Original Article

Vascular aging and its relationship with lifestyles and other risk factors in the general Spanish population: Early Vascular Ageing Study

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Objectives: To describe the prevalence of healthy vascular aging (HVA), normal vascular aging and early vascular aging (EVA) in a sample of Spanish population without cardiovascular disease. The relationship of vascular aging with lifestyle, cardiovascular risk factors, psychological and inflammatory risk factors is also analyzed.

Methods: A total of 501 participants were recruited (49.70% men, aged 55.90 ± 14.24 years) by random sampling. Vascular aging was defined in three steps: Step 1: participants with vascular damage in carotid arteries or peripheral artery disease were classified as EVA. Step 2: with the percentiles of carotid-to-femoral pulse wave velocity (cfPWV) we used three criteria, first, the 10th and 90th cfPWV percentiles of the population studied by age and sex; second, the 10th and 90th percentiles of the European population reference values and third, the 25th and 75th cfPWV percentiles of the population studied by age and sex. Step 3: participants with hypertension or type 2 diabetes mellitus included in HVA were reclassified as normal vascular aging. Arterial stiffness was assessed with cfPWV using a Sphygmocor device. Physical activity was measured with an accelerometer. Psychological factors, lifestyle and other clinical information were obtained by standard questionnaire.

Results: The global prevalence of HVA was 8 and 14% (men 8 and 10%, women 9 and 18%), and 22 and 18% (men 26 and 23%, women 17 and 12%) for EVA, using criteria a and b, respectively. In the logistic regression analysis, vascular aging maintains positive associations with more sedentary time [odds ratio (OR) = 2.37 and 4.51], having triglycerides above 150 mg/dl (OR = 6.55 and 4.06), abdominal obesity (OR = 2.73 and 2.90), increased uric acid (OR = 4.63 and 2.98) and insulin resistance index homeostatic model assessment (OR = 4.05 and 6.78), and a negative association with less physical activity (OR = 0.29 and 0.28) using criteria a and b, respectively.

Conclusion: One in 10 has HVA and one in five EVA. The prevalence of EVA is higher in men. Study results suggest that preventive strategies aimed at increasing physical activity, reducing sedentary time and decreasing obesity and insulin resistance improve vascular aging.

Keywords: cardiovascular risk factors, early vascular aging, healthy vascular aging, inflammatory factors, lifestyles, normal vascular aging, psychological factors

Abbreviations: BP, blood pressure; cfPWV, carotid-to-femoral aortic pulse wave velocity; c-IMT, intima–median thickness carotid; CVR, cardiovascular risk; CVRF, cardiovascular risk factors; EVA, early vascular aging; HbA1c, glycosilated hemoglobin; HDL-c, HDL cholesterol; HOMA-IR, insulin resistance index homeostatic model assessment; HVA, healthy vascular aging; LDL-c, LDL cholesterol; MARE, Metabolic syndrome and Artery REsearch Consortium; MBP, mean blood pressure; NVA, normal vascular aging; OR, odds ratio

INTRODUCTION

Maintaining a normal vascular aging (NVA) process is essential for preserving vascular health and delaying the onset of cardiovascular disorders [1]. In industrialized societies, it is assumed that the phenomena of vascular aging, arterial stiffness or high blood pressure (BP) are inevitable aspects of the general aging

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process [2]. However, an association between increased age and increased BP has not been shown in early civilizations [3]. Such findings suggest that increased BP and arterial stiffness are not a direct and inevitable consequence of aging, but rather the result of the interaction between lifestyles and the biological aging process. [4]. In this sense, it is known that early vascular aging (EVA) is related to the impairment of arterial function, classical cardiovascular risk factors (CVRF), lifestyles and inflammatory factors [1,5–10]. On the other hand, the benefits of the Mediterranean diet and the influence of psychological factors on cardiovascular morbidity and mortality are known [11,12], but the relationship of these factors with vascular aging has not been studied.

Arterial stiffness reflects the dissociation between the chronological and biological age of the great arteries, with impairment preceding the occurrence of cardiovascular events [13]. Different definitions of healthy vascular aging (HVA) and EVA have been used in recent years [14]. The Metabolic syndrome and Artery REsearch Consortium (MARE) study [6] defined HVA as describing participants with carotid-to-femoral pulse wave velocity (cfPWV) standardized by age intervals below the 10th percentile, and EVA as those above the 90th percentile [9]. The Shanghai study [9] used cfPWV values based on BP in people without hypertension as a criterion for defining HVA. In the Framingham study [4], participants were defined as having HVA if they lacked hypertension and had cfPWV values less than 7.6 m/s based on a sample of healthy individuals aged under 30 years. In a study conducted in the general population of northern Portugal [15], EVA was defined as a cfPWV value of at least percentile 97.5 of the *z*-score for mean cfPWV values adjusted for age, using as reference values those published for the European population [16]. Finally, Laurent [17] considers that the use of the 10th and 90th or 25th and 75th percentiles of cfPWV, by age group, to define the threshold values is more appropriate than establishing a fixed cutoff point (cfPWV $>$ 10 m/s) since reference values based on percentiles are more precise in identifying an increase in cardiovascular risk (CVR) because the cfPWV is influenced by age and sex. However, there is still no consensus on a definition of HVA and EVA, and the understanding of vascular aging is far from sufficient [1].

The use of definitions for HVA and EVA which take into account the above-mentioned variables will allow better identification of individuals with HVA, NVA and EVA. To date, the prevalence and determinants of vascular aging in the Spanish population without cardiovascular disease have not been studied.

Thus, the main objective of this study was to describe the prevalence of HVA, NVA and EVA in the Spanish population free of cardiovascular disease. We also analyze the relationship of vascular aging with lifestyles, cardiovascular, psychological and inflammatory risk factors, as well as the determinants of vascular aging.

METHODS

Design

Cross-sectional study of individuals recruited in the Influence of Different Risk Factors in Vascular Accelerated Aging (EVA Study) (NCT02623894) [18].

Participants

The sample is from an urban population of 43 946 people. By random sampling with replacement stratified by age groups (35, 45, 55, 65 and 75 years) and sex, 501 individuals were selected, approximately 100 in each of the groups, half of each sex. Recruitment was carried out from June 2016 to November 2017. A detailed description of the study procedures, as well as the inclusion and exclusion criteria and response rate have been previously published [18,19].

Ethical principles

All participants provided written informed consent. The study was approved on 4/5/2015 by the Salamanca Ethics Committee for Research with Medicines. The Declaration of Helsinki guidelines were followed throughout the study [20].

Definition of healthy vascular aging, normal vascular aging and early vascular aging

Vascular aging was defined in three steps: Step 1: participants with vascular damage in carotid arteries or peripheral artery disease were classified as EVA. Step 2: with the percentiles of cfPWV, we used three criteria, first, the 10th and 90th cfPWV percentiles of the population studied by age and sex, second, the 10th and 90th percentiles of the European population reference values [16], classified thus: more than P90 was considered EVA, between P10 and P90 was considered NVA and less than P10 was considered HVA and third, the 25th and 75th cfPWV percentiles of the population studied by age and sex, classified thus: more than P75 EVA, P25–P75 NVA and less than P25 HVA. Step 3: participants with hypertension or type 2 diabetes mellitus included in HVA were reclassified as NVA. The distribution of participants with the three criteria in each of the groups is shown in Fig. 1. Figure 2 shows the cfPWV percentiles of the participants included in the study.

Arterial stiffness

This was measured using the *Sphygmo Cor* device (AtCor-Medical Pty Ltd, Head Office, West Ryde, Australia). The carotid and femoral pulse waves were analyzed with the patient supine, estimating the delay time compared with the electrocardiogram wave and calculating the cfPWV. The distance measurements were made with a tape measure from the sternal notch to the point where the sensor was placed on the carotid and femoral arteries and multiplied by 0.8 [21].

Measurement of cardiovascular risk factors

Office BP measurement involved three measurements of SBP and DBP, using the average of the last two measurements, with a validated *OMRON* model M10-IT sphygmomanometer (Omron Healthcare, Kyoto, Japan), following the recommendations of the European Society of Hypertension [13]. Mean arterial pressure (MBP) was estimated with the formula $MBP = (2 \times DBP + SBP)/3$.

Two weight measurements were taken with a calibrated electronic scale (accuracy $\pm$ 0.1 kg) (*Seca 770,* Medical Scale and Measurement Systems, Birmingham, UK). Height was measured twice with a stadiometer (Seca 222), rounded

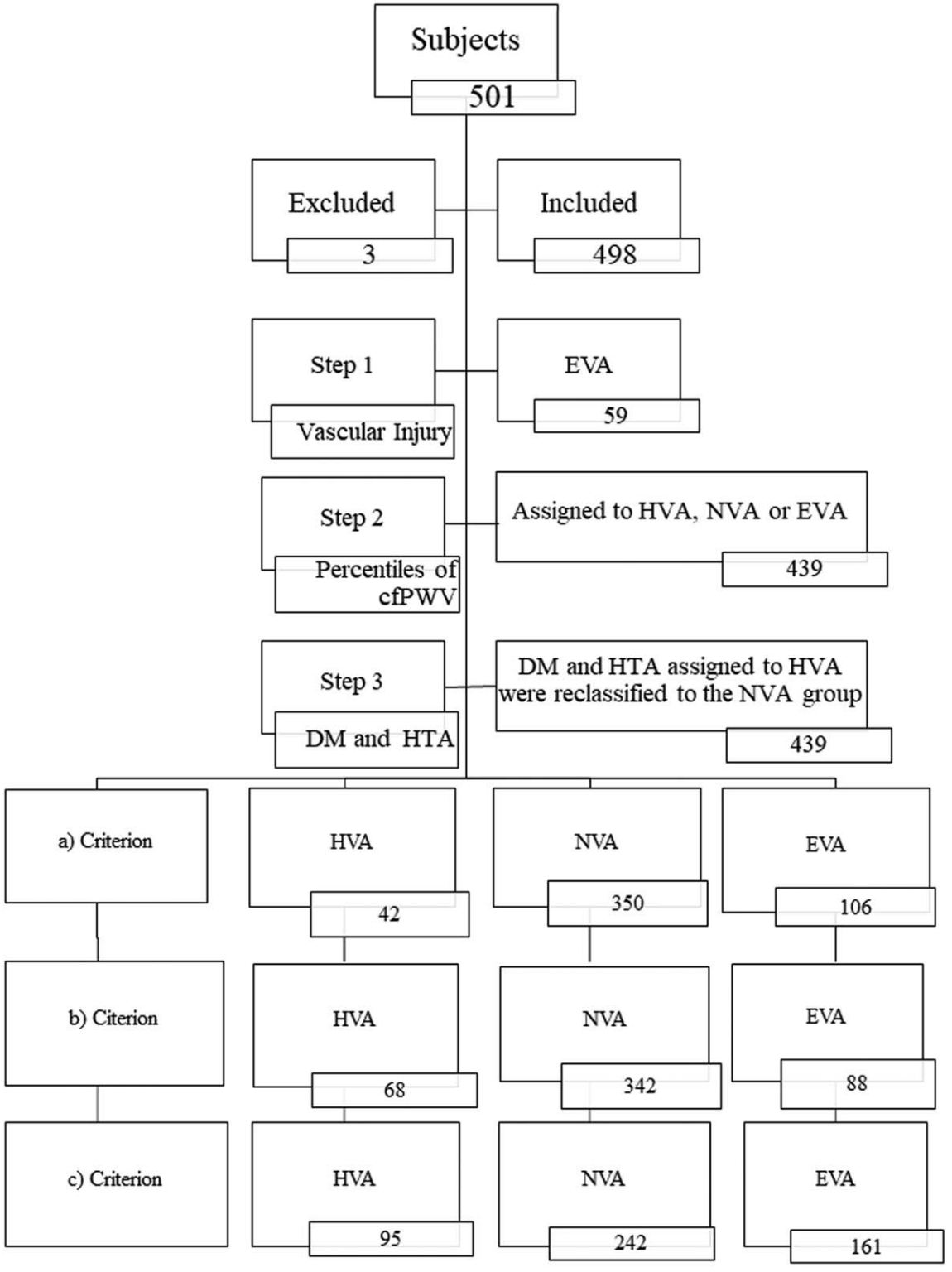

FIGURE 1 Distribution of participants with the three criteria in each of the groups healthy vascular aging, NHV and early vascular aging. (a) The 10th and 90th carotid-to-femoral pulse wave velocity percentiles of the population studied by age and sex, (b) the 10th and 90th percentiles of the European population reference values, classified thus: more than P90 was considered early vascular aging, between P10 and P90 was considered normal vascular aging and less than P10 was considered healthy vascular aging and (c) the 25th and 75th carotid-to-femoral pulse wave velocity percentiles of the population studied by age and sex, classified thus: more than P75 early vascular aging, P25–P75 normal vascular aging and less than P25 healthy vascular aging. EVA, early vascular aging; HVA, healthy vascular aging; NVA, normal vascular aging.

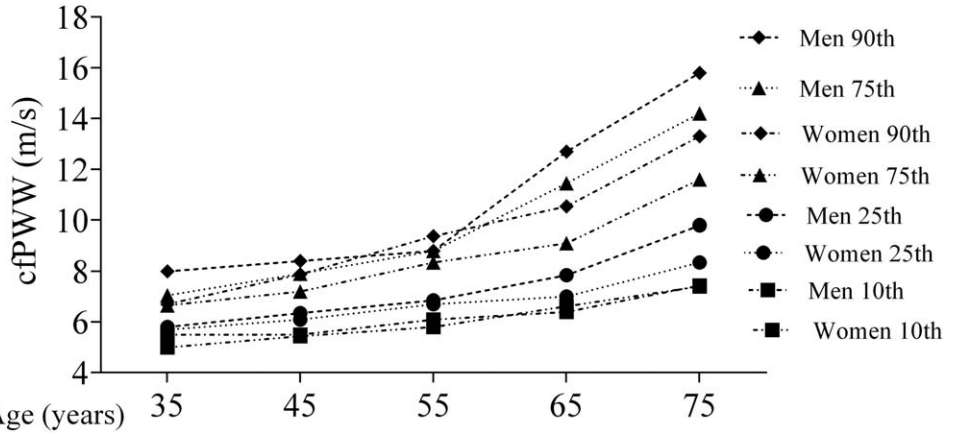

FIGURE 2 Age-specific 10th, 25th, 75th and 90th percentile for carotid-to-femoral pulse wave velocity in participants without prevalent cardiovascular disease. cfPWV, carotid-to-femoral aortic pulse wave velocity; *P*, percentile.

to the nearest centimeter, with the individual standing. The means of the two respective weight and height measurements were taken as reference measurements. The BMI was calculated by dividing weight in kg by height in m^2. A value of BMI at least 30 kg/m^2 was used to define obesity. Waist circumference was measured following the 2007 recommendations of the Spanish Society for the Study of Obesity [22]. A value of waist circumference at least 88 cm in females and at least 102 cm in males was used to define abdominal obesity [13].

Participants were considered to have hypertension if they were taking antihypertensive drugs, or had BP values at least 140/90 mmHg; to have diabetes if taking hypoglycemic or fasting plasma glucose at least 126 mg/dl or glycosilated hemoglobin (HbA1c) at least 6.5%; to have dyslipidemia if taking lipid-lowering drugs or had fasting total cholesterol (TC) at least 240 mg/dl or LDL cholesterol (LDL-c) at least 160 mg/dl or HDL cholesterol (HDL-c) of 40 mg/dl or less in men and 50 mg/dl or less in women or triglycerides at least 150 mg/dl; and to be smokers if smoking at the time of evaluation or having stopped within the last year [13]. CVR was assessed with the Systematic Coronary Risk Evaluation equation [13].

Measurement of vascular injury

Measurement of the carotid intima-media thickness (c-IMT) was carried out using the *Sonosite Micromaxx* ultrasound (Sonosite Inc., Bothell, Washington, USA), with a 5–10 MHz multifrequency high-resolution linear transducer with Sonocal software. The common carotid artery was measured after examining a 10 mm longitudinal section at a distance of 1 cm from the fork, and measurements were taken on the proximal and distal walls in the lateral (90°), anterior (45°) and posterior projections (135°). The measurements were obtained with the participant lying down, with the head extended and slightly turned in the direction away from the carotid artery being examined. Carotid injury was considered present when c-IMT more than 0.9 mm or in occurrence of plaque, this being the case if c-IMT at least 1.5 mm or if there is focal increase in c-IMT of 0.5 mm or 50% of the c-IMT value of the adjacent carotid, following the criteria of the 2018 ESC/ESH Guidelines for diagnosing and treating hypertension [13]. The presence of peripheral artery disease was assessed by calculating the ankle-brachial index using *VaSera VS-1500* (Fukuda Denshi, Denshi Co. Ltd, Tokyo, Japan) following the manufacturer's instructions.

Lifestyle assessment

Smoking status was recorded using a standardized questionnaire (asking whether the respondent smoked and if so, how much). For smokers and ex-smokers, the number of years of smoking was recorded. Alcohol consumption was reported with a standardized questionnaire (recording the type and amount of alcohol ingested during a week, measuring it in g/week). Drinking was considered free of risk if the quantity was less than 140 g/week for women and below 210 g/week for men. These were the cutoff points used in the logistic regression analysis. Adherence to the Mediterranean diet was assessed with a 14-item questionnaire, validated in Spain and used in the PREDIMED study. Scores at least 9 were considered 'good adherence' [23]. Physical activity was assessed objectively, using an accelerometer (*Actigraph*; Shalimar, Florida, USA), which had been previously validated [24]. Participants wore the accelerometer attached to the right side of the waist for 7 consecutive days, except for bathing and water activities. The data were recorded at 1-min intervals. Total physical activity was expressed in hours/week. The accelerometer gives us data on the intensity of the activity carried out by the participant and sedentary time in hours/day. The variables analyzed in this study were total physical activity (hours/week) and sedentary time (hours/week).

Evaluation of psychological factors

Depression was assessed with the Hamilton Depression Scale [25]. Anxiety was measured with the Hamilton Anxiety Scale [26] and stress with the Cohen Perceived Stress Scale [27].

Evaluation of inflammatory factors and laboratory determinations

Venous blood sampling was performed between 0800 and 0900 h after the individuals had fasted and abstained from smoking and drinking alcohol and caffeinated beverages

for the previous 12 h. Hemogram, plasma glucose, serum TC, HDL-c concentrations and triglyceride concentrations were measured using standard enzymatic automated methods. LDL-c was estimated by the Friedewald equation when the direct parameter was not available.

The atherogenic index was calculated with the following formula (Atherogenic index = cholesterol total/HDL-c). High ultrasensitive C-reactive protein, fibrinogen, insulin resistance, uric acid and neutrophil-to-lymphocyte ratio were measured in venous blood. Blood samples were collected in the primary healthcare centre and analyzed at the hospital of reference, which was approved by the external quality assurance programs of the Spanish Society of Clinical Chemistry and Molecular Pathology.

The researchers who collected the biological samples, performed the examinations and collected the questionnaires analyzed in the EVA study were previously trained according to a standardized protocol.

Statistical methods

Data for the continuous variables are shown as means ± SD and those for the categorical variables as number and percentage. The comparison of means between two independent groups was carried out with Student's *t* test and between more than two groups by a one-way analysis of variance. Post-hoc analysis to analyze the differences between more than two groups was performed with the Least Significant Difference test. When comparing categorical variables with each other, the χ^2 test and Fisher's exact test were used.

To analyze the determinants of vascular aging, three logistic regression models were applied, one for each of the criteria used with the cfPWV percentiles by age and sex of the participants studied, using 10th and 90th percentiles by age of the European population reference values [16] and with the 25th and 75th cfPWV percentiles by age and sex of the participants included in the study. We used the vascular aging as dependent variable (HVA = 0 and EVA = 1). The different lifestyles, CVRF and inflammatory factors were taken as independent variables (1 = Yes, 0 = No) using the stepwise method with backward selection, retaining the covariates with *P* less than 0.05. Adjustment variables included age, sex (0 = female, 1 = male), MBP and the use of lipid-lowering drugs (1 = Yes, 0 = No). For the variables in which a cutoff point indicating greater risk is not established (years of smoking, total physical activity and sedentary hours per week, and inflammatory factors), we used P75 as the cutoff point in men and women. Odds ratios (OR) and 95% confidence intervals were calculated. Only the variables which showed significant associations in any of the models are presented. Data were analyzed using SPSS Statistics for Windows, Version 25.0 software (IBM Corp, Armonk, New York, USA). A *P* value of 0.05 was considered as the level of statistical significance.

RESULTS

Participants and prevalence of vascular aging

Global characteristics of participants by sex ($n = 501$; mean age 55.90 ± 14.24 years; 49.70% men) are presented in Table 1, including lifestyle, conventional CVRF, CVR psychological, inflammatory factors and structure and vascular function parameters. The flow diagram describing the reference population (43 946), those included and excluded, as well as exclusion criteria by age group and sex, is shown in Fig. 1S, http://links.lww.com/HJH/B263 in the supplementary material.

The prevalence of participants with HVA, NVA and EVA overall, by sex and by age group using criteria a and b are shown in Fig. 3. With criteria a and b, the global prevalence of HVA was 8 and 14% respectively (men 8 and 10%, women 9 and 18%), and 22 and 18%, respectively (men 26 and 23%, women 17 and 12%) for EVA. The prevalence of EVA increases with age. The prevalence of participants with EVA increases with rising CVR and is greater than the prevalence of participants with HVA when CVRF is present (Fig. 4). Results when criterion c is applied (percentiles 25 and 75) are shown in Fig 2S, http://links.lww.com/HJH/B264 in the supplementary material.

The diagnostic reclassification of participants as HVA, NVA and EVA taking European population values for reference with respect to vascular aging values using 10th and 90th percentiles and vascular aging using 25th and 75th percentiles is shown in Table 1S, http://links.lww.com/HJH/B262.

Relationship of vascular aging with lifestyle, cardiovascular risk factors, psychological factors and inflammatory factors

Tables 2 and 3 show the mean values for the different lifestyle factors, for CVRF, for psychological and inflammatory factors in participants with HVA, NVA and EVA using criteria a and b. Vascular aging deteriorates as sedentary time increases and physical activity decreases ($P < 0.05$). Likewise, the increase in vascular aging is associated with the increase in age and values for BP, triglycerides, uric acid, glucose, HbA1c, insulin resistance, BMI and waist circumference levels, ($P < 0.05$). We did not find differences between any of the three groups in the psychological factors analyzed. Similar results with the third criterion are shown in Table 2S, http://links.lww.com/HJH/B262.

Participants classified as having EVA show higher values for age, BP, triglycerides, glycemia, HbA1c, BMI, waist circumference, and CVR, uric acid, drink more alcohol, perform less physical activity, and have greater insulin resistance than participants classified as HVA, using the criteria as reflected in Tables 4 and 5 and 3S, http://links.lww.com/HJH/B262.

Association of cardiovascular risk factors with healthy vascular aging

There were three logistic regression models which differ in the definition of vascular aging categories as a dependent variable, HVA = 0 and EVA = 1 (Fig. 5 and 3S, http://links.lww.com/HJH/B265). In the three models, the independent variables included are lifestyles, CVRF and inflammatory factors. After adjusting for age, sex, mean BP and lipid lowering drugs, the associations are maintained between vascular aging and greater sedentary lifestyle. With the three criteria considered, a, b and c, vascular aging maintains positive associations with more sedentary time (OR = 2.37, 4.51 and 1.96, respectively), having triglycerides above 150 mg/dl (OR = 6.55, 4.06 and 8.14), abdominal obesity (OR = 2.73, 2.90 and 2.14), increased

TABLE 1. General characteristics of the participants included in global and by sex

	Global (501)	Men (249)	Women (252)	*P* value
Lifestyles				
Alcohol (g/week)	46.12 ± 78.25	71.83 ± 95.54	20.71 ± 43.30	<0.001
Adequate alcohol consumption, *n* (%)	451 (90.00)	215 (86.30)	236 (93.70)	0.006
Smoking, *n* (%)	90 (18.00)	49 (19.70)	41 (16.30)	0.190
Smoking (years)	29.16 ± 14.44	31.51 ± 15.54	26.69 ± 12.80	0.012
Mediterranean diet	7.15 ± 2.07	6.68 ± 1.96	7.70 ± 6.08	<0.001
Adherence to the MD, *n* (%)	127 (25.30)	42 (16.9)	85 (33.70)	<0.001
Total physical activity (h/week)	13.84 ± 35.39	19.17 ± 44.36	8.48 ± 22.02	<0.001
Sedentary time (h/week)	140.75 ± 9.46	141.78 ± 9.44	139.42 ± 9.35	0.017
Conventional risk factors				
Age (years)	55.90 ± 14.24	55.95 ± 14.30	55.85 ± 14.19	0.935
SBP (mmHg)	120.69 ± 23.13	126.47 ± 19.52	114.99 ± 24.96	<0.001
DBP (mmHg)	75.53 ± 10.10	77.40 ± 9.37	73.67 ± 10.46	<0.001
Central SBP (mmHg)	110.15 ± 16.12	114.14 ± 15.13	106.20 ± 16.13	<0.001
Central DBP (mmHg)	74.71 ± 11.82	76.77 ± 11.29	72.68 ± 11.99	<0.001
Hypertension, *n* (%)	147 (29.34)	82 (32.93)	65 (25.79)	<0.001
Hypertension (years)	4.60 ± 4.19	4.98 ± 4.31	4.30 ± 4.08	0.434
Hypertension ≤140/90 mmHg, *n* (%)	62 (42.20)	27 (23.90)	35 (53.80)	0.009
Antihypertensive drugs, *n* (%)	96 (19.20)	50 (20.10)	46 (18.30)	0.650
Total cholesterol (mg/dl)	194.76 ± 32.50	192.61 ± 32.26	196.88 ± 32.64	0.142
LDL cholesterol (mg/dl)	115.51 ± 29.37	117.43 ± 14.12	113.61 ± 28.54	0.148
HDL cholesterol (mg/dl)	58.75 ± 16.16	53.19 ± 14.12	64.22 ± 28.54	<0.001
Atherogenic index (mg/dl)	3.53 ± 1.07	3.84 ± 1.11	3.23 ± 0.93	<0.001
Triglycerides (mg/dl)	103.06 ± 53.19	112.28 ± 54.39	93.95 ± 50.50	<0.001
Dyslipidemia, *n* (%)	191 (38.10)	95 (38.10)	96 (38.20)	0.989
Lipid-lowering drugs, *n* (%)	102 (20.40)	49 (19.70)	53 (21.00)	0.396
Fasting plasma glucose (mg/dl)	88.21 ± 17.37	90.14 ± 18.71	86.30 ± 15.73	0.013
HbA1c (%)	5.49 ± 0.56	5.54 ± 0.63	5.44 ± 0.47	0.044
Diabetes mellitus, *n* (%)	38 (7.60)	26 (10.50)	12 (4.80)	0.012
Diabetes mellitus (years)	6.11 ± 5.35	7.35 ± 5.97	3.75 ± 2.80	0.057
HbA1c ≤ 7%, *n* (%)	28 (73.70)	19 (73.10)	9 (75.00)	0.615
Hypoglycaemic drugs, *n* (%)	35 (7.00)	23 (9.20)	12 (4.80)	0.055
BMI (kg/m^2)	26.52 ± 4.23	26.90 ± 4.08	26.14 ± 4.79	0.044
Waist circumference (cm)	93.33 ± 12.01	98.76 ± 9.65	87.93 ± 11.70	<0.001
Obesity, *n* (%)	94 (18.80)	42 (16.90)	52 (20.60)	0.304
Abdominal obesity, *n* (%)	193 (38.60)	78 (45.80)	115 (31.30)	0.001
CVR score (%)	1.85 ± 0.80	2.05 ± 0.80	1.65 ± 0.76	<0.001
Psychological factors				
Hamilton depression scale	1.58 ± 2.60	1.18 ± 2.25	1.97 ± 2.85	<0.001
Hamilton anxiety scale	2.11 ± 3.33	2.09 ± 3.13	2.11 ± 3.52	0.876
Cohen stress scale	17.59 ± 8.17	20.56 ± 8.31	14.65 ± 6.86	<0.001
Inflammatory factors				
Fibrinogen (mg/dl)	314 ± 60	298 ± 65	330 ± 71	<0.001
Ultrasensitive CRP (mg/dl)	0.25 ± 0.46	0.23 ± 0.37	0.27 ± 0.53	0.403
HOMA-IR index (μU/ml)	1.87 ± 1.17	1.77 ± 1.16	1.97 ± 1.18	0.050
Uric acid (mg/dl)	5.11 ± 1.37	5.80 ± 1.25	4.42 ± 1.12	<0.001
N/L ratio (ml/μl)	1.72 ± 0.74	1.74 ± 0.80	1.70 ± 0.77	0.532
Vascular structure and function				
cfPWV (m/s)	6.53 ± 2.03	6.86 ± 2.20	6.21 ± 1.79	<0.001
baPWV (m/s)	12.93 ± 2.68	13.16 ± 2.46	12.71 ± 2.86	0.064
CAVI	8.01 ± 1.44	8.13 ± 1.49	7.87 ± 1.39	0.043
CAIx (%)	26.84 ± 12.79	22.09 ± 13.57	31.87 ± 9.97	<0.001
PAIx (%)	89.77 ± 20.50	82.74 ± 18.75	96.57 ± 19.85	<0.001
CACs (%)[a]	119.57 ± 381.67	191.92 ± 493.0	26.11 ± 73.26	<0.001

Values are means ± SDs for continuous data and number and proportions for categorical data. Adequate alcohol consumption in women were less than 140 g/week and in men less than 210 g/week. *P* value: differences between men and women. baPWV, brachial–ankle pulse wave velocity; CACs, coronary artery calcium score; CAIx, central augmentation index; CAVI, cardio-ankle vascular index; cfPWV, carotid-to-femoral aortic pulse wave velocity; CRP, C-reactive protein; CVR, cardiovascular risk; HbA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance index homeostatic model assessment; MD, Mediterranean diet; *N/L* ratio, neutrophil-to-lymphocyte ratio; PAIx, peripheral augmentation index.
[a]Coronary artery calcium score was only evaluated in 220 participants.

uric acid (OR = 4.63, 2.98 and 3.15) and insulin resistance index homeostatic model assessment (HOMA-IR) (OR = 4.63, 6.78 and 2.95), and a negative association with less physical activity (OR = 0.29, 0.28 and 0.41).

The distribution of participants classified as HVA, NVA and EVA, applying the three criteria used by risk group as established in the 2019 ESC guidelines on the management of dyslipidemias [28], are shown in Table 4S, http://links.lww.com/HJH/B262.

DISCUSSION

The current study is the first to analyze vascular aging in a Spanish population free of cardiovascular disease, studying

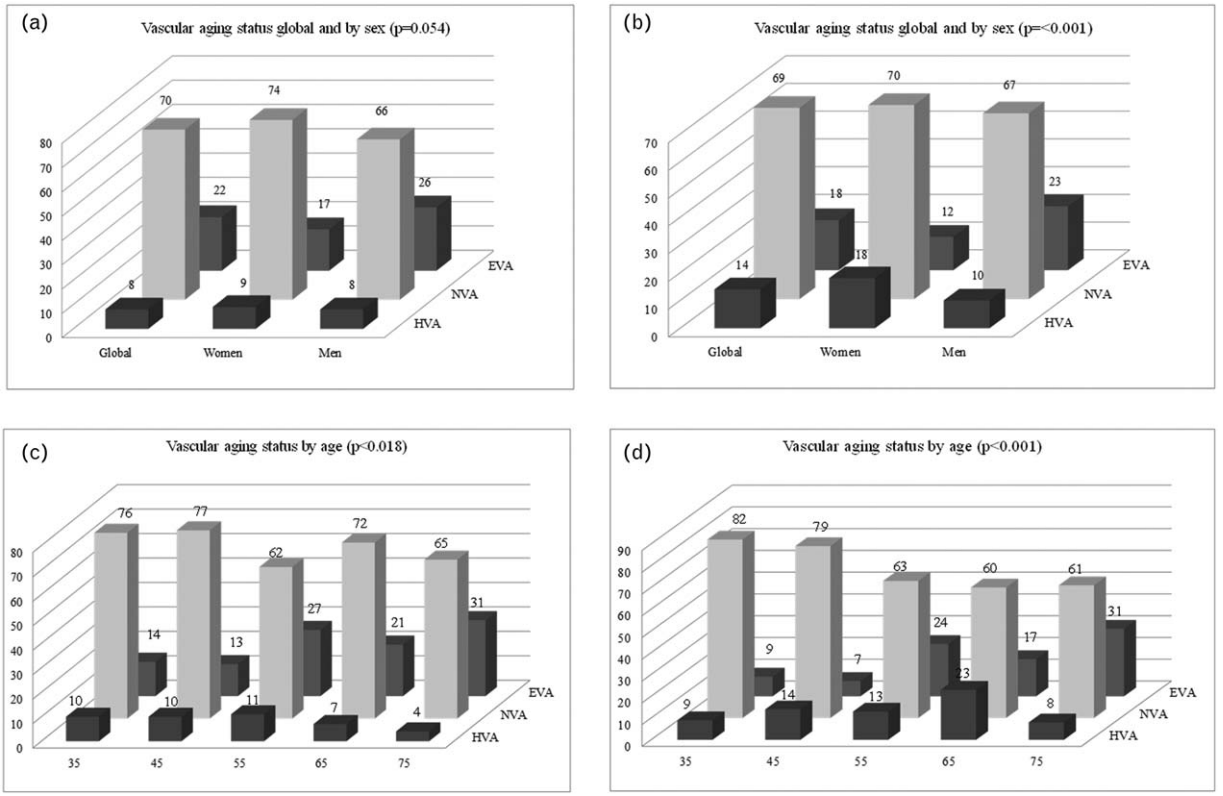

FIGURE 3 Global prevalence in percentage of vascular aging status with first and second criteria, by sex (a and b) and by decades of age (c and d). EVA, early vascular aging; HVA, healthy vascular aging; NVA, normal vascular aging.

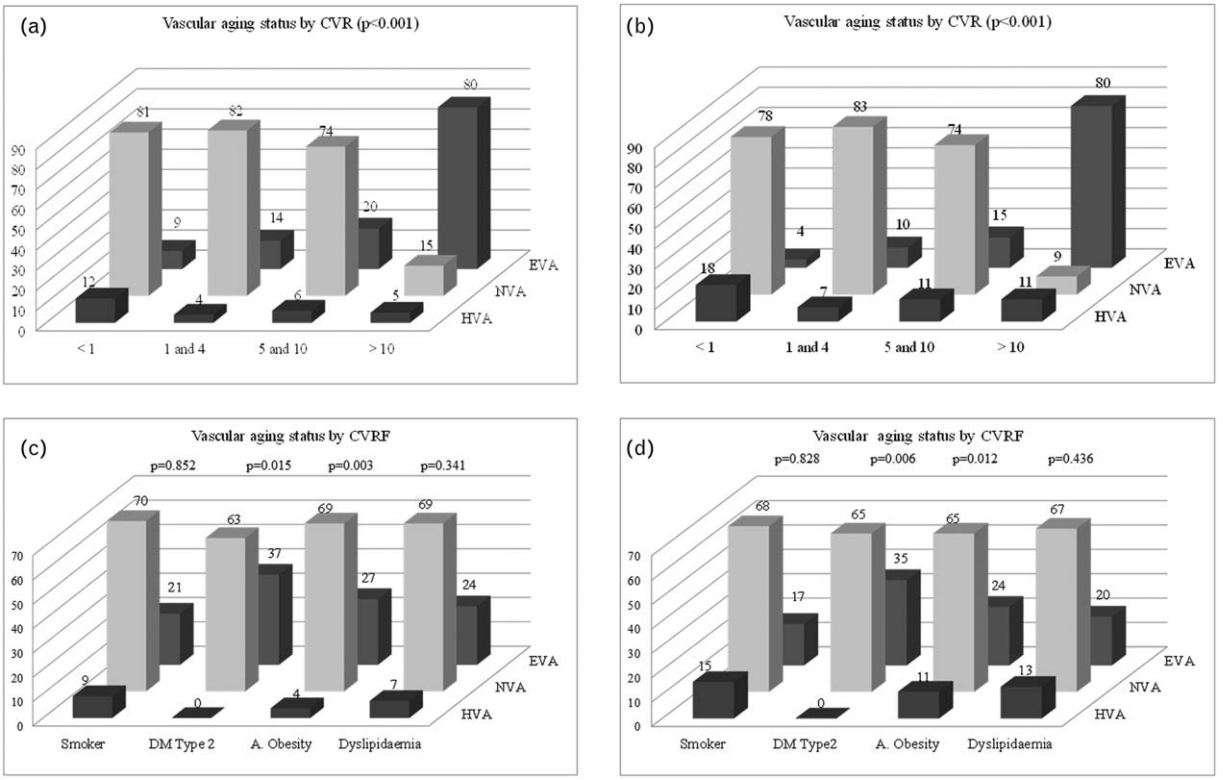

FIGURE 4 Prevalence in percentage of vascular aging status with first and second criteria, by cardiovascular risk (a and b) and by cardiovascular risk factors (c and d). A value of BMI at least 30 kg/m^2 was used to define obesity. A value of waist circumference at least 88 cm in females and at least 102 cm in males was used to define abdominal obesity. A, abdominal; CVR, cardiovascular risk; CVRF, cardiovascular risk factors; DM, diabetes mellitus; EVA, early vascular aging; HVA, healthy vascular aging; NVA, normal vascular aging.

TABLE 2. Characteristics of participants with healthy vascular aging, normal and early vascular aging using 10th and 90th percentile

	HVA, 42 (8%)	NVA, 350 (70%)	EVA, 106 (22%)	*P* value
Lifestyles				
Alcohol (g/week)	20.48 ± 43.12	46.77 ± 80.42	54.95 ± 80.95	0.053
Smoking (years)	12.86 ± 16.89	12.04 ± 16.20	15.35 ± 20.49	0.226
Mediterranean diet	6.55 ± 2.10	7.27 ± 2.01	6.97 ± 2.25	0.062
Total physical activity (h/week)*,**	26.98 ± 57.78	13.91 ± 34.32	8.54 ± 25.56	0.019
Sedentary time (h/week)**	140.07 ± 10.25	141.27 ± 9.50	142.63 ± 9.35	0.046
Conventional risk factors				
Age (years)**,***	52.27 ± 13.00	55.16 ± 14.31	59.77 ± 13.72	0.003
SBP (mmHg)*,**,***	108.18 ± 13.55	118.51 ± 21.96	133.03 ± 25.15	<0.001
DBP (mmHg)*,**,***	69.49 ± 8.48	74.61 ± 9.24	80.93 ± 11.21	<0.001
Atherogenic index (mg/dl)	3.34 ± 1.12	3.53 ± 1.09	3.63 ± 0.96	0.319
HDL cholesterol (mg/dl)	59.62 ± 16.39	59.25 ± 16.40	56.52 ± 15.25	0.302
LDL cholesterol (mg/dl)	110.07 ± 26.82	116.39 ± 30.36	114.27 ± 26.94	0.383
Triglycerides (mg/dl)*,**,***	78.61 ± 30.78	101.40 ± 50.98	118.18 ± 62.68	<0.001
FPG (mg/dl)**,***	83.07 ± 10.53	87.00 ± 913.85	94.56 ± 26.36	<0.001
HbA1c (%)**,***	5.29 ± 0.32	5.45 ± 0.48	5.69 ± 0.78	<0.001
BMI (kg/m^2)*,**	23.64 ± 3.37	26.68 ± 4.14	27.12 ± 4.45	<0.001
WC (cm)*,**,***	87.05 ± 9.49	93.11 ± 11.84	96.52 ± 12.46	<0.001
CVR score (%)**,***	1.50 ± 0.97	1.53 ± 0.77	2.96 ± 1.26	<0.001
Psychological factors				
Hamilton depression scale	1.64 ± 2.46	1.60 ± 2.57	1.52 ± 2.80	0.949
Hamilton anxiety scale	2.19 ± 3.19	2.24 ± 3.56	1.66 ± 2.52	0.287
Cohen stress scale	17.00 ± 7.75	17.63 ± 7.96	17.58 ± 9.08	0.894
Inflammatory factors				
Fibrinogen (mg/dl)	317.86 ± 64.21	312.15 ± 67.14	318.36 ± 79.43	0.698
U-CRP (mg/dl)***	0.26 ± 0.35	0.22 ± 0.24	0.37 ± 0.89	0.022
HOMA-IR (μU/ml)*,**,***	1.36 ± 0.64	1.85 ± 1.14	2.18 ± 1.38	0.001
Uric acid (mg/dl)*,**,***	4.64 ± 1.16	5.05 ± 1.36	5.49 ± 1.42	0.001
N/L ratio (ml/μl)	1.70 ± 0.67	1.72 ± 0.66	1.76 ± 0.97	0.818

Values are means (SDs) for continuous data. Differences among groups: continuous variables analysis of variance and *post hoc* using the least significant difference tests. CVR, cardiovascular risk; EVA, early vascular aging; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance index homeostatic model assessment; HVA, healthy vascular aging; *N/L* ratio, neutrophil-to-lymphocyte ratio; NVA, normal vascular aging; U-CRP, ultrasensitive C-reactive protein; WC, waist circumference.
**P* value less than 0.05 between HVA and NVA.
***P* value less than 0.05 between NVA and EVA.
****P* value less than 0.05 between HVA and EVA.

TABLE 3. Characteristics of participants with healthy vascular aging, normal and early vascular aging using 10th and 90th percentile of European population

	HVA, 68 (14%)	NVA, 342 (68%)	EVA, 88 (18%)	*P* value
Lifestyles				
Alcohol (g/week)*	34.56 ± 79.24	44.82 ± 76.47	61.08 ± 83.95	0.022
Smoking (years)**	13.22 ± 17.33	11.53 ± 15.83	17.48 ± 21.49	0.015
Mediterranean diet	7.22 ± 2.15	7.151 ± 2.03	7.07 ± 2.20	0.898
Total physical activity (h/week)*	19.63 ± 47.80	14.32 ± 34.60	7.66 ± 26.10	0.047
Sedentary time (h/week)*,**	138.86 ± 9.37	140.52 ± 9.55	143.30 ± 9.31	0.008
Conventional risk factors				
Age (years)*,**	57.05 ± 12.61	54.05 ± 14.37	61.95 ± 13.18	<0.001
SBP (mmHg)*,**,***	109.76 ± 13.75	118.95 ± 22.04	136.49 ± 25.61	<0.001
DBP (mmHg)*,**,***	70.92 ± 8.32	74.86 ± 9.38	81.70 ± 11.38	<0.001
Atherogenic index (mg/dl)*,***	3.25 ± 0.93	3.54 ± 1.11	3.73 ± 0.98	0.021
HDL cholesterol (mg/dl)*,**	63.79 ± 18.28	58.61 ± 15.80	55.05 ± 15.00	0.004
LDL cholesterol (mg/dl)	115.44 ± 29.92	115.43 ± 29.76	116.01 ± 27.80	0.962
Triglycerides (mg/dl)*,**,***	83.19 ± 33.55	103.26 ± 55.15	117.69 ± 53.61	<0.001
FPG (mg/dl)*,**	85.25 ± 11.35	86.67 ± 13.90	96.88 ± 27.92	<0.001
HbA1c (%)*,**	5.33 ± 0.32	5.45 ± 0.48	5.76 ± 0.83	<0.001
BMI (kg/m^2)*,***	24.53 ± 3.26	26.65 ± 4.22	27.53 ± 4.48	<0.001
WC (cm)*,***	87.93 ± 8.40	93.23 ± 11.98	97.83 ± 12.27	<0.001
CVR score (%)*,**	1.59 ± 1.04	1.51 ± 0.73	3.26 ± 1.14	<0.001
Psychological factors				
Hamilton depression scale	1.78 ± 2.70	1.56 ± 2.50	1.55 ± 2.94	0.809
Hamilton anxiety scale	2.10 ± 4.22	2.22 ± 3.30	1.73 ± 2.61	0.472
Cohen stress scale	16.51 ± 7.24	17.73 ± 8.04	17.77 ± 9.30	0.520
Inflammatory factors				
Fibrinogen (mg/dl)	323.65 ± 62.50	309.51 ± 67.57	324.49 ± 80.62	0.119
U-CRP (mg/dl)	0.24 ± 0.29	0.23 ± 0.44	0.25 ± 0.61	0.216
HOMA-IR (μU/ml)*,**,***	1.46 ± 0.84	1.85 ± 1.15	2.28 ± 1.35	<0.001
Uric acid (mg/dl)*,**,***	4.56 ± 1.05	5.07 ± 1.41	5.66 ± 1.25	<0.001
N/L ratio (ml/μl)	1.62 ± 0.62	1.72 ± 0.66	1.81 ± 1.04	0.283

Values are means (SDs) for continuous data. Differences among groups: continuous variables analysis of variance and post hoc using the least significant difference tests. CVR, cardiovascular risk; EVA, early vascular aging; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance index homeostatic model assessment; HVA, healthy vascular aging; *N/L* ratio, neutrophil-to-lymphocyte ratio; NVA, normal vascular aging; U-CRP, ultrasensitive C-reactive protein; WC, waist circumference.
**P* value less than 0.05 between NVA and EVA.
***P* value less than 0.05 between HVA and EVA.
****P* value less than 0.05 between HVA and NVA.

TABLE 4. Differences between participants with healthy vascular aging and participants with early vascular aging in lifestyles and other cardiovascular risk factors, using 10th and 90th percentile

	Difference	95% CI
Lifestyles		
Alcohol (g/week)	−34.48	(−60.45; −8.40)
Smoking (years)	−2.49	(−9.53; 4.56)
Mediterranean diet	−0.40	(−1.22; 0.37)
Total physical activity (h/week)	18.43	(4.77; 32.09)
Sedentary time (h/week)	−2.44	(−6.11; 1.24)
Cardiovascular risk factors		
Age (years)	−7.50	(−12.38; −2.71)
SBP (mmHg)	−24.85	(−32.96; −16.74)
DBP (mmHg)	−11.45	(−15.24; −7.66)
Atherogenic index (mg/dl)	−0.30	(−0.66; 0.72)
LDL cholesterol (mg/dl)	−4.20	(−13.99; 5.59)
HDL cholesterol (mg/dl)	3.09	(−2.77; 8.95)
Triglycerides (mg/dl)	−39.57	(−58.84; −19.30)
Fasting plasma glucose (mg/dl)	−11.48	(−19.79; −3.18)
HbA1c (%)	−0.40	(−0.58; −0.22)
BMI (kg/m^2)	−3.48	(−4.82; −2.14)
Waist circumference (cm)	−9.47	(−13.24; −7.70)
CVR score (%)	−1.46	(−1.89; −1.03)
Inflammatory factors		
Fibrinogen (mg/dl)	−0.49	(−29.68; 28.64)
Ultrasensitive CRP (mg/dl)	−0.11	(−0.32; 0.10)
HOMA-IR (μU/ml)	−0.82	(−1.27; −0.37)
Uric acid (mg/dl)	−0.85	(−1.30; −0.40)
Neutrophil-to-lymphocyte ratio (ml/μl)	−0.06	(−0.39; 0.25)

CI, confidence interval; CRP, C-reactive protein; CVR, cardiovascular risk; HbA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance index homeostatic model assessment.

TABLE 5. Differences between participants with healthy vascular aging and participants with early vascular aging in lifestyles and other cardiovascular risk factors, using 10th and 90th percentile of European population

	Difference	95% CI
Lifestyles		
Alcohol (g/week)	−26.52	(−52.65; −0.39)
Smoking (years)	−4.26	(−10.56; 2.06)
Mediterranean diet	0.15	(−0.54; 0.85)
Total physical activity (h/week)	11.97	(0.89; 24.82)
Sedentary time (h/week)	−4.64	(−7.64; −1.64)
Cardiovascular risk factors		
Age (years)	−4.90	(−9.02; −0.77)
SBP (mmHg)	−26.73	(−33.51; −19.94)
DBP (mmHg)	−10.78	(−14.02; −7.54)
Atherogenic index (mg/dl)	−0.48	(−0.78; −0.17)
LDL cholesterol (mg/dl)	0.08	(−9.16; 9.33)
HDL cholesterol (mg/dl)	8.75	(3.43; 14.06)
Triglycerides (mg/dl)	−34.49	(−48.45; −20.54)
Fasting plasma glucose (mg/dl)	−11.62	(−18.73; −4.52)
HbA1c (%)	−0.43	(−0.64; −0.21)
BMI (kg/m^2)	−2.99	(−4.27; −1.72)
Waist circumference (cm)	−9.90	(−13.33; −6.47)
CVR score (%)	−1.67	(−2.01; −1.33)
Inflammatory factors		
Fibrinogen (mg/dl)	−0.84	(−26.04; 24.35)
Ultrasensitive CRP (mg/dl)	−0.09	(−0.25; 0.08)
HOMA-IR (μU/ml)	−0.81	(−0.19; −0.83)
Uric acid (mg/dl)	−1.10	(−1.47; −0.73)
Neutrophil-to-lymphocyte ratio (ml/μl)	−0.19	(−0.47; 0.09)

CI, confidence interval; CRP, C-reactive protein; CVR, cardiovascular risk; HbA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance index homeostatic model assessment.

the relationships between vascular aging and the main lifestyle aspects and inflammatory and psychological CVRF.

The main findings of this study are: the prevalence of HVA was 8 and 14% (higher in women), and that of EVA was 22 and 18% (higher in men). The prevalence of participants with EVA increased with CVR and the presence of CVRF. Vascular aging is associated with sedentary time, total physical activity performed, triglyceride levels greater than 150 mg/dl, abdominal obesity, uric acid plasma levels and HOMA-IR. We found no association of vascular aging with adherence to the Mediterranean diet, alcohol consumption, years of smoking, psychological factors and fibrinogen levels.

Vascular aging is a gradual process involving biochemical, enzymatic and cellular phenomena in the vascular wall, combined with epigenetic and molecular alterations, which generally reflects biological aging. Vascular aging causes a decrease in elastin content and collagen accumulation on the wall, leading to an increase in arterial stiffness and a reduction in distensibility [14,29].

Several studies have been published over the last decade which analyzed the prevalence of HVA and EVA. In the MARE study [6], 10.0% of the 18 490 participants had HVA. The figures for HVA in the Shanghai study [9] was 30.6% of the 2098 participants, and 17.7% of the 3196 participants in the Framingham study cohort [4]. In the OPTIMO study [5], 5.7% of the 1416 participants had EVA. Finally, in the study by Cunha *et al.* [15], 12.5% presented EVA. It should be noted, however, that the prevalences found in the previous studies are not directly comparable because of the variation across the studies in the criteria used to define HVA and EVA, the distribution of the population according to age and sex, and their characteristics regarding the presence of risk factors and morbidity, reflecting the need to establish a consensus and a common definition of HVA, NVA and EVA.

Link to lifestyle

The results of this study show that individuals who perform more physical activity and do not have a sedentary lifestyle show less vascular aging. This association had not been found previously [2]. These discrepancies are probably due to the way in which physical activity was measured, objectively with accelerometry in this study and subjectively in others. The results of our research are supported by previous studies, which have reported that greater physical activity (measured by accelerometry) is associated with lower vascular stiffness [30]. However, some studies suggest that moderately intense aerobic exercise lacks efficacy in reducing cfPWV [4]. Nevertheless, not all behaviors related to lifestyles are linked, since although the years of smoking and the amount of alcohol increased with increasing vascular aging, the logistic regression analyses performed did not show this association to be significant. These results coincide with those published by Niiranen *et al.* [2], who found no link between smoking and HVA; results of the OPTIMO study [5] observed a beneficial relationship between drinking alcohol and EVA in young adults, an effect which disappeared when adults were included in the

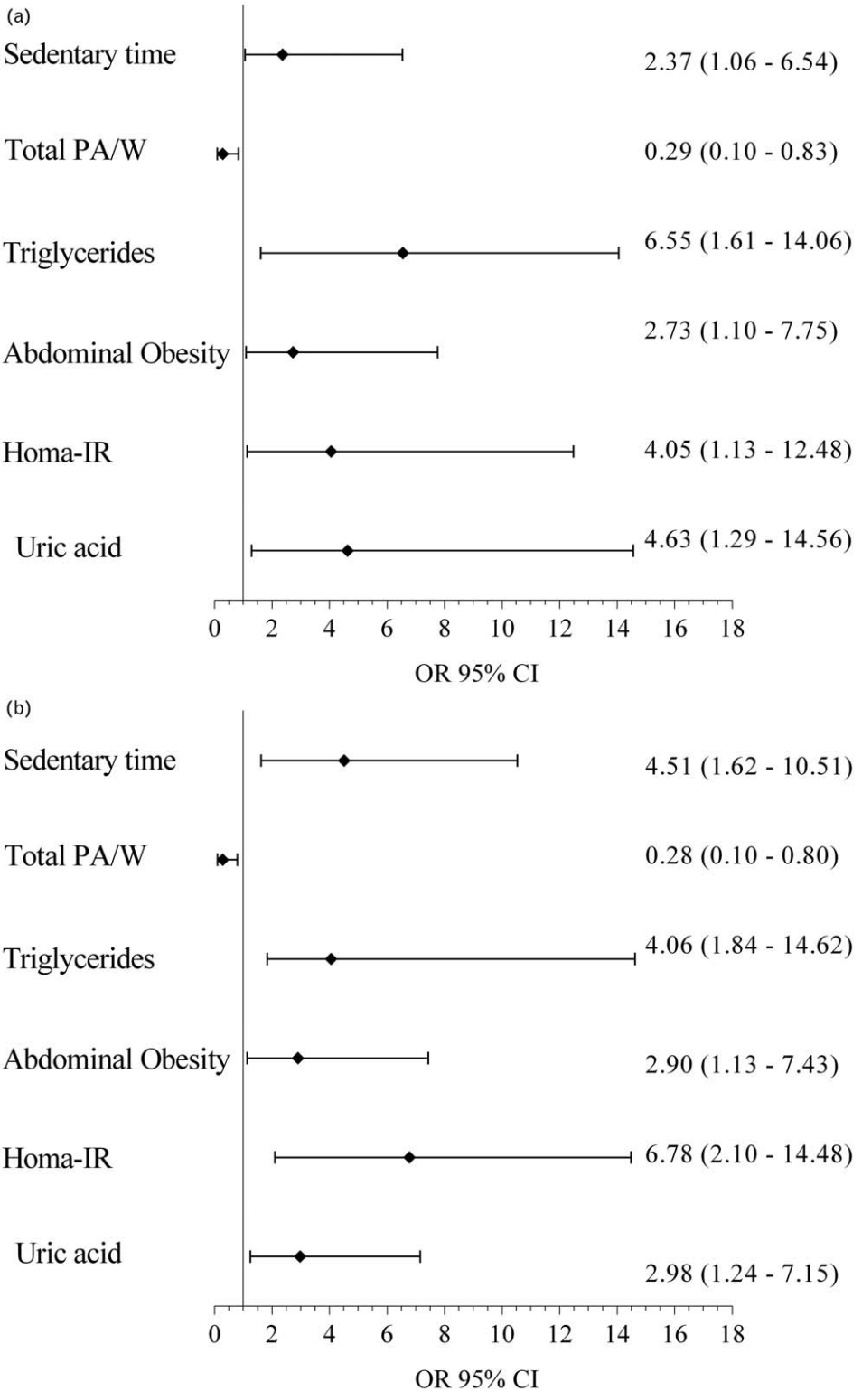

FIGURE 5 Odds ratio of determinants of healthy vascular aging = 0 vs. early vascular aging = 1 with the first criterion (a) and the second criterion (b) for lifestyles, cardiovascular risk factors and inflammatory factors. Adjusted confounders include age, sex, median blood pressure and lipid-lowering drugs. CI, confidence interval; EVA, early vascular aging; H/sitting/W, hours sitting/week; HVA, healthy vascular aging; IR, insulin resistance; OR, odds ratio; PA/W, physical activity/week.

analysis. Similarly, the participants included in the EVA group showed greater adherence to the Mediterranean diet than those classified as NVA and HVA; this association disappears, however, in the logistic regression analysis, in line with the results of the Framingham heart study [2]. These findings can be explained by the mediating effects of BMI on the relationships between diet and vascular aging [31].

Relationship with cardiovascular risk factors

In this study, the prevalence of Early Vascular Ageing (EVA) is higher in men and increases with age; conversely, the prevalence of HVA is higher in women. However, in the OPTIMO study [5], the frequency of EVA was higher in participants under 30 (18.7 vs. 4.5%) than in participants over 60. Along the same lines, in a study carried out in Portugal [15], the prevalence of EVA was higher in young people under 30 (26.1 vs. 6%) than in the overall sample. These two studies found a high frequency of EVA in young adults, thereby highlighting the importance of diagnosing EVA in young people and supporting the results published in a meta-analysis [32], which concluded that the power of cfPWV to predict cardiovascular disease and mortality events was stronger in younger and middle-aged participants than in older ones. This could be explained by changes in eating habits and social behavior that have led to an increase in childhood obesity, as well as a decrease in physical activity in Western countries [15].

In the Framingham cohort [2], the prevalence of HVA decreased from 30.3% in people aged 50–59 to 1.0% in people at least 70 years, and the regression analysis showed that age had an inverse relationship with EVA (OR = 0.93), which implies a stronger association in younger rather than older individuals. On the other hand, in the MARE study [6] the increase in age was associated with a lower probability of having HVA, so for every 5-year increase in age, there was an approximately 7% smaller chance of having HVA.

We also observed that vascular aging was associated with triglyceride levels and the presence of obesity. In general, we found that participants characterized by HVA had a more favorable CVR profile than participants characterized by EVA, which is consistent with the data of other studies [2,5,6,9,15]. In the OPTIMO study [5], an association of EVA with dyslipidaemia and BP was found, while the Framingham heart study [2] revealed that lower BMI, the use of lipid-lowering drugs and the absence of diabetes are associated with the presence of HVA, and in the prospective HVA analysis it was independently associated with a lower risk of new cardiovascular events, even after taking into account traditional CVRF. In the Shanghai study [9], greater BMI and metabolic syndrome were also associated with EVA. In the MARE study [6], the components of metabolic syndrome were associated with HVA, although this association varied with age. In all these studies, it was observed that in addition to non-modifiable CVRF, obesity, insulin resistance and BP are the main determinants of vascular aging, and considering that more than 80% of people with type 2 diabetes are also obese, the available evidence suggests the importance of maintaining normal body weight in preventing vascular aging. In fact, weight loss interventions based on caloric restriction could have a consistent effect on reducing cfPWV and SBP, and should be considered as a strategy for maintaining HVA in overweight and obese adults [4,33,34].

Relationship with inflammatory factors

In this study, the increase in uric acid and HOMA-IR was associated with vascular aging; in the same way, participants with HVA showed lower levels of ultrasensitive C-reactive protein than participants with EVA, results which are in line with those published in the Framingham heart study [2], where it was found that people with HVA had lower IL-6, high-sensitivity PCR and HOMA-IR than participants without HVA, and it is known that effective control of inflammation can reduce arterial stiffness [35].

Although this study found no relationship between vascular aging and psychological factors, the recently published Paris Prospective Study [36] concludes that greater carotid stiffness is associated with a higher incidence of depressive symptoms, supporting the hypothesis that carotid stiffness may contribute to the development of late depression.

In sum, there are currently two possible theories regarding vascular aging. On the one hand, some authors suggest that vascular aging should not be considered part of normal aging, based on studies conducted on early civilizations [3] which show that BP figures and arterial stiffness in these populations increased with the degree of civilization [4], suggesting that vascular aging is more linked to civilization-related lifestyles than to genetic determinants [2]. On the other hand, there are authors who consider vascular aging to be an inevitable process which we can slow down, but not reverse, by controlling CVRFs and having healthy lifestyle habits [6]. With respect to both theories, the results of this study suggest that healthy habits should indeed be encouraged, mainly in terms of increased physical activity, decreased sedentary lifestyle and obesity prevention as the main factors related to vascular aging [37] and HVA.

Limitations of the study

The current study has some limitations. In the first place, the analysis was of a transversal nature, which does not allow causal inference. Second, results refer only to the Spanish urban population and may not be generalizable to other races/ethnicities. Finally, the validated questionnaires used in this study may not be the most accurate methods for assessing food intake and psychological risk factors since these are subjective measures, self-reported by the participants.

In conclusion, one in ten has HVA and one in five EVA. The prevalence of EVA is higher in men. Study results suggest that preventive strategies aimed at increasing physical activity, reducing sedentary time and decreasing obesity and insulin resistance improve vascular aging.

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Conflicts of interest

There are no conflicts of interest.

Trial registration number: https://clinicaltrials.gov/ct2/show/NCT02623894.

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