Revista Iberoamericana de Neuropsicología, Vol. 5, No. 1: 1-9, enero-junio, 2022.

Acute coronary syndrome and neurocognition: Determinants and moderators

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Abstract

Objective. *This study aims to characterize neurocognitive functioning after acute coronary syndrome (ACS), and to determine the relations between sociodemographic, cardiovascular risk factors and clinical variables with different aspects of neurocognitive functioning. Moderation effects regarding those relations will be determined.*

Methods. *The Addenbrooke's Cognitive Examination-III (ACE-III) was administered to 60 participants with history of ACS, selected at the first consult of cardiac rehabilitation and at the cardiology outpatient consult. Univariate analysis was preformed through Spearman correlations and Mann-Whitney U test. The moderation hypothesis was tested through Haye's PROCESS, version 3 for SPSS.*

Results. *Neurocognitive function is correlated to age, however this relation is moderated by the number of previous cardiovascular risk factors, body mass index and waist circumference; Verbal fluency domain correlates with years of education and this correlation is moderated by previous alcohol consumption and ventricular ejection fraction; Language domain is correlated to diastolic blood pressure, however this relation is moderated by years of education.*

Conclusions. *This study unveils some of the complex interactions between ACS and neurocognitive functioning. In this context, a focal predictor could have different repercussions on neurocognitive functioning according to a moderator*

Keywords.

Cardiovascular Diseases; Risk Factors; Blood Pressure; Body Mass Index; Verbal Fluency; Neuropsychology.

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Introduction

Acute coronary syndrome (ACS) is the most prevalent cardiovascular disease in developed countries [1]. ACS is the result of the rupture or erosion of the atherosclerotic plaque, with several degrees of thrombosis and distal embolization [2].

The incidence of neurocognitive dysfunction in ACS patients without dementia ranges between 10.51% and 85% [3] [4]. Moreover, deficits in general cognitive functioning, verbal fluency, verbal memory, executive functioning, decrease in simple attention tasks, psychomotor speed, mental flexibility and mental processing speed have been reported [4] [5] [6]. A six years follow-up of ACS patients showed a mild but significant decrease of visual memory, visuoconstructive ability, verbal fluency, executive and global cognitive functioning [5]. In addition to the association between ACS and non-amnestic mild cognitive impairment [7], ACS constitutes a five-time higher risk for the development of dementia [8].

In comparison to healthy controls, ACS patients exhibit loss of grey matter volume in several essential areas for high demanding cognitive tasks: left medial frontal cortex, left cingulate and precuneus, left and right parahippocampal gyri and right and left middle temporal gyri [9]. Advanced medial temporal lobe atrophy, observed in ACS patients with heart failure, seems to be related to memory and attention impairments [10]. Moreover, deficits in executive functions seem to be related to an increased connectivity in the middle-orbito-frontal regions [11].

The factors that may underlie these associations are extensive and far from being understood [12]. The severity of the atherosclerotic disease and subsequent ischemia, hypoperfusion due to reduced systemic cardiac output, a persistent low-grade inflammatory activation, oxidative stress, multiple cardiovascular risk factors such as diabetes, central obesity, hypertension and dyslipidemia, are some of the variables of this complex equation. In addition, psychosocial and behavioral aspects have been frequently reported has being based on these relations [9].

This study aims to characterize neurocognitive functioning after acute coronary syndrome, and to determine the relations between sociodemographic, cardiovascular (CV) risk factors and clinical variables and different aspects of neurocognitive functioning. Moderation effects regarding those relations will be determined.

Methods

Sample

The study comprised a consecutive sample of 60 patients (53 males) with ACS history, from two hospitals in the north of Portugal (Cardiovascular Rehabilitation Unit, Department of the Physical Medicine and Rehabilitation Service, *Centro Hospitalar de São João*/ Porto; Clinical Department of Cardiology of the *Centro Hospitalar do Tâmega e Sousa*/ Penafiel) (Table 1). Clinical data were extracted from the patient's records. Besides the history of ACS, participants had to be literate with no uncorrected sensory deficit and completely independent in daily life activities. Patients with any medical history of major systemic or neuropsychiatric problems (e.g.: minor and major stroke, dementia) prior to the ACS, were not included in the study.

Neuropsychological Assessment

Addenbrooke's Cognitive Examination-III (ACE-III) was administered to all participants. ACE-III is a neurocognitive screening test, evaluating different cognitive dimensions and enabling an overall measure of neurocognitive functioning. ACE-III assesses five cognitive domains: Attention; Memory; Verbal fluency; Language; Visuospatial [13] [14]. With the sum of the domains, a global indicator of cognitive functioning is obtained.

The raw scores were converted into *z* scores, according to age and years of education of the participants [15]. ACE-III has high sensitivity and specificity for detecting cognitive impairment [14].

Procedure

This study was approved by the ethics committees of the *Centro Hospitalar de São João, EPE* and *Centro Hospitalar do Tâmega e Sousa, EPE*.

Table 1. Characteristics of the sample

	M	SD	[Min.-Max.]	n	%
Age	52.93	11.01	[34-79]		
Education (years)	8.45	3.92	[3-16]		
Professional activity					
Blue collar				32	53.3
White collar				28	46.7
Number of CV risk factors	2.23	1.17	[0-4]		
Previous daily number of cigarettes	14.59	15.75	[0-60]		
Actual daily number of cigarettes	0.93	3.01	[0-17]		
Previous daily alcohol consumption (g)	20.98	31.37	[0-137.5]		
Actual daily alcohol consumption (g)	7.27	13.45	[0-72]		
Time since ACS (months)	11.74	38.95	[1-274]		
Diagnosis					
With ST* segment elevation				42	70
Without ST* segment elevation				18	30
Ventricular ejection fraction (%)	45.51	15.88	[14-70]		
Triglycerides (mg/dl)	148.4	73.34	[47-374]		
Cholesterol (mg/dl)					
HDL	39.17	7.94	[28-57]		
LDL	115.73	39.32	[44-224]		
Glucose (mg/dl)	98.90	29.94	[70-216]		
Mean blood pressure (mmHg)					
Systolic	116.32	15.70	[90-153]		
Diastolic	69.48	9.95	[58-93]		
BMI (Kg/m2)	27.58	4.21	[20-41]		
Waist circunference (cm)	96.24	11.71	[68-127]		
Medication					
Antiplatelet				60	100
Statines				60	100
Angiotensin inhibitors				56	93
Betablockers				54	90
Nitroglycerine (SOS)				49	81
Anxiolytics				28	46
Diuretics				18	30
Antidiabetics				20	33
Other				58	96

Participants were flagged by the medical doctor at the time of their first appointment at the cardiac rehabilitation consult or at the follow-up cardiology outpatient consult and then checked by the researchers before the inclusion in the study. Immediately after the scheduled appointment, the interview for sociodemographic and health behaviors information and neurocognitive assessment was performed in one session.

All participants gave their informed consent.

Statistical analysis

Statistical analysis was carried out using the *IBM Statistics* version 24 for *Windows* software.

Table 2. Results (z scores) obtained on ACE-III and its domains

	M	SD	[Min.-Max]
ACE-III	-1,91	1,01	[-6.13- 0.69]
Attention	-0,53	1,04	[-2.97- 1.18]
Memory	-1,65	1,79	[-5.59- 1.42]
Verbal fluency	-2,27	1,19	[-5.8- -0.11]
Language	-0,74	1,40	[-5.47-1.7]
Visuospatial	-0,75	1,57	[-8.67-1.56]

Measures of central tendency and frequency were used to describe the obtained results.

The study of the relations between continuous variables was determined by Spearman's correlations. The relation between nominal and continuous variables was studied through the Mann-Whitney *U* test. For each identified relation the hypotheses of moderation were tested with Hayes's PROCESS version 3 for SPSS. The PROCESS macro simplifies this procedure determining the values of the predictor and of the moderator, generating estimates of the dependent variable and the combinations of these values. [16]. As interactions can take many forms it is important to visualize the model in order to understand how the predictor effect varies with the moderator [16]. As the moderation is a regression analysis of the interaction between two variables on the dependent variable, we have followed the recommendations that point that up to 10 predictors, a sample of 60 participants will suffice if a large effect is expected [17]. For the determination of the statistical significance (or interval estimates) of the effect of the predictor for all values of the moderator, the Johnson-Neyman technique was used and the lower (LLCI) and upper (ULCI) limit confidence intervals were included [16].

Results with $p \leq .05$ were considered significant.

Results

The results obtained on ACE-III and its domains are shown in table 2.

ACE-III overall score showed a negative correlation with age (ρ=-.332; p=.011). Verbal fluency was influenced by years of education (ρ=.239; p=.021). Language domain was positively correlated with mean diastolic pressure (ρ=.373; p=.006). Visuospatial domain was correlated with years of education (ρ=-.641; p<.001).

The relation between age and results on ACE-III is moderated by the number of previous risk factors (interaction coefficient -.3; standard error -.1; *t*=-2.41, *p*=.02). The model has identified having one (*t*= 3.29; *p*<.001; confidence interval: .02 - .1) or two (*t*= 2.48; *p*=.02; confidence interval: .01 - .06) risk factors as

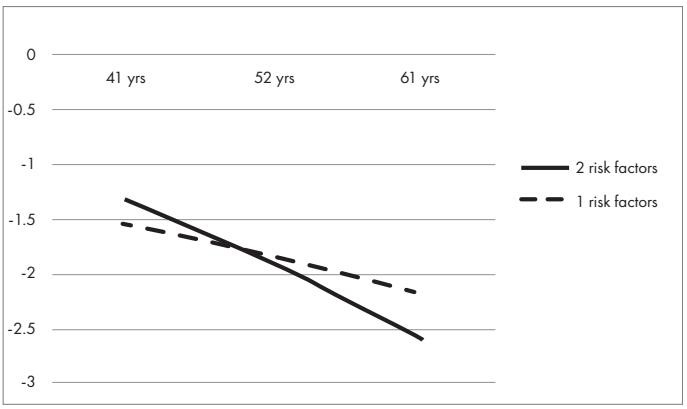

Image 1. Moderation effect of the number of risk factors on the interaction between age and level of general neurocognitive functioning.

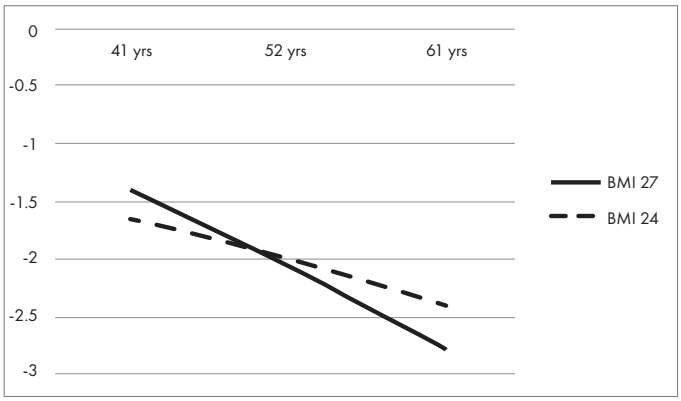

Image 2. Moderation effect of body mass index (kg/m2) on the relation between age and general neurocognitive functioning.

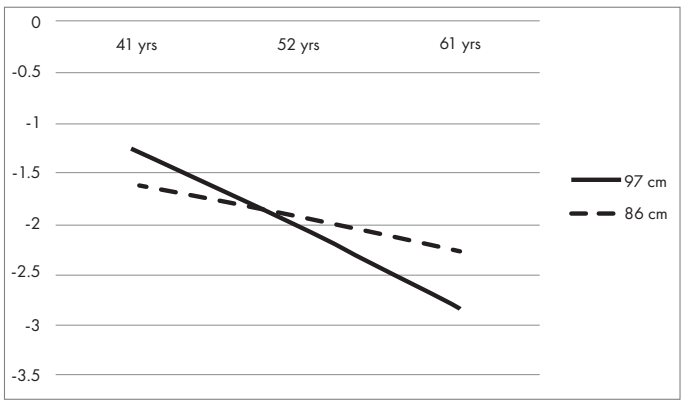

Image 3. Moderation effect of waist circumference (cm) on the relation between age and general neurocognitive functioning.

the moderator values with conditional effects on age (Image 1). Body mass index (BMI) also moderates the relation between age and general neurocognitive functioning (interaction coefficient -.1; standard error 0; t=-3.07, p<.001). BMI values of 24 Kg/m² (t= 3.15; p<.001; confidence interval: .04 - .01) and 27 Kg/m² (t= 4.27; p<.001; confidence interval: .01 - .05) have impact in this relation (Image 2). Waist circumference moderates the impact of age on ACE-III performance (interaction coefficient -.4; standard error .011; t=-3.82, p=.004), 97 cm of waist circumference is related to higher impact of age on cognition (t= 4.76; p<.001; confidence interval: .01 - .05) in comparison to a waist perimeter of 86 cm (t= 2.68; p=.01; confidence interval: .5 - .11) (Image 3).

The relation between verbal fluency and years of education is moderated by previous alcohol consumption (interaction coefficient -.035; standard error .0015; t=-2.33, p=.002). Education exerts a lesser positive effect on verbal fluency with a previous daily consumption of 11g/dl of alcohol (t= 3; p<.001; confidence interval: .02 - .04) (Image 4). This relation it is also moderated by ejection fraction (interaction coefficient .0062; standard error .003; t=2.0494, p=.004). The years of education has a higher impact on verbal fluency with an ejection fraction of 63% (t= 3.1706; p=.0062; confidence interval: .06 - .2724) (Image 5).

Diastolic pressure and language correlation is moderated by years of education (interaction coefficient -.011; standard error .0048; t=-2.3247, p=.004). With significant interaction at 4 (t= 2.904; p=.0053; confidence interval: .0285 - .116) and 9 (t= 2.264; p=.0027; confidence interval: .0046 - .0772) years of education (image 6).

Mann-Whitney U tests did not reveal any significant differences in neurocognitive functioning regarding sex (U=176; p=.952), type of profession (U=262; p=.327) and severity of the ACS (with or without ST wave segment elevation on the electrocardiogram) (U=378; p=.170).

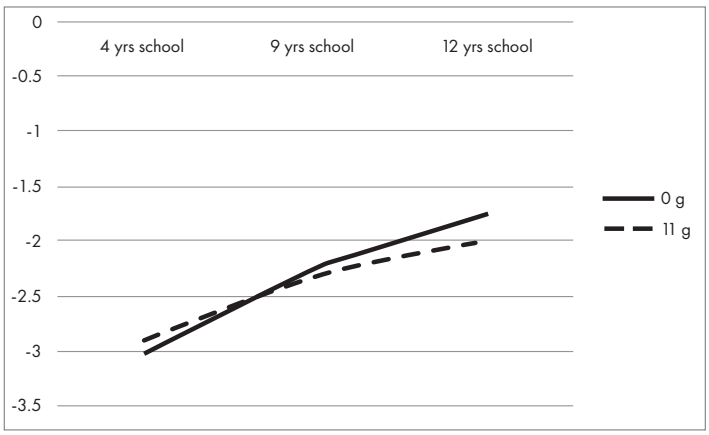

Image 4. Moderation effect of previous alcohol consumption (g) on the relation between years of education and verbal fluency.

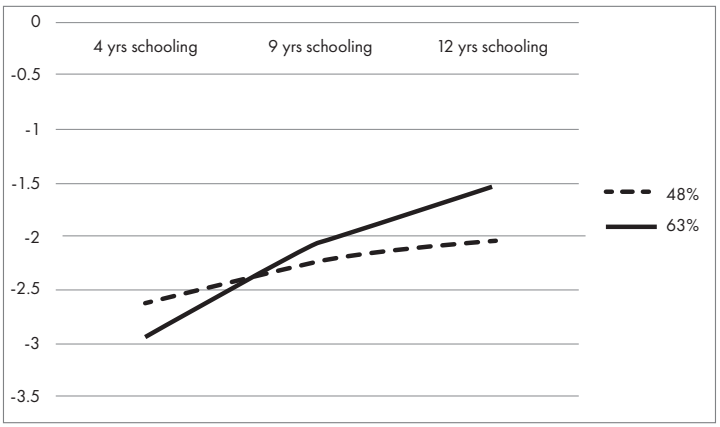

Image 5. Moderation effect of ejection fraction on the relation between years of education and verbal fluency.

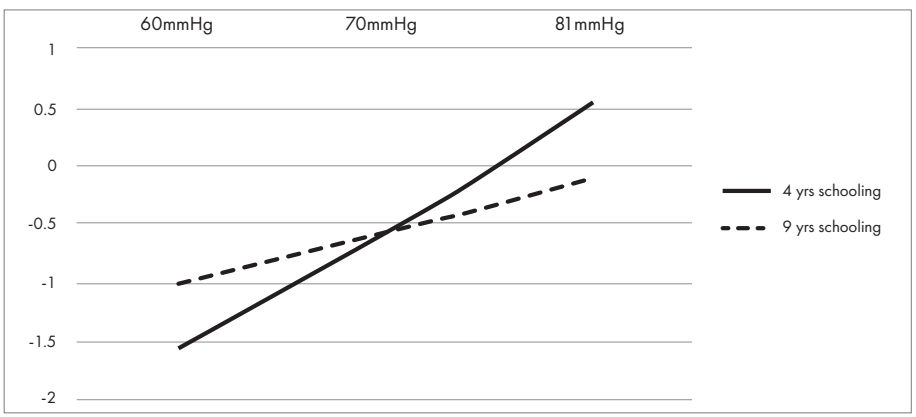

Image 6. Moderation effect of years of education on the relation between diastolic blood pressure and language.

Discussion

The first objective of this study was to characterize neurocognitive functioning after acute coronary syndrome. The global performance of the sample on ACE-III and on memory domain can be classified as below average [18], these aspects have already been pointed [15] even when the performance of ACS patients is compared to transient ischemic attack and minor stroke patients [19]. Verbal fluency is the most

affected domain, with a mean score exceptionally low [18], therefore highly suggestive of impairment. Verbal fluency refers to non-motor processing speed and language generation [20], in fact verbal fluency tasks are related to multiple dimensions of executive functions [21]. It relies on left dorsolateral prefrontal cortex and temporal lobes [20], which are structurally and connectively affected in ACS [9] [11].

This neurocognitive profile is in line with previous studies [4] [6].

General cognitive functioning, measured through ACE-III total score, was negatively correlated with age. Since the results on ACE-III were transformed (*z* scores) according to age and years of education, this cannot be attributed to neurocognitive alterations in aging. Instead, this correlation is suggestive of an increased impact of higher age on cognition after ACS, has it can be seen, for instance, in acquired brain injury where younger adults are more resilient to the effects of recent brain injury than older adults [22]. The number of cardiovascular risk factors moderate this relation; therefore, having two risk factors augments this correlation in comparison to having just one. It is well known the role of cardiovascular risk factors as etiological factors in cognitive decline in ageing, and also their independent role on both cardiovascular and neurodegenerative diseases [23]. The cumulative exposure to cardiovascular risk factors from early to middle adulthood is associated with worse cognition [24] and having two or more midlife vascular risk factors compared with none is significantly associated with elevated amyloid deposition in the brain [25]. Among the risk factors, our study points to moderation effects of BMI and waist circumference. Higher midlife BMI is associated with higher risk of dementia [26] and loss of lean mass and gain of fat mass, as measured by waist circumference adjusted for BMI, are associated with elevated risk of cognitive decline in the elderly [27]. In this context, neurocognitive functioning after ACS is negatively correlated with age, and this correlation is augmented independently in the presence of more than one cardiovascular risk factor, a BMI of 27 Kg/m² (overweight) and a waist circumference of 97 cm. The same correlation is reduced independently by having just one cardiovascular risk factor, a BMI of 24 Kg/m² (normal weight) and a waist circumference of 86 cm.

Verbal fluency was positively correlated with years of education, a well-known factor of cognitive reserve [28]. However, this relation is moderated by alcohol consumption and ejection fraction. Heavy alcohol consumption has been associated to adverse effects on brain structure and neurocognition [29], however, moderate consumption has been somehow controversial with some pointing to negative effects [30] while others associate moderate alcohol use in middle to late adulthood with a decreased risk of cognitive impairment and dementia [31]. In our study, a mean daily consumption of 11 g of alcohol (moderate pattern), reduced the positive correlation between verbal fluency and years of education, suggesting that a moderate consumption could have a negative impact in this cognitive function specially in subjects with higher cognitive reserve. Perhaps this finding could account for the cleavage on literature regarding alcohol consumption and cognition. In this context, alcohol can acts like a moderator reducing the effect of years of education on verbal fluency.

Ejection fraction of 63%, which is in the normal range [32], is associated with an augmented conditional effect of years of education on verbal fluency, while a borderline level of ventricular ejection (48%) reduces this effect. This moderation clearly indicates that a better arterial perfusion enhances the effect cognitive reserve on verbal fluency.

A positive correlation was observed between language and diastolic blood pressure and this relation is moderated by years of education. It has been suggested a link between hypotension and cognitive impairment mediated by cerebral hypoperfusion [33], however our data suggests that individuals with lesser cognitive reserve (4 years of education) are more vulnerable to this effect.

This study has as major limitations the reduced number of participants and their clinical heterogeneity. Some were recruited at the beginning of the phase II cardiac rehabilitation program (exercise reconditioning), therefore approximately three weeks after hospital discharge, while others

at the cardiology outpatient clinic with more variable time window since the ACS.

In conclusion, this study unveils some of the complex interactions between ACS and neurocognitive functioning. In this context, a focal predictor could have different repercussions on neurocognitive functioning according to a moderator. Neurocognitive function is correlated to age, however this relation is moderated by the number of previous cardiovascular risk factors, BMI and waist circumference; Verbal fluency domain correlates with years of education and this correlation is moderated by previous alcohol consumption and ventricular ejection fraction; Language domain is correlated to diastolic pressure, however this relation is moderated by years of education.

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