





Article

Association of Insulin Resistance with Vascular Ageing in a General Caucasian Population: An EVA Study

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- ‡ Membership of the EVA Investigators is provided in the Acknowledgments.



Citation: Gómez-Sánchez, L.; Gómez-Sánchez, M.; Lugones-Sánchez, C.; Tamayo-Morales, O.; González-Sánchez, S.; Rodríguez-Sánchez, E.; García-Ortiz, L.; Gómez-Marcos, M.A.; on behalf of the EVA Investigators. Association of Insulin Resistance with Vascular Ageing in a General Caucasian Population: An EVA Study. *J. Clin. Med.* **2021**, *10*, 5748. <https://doi.org/10.3390/jcm10245748>

Academic Editor: Nandu Goswami

Received: 22 November 2021

Accepted: 7 December 2021

Published: 8 December 2021

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Abstract: The data on the relationship between insulin resistance and vascular ageing are limited. The aim of this study was to explore the association of different indices of insulin resistance with vascular ageing in an adult Caucasian population without cardiovascular disease. We selected 501 individuals without cardiovascular disease (mean age: 55.9 years, 50.3% women) through random sampling stratified by sex and age. Arterial stiffness was evaluated by measuring the carotid-to-femoral pulse wave velocity (cfPWV) and brachial-to-ankle pulse wave velocity (baPWV). The participants were classified into three groups according to the degree of vascular ageing: early vascular ageing (EVA), normal vascular ageing (NVA) and healthy vascular ageing (HVA). Insulin resistance was evaluated with the homeostatic model assessment of insulin resistance (HOMA-IR) and another five indices. The prevalence of HVA and EVA was 8.4% and 21.4%, respectively, when using cfPWV, and 7.4% and 19.2%, respectively, when using baPWV. The deterioration of vascular ageing, with both measurements, presented as an increase in all the analysed indices of insulin resistance. In the multiple regression analysis and logistic regression analysis, the indices of insulin resistance showed a positive association with cfPWV and baPWV and with EVA.

Keywords: insulin resistance; vascular ageing; arterial stiffness

1. Introduction

Insulin resistance produces hyperglycaemia and dyslipidaemia, and is characterised by high levels of plasma triglycerides and low levels of high-density lipoproteins (HDLs) [1,2]. All this, together with abdominal obesity [3], leads to endothelial dysfunction [4] and increases arterial stiffness [5–7], atherosclerosis [2,8] and morbimortality from cardiovascular diseases [1,2,9–11]. The homeostatic model assessment of insulin resistance (HOMA-IR) is the method most commonly used to evaluate insulin resistance in clinical practice [12]. However, this method is expensive [13]. Therefore, based on anthropometric, glycaemic and/or biochemical parameters gathered routinely in clinical practice, new indices have been created to evaluate insulin resistance, such as the triglyceride and glucose index (TyG index) [8,14,15], triglyceride-to-high-density lipoprotein cholesterol ratio (T/HDL-c ratio) [16], lipid accumulation product index (LAP index) [17,18], waist-to-height ratio (WHt ratio) and visceral adiposity index (VA index) [19]. These indices have shown good correlation with HOMA-IR [14,17,19,20] and an independent association between insulin

resistance and cardiovascular events [21]; thus, they can be used as substitute measures to assess insulin resistance [5,22,23].

Furthermore, increases in central arterial stiffness, evaluated with carotid-to-femoral pulse wave velocity (cfPWV) [24,25], and peripheral arterial stiffness, evaluated with brachial ankle pulse wave velocity (baPWV) [26], can be used to predict morbimortality by cardiovascular diseases. It is also known that increases in insulin resistance increase arterial stiffness [27]. Vascular ageing is influenced by arterial stiffness, reflecting a dissociation between the chronological age and biological age of the main arteries, with such alterations preceding the appearance of cardiovascular events [28–30]. Numerous epidemiological studies have been carried out to determine the influencing factors of vascular ageing, which have attracted considerable interest because they show a stronger relationship with morbimortality from cardiovascular diseases than biological ageing [28,30]. However, few studies have analysed the relationship between vascular ageing and insulin resistance [31,32].

Therefore, it is of increasing research interest to determine the interactions that link insulin resistance to vascular ageing, as well as to evaluate which insulin resistance index is the most adequate to predict vascular ageing. This relationship has not been explored in the Caucasian population; thus, the main objective of the present study was to analyse the association between different insulin resistance indices and vascular ageing in an adult Caucasian population without cardiovascular disease. As a secondary objective, we analysed whether this association differs depending on the arterial stiffness measurements used to define vascular ageing.

2. Materials and Methods

2.1. Study Population

This was a cross-sectional descriptive study with individuals recruited from the association between different risk factors and vascular accelerated ageing study (EVA study) (NCT02623894) [33].

The included individuals were from an urban population of 43,946 people. Through random sampling with replacements stratified by sex and age group (35, 45, 55, 65 and 75 years), 501 Spanish individuals were selected, with approximately 100 in each of the groups (50 women and 50 men). The recruitment was carried out between June 2016 and November 2017. Inclusion criteria: patients aged 35–75 years who agreed to participate in the study and did not meet any of the exclusion criteria. Exclusion criteria: participants who were in terminal condition, could not travel to the health centres to undergo the corresponding examinations, or did not wish to sign the informed consent; participants with a medical history of CVD (ischaemic heart disease or stroke, peripheral arterial disease or heart failure), a diagnosis of renal failure in terminal stages (glomerular filtration rate below 30%), chronic inflammatory disease or acute inflammatory process in the past three months; and patients treated with oestrogens, testosterone or growth hormones. A detailed description of the reference population, as well as the inclusion and exclusion criteria and the causes by age group and sex, is presented in Figure 1.

Before the participants were included in the study, we informed them about its content, and they all signed informed consent. The study was approved on 4 May 2015 by the Drug Research Ethics Committee of Salamanca. Throughout the course of the study, the recommendations of the Declaration of Helsinki were followed [34].

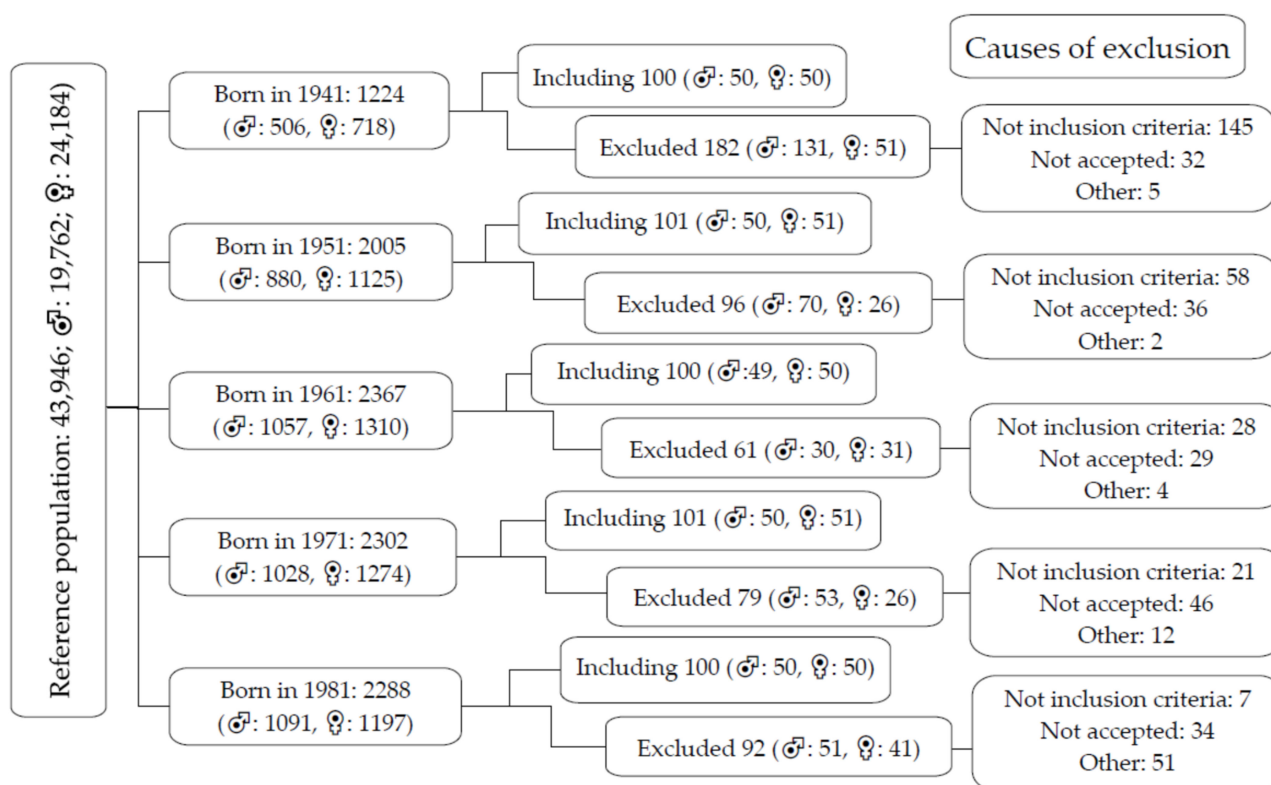


Figure 1. Flow diagram describing the reference population (43,946), those included and excluded, as well as exclusion criteria by age group and sex. A total of 259 subjects did not meet the inclusion criteria; 177 did not agree to participate in the study; 74 (other) subjects were not located due to changes in address or telephone number.

2.2. Variables and Measurement Instruments

A detailed description of the study procedures, as well as the inclusion and exclusion criteria and the response rate, have previously been published [33,35]. Before initiating the study, two healthcare professionals were trained to record the measurements and gather the necessary questionnaires, following a standardised protocol.

2.3. Measurement of Arterial Stiffness

cfPWV was measured in the supine position, using a SphygmoCor® device (AtCor Medical Pty Ltd., Head Office, West Ryde, Australia) [36]. The carotid and femoral pulse waves were recorded, estimating the time of delay in comparison with the ECG wave and calculating the pulse wave velocity. The distances were measured using a measuring tape from the sternal notch to the point where the sensor was placed over the carotid and femoral arteries [36]. The pulse wave was evaluated by flattening tonometry, using a sensor over the radial artery; through a mathematical transformation, the device estimated the aortic pulse wave.

baPWV was measured using a VaSera VS-1500® device (Fukuda Denshi, Denshi Co. Ltd., Tokyo, Japan), which employs an oscillometer method, following the manufacturer’s instructions. The participants were asked not to smoke or consume caffeine 1 h before the test; they wore comfortable clothing and rested for at least 10 min before the test. The cuffs were adapted to the circumference of the arms and ankles in both the left and right limbs. baPWV was estimated using the following equation: $baPWV = (0.5934 \times \text{height (cm)} + 14.4724) / TBA$, where TBA is the time interval between the waves of the arm and ankle [37].

2.4. Definition of Vascular Ageing

Vascular ageing was defined in three steps:

- Step 1: the participants who presented with vascular injury in the carotid artery or peripheral arteriopathy, using the criteria established in the 2018 clinical practice guidelines of the European Societies of Hypertension and Cardiology for the treatment of arterial hypertension [38], were classified as early vascular ageing (EVA);
- Step 2: with the percentiles of arterial stiffness, we used two criteria: the 10th and 90th percentiles of cfPWV and the 10th and 90th percentiles of baPWV of the population studied by age and sex. The individuals with values of cfPWV or baPWV over p90 were considered EVA; those between p10 and p90 were classified as normal vascular ageing (NVA); and those with values below p10 were classified as healthy vascular ageing (HVA);
- Step 3: the individuals diagnosed with type 2 diabetes mellitus or hypertension were included in the HVA group; those with the criteria in the percentiles for cfPWV or those of baPWV were classified as NVA [39]. The distribution of participants fitting the two criteria in each of the groups is shown in Figure 2. The percentiles by age groups and sex of cfPWV and baPWV are shown in Supplementary Materials: Figure S1.

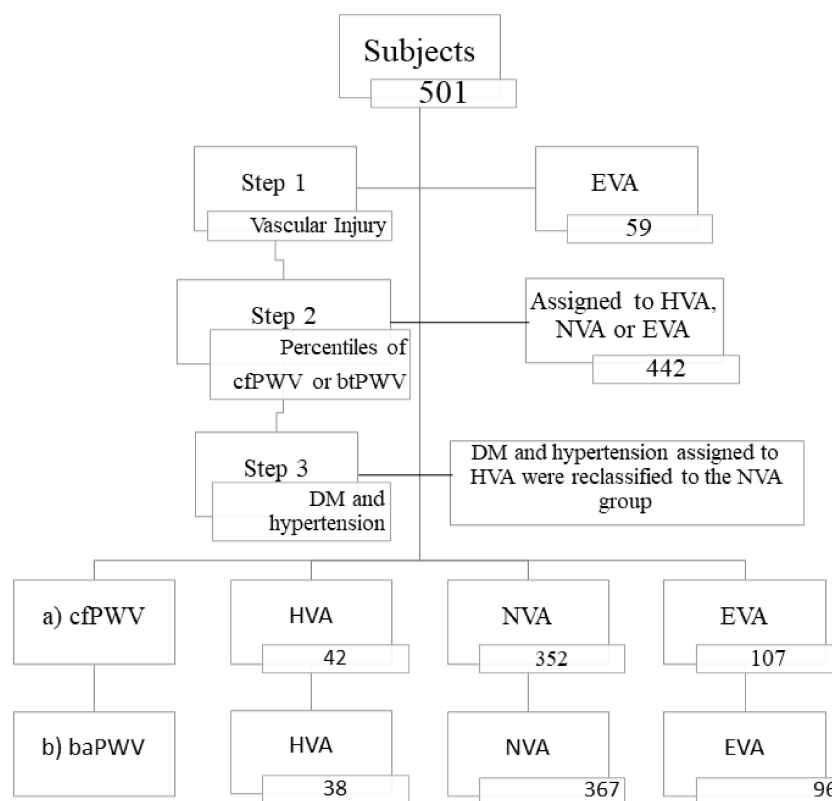


Figure 2. Distribution of participants fitting the two criteria in each of the groups: healthy vascular ageing, normal vascular ageing, and early vascular ageing. (a) The 10th and 90th carotid-to-femoral pulse wave velocity percentiles of the population studied by age and sex; (b) the 10th and 90th brachial-to-ankle pulse wave velocity percentiles of the population studied by age and sex, classified thus: above the 90th percentile was considered early vascular ageing; between the 10th and 90th percentiles was considered normal vascular ageing; and below the 10th percentile was considered healthy vascular ageing. Abbreviations: EVA, early vascular ageing; HVA, healthy vascular ageing; NVA, normal vascular ageing; cfPWV, carotid-to-femoral pulse wave velocity, baPWV brachial-to-ankle pulse wave velocity; DM, diabetes mellitus.

2.5. Insulin Resistance Indices

The homeostatic model assessment of insulin resistance (HOMA-IR) was estimated using the following formula: (fasting glucose in mmol/L) \times (fasting insulin in μ U/mL)/22.5 [12]. The triglyceride-to-high-density lipoprotein cholesterol ratio (T/HDL-C ratio) was calculated using the following equation: (triglyceride in mg/dL)/(high-density lipoprotein cholesterol in mg/dL) [16]. The triglyceride and glucose index (TyG index) was calculated using the following formula: $\text{Ln} [(fasting triglyceride in mg/dL \times fasting glucose in mg/dL)/2]$ [14]. The lipid accumulation product index (LAP index) was calculated using the following formula: [(waist circumference (WC) in cm – 65) \times (triglyceride in mmol/L)] in men and [(WC in cm – 58) \times (triglyceride in mmol/L)] in women [17]. The waist-to-height ratio (WHt ratio) was calculated using the following formula: WHt ratio = (WC in cm/height in cm). The visceral adiposity index (VA index) [19] was calculated using the following formula: VA index = (WC/(39.68 + 1.88 \times BMI)) \times (triglyceride/1.03) \times (1.31/LDL-c) in men and VA index = (WC/(36.58 + 1.89 \times BMI)) \times (triglyceride/0.81) \times (1.52/LDL-c) in women, measuring triglycerides and LDL-c mmol/L [19].

2.6. Measurement of Vascular Injury

The carotid intima–media thickness was measured using a Sonosite Micromaxx ultrasound device (Sonosite Inc., Bothell, Washington, DC, USA), 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 of the proximal and distal walls were taken. 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 criteria of the 2018 ESC/ESH Guidelines for diagnosing and treating hypertension in order to establish the presence of vascular injury [29].

2.7. Laboratory Analyses

Blood samples were collected at the Primary Healthcare Research Unit between 8 am and 9 am, with the participants fasting for at least 12 h beforehand, using a standardised venepuncture protocol; the blood samples were processed in the laboratory of the reference hospital. Glucose, triglycerides, total cholesterol and HDL-c were analysed using enzymatic methods. LDL-c was estimated with the Friedewald equation. Fasting insulin was analysed through immunoassay methods.

We considered that the individuals presented normal glucose metabolism if fasting glycemia < 100 mg/dL, HbA1c < 5.7% and no antidiabetic drugs were being administered. Prediabetes was considered if fasting glycemia values were between 100 and 125 mg/dL, or HbA1c was between 5.7% and 6.4% and no antidiabetic drugs were being administered. Type 2 diabetes mellitus was considered if fasting glycemia \geq 126 mg/dL, HbA1c \geq 6.5%, or the participant was receiving antidiabetic drugs.

The rest of the variables used in this study were analysed, as reflected in the protocol [33].

2.8. Statistical Analysis

The data of the continuous variables are shown as mean \pm standard deviation, and those of the categorical variables are numbers and percentages. Comparison of means between two independent groups was performed with Student's *t*-tests; for more than two groups, a one-way analysis of variance (ANOVA) was used. A post hoc analysis to assess the differences between more than two groups was performed with the least significant difference (LSD) test. In the comparison between categorical variables, the χ^2 test was used. Correlations between cfPWV and baPWV with the indices of insulin resistance were assayed with Pearson's correlation coefficient. The association between the insulin resistance indices and the stiffness measurements used was evaluated through a multiple regression analysis. To analyse the association of the insulin resistance indices with vascular ageing, a logistic regression model was developed for each of the studied

indices. We used HVA, NVA and EVA as dependent variables. In model 1, we coded HVA and NVA = 0 and EVA = 1. In model 2, we coded HVA = 0, and NVA and EVA = 1. Lastly, in model 3, we coded HVA = 0 and EVA = 1. We used the six insulin resistance indices analysed as independent variables. The three models were repeated with the two classifications of vascular ageing conducted using cfPWV and baPWV. In all multiple and logistic regression models, the adjustment variables were age, sex (0 = woman, 1 = man) and the intake of antihypertensive, lipid-lowering and hypoglycaemic drugs (no drug intake = 0, and drug intake = 1). In the hypothesis test, an α risk of 0.05 was established as the limit of statistical significance. All analyses were carried out using SPSS statistical software for Windows, v.25.0 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Baseline Characteristics

The clinical measures, cardiovascular risk factors, arterial stiffness measures, drug intake and parameters to measure insulin resistance, globally and by sex, are described in Table 1. The mean age was 55.90 ± 14.24 years. The insulin resistance indices were greater in men, except for HOMA-IR and the VA index.

Table 1. General characteristics of the subjects, globally and by sex.

	Global (501)	Men (248)	Women (251)	p Value
Age, years	55.90 \pm 14.24	55.95 \pm 14.31	55.85 \pm 14.19	0.934
Clinical measures, mean (SD)				
SBP, mmHg	121 \pm 23	126 \pm 20	115 \pm 25	<0.001
DBP, mmHg	76 \pm 10	77 \pm 9	74 \pm 10	<0.001
Total cholesterol, mg/dL	195 \pm 32	191 \pm 32	197 \pm 31	0.142
LDL cholesterol, mg/dL	116 \pm 29	117 \pm 30	114 \pm 29	0.148
HDL cholesterol, mg/dL	59 \pm 16	53 \pm 14	64 \pm 16	<0.001
Triglyceride, mg/dL	103 \pm 53	112 \pm 54	94 \pm 50	<0.001
Fasting glucose, mg/dL	88 \pm 17	90 \pm 19	86 \pm 16	0.013
HbA1c, (%)	5.49 \pm 0.56	5.54 \pm 0.63	5.44 \pm 0.47	<0.001
Fasting insulin, μ U/mL	8.45 \pm 4.66	8.78 \pm 4.59	8.11 \pm 4.71	0.110
Weight, kg	72 \pm 14	79 \pm 12	66 \pm 12	<0.001
Height, cm	165 \pm 10	172 \pm 7	159 \pm 7	<0.001
BMI, kg/m ²	26.52 \pm 4.23	26.90 \pm 3.54	26.14 \pm 4.79	0.044
Waist circumference, cm	93.33 \pm 12.00	98.76 \pm 9.65	87.95 \pm 11.68	<0.001
Arterial stiffness, mean (SD)				
cfPWV, m/s	8.17 \pm 2.53	8.58 \pm 2.74	7.77 \pm 2.24	0.043
baPWV, m/s	12.93 \pm 2.68	13.16 \pm 2.46	13.16 \pm 2.46	0.064
Cardiovascular Risk factors, n (%)				
Smoker	90 (17.96)	49 (9.80)	41 (8.20)	0.353
Hypertension	147 (29.34)	82 (32.93)	65 (25.79)	0.095
Dyslipidaemia	191 (38.12)	95 (38.10)	96 (38.20)	0.989
Normal glucose	358 (71.42)	174 (69.90)	184 (73.00)	0.314
Prediabetes	105 (21.00)	49 (19.70)	56 (22.20)	0.459
Diabetes mellitus	38 (7.58)	26 (10.40)	12 (4.80)	0.018
Obesity	94 (18.76)	42 (16.90)	52 (20.60)	0.304
Abdominal obesity	193 (38.52)	78 (31.30)	115 (45.80)	0.001
Medication use, n (%)				
Antihypertensive drugs	147 (29)	82 (33)	65 (26)	0.095
Lipid-lowering drugs	102 (20)	49 (20)	53 (21)	0.740
Hypoglycaemic drugs	35 (7)	23 (9)	12 (5)	0.055
Insulin resistance indexes, mean (SD)				
HOMA-IR	1.87 \pm 1.18	1.98 \pm 1.18	1.77 \pm 1.17	0.052
TyG index	10.12 \pm 1.15	10.37 \pm 1.06	9.86 \pm 1.18	<0.001
T/HDL-c ratio	2.01 \pm 1.49	2.36 \pm 1.59	1.66 \pm 1.29	<0.001
LAP index	43.10 \pm 31.08	48.68 \pm 30.51	37.39 \pm 30.67	<0.001
WHt ratio	0.57 \pm 0.07	0.58 \pm 0.06	0.56 \pm 0.08	0.001
VA index	3.27 \pm 2.44	3.31 \pm 2.26	3.21 \pm 2.61	0.656

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; cfPWV, carotid-to-femoral aortic pulse wave velocity; baPWV, brachial-to-ankle aortic pulse wave velocity; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycosylated haemoglobin; TyG index, triglyceride and glucose index; T/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio; LAP index, lipid accumulation product index; WHt ratio, waist-to-height ratio; VA index, visceral adiposity index.

Using cfPWV, the global prevalence of HVA was 8.4% (8.0% in men and 8.7% in women), and that of EVA was 21.4% (25.7% in men and 17.1% in women). Using baPWV, the global prevalence of HVA was 7.4% (6.4% in men and 8.4% in women), and that of EVA was 19.2% (22.9% in men and 15.5% in women) (Figure 3).

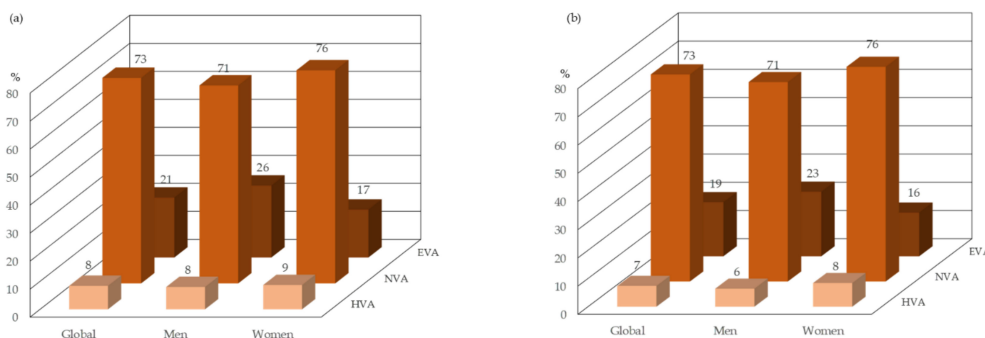


Figure 3. Proportion of vascular ageing status global and by sex. (a) cfPWV and (b) baPWV. Abbreviations: EVA, early vascular ageing; HVA, healthy vascular ageing; NVA, normal vascular ageing; cfPWV, carotid-to-femoral pulse wave velocity; baPWV, brachial-to-ankle pulse wave velocity.

3.2. Relationship of the Insulin Resistance Indices with Vascular Ageing

Table 2 shows the mean values of the insulin resistance indices analysed in individuals with HVA, NVA and EVA, using the percentiles of cfPWV as a measurement of arterial stiffness to classify the individuals according to the degree of vascular ageing. Globally and in women, the deterioration of vascular ageing presented with an increase in all the insulin resistance indices. In men, the increases in the T/HDL-c ratio and VA index were not significant ($p > 0.05$).

Table 2. Insulin resistance indexes to the degree of vascular ageing using the 10th percentile and 90th percentile of cfPWV.

	HVA (42)	NVA (253)	EVA (107)	p Value
Global, mean (SD)				
HOMA-IR, *,¥,&	1.36 ± 0.64	1.85 ± 1.14	2.17 ± 1.37	0.001
TyG index, *,¥,&	179 ± 30	197 ± 40	220 ± 70	<0.001
T/HDL-c ratio, ¥,&	1.54 ± 0.99	1.95 ± 1.43	2.38 ± 1.73	0.003
LAP index, *,¥,&	26.26 ± 15.54	42.52 ± 31.20	51.62 ± 32.37	<0.001
WHt ratio, *,¥,&	0.53 ± 0.06	0.57 ± 0.07	0.58 ± 0.08	0.019
VA index, *,¥,&	2.39 ± 1.31	3.20 ± 2.40	3.85 ± 2.79	0.004
Men, mean (SD)				
HOMA-IR, *,¥	1.39 ± 0.80	1.98 ± 1.22	2.16 ± 1.13	0.038
TyG, mg/dL, *,¥,&	187 ± 28	204 ± 38	228 ± 73	0.001
T/HDL-c ratio	2.05 ± 1.18	2.28 ± 1.56	2.67 ± 1.74	0.165
LAP index, *,¥	32.25 ± 15.43	47.73 ± 30.40	56.28 ± 32.25	0.007
WHt ratio, *,¥	0.54 ± 0.04	0.58 ± 0.06	0.59 ± 0.06	0.005
VA index	2.77 ± 1.65	3.18 ± 2.22	3.86 ± 2.46	0.067
Women, mean (SD)				
HOMA-IR, ¥,&	1.33 ± 0.44	1.73 ± 1.05	2.18 ± 1.68	0.015
TyG index, *, ¥, &	172 ± 32	191 ± 41	209 ± 64	0.006
T/HDL-c ratio, *, ¥	1.07 ± 0.43	1.67 ± 1.25	1.94 ± 1.63	0.033
LAP index, *, &	20.83 ± 13.81	37.93 ± 31.25	44.69 ± 31.64	0.011
WHt ratio, *, ¥	0.51 ± 0.07	0.56 ± 0.08	0.58 ± 0.09	0.012
VA index, *, &	2.06 ± 0.82	3.21 ± 2.55	3.80 ± 3.23	0.039

HVA, healthy vascular ageing; NVA, normal vascular ageing; EVA, early vascular ageing; cfPWV, carotid-to-femoral aortic pulse wave velocity; HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride and glucose index; T/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio; LAP index, lipid accumulation product index; WHt ratio, waist-to-height ratio; VA index, visceral adiposity index. Differences among groups: continuous variables analysis of variance and post hoc using the least significant difference tests. * 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 shows the mean values of the insulin resistance indices analysed in individuals with HVA, NVA and EVA, using the percentiles of baPWV as a measurement of arterial stiffness to classify the individuals according to the degree of vascular ageing. Globally, vascular deterioration presented with an increase in all the insulin resistance indices. In men, increases in the T/HDL-c ratio, LAP index and VA index, as well as those in the WHt ratio and LAP index in women, were not significant ($p > 0.05$).

Table 3. Insulin resistance indexes to the degree of vascular ageing using the 10th percentile and 90th percentile of baPWV.

	HVA (38)	NVA (367)	EVA (96)	<i>p</i> Value
Global, mean (SD)				
HOMA-IR, *,¥,&	1.23 ± 0.61	1.85 ± 1.13	2.20 ± 1.38	<0.001
TyG index, *,¥,&	180 ± 28	198 ± 42	219 ± 68	<0.001
T/HDL-c ratio, ¥,&	1.63 ± 1.16	1.93 ± 1.39	2.47 ± 1.84	0.002
LAP index, *,&	34.30 ± 23.60	41.66 ± 31.01	51.76 ± 32.27	0.004
WHt ratio, ¥,&	0.54 ± 0.06	0.56 ± 0.07	0.58 ± 0.07	0.019
VA index, ¥,&	2.63 ± 1.80	3.15 ± 2.31	3.95 ± 2.97	0.005
Men, mean (SD)				
HOMA-IR, *,¥	1.15 ± 0.59	1.98 ± 1.20	2.20 ± 1.15	0.007
TyG index, *,¥,&	192 ± 23	204 ± 39	228 ± 74	0.002
T/HDL-c ratio	2.13 ± 1.20	2.27 ± 1.52	2.69 ± 1.86	0.186
LAP index	38.95 ± 21.16	47.12 ± 30.53	56.23 ± 31.57	0.061
WHt ratio, *,¥	0.54 ± 0.05	0.58 ± 0.06	0.59 ± 0.06	0.010
VA index	2.96 ± 1.81	3.19 ± 2.16	3.82 ± 2.63	0.158
Women, mean (SD)				
HOMA-IR, ¥,&	1.29 ± 0.64	1.73 ± 1.06	2.19 ± 1.68	0.014
TyG index, *,¥,&	171 ± 29	192 ± 44	206 ± 56	0.017
T/HDL-c ratio, ¥,&	1.25 ± 0.99	1.61 ± 1.18	2.14 ± 1.77	0.019
LAP index	30.76 ± 25.22	36.63 ± 30.68	45.23 ± 32.57	0.162
WHt ratio	0.55 ± 0.07	0.55 ± 0.08	0.56 ± 0.09	0.685
VA index, ¥,&	2.39 ± 1.80	3.11 ± 2.45	4.13 ± 3.43	0.027

HVA, healthy vascular ageing; NVA, normal vascular ageing; EVA, early vascular ageing; baPWV, brachial-to-ankle aortic pulse wave velocity; HOMA-IR, homeostatic model assessment of insulin resistance; T/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio; LAP index, lipid accumulation product index; WHt ratio, waist-to-height ratio; VA index, visceral adiposity index. Differences among groups: continuous variables analysis of variance and post hoc using the least significant difference tests. * 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.

Correlations between the measures of arterial stiffness and the insulin resistance indices are shown in Supplementary Materials: Table S1; there was a positive correlation in all cases, except between cfPWV and the T/HDL-c ratio in men. The correlation persisted in all cases after controlling for age and sex, as can be observed in Supplementary Materials: Table S2.

The values of the two measurements of arterial stiffness in both sexes, according to impaired glucose metabolism, are shown in Supplementary Materials: Figure S2.

3.3. Association of the Insulin Resistance Indices with Arterial Stiffness and Vascular Ageing

In the multiple regression analysis, all the insulin resistance indices showed a positive association with the two stiffness measurements analysed, after controlling for possible confounders (Table 4).

Table 4. Association of arterial stiffness parameters with insulin resistance indices.

	β	95% IC	<i>p</i>
cfPWV, m/sec			
HOMA-IR	0.196	(0.049–0.344)	0.009
TyG index	0.012	(0.004–0.020)	0.004
T/HDL-c ratio	0.137	(0.026–0.248)	0.015
LAP index	0.011	(0.005–0.016)	<0.001
WHt ratio	3.798	(1.293–6.304)	0.003
VA index	0.091	(0.024–0.158)	0.008
baPWV, m/sec			
HOMA-IR	0.203	(0.060–0.346)	0.005
TyG index	0.007	(0.003–0.011)	0.002
T/HDL-c ratio	0.227	(0.118–0.335)	<0.001
LAP index	0.009	(0.004–0.014)	0.001
WHt ratio	2.848	(0.365–5.331)	0.025
VA index	0.134	(0.069–0.199)	<0.001

cfPWV, carotid-to-femoral aortic pulse wave velocity; baPWV, brachial-to-ankle aortic pulse wave velocity; HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride and glucose index; T/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio; LAP index, lipid accumulation product index; WHt ratio, waist-to-height ratio; VA index, visceral adiposity index. Multiple regression analysis using cfPWV m/sec and baPWV m/sec as dependent variables, insulin resistance indices (HOMA-IR, HbA1c, TyG, TG/HDL and WHt ratio) as independent variables, and age, sex, hypotensive, hypoglycaemic, and lipid-lowering drugs as adjustment variables.

In model 1 of the logistic regression analysis, there were high OR values with GyT index (OR = 1.01 and OR = 1.02), T/HDL-c ratio (OR = 1.15 and OR = 1.21), LAP index (OR = 1.02 and OR = 1.01) and VA index (OR = 1.09 and OR = 1.12) using cfPWV and baPWV as measurements of arterial stiffness in individuals with EVA with respect to the remaining participants (Figure 4).

The results obtained from the logistic regression analysis using model 2 and model 3 can be seen in Supplementary Materials: Figure S3 and Figure S4.

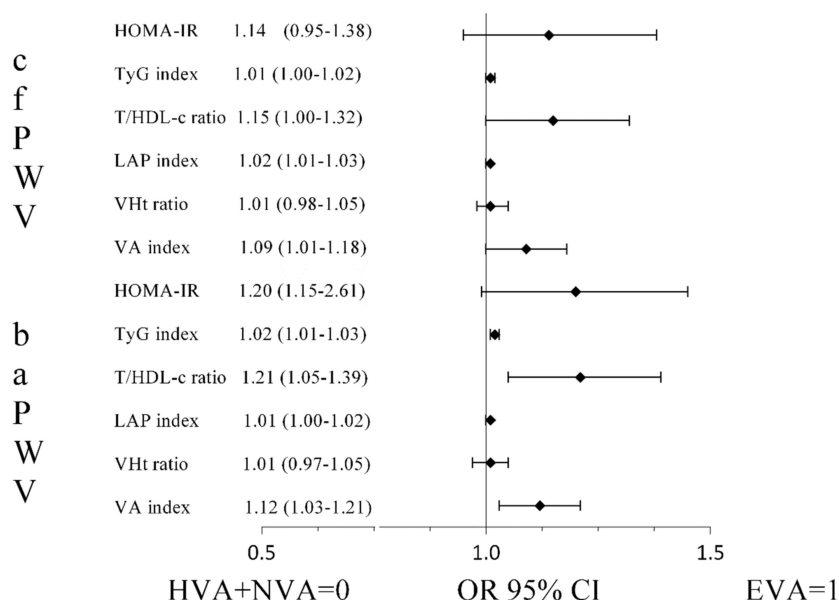


Figure 4. Odds ratio of determinants of EVA vs. HVA + NVA with insulin resistance indexes in adults aged 35–75 years. Adjusted for age, sex, antihypertensive, lipid-lowering and hypoglycaemic drugs. Abbreviations: EVA, early vascular ageing; HVA, healthy vascular ageing; NVA, normal vascular ageing; cfPWV, carotid-to-femoral pulse wave velocity; baPWV, brachial-to-ankle pulse wave velocity; HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride and glucose index; T/HDL-c ratio, triglyceride-to-high-density lipoprotein cholesterol ratio; LAP index, lipid accumulation product index; WHt ratio, waist-to-height ratio; VA index, visceral adiposity index.

4. Discussion

This study analysed the association between different insulin resistance indices and vascular ageing and arterial stiffness measurements using cfPWV and baPWV in an adult Caucasian population without cardiovascular disease. Regarding the main findings of this study, the insulin resistance indices showed a positive association with vascular ageing, although there were differences between them. All the insulin resistance indices analysed were related to central and peripheral arterial stiffness.

The prevalence of HVA and EVA has been analysed in previous studies [32,40–43], all of which agree with the results of the present study, indicating that the prevalence of EVA is greater in men, and that of HVA is greater in women. However, the prevalence rates found between the studies are different and cannot be compared, because the cut-off points used, the mean age and the distribution by sex, as well as the prevalence of the different cardiovascular risk factors and race differ from one study to another.

The positive correlations found in this study between the arterial stiffness measurements (cfPWV and baPWV for the evaluation of central and peripheral arterial stiffness, respectively) and the different indices that reflect peripheral or hepatic insulin resistance are in line with those reported in previous studies. For example, the recent study of Poon et al. [5], conducted in US adults without diabetes, found that HOMA-IR, the T/HDL-c ratio and the TyG index were positively related to central arterial stiffness. This association between central arterial stiffness and insulin resistance has also been found in Chinese adults without diabetes mellitus [44] or with arterial hypertension [45]. In Korean adults, HOMA-IR and the TyG index have been shown to exhibit a positive association with peripheral arterial stiffness [21,46]. Lastly, the results of the study entitled “elderly individuals: the Northern Shanghai Study” [20] demonstrated an association between the TyG index and central and peripheral arterial stiffness. However, this study complements the existing information, because it analysed the association of central and peripheral arterial stiffness evaluated with cfPWV and baPWV with the indices of peripheral and hepatic insulin resistance in the same sample of individuals without previous cardiovascular disease. Therefore, we have confirmed a relationship between insulin resistance and central and peripheral arterial stiffness in an adult population, using indices that reflect more than one aspect of insulin resistance.

The participants characterised by HVA had lower values for the insulin resistance indices than the participants with EVA, which is in line with the results published in the study of Framingham [32]. In this study, the participants with HVA had lower values of HOMA-IR than the participants without HVA. However, most of the published studies did not analyse the association of the different insulin resistance indices with vascular ageing, focusing on the relationship of the parameters of abdominal obesity, lipid components and the glycemia values used to calculate the different indices of insulin resistance. Thus, numerous studies have shown that abdominal obesity is positively associated with vascular ageing [28,30,32,40,41,47–49]. The increase in triglycerides and the decrease in HDL-c show a correlation with vascular ageing [30,32,40–42]. In this sense, the association between glycometabolic impairment and an increase in arterial stiffness is consistent with previous studies [50], and a better control of glycemia alleviates or prevents the progression of arterial stiffness in individuals with type 2 diabetes mellitus [51]. Similarly, it has been demonstrated that glycometabolic impairment is associated with vascular ageing. The study by Framingham [32] revealed that the absence of type 2 diabetes mellitus was associated with the presence of HVA, and that the individuals with type 2 diabetes mellitus were eight times less likely to present with HVA compared to non-diabetic individuals; in the study of Shanghai [41] and in the MARE study [40], a baseline glycemia level over 100 mg/dL was associated with EVA. Lastly, in a study carried out in Chinese adults, it was found that higher fasting glucose levels and HbA1c were associated with EVA [52].

Furthermore, the different behaviours of the insulin resistance indices with vascular ageing are in agreement with the results of previous studies, which showed that the TyG

index was more strongly related to greater arterial stiffness than HOMA-IR in Korean adults [21].

In summary, this study provides further support to the available information which indicates that insulin resistance is an independent predictor of vascular ageing in the general population.

5. Conclusions

In general, all the insulin resistance indices showed a positive association with vascular ageing and with central and peripheral arterial stiffness. However, we have found differences in the associations between different indices of insulin resistance and ageing. Therefore, prospective studies are necessary to clarify these results.

6. Limits

Regarding the main limitations of this study, it is important to highlight that, firstly, the cross-sectional study design does not allow for inferring causality. Secondly, the results of this study only refer to a Caucasian urban population, and thus cannot be generalised to other races/ethnicities. Lastly, the prevalence of cardiovascular risk factors in this study was lower than in other studies conducted in a Caucasian population. The main strengths of this study were the recruitment of participants by population-based random sampling, and the fact that this is the first study to analyse the relationship between vascular ageing and different insulin resistance indices.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/jcm10245748/s1>, Figure S1: Age-specific 10th and 90th, Table S1: The correlation between insulin resistance indexes and arterial stiffness parameters globally and by sex, Table S2: The correlation between insulin resistance indexes and arterial stiffness parameters globally adjusted for age and sex, Figure S2: Values according to glucose metabolism by sex of the two measures of arterial stiffness used. Figure S3: Logistic regression analysis using model 2, Figure S4: Logistic regression analysis using model 3.

Author Contributions: L.G.-S. and M.G.-S. proposed the study, implemented the analysis, interpreted the results and composed the manuscript; E.R.-S., C.L.-S., O.T.-M. and S.G.-S. conducted the data collection; L.G.-O. and M.A.G.-M. contributed expertly to the interpretation of the results and preparation of the manuscript. All authors critically reviewed and revised the manuscript for important intellectual content and read and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the IBSAL, the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III and co-funded by European Union (ERDF/ESF, “Investing in your future”) (RD21/0016/0010), the Autonomous Government of Castilla and León (GRS 1193/B/15, GRS 1943/B/19, INT/M/02/17 e INT/M/04/15) and intensification of research programme.

Institutional Review Board Statement: The study was approved by the Drug Research Ethics Committee of the Health Area of Salamanca on 4 May 2015. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Declaration of Helsinki. All participants signed written informed consent documents prior to participation in the study.

Informed Consent Statement: Written informed consent has been obtained from all the subjects involved in the study.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: Members of the EVA group: Manuel A Gómez-Marcos, Luis García-Ortiz, José I Recio-Rodríguez, Carlos Martínez-Salgado, Jesús M Hernández-Rivas, Rogelio González-Sarmiento, Pedro L Sánchez-Fernández, Emiliano Rodríguez-Sánchez, María C Patino-Alonso, José A Maderuelo-Fernández, Leticia Gómez-Sánchez, Jesús González-Sánchez, Rosa Alonso-Domínguez, Carmela Rodríguez-Martín, Marta Gómez-Sánchez, Ángela de Cabo-Laso, Benigna Sánchez-Salgado, Natalia Sánchez Aguadero, Sara Mora-Simón, Olaya Tamayo-Morales, Cristina Agudo Conde, Cristina

Lugones Sánchez, Susana González Sánchez, José Ramón González-Porras, José María Bastida-Bermejo and Isabel Fuentes-Calvo.

Conflicts of Interest: The authors declare that they have no competing interests.

References

1. Ormazabal, V.; Nair, S.; Elfeky, O.; Aguayo, C.; Salomon, C.; Zuñiga, F.A. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc. Diabetol* **2018**, *17*, 122. [[CrossRef](#)] [[PubMed](#)]
2. Strisciuglio, T.; Izzo, R.; Barbato, E.; Di Gioia, G.; Colaiori, I.; Fiordelisi, A.; Morisco, C.; Bartunek, J.; Franco, D.; Ammirati, G.; et al. Insulin Resistance Predicts Severity of Coronary Atherosclerotic Disease in Non-Diabetic Patients. *J. Clin. Med.* **2020**, *9*, 2144. [[CrossRef](#)] [[PubMed](#)]
3. Kurniawan, L.B.; Bahrin, U.; Hatta, M.; Arif, M. Body Mass, Total Body Fat Percentage, and Visceral Fat Level Predict Insulin Resistance Better Than Waist Circumference and Body Mass Index in Healthy Young Male Adults in Indonesia. *J. Clin. Med.* **2018**, *7*, 96. [[CrossRef](#)] [[PubMed](#)]
4. Janus, A.; Szahidewicz-Krupska, E.; Mazur, G.; Doroszko, A. Insulin Resistance and Endothelial Dysfunction Constitute a Common Therapeutic Target in Cardiometabolic Disorders. *Mediat. Inflamm.* **2016**, *2016*, 3634948. [[CrossRef](#)]
5. Poon, A.K.; Meyer, M.L.; Tanaka, H.; Selvin, E.; Pankow, J.; Zeng, D.; Loehr, L.; Knowles, J.W.; Rosamond, W.; Heiss, G. Association of insulin resistance, from mid-life to late-life, with aortic stiffness in late-life: The Atherosclerosis Risk in Communities Study. *Cardiovasc. Diabetol* **2020**, *19*, 11. [[CrossRef](#)] [[PubMed](#)]
6. González-Clemente, J.M.; Cano, A.; Albert, L.; Giménez-Palop, O.; Romero, A.; Berlanga, E.; Vendrell, J.; Llauradó, G. Arterial Stiffness in Type 1 Diabetes: The Case for the Arterial Wall Itself as a Target Organ. *J. Clin. Med.* **2021**, *10*, 3616. [[CrossRef](#)] [[PubMed](#)]
7. Gagliardino, J.J.; Salazar, M.R.; Espeche, W.G.; Tolosa Chapasian, P.E.; Gomez Garizoain, D.; Olano, R.D.; Stavile, R.N.; Balbín, E.; Martinez, C.; Leiva Sisniegues, B.C.; et al. Arterial Stiffness: Its Relation with Prediabetes and Metabolic Syndrome and Possible Pathogenesis. *J. Clin. Med.* **2021**, *10*, 3251. [[CrossRef](#)] [[PubMed](#)]
8. Cho, Y.K.; Lee, J.; Kim, H.S.; Kim, E.H.; Lee, M.J.; Yang, D.H.; Kang, J.W.; Jung, C.H.; Park, J.Y.; Kim, H.K.; et al. Triglyceride Glucose-Waist Circumference Better Predicts Coronary Calcium Progression Compared with Other Indices of Insulin Resistance: A Longitudinal Observational Study. *J. Clin. Med.* **2020**, *10*, 92. [[CrossRef](#)] [[PubMed](#)]
9. Gast, K.B.; Tjeerdema, N.; Stijnen, T.; Smit, J.W.; Dekkers, O.M. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: Meta-analysis. *PLoS ONE* **2012**, *7*, e52036. [[CrossRef](#)] [[PubMed](#)]
10. Mancusi, C.; de Simone, G.; Best, L.G.; Wang, W.; Zhang, Y.; Roman, M.J.; Lee, E.T.; Howard, B.V.; Devereux, R.B. Myocardial mechano-energetic efficiency and insulin resistance in non-diabetic members of the Strong Heart Study cohort. *Cardiovasc. Diabetol* **2019**, *18*, 56. [[CrossRef](#)] [[PubMed](#)]
11. Yan, Y.; Li, S.; Liu, Y.; Bazzano, L.; He, J.; Mi, J.; Chen, W. Temporal relationship between inflammation and insulin resistance and their joint effect on hyperglycemia: The Bogalusa Heart Study. *Cardiovasc. Diabetol* **2019**, *18*, 109. [[CrossRef](#)] [[PubMed](#)]
12. Galvin, P.; Ward, G.; Walters, J.; Pestell, R.; Koschmann, M.; Vaag, A.; Martin, I.; Best, J.D.; Alford, F. A simple method for quantitation of insulin sensitivity and insulin release from an intravenous glucose tolerance test. *Diabet. Med.* **1992**, *9*, 921–928. [[CrossRef](#)]
13. Bonora, E.; Targher, G.; Alberiche, M.; Bonadonna, R.C.; Saggiani, F.; Zenere, M.B.; Monauni, T.; Muggeo, M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: Studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* **2000**, *23*, 57–63. [[CrossRef](#)] [[PubMed](#)]
14. Guerrero-Romero, F.; Simental-Mendía, L.E.; González-Ortiz, M.; Martínez-Abundis, E.; Ramos-Zavala, M.G.; Hernández-González, S.O.; Jacques-Camarena, O.; Rodríguez-Morán, M. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 3347–3351. [[CrossRef](#)] [[PubMed](#)]
15. Bikov, A.; Frent, S.M.; Meszaros, M.; Kunos, L.; Mathioudakis, A.G.; Negru, A.G.; Gaita, L.; Mihaicuta, S. Triglyceride-Glucose Index in Non-Diabetic, Non-Obese Patients with Obstructive Sleep Apnoea. *J. Clin. Med.* **2021**, *10*, 1932. [[CrossRef](#)] [[PubMed](#)]
16. Abbasi, F.; Reaven, G.M. Comparison of two methods using plasma triglyceride concentration as a surrogate estimate of insulin action in nondiabetic subjects: Triglycerides \times glucose versus triglyceride/high-density lipoprotein cholesterol. *Metabolism* **2011**, *60*, 1673–1676. [[CrossRef](#)] [[PubMed](#)]
17. Kahn, H.S. The “lipid accumulation product” performs better than the body mass index for recognizing cardiovascular risk: A population-based comparison. *BMC Cardiovasc. Disord.* **2005**, *5*, 26. [[CrossRef](#)] [[PubMed](#)]
18. Foschi, F.G.; Conti, F.; Domenicali, M.; Giacomoni, P.; Borghi, A.; Bevilacqua, V.; Napoli, L.; Berardinelli, D.; Altini, M.; Cucchetti, A.; et al. External Validation of Surrogate Indices of Fatty Liver in the General Population: The Bagnacavallo Study. *J. Clin. Med.* **2021**, *10*, 520. [[CrossRef](#)] [[PubMed](#)]
19. Amato, M.C.; Giordano, C.; Galia, M.; Criscimanna, A.; Vitabile, S.; Midiri, M.; Galluzzo, A. Visceral Adiposity Index: A reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care* **2010**, *33*, 920–922. [[CrossRef](#)] [[PubMed](#)]
20. Zhao, S.; Yu, S.; Chi, C.; Fan, X.; Tang, J.; Ji, H.; Teliewubai, J.; Zhang, Y.; Xu, Y. Association between macro- and microvascular damage and the triglyceride glucose index in community-dwelling elderly individuals: The Northern Shanghai Study. *Cardiovasc. Diabetol.* **2019**, *18*, 95. [[CrossRef](#)] [[PubMed](#)]

21. Lee, S.B.; Ahn, C.W.; Lee, B.K.; Kang, S.; Nam, J.S.; You, J.H.; Kim, M.J.; Kim, M.K.; Park, J.S. Association between triglyceride glucose index and arterial stiffness in Korean adults. *Cardiovasc. Diabetol* **2018**, *17*, 41. [[CrossRef](#)] [[PubMed](#)]
22. Fiorentino, T.V.; Marini, M.A.; Succurro, E.; Andreozzi, F.; Sesti, G. Relationships of surrogate indexes of insulin resistance with insulin sensitivity assessed by euglycemic hyperinsulinemic clamp and subclinical vascular damage. *BMJ Open Diabetes Res. Care* **2019**, *7*, e000911. [[CrossRef](#)]
23. Sánchez-García, A.; Rodríguez-Gutiérrez, R.; Mancillas-Adame, L.; González-Nava, V.; Díaz González-Colmenero, A.; Solís, R.C.; Álvarez-Villalobos, N.A.; González-González, J.G. Diagnostic Accuracy of the Triglyceride and Glucose Index for Insulin Resistance: A Systematic Review. *Int. J. Endocrinol.* **2020**, *2020*, 4678526. [[CrossRef](#)] [[PubMed](#)]
24. Ben-Shlomo, Y.; Spears, M.; Boustred, C.; May, M.; Anderson, S.G.; Benjamin, E.J.; Boutouyrie, P.; Cameron, J.; Chen, C.H.; Cruickshank, J.K.; et al. Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *J. Am. Coll. Cardiol.* **2014**, *63*, 636–646. [[CrossRef](#)] [[PubMed](#)]
25. Sequí-Domínguez, I.; Cavero-Redondo, I.; Álvarez-Bueno, C.; Pozuelo-Carrascosa, D.P.; Nuñez de Arenas-Arroyo, S.; Martínez-Vizcaíno, V. Accuracy of Pulse Wave Velocity Predicting Cardiovascular and All-Cause Mortality. A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2020**, *9*, 2080. [[CrossRef](#)]
26. Ohkuma, T.; Ninomiya, T.; Tomiyama, H.; Kario, K.; Hoshida, S.; Kita, Y.; Inoguchi, T.; Maeda, Y.; Kohara, K.; Tabara, Y.; et al. Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. *Hypertension* **2017**, *69*, 1045–1052. [[CrossRef](#)] [[PubMed](#)]
27. Webb, D.R.; Khunti, K.; Silverman, R.; Gray, L.J.; Srinivasan, B.; Lacy, P.S.; Williams, B.; Davies, M.J. Impact of metabolic indices on central artery stiffness: Independent association of insulin resistance and glucose with aortic pulse wave velocity. *Diabetologia* **2010**, *53*, 1190–1198. [[CrossRef](#)] [[PubMed](#)]
28. Laurent, S.; Boutouyrie, P.; Cunha, P.G.; Lacolley, P.; Nilsson, P.M. Concept of Extremes in Vascular Aging. *Hypertension* **2019**, *74*, 218–228. [[CrossRef](#)]
29. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J. Hypertens.* **2018**, *36*, 1953–2041. [[CrossRef](#)] [[PubMed](#)]
30. Nowak, K.L.; Rossman, M.J.; Chonchol, M.; Seals, D.R. Strategies for Achieving Healthy Vascular Aging. *Hypertension* **2018**, *71*, 389–402. [[CrossRef](#)]
31. Liu, J.; Wu, Y.Y.; Huang, X.M.; Yang, M.; Zha, B.B.; Wang, F.; Zha, Y.; Sheng, L.; Chen, Z.P.; Gu, Y. Ageing and type 2 diabetes in an elderly Chinese population: The role of insulin resistance and beta cell dysfunction. *Eur. Rev. Med. Pharm. Sci.* **2014**, *18*, 1790–1797.
32. Niiranen, T.J.; Lyass, A.; Larson, M.G.; Hamburg, N.M.; Benjamin, E.J.; Mitchell, G.F.; Vasan, R.S. Prevalence, Correlates, and Prognosis of Healthy Vascular Aging in a Western Community-Dwelling Cohort: The Framingham Heart Study. *Hypertension* **2017**, *70*, 267–274. [[CrossRef](#)]
33. Gomez-Marcos, M.A.; Martinez-Salgado, C.; Gonzalez-Sarmiento, R.; Hernandez-Rivas, J.M.; Sanchez-Fernandez, P.L.; Recio-Rodriguez, J.I.; Rodriguez-Sanchez, E.; Garcia-Ortiz, L. Association between different risk factors and vascular accelerated ageing (EVA study): Study protocol for a cross-sectional, descriptive observational study. *BMJ Open* **2016**, *6*, e011031. [[CrossRef](#)] [[PubMed](#)]
34. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* **2013**, *310*, 2191–2194. [[CrossRef](#)] [[PubMed](#)]
35. Gómez-Sánchez, M.; Patino-Alonso, M.C.; Gómez-Sánchez, L.; Recio-Rodríguez, J.I.; Rodríguez-Sánchez, E.; Maderuelo-Fernández, J.A.; García-Ortiz, L.; Gómez-Marcos, M.A. Reference values of arterial stiffness parameters and their association with cardiovascular risk factors in the Spanish population. The EVA Study. *Rev. Esp. Cardiol. (Engl. Ed.)* **2020**, *73*, 43–52. [[CrossRef](#)]
36. Van Bortel, L.M.; Laurent, S.; Boutouyrie, P.; Chowienczyk, P.; Cruickshank, J.K.; De Backer, T.; Filipovsky, J.; Huybrechts, S.; Mattace-Raso, F.U.; Protogerou, A.D.; et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J. Hypertens.* **2012**, *30*, 445–448. [[CrossRef](#)] [[PubMed](#)]
37. Shirai, K.; Hiruta, N.; Song, M.; Kurosu, T.; Suzuki, J.; Tomaru, T.; Miyashita, Y.; Saiki, A.; Takahashi, M.; Suzuki, K.; et al. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: Theory, evidence and perspectives. *J. Atheroscler. Thromb.* **2011**, *18*, 924–938. [[CrossRef](#)]
38. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.; Coca, A.; De Simone, G.; Dominiczak, A.; et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J. Hypertens.* **2018**, *36*, 2284–2309. [[CrossRef](#)] [[PubMed](#)]
39. Gomez-Sanchez, M.; Gomez-Sanchez, L.; Patino-Alonso, M.C.; Cunha, P.G.; Recio-Rodriguez, J.I.; Alonso-Dominguez, R.; Sanchez-Aguadero, N.; Rodriguez-Sanchez, E.; Maderuelo-Fernandez, J.A.; Garcia-Ortiz, L.; et al. Vascular aging and its relationship with lifestyles and other risk factors in the general Spanish population: Early Vascular Ageing Study. *J. Hypertens.* **2020**, *38*, 1110–1122. [[CrossRef](#)]

40. Nilsson, P.M.; Laurent, S.; Cunha, P.G.; Olsen, M.H.; Rietzschel, E.; Franco, O.H.; Ryliškytė, L.; Strazhesko, I.; Vlachopoulos, C.; Chen, C.H.; et al. Characteristics of healthy vascular ageing in pooled population-based cohort studies: The global Metabolic syndrome and Artery REsearch Consortium. *J. Hypertens.* **2018**, *36*, 2340–2349. [[CrossRef](#)] [[PubMed](#)]
41. Ji, H.; Teliewubai, J.; Lu, Y.; Xiong, J.; Yu, S.; Chi, C.; Li, J.; Blacher, J.; Zhang, Y.; Xu, Y. Vascular aging and preclinical target organ damage in community-dwelling elderly: The Northern Shanghai Study. *J. Hypertens.* **2018**, *36*, 1391–1398. [[CrossRef](#)]
42. Botto, F.; Obregon, S.; Rubinstein, F.; Scuteri, A.; Nilsson, P.M.; Kotliar, C. Frequency of early vascular aging and associated risk factors among an adult population in Latin America: The OPTIMO study. *J. Hum. Hypertens.* **2018**, *32*, 219–227. [[CrossRef](#)] [[PubMed](#)]
43. Cunha, P.G.; Cotter, J.; Oliveira, P.; Vila, I.; Boutouyrie, P.; Laurent, S.; Nilsson, P.M.; Scuteri, A.; Sousa, N. Pulse wave velocity distribution in a cohort study: From arterial stiffness to early vascular aging. *J. Hypertens.* **2015**, *33*, 1438–1445. [[CrossRef](#)]
44. Fu, S.; Lin, Y.; Luo, L.; Ye, P. Relationship between Central Arterial Stiffness and Insulin Resistance in Chinese Community-Dwelling Population without Diabetes Mellitus. *Int. J. Endocrinol.* **2017**, *2017*, 1073919. [[CrossRef](#)] [[PubMed](#)]
45. Li, M.; Zhan, A.; Huang, X.; Hu, L.; Zhou, W.; Wang, T.; Zhu, L.; Bao, H.; Cheng, X. Positive association between triglyceride glucose index and arterial stiffness in hypertensive patients: The China H-type Hypertension Registry Study. *Cardiovasc. Diabetol* **2020**, *19*, 139. [[CrossRef](#)] [[PubMed](#)]
46. Won, K.B.; Park, G.M.; Lee, S.E.; Cho, I.J.; Kim, H.C.; Lee, B.K.; Chang, H.J. Relationship of insulin resistance estimated by triglyceride glucose index to arterial stiffness. *Lipids Health Dis.* **2018**, *17*, 268. [[CrossRef](#)] [[PubMed](#)]
47. Li, P.; Wang, L.; Liu, C. Overweightness, obesity and arterial stiffness in healthy subjects: A systematic review and meta-analysis of literature studies. *Postgrad. Med.* **2017**, *129*, 224–230. [[CrossRef](#)]
48. Cunha, P.G.; Boutouyrie, P.; Nilsson, P.M.; Laurent, S. Early Vascular Ageing (EVA): Definitions and Clinical Applicability. *Curr. Hypertens. Rev.* **2017**, *13*, 8–15. [[CrossRef](#)] [[PubMed](#)]
49. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* **2016**, *387*, 1377–1396. [[CrossRef](#)]
50. McEniery, C.M.; Wilkinson, I.B.; Johansen, N.B.; Witte, D.R.; Singh-Manoux, A.; Kivimaki, M.; Tabak, A.G.; Brunner, E.J.; Shipley, M.J. Nondiabetic Glucometabolic Status and Progression of Aortic Stiffness: The Whitehall II Study. *Diabetes Care* **2017**, *40*, 599–606. [[CrossRef](#)] [[PubMed](#)]
51. Ferreira, M.T.; Leite, N.C.; Cardoso, C.R.; Salles, G.F. Correlates of aortic stiffness progression in patients with type 2 diabetes: Importance of glycemic control: The Rio de Janeiro type 2 diabetes cohort study. *Diabetes Care* **2015**, *38*, 897–904. [[CrossRef](#)] [[PubMed](#)]
52. Yu, J.; Sun, H.; Shang, F.; Wu, H.; Shi, H.; Ren, L.; He, Y.; Zhang, M.; Peng, H. Association Between Glucose Metabolism And Vascular Aging In Chinese Adults: A Cross-Sectional Analysis In The Tianning Cohort Study. *Clin. Interv. Aging.* **2019**, *14*, 1937–1946. [[CrossRef](#)] [[PubMed](#)]