

## Risk Factors for Cerebrovascular Disease and Cognitive Function in the Elderly

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### Summary

**Objective:** To determine whether stroke risk factors and cognitive dysfunction are concomitant in individuals over the age of 60.

**Methods:** The cognitive abilities of elderly individuals with different degrees of risk as per the Framingham stroke risk profile were compared. The Framingham stroke risk profile was used to calculate the risk of an ischemic cerebral event. Neuropsychological tests included the Buschke Selective Reminding Test, verbal fluency (animals), clock drawing, Rey Auditory Verbal Learning, digit span and vocabulary. A random and typical population sample was used in the study, selected from the 200 elderly residents in the area surrounding the primary health care facility (Morada das Flores Clinic, Porto Alegre). Forty-six elderly individuals were included in the study.

**Results:** The elderly individuals with a risk profile, had lower memory test performance levels (NF,  $p=0.02$ ) and planning capacity (clock drawing test,  $p=0.03$ ). Diabetes proved to be related to delayed recall performance in the Rey auditory verbal learning test ( $p=0.04$ ).

**Conclusion:** The presence of stroke risk factors in the elderly was associated with worse cognitive performance for memory and executive functions. (Arq Bras Cardiol 2007;89(3):142-146)

**Key words:** Framingham's stroke risk profile, cognitive functions, neuropsychological tests.

### Introduction

It is agreed that cerebrovascular disease (CVD) represents a significant risk factor for vascular dementia. Recent evidence has indicated that CVD is also related to a higher risk for Alzheimer dementia (AD). Findings such as greater cortical senile plaque density in non-demented patients with severe coronary artery disease<sup>1</sup>, a significant positive association between the atherosclerotic index and the AD diagnosis<sup>2</sup>, a positive association between elevated homocysteine levels and the prevalence of AD<sup>3</sup>, a negative association between the use of statins and AD prevalence<sup>4</sup>, and less cognitive decline in AD patients using atorvastatina<sup>5</sup> have led to the belief that there is an association between cardiovascular risk factors and the AD pathogenesis.

Isolated studies indicate that CVD could also be a risk factor for minimal cognitive loss (MCI), and more specifically, it could be associated with the mild cognitive impairment subtype called "multiple domains"<sup>6</sup>. Given the associations between CVD and the various dementia syndromes (Alzheimer, vascular) or "pre-dementia" (MCI), two recent studies attempted to determine whether CVD risk factors such as hypertension and diabetes mellitus – in an isolated manner – are associated with cognitive impairment<sup>7-8</sup>. According to these studies, elderly individuals

with stroke risk factors, but without CVD or dementia at the beginning of the longitudinal follow-up, were inclined to suffer greater cognitive loss over time. It is speculated that individuals with stroke risk factors, who have not suffered a marked vascular event, present microscopic cerebrovascular lesions that can be identified in neuroimage studies, even though the patient does not present any clinical repercussions other than mild cognitive loss<sup>9,10</sup>.

These two initial studies conducted in 2004, indicated some potentially important implications in relation to prevention and therefore should be validated in various populations, particularly the elderly, since the mean participant age in one of the studies was of only 60 years.

The objective of the present study is to verify whether the association indicated in these two studies between stroke risk factors and cognitive loss is reproducible.

### Methods

**Population and sample** - The study population was comprised of individuals over 60 years of age, who lived in the neighborhood where the primary health care facility was located (Morada da Hípica Clinic, Porto Alegre). A typical cross section (46 participants) of the district's elderly population (200 individuals) were included in the study. The alpha value was established as 5% with a margin of error up to 10%. The sample was randomly selected.

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**Statistics** - The computer program, Statistical Package for the Social Sciences (SPSS) version 11.5 was used to process and analyze the data. The Student's t-test was used for the statistical analysis of the parametric variables. The Mann-Whitney U test (two independent samples) and chi square test (analysis of the association between different variables) were used for the non-parametric variables. In all cases, statistical significance was established as the probability of a type I error (p) less than 5%.

**Ethical aspects** - All study participants or their designated representatives were required to sign a free and informed consent form. The project was submitted to the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul and was approved in November 2004.

**Procedures** - The interviews were conducted at the clinic and lasted, on average, for one hour. Study participants who were unable to travel to the clinic, were assessed in their homes. In addition to the tests listed below, questionnaires on the participants' medical histories, socio-demographic variables, alcohol and cigarette use were used.

The tests were used for both the cognitive investigation and the presence of cerebrovascular risk.

**Mini-Mental Status Exam<sup>11</sup> (MMSE)**: This exam is a short mental status examination which evaluates orientation, memory, attention and calculation, language and constructive praxis (maximum score 30).

**Free and Cued Selective Reminding Test<sup>12</sup> (Buschke)**: This test evaluates memory storage, retention and recall (maximum score 96).

**Clock Drawing Test<sup>13</sup>**: This test assesses visual constructive abilities, planning and visual neglect. The individual is asked to draw a clock with the numbers and afterwards to draw the hands to depict a time of a quarter to three (maximum score 4).

**Verbal Fluency for Category (animals)<sup>14</sup>**: This test assesses long term memory recall and retrieval, which requires organizational, self-regulation and operational memory abilities.

**Vocabulary (WAIS-III subtest)<sup>13</sup>**: This test evaluates language development and word knowledge. It is considered to be the best individual measurement of overall intelligence.

**Digit Span (WAIS-III subtest)<sup>15</sup>**: This test assesses attention and immediate memory, and is divided in two stages. During the first stage the individual is asked to repeat increasingly larger series of numbers in the same order spoken by the examiner (direct order). During the second stage the individual is asked to repeat the series in the opposite order from the presentation (reverse order).

**Rey's Auditory Verbal Learning Test<sup>16</sup>**: This test checks the ability to learn and retain a series of words, the extent of the verbal memory, susceptibility to distractions and recall memory. A list of fifteen words (list A) is read slowly, five times. The individual should repeat the words in any order, after each reading of the list. In this study, only list A and delayed recall of list A were used.

The Framingham Stroke Risk Profile (Cerebrovascular Risk Table)<sup>17,18</sup> is a validated score that combines the greatest cardiovascular risk factors, giving them different weights, in order to produce a risk score of the probability to have a

stroke over the next 10 years. The Cerebrovascular Risk Table determines a score for cerebrovascular events over the next 10 years, based on the vascular risk factor data of the Framingham Study that comprises the following determinant risk factors: age, gender, total and HDL cholesterol levels, systolic and diastolic blood pressure, presence or not of diabetes mellitus and whether or not the individual is a smoker.

Using the score, we determined the "presence" of risk for an ischemic event during the next 10 years as: a score greater than or equal to 15 on the Framingham table for females and a score greater than or equal to 10 for males.

## Results

The socio-demographic characteristics of the sample are shown in table 1. The percentile of women was 65.2% and the mean age was 68.6 years (minimum of 60 years and maximum of 81 years). The level of education for most of the participants (63%) was low (1-5 years of formal education). Ex-smokers were classified as non-smokers.

A comparison of the risk profiles for cerebrovascular events for males and females is shown in table 2. This table demonstrates the profile for males and females in relation to

**Table 1 – Socio-demographic data of the sample**

Characteristic	Participants n=46
<b>Gender</b>	
Female	30 (65.2%)
Male	16 (34.8%)
Age, years	68.6 ± 5.9
Marital Status	99.9%
Married	25 (54.3%)
Widow	11 (23.9%)
Divorced	8 (17.4%)
Single	2 (4.3%)
Formal Education	99.8%
0 years	7 (15.2%)
1-5 years	35 (76.0%)
6-8 years	4 (8.6%)
9-11 years	-
<b>Current Situation</b>	
Active Retiree	13 (28.3%)
Sedentary Retiree	33 (71.7%)
<b>Leisure Activities</b>	
Yes	34 (73.9%)
No	12 (26.1%)
<b>Tobacco</b>	
Smoker	3 (6.5%)
Non-Smoker	43 (93.5%)

Table 2 – Distribution of the Framingham risk profile components according to gender

Risk factors included in the Framingham score	Males n=16	Females n =30	p
Presence of Diabetes	8 (50%)	6 (20%)	0.048
Tobacco	1 (6%)	2 (6%)	0.999§
Age	66 ± 3	70 ± 6	0.006
Between 60 and 64	7 (43%)	8 (26%)	
Between 65 and 69	6 (37%)	7 (23%)	
Between 70 and 74	4 (25%)	5 (16%)	
Between 75 and 79		7 (23%)	
Between 80 and 84		2 (6%)	
Blood Pressure			
<b>SBP</b>			
<139	11 (69%)	28 (93%)	
>140	5 (31%)	2 (7%)	0.040
Mean Framingham score	11.1 ± 4.0	12.8 ± 6.8	0.128#
Number of individuals with risk of an ischemic event during the next 10 years according to the Framingham score	12 (75%)	8 (25%)	0.002

Exact Fisher Test <sup>(1)</sup> Values expressed as mean ± standard deviation (percentage of risk to suffer a stroke during the next ten years). # Student's t-test. \* Using the Framingham Cerebrovascular Risk Table score, we determined the "presence" of risk for an ischemic event during the next 10 years as: a score greater than or equal to 15 for females and a score greater than or equal to 10 for males. SBP - systolic blood pressure; DBP - diastolic blood pressure.

the Framingham score risk components, the mean score based on gender and the percentile of men and women with high risk as per the score. Even though the mean risk for cerebrovascular events was the same for both males and females over the next ten years, a breakdown of the Framingham score by components, revealed different gender risk profiles for each item. Even though the mean age of the males was lower (therefore a lower age factor risk) there was a significantly greater number of males with altered blood pressure and diabetes when compared to the females. A greater percentile of males, when compared to the females, had a high risk for stroke ( $p=0.002$ ): in the sample, 75% of the males presented a risk of stroke in comparison to 25% of the females.

Through the multivariate analysis, we investigated if any of the Framingham score components (smoking, diabetes, blood pressure and age) had a more significant impact on the neuropsychological test scores. In this calculation, only the presence of diabetes proved to be directly related to delayed recall performance in the Rey auditory verbal learning test.

Table 3 compares the cognitive performance of the elderly individuals with and without stroke risk factors. Individuals with a higher Framingham score had worse performance in the memory ability tests. Performance was lower for both the number of free recalls in the six Buschke test verifications ( $p=0.02$ ) and the delayed recall in the Rey auditory verbal learning test ( $p=0.05$ ).

The individuals with greater risk profiles for cerebrovascular events also presented executive dysfunction: when evaluated using the clock test, individuals with stroke risk factors had significantly lower scores ( $p=0.03$ ) than those with no risk factors.

## Discussion

The data indicate that there is an association between stroke risk factors and cognitive impairment. Individuals with risk factors for cerebrovascular events as per the Framingham risk profile presented impairment in both memory function (Rey and Buschke tests) and planning ability (clock test).

These results agree with previous studies that demonstrate that stroke risk factors are associated with both memory loss<sup>19-21</sup> and executive dysfunction. As described by Alexopoulos<sup>22</sup>, this executive dysfunction, without the presence of evident stroke sequelae, would be the subtle clinical manifestation of microscopic encephalic vascular lesions, that can be identified with neuroimage tests.

In our sample, we observed that the mean risk of stroke was the same for males and females, since the Framingham scores for both genders were similar. Nevertheless, this final score conceals the considerably different profiles for each component in the Framingham risk profile: the males presented more cases of diabetes and hypertension, that led us to assume that their final score was similar to the females due to their significantly younger ages. In addition, it was also shown that three quarters of the males in this sample had an "elevated" risk of stroke as per the Framingham criteria, while only one quarter of the females had the same risk.

Analysis of the relative impact of each factor of the Framingham final score, revealed that diabetes is associated with a worse memory performance. Nevertheless, the sample size greatly limits the ability to conclude whether or not there is an association between the other components (hypertension, age) and the various cognitive fields. In this

**Table 3 – Comparison of neuropsychological test performance among the elderly individuals with and without stroke risk factors in accordance with the Framingham Risk Profile**

Tests	Framingham Risk Profile		p*
	Risk for stroke n=20 (median)	No risk for stroke n=26 (median)	
Mini Mental Status Exam	25.00	26.50	0.27
<b>Buschke Selective Reminding Test</b>			
Cued and Free Recall	95.50	96.00	0.26
Free Recall	59.50	72.00	0.02*
Delayed Recall	16.00	16.00	0.19
Clock Drawing Test	2.50	4.00	0.03*
Verbal Fluency (animals)	11.50	13.50	0.10
Vocabulary (WAIS-III)	17.00	23.00	0.08
<b>Rey Auditory Verbal Learning Test</b>			
Verbal Learning	34.00	37.50	0.07
Delayed Recall	4.50	7.00	0.05*
Digit Span (WAIS-III)	7.00	8.00	0.13
Direct Order	4.00	4.00	0.12
Reverse Order	3.00	4.00	0.31

\* Mann Whitney statistical test.

study, the relative gender impact on the Framingham risk profile was not calculated, since the profile has already taken this into account and gives different relative weights to each risk factor based on gender.

A longitudinal study conducted with 238 elderly diabetics and 36 controls, demonstrated that a greater percentage of elderly diabetics develop dementia in relation to the control group. Another important finding in this study was that the neuropsychological tests that demonstrated the greatest sensitivity for the early onset of cerebral changes associated with diabetes were those that involve episodic memory and processing speed<sup>21</sup>.

Further longitudinal studies are required to fully understand the association between stroke risk factors and cognitive loss. A multivariate analysis with larger samples will make it possible to identify whether or not there is a particular risk

factor that has a greater impact on cognitive function. It will also be possible to investigate whether different risk factors have a greater impact on the memory, and if other factors cause greater risk for executive function.

#### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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#### Study Association

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