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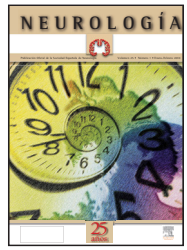

ORIGINAL ARTICLE

Vascular Risk Factors and Cognitive Performance in Patients 50 to 65 Years-Old

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KEYWORDS
Cognition;
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Risk factor;
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Abstract
Introduction: Vascular risk factors (VRF) have been related to cognitive deficits and an increased risk of dementia. Cognitive impairment is considered to be one of the earliest manifestations of cerebrovascular disease. In Spain there is a high prevalence of VRF, but also one of the lowest incidences of cerebrovascular disease in Europe. This is the first study that investigates the relationship between VRF and cognition in a Spanish sample.
Methods: A total of 90 people aged between 50-65 years with a low-to-moderate cardiovascular risk underwent a neuropsychological evaluation. None of them had a history of cardiovascular disease. The battery included tests assessing executive, attentional, mnesic, visuospatial and motor-speed/coordination functions. We used correlation and inter-groups comparison to relate VRF to multiple cognitive domains[24].
Results: Higher stroke risk was significantly related to a lowered profile in visuo-constructive functions and motor-speed/coordination. Moreover, the group with moderate cardiovascular risk showed a lower performance in visuoconstructive functions compared to the low-risk group. After statistical adjustment for age, sex and years of scholarship VRF were only related to motor-speed/coordination.
Conclusions: In healthy, middle-aged adults, VRF are related with impairment in two cognitive domains. This effect is slight and tends to appear in people with moderate cardiovascular risk.

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PALABRAS CLAVE
Cognición;
Estudio Barcelona-ASIA;
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Neuropsicología;
Paradoja mediterránea

Factores de riesgo vascular y rendimiento cognitivo en personas de 50 a 65 años

Resumen
Introducción: Los factores de riesgo vascular (FRV) se han relacionado con déficit cognitivos e incremento del riesgo de demencia. De hecho, el deterioro cognitivo es considerado como una de las primeras manifestaciones de enfermedad cerebrovascular. En nuestro país se ha registrado una elevada prevalencia de FRV junto a una incidencia de ictus de las más bajas de Europa. Éste es el primer estudio con población española que investiga la relación entre los FRV y el rendimiento cognitivo en la edad adulta.
Métodos: Se ha realizado evaluación neuropsicológica a 90 personas de 50-65 años de edad con riesgo cardiovascular bajo, leve y moderado, sin historia de enfermedad cardiovascular. Se les administró una batería de test sensible a funciones ejecutivas, atencionales, mnésicas, visuoconstructivas y de velocidad/coordinación visuomotriz. Se han hecho análisis de correlación y comparación entre grupos para estudiar la relación entre los FRV y las diferentes funciones cognitivas.
Resultados: Se observó una relación estadísticamente significativa entre un mayor riesgo vascular y un peor rendimiento en funciones visuoconstructivas y en velocidad/coordinación visuomotriz. Además, el grupo de riesgo moderado presentó un rendimiento significativamente inferior respecto al de riesgo bajo en funciones visuoconstructivas. Tras covariar por edad, sexo y años de escolaridad los FRV únicamente se relacionaron con velocidad/coordinación visuomotriz.
Conclusiones: Los FRV en personas de mediana edad están relacionados con disminución del rendimiento en dos funciones cognitivas. La afectación es leve y tiende a evidenciarse en personas con un riesgo moderado.

Introduction

Cognitive deterioration is considered to be the first manifestation of cerebrovascular disease.[1] Vascular disease is the second most common cause of dementia after Alzheimer's disease.[2] In fact, the risk factors that increase the probability of stroke,[3] such as hypertension (HT), dyslipidemia, diabetes mellitus (DM) or smoking, for example, have been linked to cognitive deficits[4-6] and a greater risk of dementia.[7,8] Vascular risk factors (VRF) have also been related to cerebral atrophy, white matter lesions and lacunar stroke.[9-12] The relationship between the factors mentioned and cognitive deterioration could be explained by subclinical pathological cerebrovascular processes.[5,13]

Although Spain has a high prevalence of VRF,[14-16] studies on cerebral vascular disease in our country have show one of the lowest stroke incidence rates registered in Europe.[17,18] This trend is similar to that described by the phenomenon called "southern Europe paradox" or "Mediterranean paradox", characterised by a coronary disease incidence rate lower than expected from the VRF in southern European countries, compared to those in the north of Europe.[19-21] The causes are unknown, but it has been suggested that genetic and/or environmental factors, such as the Mediterranean diet, could grant some protection.[22,23] It has recently been demonstrated that a greater adherence to the Mediterranean diet also reduces the risk of cognitive deterioration and Alzheimer's disease.[23-25]

The cognitive deterioration associated with vascular risk factors has been insufficiently explored in the Spanish population. The main aim of this study was to determine the link between VRF and cognitive performance in a sample of people between 50 and 65 years of age with no history of cardiovascular events.

Subjects and Methods

Subjects

The sample was composed of 90 individuals between 50 and 65 years of age, grouped by gender and educational level according to population ratios. These subjects were part of the Barcelona-ASIA-neuropsychological study; 30 had a low cardiovascular risk (REGICOR<5) and 60 between mild and moderate (REGICOR=5). They were randomly selected from a sample of 3,010 individuals from the PERART population database on peripheral arterial disease in the north Barcelona-Maresme area.[26] This is an area that includes both urban and rural populations, totalling about 600,000 inhabitants.

Individuals with a history of stroke, transient ischemic attacks, cardiovascular events, cognitive deterioration (MMSE<25), neurological or psychiatric affectation or with any other medical condition that could interfere with the results of the evaluation were excluded. Following the protocol of the Barcelona-ASIA-neuropsychological study, incompatibility with magnetic resonance (MRI) was also

considered as a criterion for exclusion. Two people were excluded *a posteriori* due to neuroanatomical alterations revealed by their MRI.

Socioeconomic variables such as age, gender and economic and educational level were collected. Premorbid intelligence, general cognitive level and depressive symptomatology were estimated through the Vocabulary (WAIS-III),[27] Mini-Mental State Examination (MMSE)[28] and Geriatric Depression Scale GDS)[29] tests, respectively (table 1).

Assessment of Cardiovascular Risk

Cardiovascular risk was calculated from the REGICOR[30] function, which is a calibrated scale validated for the Spanish population,[31] of the Framingham-Wilson equation (Framingham Coronary Heart Disease Risk Function).[32] This scale, widely used in the clinical environment, makes it possible to quantify the risk of suffering a coronary event within 10 years. The REGICOR scale is based on the following VRF: age, gender, arterial pressure, DM, smoking habit and cholesterol. The diagnosis of metabolic syndrome was also determined using the criteria of the American Heart Association (AHA),[33] as were the classic VRF and their prevalence: HT,[34] dyslipidemia,[35] DM[3] and smoking habit (the current consumption of any amount of tobacco is the guideline for considering patients as smokers). The determinations of the VRF took place at the Neurology Department of the Hospital Universitario Germans Trias i Pujol in Badalona. Total cholesterol and baseline glycaemia measurements were obtained from a blood extraction while the patient was fasting, and the systolic arterial pressure was calculated as the worst obtained from the patient's arms, after at least 5 minutes of rest.

Neuropsychological Evaluation

The assessment consisted of a single session approximately two and a half hours long. It took place at the Hospital Universitario Germans Trias i Pujol in Badalona between January and October 2008. All participants were submitted to a battery of neuropsychological tests that evaluated different cognitive skills. The majority of tests included had been recommended by the board of specialists of the National Institute for Neurological Disorders (NINDS) and the Canadian Stroke Network for their suitability and sensitivity in the diagnosis of vascular cognitive deterioration.[1] Specifically, planning, cognitive flexibility and inhibition were assessed using the computerized version of the 64-item Wisconsin Card Sorting Test (WCST-64)[36] and the interference score of the Stroop test.[37] Verbal fluency was explored through the phonetic (P, M, R) and semantic (animals)[29] fluency tasks. Working memory was determined from the scores obtained in Inverted Digits in the Wechsler intelligence scale for adults (WAIS-III)[27] and part B of the Trail Making Test.[29] Attention functions were assessed by subtests such as the Symbols Search, Direct Digits and Numbers Code from WAIS-III, the Trail Making Test (part A) and the Continuous Performance Test (CPT-II).[38] The List of Words and Pictures tests from the Wechsler-III (WMS-III)[39] memory scale were used as verbal and visual memory indices, respectively. Finally, visuoconstructive functions were assessed with the Drawing Copy section from the WMS-III and visuomotor speed/coordination with the Grooved Pegboard Test.[40] This project was approved by the Ethics Committee of the University of Barcelona and all subjects gave their informed consent.

Statistical Analysis

The analysis of demographic, clinical and neuropsychological variables was carried out with SPSS 15.0 (SPSS Win.; v 15.0) software for Windows. To obtain a single general score for each of the cognitive functions, the direct scores from each neuropsychological test were transformed into standard z scores. These were generated from the scores obtained from the low risk group (REGICOR<5). The general score of each of the functions was calculated from the mean of the z scores for each of the tests that composed them (table 2). The z scores of the tests in which a greater score implied a worse performance were inverted.

The study of the relation between the REGICOR scale score and the performance on the different cognitive functions was carried out by Pearson's product-moment linear correlation coefficient. In a second analysis, a partial correlation coefficient was used to control the age, gender and years of education variables, as these were the sociodemographic variables that most affected cognitive performance. Furthermore, although age and gender were components of the REGICOR index, they were controlled in the partial correlation analysis because they were classic VRF that could not be modified.

The statistical tests ANOVA and MANOVA were used for the comparison of means between the groups with low risk (REGICOR<5%), mild risk (REGICOR, 6%9%) and moderate risk (REGICOR, 10%19%), applying Bonferroni as *a posteriori* contrast. If the pertinent assumptions for each test were not fulfilled, non-parametric tests were used. The contrasts were considered statistically significant when $p<.05$.

Results

Clinical and Demographic Characteristics

Table 1 details the clinical and sociodemographic variables for each of the cardiovascular risk groups. The mean ± standard deviation for age was 59.83±3.42 years. The population was 39.8% male and 60.2% female. Their socioeconomic level was average-low. The mean length of education was 7.53±3.27 years and they had a normal level of premorbid intelligence and general cognitive performance. They did not present any clinically significant depressive symptoms; 30 people had a low coronary risk level; 48, mild; and 10, moderate. There were no individuals with a high or very high risk level (REGICOR=20).

The data obtained from the confidence intervals for the sociodemographic variables prove that the various groups were similar (table 1). Figure 1 shows the prevalence of VRF in each of the groups.

Neuropsychological Characteristics

A significant statistical relation was detected between higher vascular risk and worse performance in

Table 1 Clinical and sociodemographic characteristics of the study sample

Variables	Grouping by degrees of coronary risk					
	Low (n=30)		Mild (n=48)		Moderate (n=10)	
REGICOR. Mean±SD	3.2±0.71		6±11.1		11.17±1.49	
Metabolic syndrome. n (%) CI	2 (6.7)	0-15.65	10 (20.8)	9.32-32.28	7 (70)	41.6-98.4
Individual VRF						
Age (years). Mean±SD CI	58.73±3.41	57.51-59.95	60.13±3.46	59.15-61.11	61.7±2.16	60.15-63.25
Males. n (%) CI	12 (40)	22.47-57.53	17 (35.4)	21.87-48.92	6 (60)	29.64-90.36
Systolic arterial pressure (mm Hg). Mean±SD CI	147.68±17.17	141.62-154.1	152.31±23.09	145.79-158.83	157.7±14.21	148.89-166.51
Treatment of HT. n (%) IC	8 (26.7)	10.87-42.53	18 (37.5)	23.8-51.19	7 (70)	41.6-98.4
Total cholesterol (mg/dl). Mean±SD CI	193.8±37.59	180.13-207.47	203.72±41.9	191.87-215.57	188.9±36.88	166.03-211.77
Baseline glycaemia (mg/dl). Mean±SD CI	90.53±12.87	95.21-85.85	101.54±26.69	93.99-109.09	105.1±28.65	87.33-122.87
Additional variables						
Educational level. Mean±SD CI	8.27±3.27	7.1-9.44	7.23±3.23	6.32-8.14	6.8±3.36	4.4-9.2
Monthly gross income (€). Mean±SD CI	1.716.83±807.66	1.427.81-2.005.85	1.404.17±685.16	1.210.34-1.598	1.470±477.96	1.128.11-1.811.89
MMSE[28]. Mean±SD CI	28.9±1.4	28.4-29.4	29.06±1.3	28.69-29.42	29±1.16	28.17-29.83
Vocabulary (WAIS-III)[27]. Mean±SD CI	39.57±8.55	36.51-42.63	38.35±7.85	36.13-40.57	40±10.27	32.65-47.35
GDS-15[29]. Mean±SD CI	2.3±2.15	1.53-3.07	2.1±2.3	1.45-2.75	2.4±1.96	0.99-3.8

CI: confidence interval; GDS-15: Geriatric Depression Scale; HT: hypertension; MMSE: Mini-Mental State Examination; SD: standard deviation; VRF: vascular risk factor.

Table 2 Results of the neuropsychological tests administered

Cognitive functions and tests	Risk groups according to REGICOR			Statistical* (gl). size of the effect	p
	Low (n=30)	Mild (n=48)	Moderate (n=10)		
Executive (n=78)					
Stroop (interference)[37]	0.87±6.73	1.75±7.51	−3.3±10.87	F=1.793 (2.85)	0.173
WCST-64 (perseverative errors)[36]	13.1±5.78	14.35±6.54	12±6.16	F=0.769 (2.85)	0.467
Phonetic fluency PMR[29]	29.5±11.52	28.15±10.34	28.8±9.09	F=0.150 (2.85)	0.861
Semantic fluency [29]	17.07±3.7	16.88±3.61	17.9±4.91	F=0.302 (2.85)	0.74
TMT-B (n=78)[29]	119.93±46.87	149.93±74.97	148.5±44.14	F=1.915 (2.75)	0.154
Inverse digit WAIS-III *(span)*[27]	4.07±1.41	4.04±1.5	4.5±1.35	z=1.221 (2)	0.543
Attention					
Symbol search WAIS-III[27]	21.1±6.79	19.42±7.28	23.5±8	F=1.514 (2.85)	0.226
Numbers key WAIS-III[27]	42.97±14.56	38.85±11.82	38.2±18.62	F=0.957 (2.85)	0.388
TMT-A (n=78)[29]	46.13±16.63	51.63±17.51	51±23.88	F=0.888 (2.85)	0.415
CPT (commission errors)[38]	12.53±7.61	11.75±7.13	13.4±3.41	z=1.185 (2)	0.553
CPT (reaction time)[38]	437.42±87.81	442.1±74.77	424.34±49.56	z=0.806 (2)	0.668
Direct digits *(span)*[27]	5.4±1.25	5.35±1.16	5.6±1.51	F=0.165 (2.85)	0.848
Verbal memory					
List of words I WMS-III[39]	27±5.36	26±4.98	26.5±4.86	F=0.124 (2.85)	0.883
List of words II WMS-III[39]	5.57±2.48	5.92±1.94	5.9±2.13	F=0.255 (2.85)	0.776
Visual memory					
Drawings I WMS-III[39]	64.77±16.01	63.13±15.91	66.5±18.91	F=0.22 (2.85)	0.803
Drawings II WMS-III[39]	45.9±21.91	39.56±16.75	39.8±18.98	F=1.098 (2.85)	0.338
Visuoconstructive					
Drawings copy WMS-III[27]	95.7±5.03	94.56±4.9	90.1±11.91	F=3.203 (2.85) η =0.07	0.046
Visuomotor speed and coordination					
Grooved Pegboard (n=86)[40]	72.3±10.75	74.04±10.29	81±23.44	z=1.195 (2)	0.55

*ANOVA or Kruskal-Wallis tests. The data express mean ± standard deviation.

Table 3 Means and standard deviations of the sample as a whole for each of the cognitive domains. Values of Pearson correlation coefficients and partial

Cognitive functions	Mean±SD	Non-corrected model		Corrected model [a]	
		r	p [b]	$r_{ab.cd}$	p [b]
Executive functions	−0.07±0.6	−0.047	0.341	0.111	0.174
Attention	−0.08±0.57	< 0.001	0.499	−0.01	0.467
Verbal memory	0.01±0.81	0.011	0.46	0.072	0.274
Visual memory	−0.21±0.87	< 0.001	0.5	0.012	0.459
Visuoconstructive functions	−0.25±1.24	−0.295	0.003[c]	−0.129	0.139
Visuomotor speed and coordination	−0.17±1.16	−0.294	0.003[c]	−0.128	0.032[d]

SD: standard deviation.
[a] For age, gender and years of schooling.
[b] Degree of significance for the Pearson correlation (unilateral) and partial correlation.
[c] Significance p<.01.
[d] Significance p<.05.

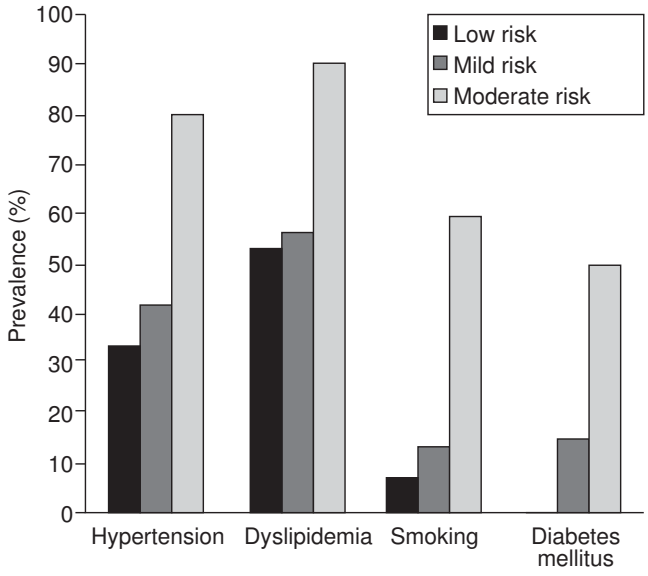

Figure 1 Prevalence of vascular risk factors in each risk group based on the REGICOR scale.

visuoconstructive functions (r=–0.295; p=0.003; R^2=0.087) and in visuomotor speed/coordination (r=–0.294; p=0.003; R^2=0.086). When corrected by age, gender and years of education, the detected pattern continued only in visuomotor speed/coordination (r=–0.218; p=0.032; $R^2_{ab.cd}$=0.047). No significant correlation was established between the other functions. Table 3 shows the data from Pearson's correlation and the partial correlation co-varying by age, gender and years of education between the REGICOR scale score and performance on the different cognitive functions.

When comparing the scores obtained in the tests by the different risk groups, a significant difference was detected in the Drawing Copy test (F=3.203; p=0.046; η =0.07). In particular, the moderate risk group performed worse than the low risk group (F=5.6; p=0.041) (table 2). Nevertheless, this difference was not detected adjusting by age, gender and years of education.

Figure 2 shows the neuropsychological profile of the low, mild and moderate risk groups in the different assessed functions. The moderate risk group performed worse in visuoconstructive and visuomotor speed/coordination functions. However, this difference was significant only in visuoconstructive functions (F=–1.11; p=0.041; η =0.07). The difference was not detected after correcting by age, gender and years of education.

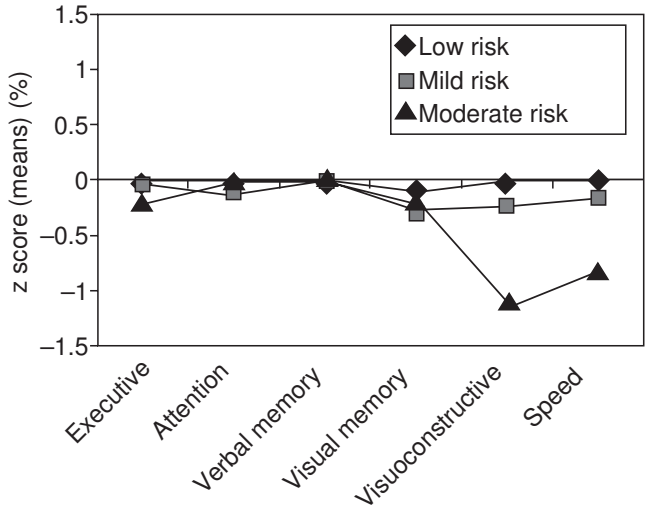

Figure 2 Neuropsychological profile of the three cardiovascular risk groups based on the REGICOR scale.

Discussion

This is the first study in Spain to investigate the relationship between VRF and cognitive performance in people between 50 and 65 years of age with no history of cardiovascular disease. A statistically significant relationship has been found between higher cardiovascular risk according to the REGICOR scale and reduced performance in two cognitive functions: visuoconstructive and visuomotor speed/coordination. It should be emphasised that the number of functions and the degree of affectation observed were inferior to those described in previous population studies from the northern Europe and the United States.[4,5] In particular, the study with the Framingham cohort showed alterations in visuospatial memory, organisation and tracking, attention, concentration and abstract reasoning.[4] The English ELSA study (English Longitudinal Study of Aging),[5] described a reduction of performance in verbal memory, semantic verbal fluency, processing speed and general cognitive function. The differences between the present study and the Framingham and ELSA studies could be partly explained by our sample being younger (age interval, 50-65 years) and, therefore, having a lower cardiovascular risk. In the Framingham and ELSA studies, participants were 50 years old or more. In addition, those studies did not exclude people with mild cognitive deterioration (MMSE, 23-25), so cognitive affectation could have been overestimated.[4,5] Nevertheless, recent investigations have also found that VRF, especially HT and DM, already cause cognitive effects on adults in that age group.[41-43] The lower cognitive affectation found in the present study could also be related to the Mediterranean paradox, which assumes a low incidence rate of coronary disease in countries with a higher prevalence of VRF.[19-21] This discovery puts forward, firstly, the need to carry out population studies with older people and with a higher cardiovascular risk and, secondly, it highlights the importance of investigating the genetic and environmental interactions which could act as protective mechanisms of cerebrovascular disease and cognitive deterioration.

On the other hand, the correction due to age and gender allowed for the exclusive assessment of the effect of the treatable VRF (HT, DM, smoking and dyslipidemia), which are the target of primary prevention strategies.[3] If we take into account only the mentioned modifiable VRF, the association of VRF with cognitive performance is reduced, but persists in visuomotor speed/coordination. It must highlighted that this capacity is one of the most intimately related to the integrity of the cerebral white matter,[44,45]

which is particularly sensitive to cerebral blood hypoperfusion.[46] The results indicate that speed is the cognitive function most sensitive to treatable VRF and the first in which performance reduction can be detected. In all likelihood, the negative effect of these VRF on the integrity of the cerebral white matter would be the implicated physiopathological mechanism.

A comparison between the low, mild and moderate risk groups indicated that the moderate risk group was the only one that showed cognitive differences. In particular, its performance in visuoconstructive functions was significantly lower than that of the low risk group. A limitation of the study was the small number of people at moderate risk (n=10). Moreover, although the data obtained show that the groups were equivalent with respect to their sociodemographic variables, the moderate risk group showed a higher mean age and percentage of older males, compared to those at low or mild risk, as well as a lower educational level. These peculiarities, which could be relevant in the results obtained, have been controlled by introducing age, gender and education time as co-variables in the statistical analysis. It is also worth mentioning that the proportion of people with a moderate cardiovascular risk in our sample was similar to that previously described in the literature. Specifically, 6.7% of the people between 40 and 65 years of age in Spain present a moderate or high vascular risk.[47,48] Consequently, it appears that it is approximately in this 7% of the population in which the VRF can begin to have an effect on cognitive performance. Monitoring of the cognitive state of the sample would allow us to ascertain if a greater middle to long term incidence of cognitive deterioration and dementia takes place in this group of patients, compared to the low and mild risk groups. In future studies, with a larger sample size, it would also be advisable to group the participants according to different sociodemographic criteria such as age, gender and educational level.

Recently, a cut-off point at which pharmacological intervention is indicated has been established for cardiovascular risk according to the REGICOR>10% scale. This is equivalent to moderate or high risk.[49] The results obtained support such recommendations, for they indicate that cognitive deficit begins to be evident in this moderate risk group. The results also indicate that prevention of VRF not only reduces the risk of suffering a cardiovascular event, it could also reduce the risk of suffering cognitive deterioration.

In short, the results show that VRF in middle-aged people without any history of cardiovascular disease are related to cognitive performance even when there have been no clinical manifestations of cerebrovascular disease. Age and gender would be the VRF with the greatest influence in this age range. The cognitive functions most sensitive to VRF would be the visuoconstructive and visuomotor speed/coordination. This affectation is mild and tends to appear in people at moderate risk (REGICOR>10).

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Conflict of interests

The authors declare no conflict of interests.

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