 mmHg and diastolic arterial pressure > 90 mmHg or history of as well as use of antihypertensive medication based on the WHO guidelines for the management of hypertension. Dyslipidemia was defined as total cholesterol level > 200 mg/dl, LDL cholesterol level > 100 mg/dl, HDL cholesterol level < 40 mg/dl for male subjects or < 50 mg/dl for female subjects, and triglyceride level $\geq$ 150 mg/dl. Diabetes mellitus was defined at baseline as fasting plasma glucose levels of 126 mg/dl (7 mmol/l) or higher, nonfasting plasma

glucose levels of 200 mg/dl (11.1 mmol/l) or higher, or a history of or treatment for diabetes. Impaired fasting plasma glucose level was defined as 110 mg/dl (6.1 mmol/l) or higher but lower than 126 mg/dl (7 mmol/l). The presence of metabolic syndrome was ascertained by using the criteria suggested by the International Diabetes Federation (IDF). Characteristics included in the IDF definition are central obesity (defined as waist circumference, males $\geq$ 94 cm and females $\geq$ 80 cm; when BMI is $>$ 30 kg/m^2 central obesity can be assumed and waist circumference does not need to be measured), triglycerides $\geq$ 150 mg/dl or specific treatment for this lipid abnormality, HDL-cholesterol $<$ 40 mg/dl in males and $<$ 50 mg/dl in females, blood pressure $\geq$ 130/85 mmHg or treatment for previously diagnosed hypertension, and fasting plasma glucose $>$ 100 mg/dl. When central obesity plus two of the four previous criteria were met, a diagnosis of metabolic syndrome was made (1).

Echocardiographic study of epicardial adipose tissue. Transthoracic two-dimensional (2D) guided M-mode echocardiography was performed in each enrolled subject lying on the left side using an Esaote MyLab TM Gold Cardiovascular instrument (Esaote, Genova, Italy) according to the method previously described and validated (23, 25). Standard parasternal views were obtained, and the echocardiograms were recorded on videotape and analyzed offline for measures. Epicardial fat was recognized as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium at end-systole in three cardiac cycles. We measured EAT thickness on the free wall of the right ventricle from both parasternal long- and short-axis views. The maximum values at any site were measured, and the average value was considered. Great concordance of long- and short-axis epicardial fat measurement was reported. Echocardiograms were performed by the same expert sonographer (MPD), and when the ultrasonographic evaluations were performed on 2 separate days in 10 patients, the within-patient difference for the measurement of the EAT was 1.2 $\pm$ 0.4%, pointing out good reproducibility of the echocardiographic measurements.

Neuropsychological assessment. All the enrolled subjects were evaluated through MMSE administration between 0830 and 1330 by a trained researcher (FA) who worked under the supervision of a physician specialized in clinical neuropsychology (FC). Possible effects of language and culture were reduced by means of tests that contained items that were familiar to the study population.

Statistical analysis. Baseline patients' characteristics were reported as relative frequency (percentage) or mean and standard deviation (SD), for categorical and continuous variables, respectively. Normal distribution assumption for EAT thickness and MMSE was checked by means of skewness and kurtosis tests. Correlations were evaluated by linear regression between variables. General linear models (GLM) adjusted by age and sex were fitted to evaluate the independent, that is each with a different model, association between EAT thickness (outcome) and each of the following determinants: BMI, metabolic syndrome, HOMA index, fasting plasma glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, AST, ALT, Hb, blood urea nitrogen, creatininemia, weight, and height. Regression coefficients (betas), along with their 95% confidence interval (CI), were reported for each model. GLM adjusted by age and sex were also used to evaluate the independent, that is each with a different model, association between MMSE (outcome) and each variable in the same set of determinants. A series of multiple regression models was used to investigate the association between EAT thickness (as exposure) and MSSE (as outcome): first a multiple regression model adjusted by age and sex (*model 1*), second a multiple regression model adjusted by age, sex, metabolic syndrome and BMI (*model 2*), and finally a multiple regression model adjusted by age, sex, metabolic syndrome, BMI, and LDL cholesterol level (*model 3*). The association between EAT thickness (as exposure) and MSSE (as outcome) was also evaluated in strata defined by absence or presence of metabolic syndrome, absence or presence of obesity, and high ($>$2.47) or low ($<$2.47) levels of HOMA index. Interactions were tested in the multiple regression models including an interaction term between epicardial fat thickness and each hypothesized effect modifier. Following the Bonferroni correction method the significance level was set to 0.003 to avoid the inflation of type I error due to multiple comparison. For metabolic syndrome, HOMA, and BMI, we calculated the direct and indirect effect (through EAT) on MMSE using the procedure previously described (25, 26) and implemented in the mediation library in R (27). All analyses were performed using Stata (StataCorp LP, College Station, TX), and R (R Core Team 2013. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria); graphs were created using SigmaPlot 11.0 (Systat Software, San Jose, CA).

RESULTS

The description of all the variables taken into account in our study population is represented in Table 1. The mean age of the enrolled subjects was 72 $\pm$ 7.1 yr, with a ratio males/females approximately of 1. More than half of the subjects (54.7%) had metabolic syndrome, and the mean BMI level was 29.7 $\pm$ 4.5 kg/m^2 with a high prevalence (47.9%) of obese subjects. The mean levels of EAT thickness (mm) and HOMA index were 10.8 $\pm$ 2.4 mm and 2.7 $\pm$ 1.5, respectively. The mean level of MMSE results was 23.7 $\pm$ 3.0 (Table 1). The results of correlations evaluated by linear regression between variables are represented in Figs. 1 and 2. Determinants of EAT thickness are represented in Table 2. Subjects with metabolic syndrome had EAT thickness 2.97 mm (95% CI 2.06; 3.88) greater with respect to subjects without metabolic syndrome. HOMA index was associated with EAT thickness with an increase of EAT thickness of 1.89 mm (95% CI 1.55; 2.24), for a 1 SD increase in HOMA index. Obesity was associated with EAT thickness, with an increase of 1.43 mm (95% CI 0.98; 1.88) of EAT thickness for a 1 SD increase in BMI. A similar association was observed between weight and EAT thickness. Metabolic syndrome, HOMA index, and BMI were also associated with MMSE results ($P < 0.05$, Table 3). Table 4 shows the results of a series of multivariable

Table 1. *Subject characteristics*

	Mean	SD	Range
Age, yr	72.7	7.1	60; 89
Sex, *n* (% of female subjects)	36 (50.7)		
Subjects with metabolic syndrome, *n* (%)	39 (54.9)		
Height, cm	162.1	6.3	147; 177
Weight, kg	78.3	13.5	50; 105
BMI, kg/m^2	29.7	4.5	20.0; 38.1
Epicardial fat thickness, mm	10.8	2.4	6.0; 18.0
HOMA index	2.7	1.5	0.35; 6.1
MMSE result	23.7	3.0	18.5; 30.0
Fasting plasma glucose, mg/dl	117.3	28.3	73; 201
Total cholesterol, mg/dl	200.3	44.6	85; 300
LDL cholesterol, mg/dl	137.7	44.2	38.6; 225.4
HDL cholesterol, mg/dl	35.1	13.2	12; 82
Triglycerides, mg/dl	137.5	42.5	52; 300
AST, UI/l	23.9	7.3	9; 44
ALT, UI/l	23.4	8.9	6; 45
Hb, g/dl	12.4	1.3	9.5; 15.5
Blood urea nitrogen, mg/dl	42.3	12.4	21; 94
Serum creatinine, mg/dl	1.02	0.29	0.66; 1.8

CI, confidence interval; BMI, body mass index; HOMA, homeostasis model assessment; MMSE, Mini Mental State Examination; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

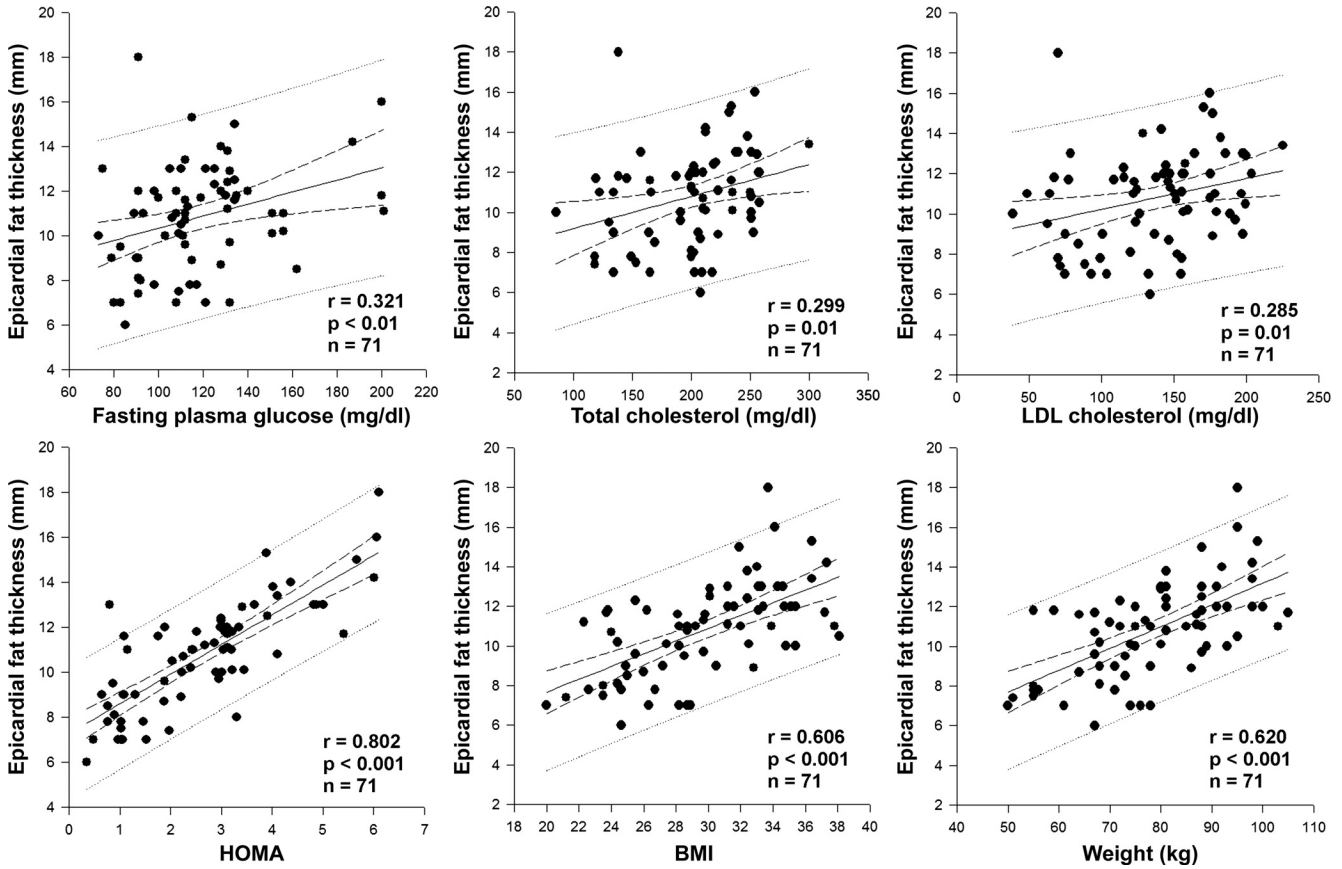

Fig. 1. The *x-y* scatterplots showing relationships of epicardial fat thickness determinants in the study population. Solid black line indicates the true linear regression line calculated to fit the population sample data points, dashed lines specify the 95% confidence intervals on the estimated mean, and dotted lines designate the 95% prediction intervals. LDL, low-density lipoprotein cholesterol; HOMA, homeostasis model assessment; BMI, body mass index.

regression models investigating the association between EAT thickness (as exposure) and MSSE results (as outcome). The model adjusted by age and sex showed a beta coefficient of −1.82 (95% CI −2.19; −1.44); the model, further adjusted by metabolic syndrome and BMI, had a beta coefficient of −1.52 (95% CI −2.01; −1.04), while BMI and metabolic syndrome showed no direct effect on MSSE results. Adjustment by LDL cholesterol level also did not have a big impact on the association between EAT thickness and MSSE results. The association between EAT thickness and MSSE results was present either in subjects with and without metabolic syndrome or in obese and nonobese subjects (Table 4), while the association between metabolic syndrome and BMI with MMSE results was present only in subjects with high level (above the median) of EAT thickness (data not shown). Given the high correlation between HOMA index and EAT thickness it was not possible to evaluate the independent effect in a multiple regression model, but EAT thickness was significantly associated with MSSE in strata with low levels of HOMA index −2.31 (95% CI −2.99; −1.64), and high level of HOMA index −1.62 (95% CI −2.29; −0.95). Interestingly, HOMA index was not associated with MSSE results in strata with low or high level of EAT thickness (data not shown).

To explore the underlying causal mechanism we specify EAT as intermediate (or mediator) variable that lies on the causal pathway between the exposure of interest (metabolic syndrome, HOMA, or BMI) and MMSE. The objective of this analysis is to decompose the total effect of the exposure into the indirect effect, which represents the hypothesized causal mechanism through EAT, and the direct effect, which represents all others mechanisms. Direct and indirect effect (through EAT) on MMSE were calculated using the mediation analysis described in the methods section. The results shown in Table 5 confirmed that under the hypothesized causal model the total effect of metabolic syndrome, HOMA, and BMI on MMSE is mainly explained by the indirect effect through EAT.

DISCUSSION

The pathophysiological effects and clinical implications related to the amount of visceral and intraorgan fat is attracting ever-growing interest in the medical field. In particular, indirect evaluation through waist-to-hip ratio assessment or BMI calculation brought to light a link between central adiposity and cognition (15, 30), as well as an association between the amount of visceral fat and increased risk of cardiovascular and cerebrovascular disease (32). Furthermore, MRI or computed tomography (CT) quantification of abdominal adiposity evidenced an inverse relationship between visceral fat amount, brain morphometry, and cognitive performance in healthy elderly, corroborating the epidemiological correlation between elevated BMI values and risk for cognitive decline or dementia

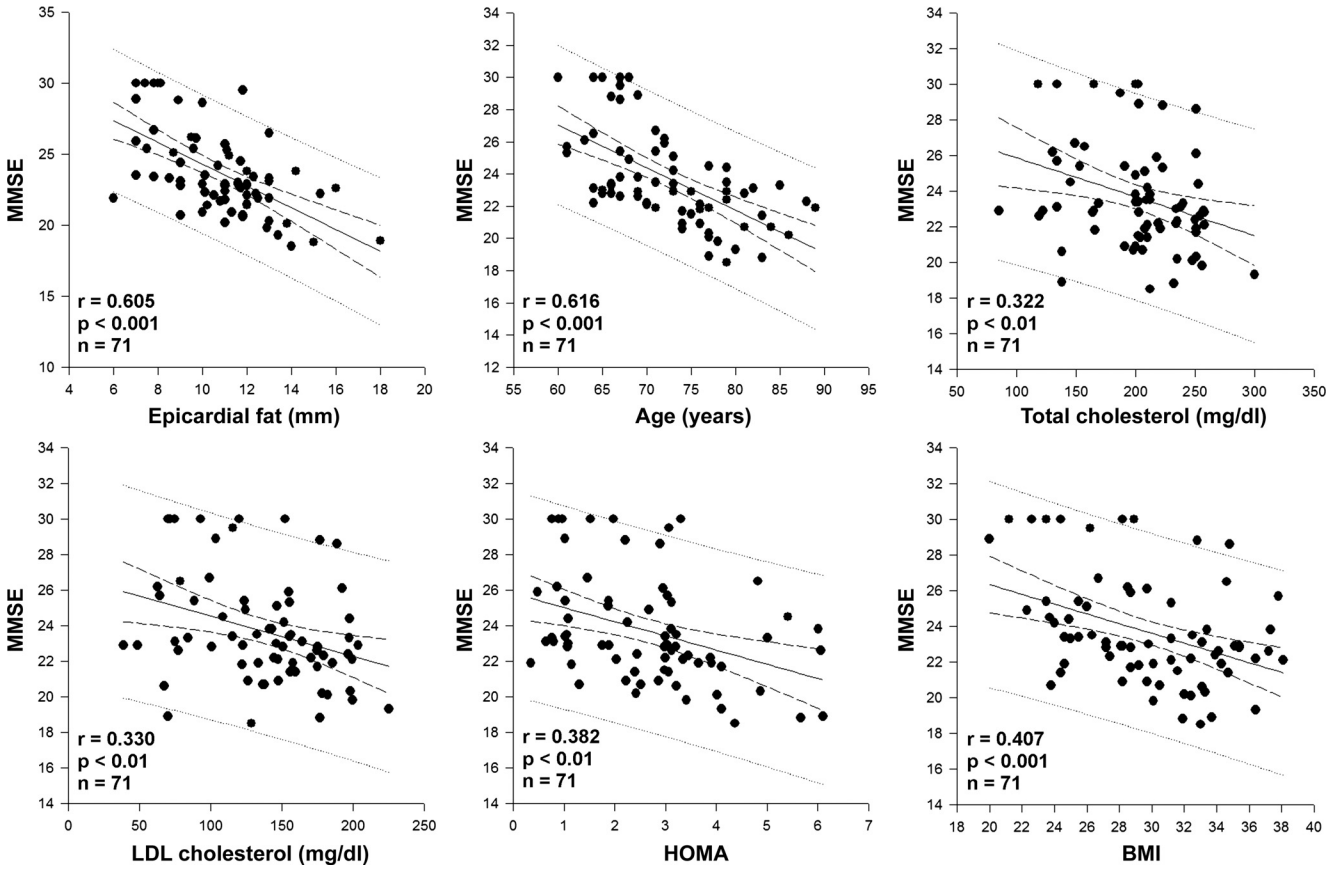

Fig. 2. The *x-y* scatterplots showing relationships of Mini Mental State Examination (MMSE) result determinants in the study population. Solid black line indicates the true linear regression line calculated to fit the population sample data points, dashed lines specify the 95% confidence intervals on the estimated mean, and dotted lines designate the 95% prediction intervals.

(8, 29, 52). Visceral adipose tissue is more metabolically active than subcutaneous adipose tissue and is considered to considerably impact on adipocytokine production and insulin resistance, and MRI or CT allow direct measurement and discrimination of abdominal adiposity into visceral and subcutaneous adipose tissue. These medical imaging techniques are not exploitable in population-based studies, and a valuable and reliable tool to evaluate visceral fat and the association with other parameters in cardiovascular and cerebrovascular risk stratification in large-scale studies is firmly needed (28). Epicardial fat thickness assessed by means of transthoracic ultrasonography is a reliable evaluation of visceral adipose tissue

Table 2. *Relations with epicardial fat thickness*

	Beta	95% CI	*P* Value
Age (years)	−0.045	(−0.605; 0.514)	0.9
Sex (female vs. male)	−0.930	(−2.062; 0.202)	0.1
Metabolic syndrome (yes vs. no)	2.971	(2.064; 3.878)	< 0.001
Height (cm)	0.437	(−0.125; 0.999)	0.1
Weight (kg)	1.449	(1.001; 1.897)	< 0.001
BMI (kg/m^2)	1.427	(0.978; 1.877)	< 0.001
HOMA index	1.894	(1.549; 2.238)	< 0.001
Fasting plasma glucose (mg/dl)	0.786	(0.252; 1.32)	0.005
Total cholesterol (mg/dl)	0.679	(0.138; 1.221)	0.016
LDL cholesterol (mg/dl)	0.655	(0.101; 1.210)	0.016
HDL cholesterol (mg/dl)	−0.150	(−0.717; 0.417)	0.6
Triglycerides (mg/dl)	0.405	(−0.148; 0.959)	0.2
AST (UI/l)	0.241	(−0.319; 0.802)	0.4
ALT (UI/l)	0.407	(−0.16; 0.974)	0.2
Hemoglobin (g/dl)	0.047	(−0.532; 0.627)	0.9
Blood urea nitrogen (mg/dl)	0.250	(−0.328; 0.827)	0.4
Serum creatinine (mg/dl)	0.360	(−0.208; 0.928)	0.2

Beta coefficients represent the impact of the various predictors on a variable in the model. Here they represent changes in epicardial fat thickness (mm) for a 1 SD increase of continuous variables.

Table 3. *Relations with MMSE*

	Beta	95% CI	*P* Value
Age (years)	−1.825	(−2.386; −1.264)	<0.001
Sex (female vs. male)	0.872	(−0.242; 1.985)	0.1
Metabolic syndrome (yes vs. no)	−2.712	(−3.669; −1.756)	<0.001
Height (cm)	−0.594	(−1.149; −0.038)	0.040
Weight (kg)	−1.438	(−1.89; −0.987)	<0.001
BMI (kg/m^2)	−1.344	(−1.809; −0.879)	<0.001
HOMA index	−1.187	(−1.682; −0.693)	<0.001
Fasting plasma glucose (mg/dl)	−0.683	(−1.226; −0.14)	0.016
Total cholesterol (mg/dl)	−0.763	(−1.344; −0.279)	0.004
LDL cholesterol (mg/dl)	−0.812	(−1.341; −0.216)	0.007
HDL cholesterol (mg/dl)	0.105	(−0.464; 0.674)	0.7
Triglycerides (mg/dl)	−0.471	(−1.022; 0.081)	0.1
AST (UI/l)	−0.272	(−0.832; 0.289)	0.3
ALT (UI/l)	−0.346	(−0.916; 0.225)	0.2
Hemoglobin (g/dl)	−0.055	(−0.635; 0.526)	0.9
Blood urea nitrogen (mg/dl)	−0.119	(−0.701; 0.462)	0.7
Serum creatinine	−0.143	(−0.717; 0.432)	0.6

Beta coefficients represent the impact of the various predictors on a variable in the model. Here they represent changes in MMSE for a 1 SD increase of continuous variables.

Table 4. *Association between MMSE results and epicardial fat thickness*

			Beta	95% CI	*P* Value		
Model 1	Epicardial fat thickness		−1.82	(−2.19; −1.44)	<0.001	Adjusted by age and sex	
Model 2	Epicardial fat thickness		−1.52	(−2.01; −1.04)	<0.001	Adjusted by age, sex, metabolic syndrome and BMI	
	Metabolic syndrome		−0.35	(−1.58; 0.89)	0.6		
	BMI		−0.30	(−0.90; 0.30)	0.3		
Model 3	Epicardial fat thickness		−1.51	(−2.00; −1.01)	<0.001	Adjusted by age, sex, metabolic syndrome, BMI and LDL cholesterol	
	Metabolic syndrome		−0.19	(−1.47; 1.09)	0.8		
	BMI		−0.30	(−0.91; 0.30)	0.3		
	LDL cholesterol		−0.22	(−0.63; 0.18)	0.3		
						Interaction P value	
Model 4	Epicardial fat thickness	HOMA index <2.47	−2.31	(−2.99; −1.64)	<0.001		Adjusted by age and sex
	Epicardial fat thickness	HOMA index >2.47	−1.62	(−2.29; −0.95)	<0.001	0.2	Adjusted by age and sex
Model 5	Epicardial fat thickness	Without metabolic syndrome	−1.61	(−2.17; −1.05)	<0.001		Adjusted by age and sex
	Epicardial fat thickness	With metabolic syndrome	−1.53	(−2.31; −0.75)	0.001	0.99	Adjusted by age and sex
Model 6	Epicardial fat thickness	Nonobese	−1.88	(−2.72; −1.05)	<0.001		Adjusted by age and sex
	Epicardial fat thickness	Obese	−1.40	(−1.99; −0.81)	<0.001	0.3	Adjusted by age and sex

Beta coefficients represent the impact of the various predictors on a variable in the model. Here they represent changes in MMSE for a 1 SD increase of continuous variables.

(12, 18). In this study we examined the cross-sectional associations of EAT thickness, body mass, biochemical parameters, and markers of metabolic status with cognitive performance in older adults. The results showed that epicardial fat thickness is inversely correlated with cognitive performance, and the association between greater amount of fat surrounding the heart and lower results of psychometric tests in apparently healthy old-aged subjects was independent from the presence or absence of metabolic syndrome or obesity. Lower cognitive performance estimated by MMSE was also associated with increasing age, presence of metabolic syndrome, elevated HOMA index, high fasting plasma glucose, high BMI values, as well as high total and LDL cholesterol. These data are in agreement with the reported evidence of an association between obesity and vascular risk factors and the risk of dementia and Alzheimer's disease; in particular, the subjects showing obesity at midlife had an increased risk for dementia when compared with subjects characterized by normal weight, also after controlling for sociodemographic characteristics and follow-up time (31). Data from previous animal studies also suggest that obesity may have negative effects on the brain regions involved in learning and memory, but the underlying mechanisms remain to be fully elucidated. Obesity is a risk factor for cerebrovascular disease, and there is evidence that high BMI is associated with a reduction in cerebral blood flow velocities and increased cerebrovascular resistance, implying that obesity can unfavorably impinge on cerebral blood flow and resistance in the cerebrovascular bed and may play a role in cerebromicrovascular disease, influencing clinical functional outcomes in the elderly (44).

Indirect evidence suggests that proinflammatory cytokines contribute to these effects. In particular, a recent study showed that adipose tissue-linked interleukin-1β (IL-1β) mediates memory deficits in a mouse model of obesity, and levels of IL-1β emerged as a correlate of adiposity and cognitive impairment, corroborating the evidence that IL-1-mediated neuroinflammation is a crucial mechanism for cognitive deficits in obesity and diabetes (9). In the elderly population obesity exerts deleterious effects on the cerebral microcirculation and on the brain and cognitive function, and aging exacerbates obesity-induced cerebromicrovascular damage and neuroinflammation, which contribute to its negative effects on learning and memory. Precisely, animal experiments in mouse evidenced that aging worsened obesity-induced systemic inflammation and blood-brain barrier disruption, as indicated by the increased circulating levels of proinflammatory cytokines and increased presence of extravasated immunoglobulin G in the hippocampus, respectively. Obesity-induced blood-brain barrier damage was associated with microglia activation, upregulation of activating Fc-gamma receptors and proinflammatory cytokines, and increased oxidative stress (50). Interestingly, an optimal cerebrovascular endothelial function is protected and successful brain aging is achieved through regular physical exercise, which requires the activation of specific brain areas that trigger a local increase in cerebral blood flow to match neuronal metabolic needs. Increase of the maximal aerobic exercise capacity ameliorates cognitive performances: they are closely related and equally decline with age, but exercise is able to preserve the endothelial function in the brain, necessary for an optimal regulation of cerebral blood flow and a healthy

Table 5. *Direct and indirect effect (through EAT) on MMSE of metabolic syndrome, HOMA, and BMI calculated using the mediation analysis*

Exposure	Total Effect	Direct Effect	Indirect Effect	Mediation %
Metabolic syndrome (yes vs. no)	−2.71 (−3.71; −1.89)	−0.74 (−1.83; 0.32)	−1.97 (−2.78; −1.30)	72.6, $P < 0.001$
Obese vs. nonobese	−2.60 (−3.45; −1.64)	−0.55 (−1.55; 0.55)	−2.05 (−2.97; 1.31)	78.9, $P < 0.001$
HOMA index >2.47 vs. <2.47	−2.19 (−3.28; −1.20)	0.25 (−0.74; 1.21)	−2.43 (−3.20; −1.79)	111.3, $P < 0.001$

EAT, epicardial adipose tissue.

cerebrovascular function (4). On the other hand, pharmacological activation of 5′-AMP-activated protein kinase is able to thwart microvascular dysfunction and exercise intolerance (2). Besides, the polyphenolic compound resveratrol has significant antiaging protective effects on the cerebromicrovasculature and counters the augmented oxidative stress that occurs with aging, ameliorating neurovascular coupling, whose damage takes part in a considerable age-related decline in higher cortical function, increasing the risk for vascular cognitive impairment (49).

The results of ultrasound imaging, anthropometric measurements of adiposity, metabolic parameters, as well as the multiple regression models and the results of mediation analysis, suggest a reasonable path on which the quantity of adipose tissue encasing the heart, an accurate gauge of abdominal visceral adipose tissue compartments, has a direct effect on the results of MMSE assessing cognitive performance, while metabolic syndrome, HOMA index, and BMI have an indirect effect mediated through epicardial fat thickness.

These results are of particular interest considering that global increase of fat mass promotes insulin resistance, dyslipidemia, and hypertension, but the visceral adipose compartment may be the major driver of cardiometabolic risk (47). Besides, visceral fat may be a leading actor in the progressive decline of cognitive functions related to altered balance of molecular events and signaling pathways in the body, promoting pathological mechanisms underlying cerebral degenerative phenomena beyond normal aging processes.

We have to consider some limitations in this study: first of all the relatively small number of enrolled subjects, although the sample size estimation and the power analysis confirmed that it was perfectly adequate to detect statistically significant differences and associations. Besides, we did not measure the waist-to-hip ratio, but we aimed to consider more specifically the visceral fat more than the subcutaneous adipose tissue compartment, and previous studies had showed that ultrasound measurement of epicardial fat thickness reliably renders intra-abdominal visceral adipose tissue.

In conclusion, the results of our study demonstrated for the first time that in elderly subjects the amount of fat surrounding the heart assessed by transthoracic echocardiography is inversely correlated with the cognitive performance assessed by psychometric tests. An enlarged visceral adipose tissue compartment has a harmful impact on metabolic balance, which influences the risk of cardiovascular and cerebrovascular disease seemingly through changed levels of chemo/cytokines mediating a chronic low-grade inflammation. The evaluation through ultrasound measurement of epicardial fat thickness provides a reliable estimate of the amount of visceral fat, affords a valuable prediction of cognitive impairment in the elderly population, and could be a useful indicator of an increased risk of dementia.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: G.M., M.P.D., and A.G. conception and design of research; G.M., F.S., and A.G. analyzed data; G.M., S.D.C., and A.G. interpreted results of experiments; G.M., M.V., and A.G. prepared figures; G.M., M.V., D.S., R.C.M., S.D.C., F.S., and A.G. drafted manuscript; G.M., M.V., D.S., R.C.M., S.D.C., F.S., and A.G. edited and revised manuscript; G.M., M.P.D., M.V., F.C., G.P., D.S., F.A., R.C.M., S.D.C., F.S., and A.G. approved final version of manuscript; M.P.D., F.C., G.P., and F.A. performed experiments.

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