Effect size for the main cognitive function determinants in a large cross-sectional study

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Original Article:

«Effect size» for the main cognitive function determinants in a large cross-sectional study.

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Abstract:

Objective: The aim of our study was to examine the «effect sizes» of different cognitive function determinants in the middle and early old age.

Methods: Cognitive functions were assessed in 11,711 volunteers (45 to 75-year-old), included in the French CONSTANCES cohort between January 2012 and May 2014, using the Free and Cued Selective Reminding Test (FCSRT), Verbal Fluency Tasks, Digit Symbol Substitution Test (DSST) and Trail Making Test (TMT), parts A and B. The «effect sizes» of socio-demographic (age, sex, education), lifestyle (alcohol, tobacco, physical activity), cardiovascular (diabetes, blood pressure) and psychological (depressive symptomatology) variables were computed as omega-squared coefficients (ω^2; part of variation of a neuropsychological score that is independently explained by a given variable).

Results: These set of variables explained from R^2=10% (semantic fluency) to R^2=26% (DSST) of the total variance. In all tests, socio-demographic variables accounted for the greatest part of the explained variance. Age explained from ω^2=0.5% (semantic fluency) to ω^2=7.5% (DSST) of the total score variance, gender from ω^2=5.2% (FCSRT) to a negligible part (semantic fluency or TMT), and education from ω^2=7.2% (DSST) to ω^2=1.4% (TMT-A). Behavioral, cardiovascular and psychological variables influenced only slightly the cognitive test results (all ω^2<0.8%, most ω^2<0.1%).

Conclusion: Socio-demographic variables (age, gender and education) are the main variables associated with cognitive performance variations between 45 and 75 years old in the general population.

The study of age-related cognitive decline has become a major public health challenge due to the ageing of the European population and the expected increase in the prevalence of dementia in the coming years (1, 2). The gradual onset of cognitive impairment is a characteristic sign of most dementias, including Alzheimer's disease. It is now accepted that dementia and cognitive impairment are the result of a pathophysiological process that begins many years or decades before symptom onset (3, 4). Specific diagnostic criteria are therefore required, in research context, to diagnose Alzheimer's disease prior to the onset of dementia using biomarkers and neuropsychological tests (5). Although the assessment of cognitive abilities is routinely performed in the elderly, the wide variability of the observed performances can sometimes lead to difficulties in interpreting the results. Therefore, a good knowledge of the variables that may affect cognitive performances in a non-pathological context could facilitate the interpretation of the obtained results.

Many studies have investigated the cross-sectional association of cognitive performance with many variables, such as socio-demographic characteristics (age (6, 7), sex (8-10) and education (11-14)), lifestyle (tobacco use (15), alcohol use (16-18) and physical inactivity (19, 20)), cardiovascular (diabetes mellitus (21-23) and blood pressure (24-26)) or psychological (depression (27-30)) variables. However, due to the high power of many of these studies, there may be confusion between the clinical and the statistical significance of these associations, and clinicians and/or psychologists might consider these factors as equally associated with cognitive functions. These associations are usually reported in separate papers with different methodologies, study populations, neuropsychological tests and statistical models. Moreover these studies tend to report their results using adjusted differences (beta coefficient) or odds ratio, which are inadequate to quantify “effect sizes”(31). Thus, none of these finding allow the comparison of the effect of a given factor on several neuropsychological tests, nor of the effect of several factors on one specific

neuropsychological test. To our knowledge, no analysis allowing the comparison of the «effect sizes» for the main variables influencing cognitive functions has been published yet.

Therefore, the aim of this cross-sectional study was to analyze the magnitude of associations between socio-demographic, lifestyle, cardiovascular and psychological variables and the scores of four neuropsychological tests in a 45 to 75 year-old population.

Material and methods

Study population

The "CONSTANCES" cohort (32) includes volunteers aged 18-69 years at inception who were randomly selected among French adults who are covered by the CNAMTS health insurance ("Caisse nationale d'assurance maladie des travailleurs salaries", the national health insurance of more than 85% of the French population). For this study, analyses were performed on data from participants aged 45 to 75 years who were included at one of the 17 Social Security Health Screening Centers (HSCs) involved in the "CONSTANCES" project between January 2012 and May 2014. This age range was chosen because it can be considered as the age of onset of cognitive decline (6). The inclusion visit included a set of self-report questionnaires and a comprehensive health examination with biological sample collection. Cognitive abilities were also assessed in standardized conditions by trained neuropsychologists (33 neuropsychologists distributed among the 17 HSCs) [32]. The CONSTANCES Cohort project has obtained the authorization of the National Data Protection Authority (Commission Nationale de L'informatique et des Libertés-CNIL-#910486), and was approved by the Institutional Review Board of the National Institute for Medical Research-INSERM (#01-011).

Socio-demographic variables

Participants were categorized in six five-year age groups. Education was categorized in seven levels according to the main stages of the French education system: no diploma (less than 5 years of education), certificate of primary or secondary education (5 to 11 years), National vocational qualifications (11 to 12 years), High School Graduation (12 to 13 years), faculty 1° or 2° cycle (14 to 15 years), first year of master degree (16 years), master degree or more (17 years of education or more)".

Lifestyle variables

Data on tobacco smoking were collected using a questionnaire on smoking status (current, past, or never).

Alcohol consumption was assessed using a questionnaire on frequency and amount of daily consumption of different alcoholic beverages (wine, beer, fortified wine, premixed spirits or cocktails) in the previous week or week-end. Alcohol consumption was classified in four categories, according to the number of alcohol units (one unit = 10–12 g of alcohol) consumed in one week: (i) abstinent (0 unit), (ii) occasional drinker (less than 7 units), (iii) moderate drinker (7 to 14 units for women, or 7 to 28 units for men) and (iv) heavy drinker (more than 14 units for women and more than 28 units for men) (33, 34).

Physical activity was assessed using a questionnaire about frequency and duration of sports practices, regular journeys on foot or by bicycle, and repairs, gardening or household chores. Physical activity was then classified as: (i) high (2 hours/week of intensive sports practice), (ii) moderate (1 hour/week of intensive sports practice, or 2 hours/week of moderate physical activity), (iii) low (1 hour/week of moderate physical activity, or 2 hours/week of low physical activity) and (iv) very low (less than in the previous category) (19).

Cardiovascular variables

Blood pressure was measured during the inclusion visit while lying on a bed after a 5-minute rest period, using an automated oscillometric sphygmomanometer. Blood pressure was measured once on each arm and a third time (reference measure) on the arm giving the highest systolic blood pressure value. For this study, the mean value between the reference measure and the initial value on the same arm was used.

Diagnosis of diabetes mellitus was based either on self-reported diabetes (self-report questionnaire or during the medical interview), or on a fasting blood glucose concentration higher or equal to 7mmol/l.

Depressive symptomatology

Depressive symptoms were measured using the French version of the Center for Epidemiologic Studies Depression Scale (CES-D)(35, 36). This widely-used 20-item scale evaluates the frequency and severity of the depressive symptoms experienced in the past week. The CES-D score ranges from 0 to 60 and was categorized in six classes (see Table 1). Scores of 17 and 23 are the reference thresholds to define "possible" and "probable" cases of depression (37).

Neuropsychological testing

The results of four neuropsychological tests were considered for the present analysis:

(1) Free and Cued Selective Reminding Test (FCSRT) (38, 39) to assess the verbal episodic memory. After the encoding phase (reading and memorization of 16 words, 4 by 4), the volunteer is asked to freely recall as many words as possible in two minutes. Then the neuropsychologist provides a cue (semantic category) for each word that has not been returned to help retrieving the remaining words. These free and cued recalls are repeated three times during the learning phase. The delayed recall phase takes place 20 minutes after the immediate recall and also includes free and cued recalls. For this study, both the free recall score (sum of the number of words retrieved at the three free recall trials; maximum score = 48), and the delayed free recall score (number of freely retrieved words during the delayed phase; maximum score = 16) were considered. The FCSRT total recall score (number of

words retrieved by free and cued recall) and the total delayed recall score (number of words retrieved by free and cued recall at the delayed phase) were not considered because of their non-Gaussian distribution and the existence of a major ceiling effect that did not allow the use of parametric statistical methods for a reliable estimate of the «effect sizes».

(2) Verbal fluencies tasks to assess the language abilities (number of words belonging to the “animals” category named in one minute for the “semantic fluency task”, and number of words starting with the letter R named in one minute for the “phonemic fluency task”).

(3) Digit Symbol Substitution Task (DSST) of the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (40) to assess the psychomotor speed. This test includes nine digit-symbol pairs, followed by a list of numerical digits. Under each digit the subject must write the corresponding symbol as fast as possible. For this study, the number of symbols correctly associated in 90 seconds was retained.

(4) Parts A and B of the Trail Making Test (41) to test executive functions and shifting abilities. This test consists of 25 circles spread over a sheet of paper. In Part A, the circles are numbered from 1 to 25, and the volunteer must connect them in ascending order by drawing a line. In Part B, circles contain either a number (1 to 13) or a letter (A to L). Participants must connect them in ascending order by alternating numbers and letters (e.g., 1-A-2-B-3-C ...). For this study, the (number of correct moves/total time)*10) was used.

The administration of neuropsychological tests was standardized in the 17 HSCs, with an initial and a continuous training of all neuropsychologists involved in the study. Testing practices were regularly monitored at each center.

Statistical analysis

The population's characteristics were described as proportions (categorical variables) and means ± standard deviation (continuous variables). «Effect sizes» were analyzed by computing the omega-squared coefficient (semi-partial omega-squared coefficient in SAS software) ($\omega 2$) (42) using multivariate linear regression models. Each $\omega 2$ value represents the proportion of the total variance of the neuropsychological score that is independently explained by a given variable. As this part of variance is independent, the sum of all the $\omega 2$ values of a model can be subtracted from the coefficient of determination R^2, which quantifies the proportion of variance explained by the full model, to determine the proportion of variance shared simultaneously by several variable with the neuropsychological score (co-explained variance). The relationships between neuropsychological scores and age or education were represented graphically using adjusted means and their 95% confidence intervals. These adjusted means were computed using the same multivariate models described above. In these graphs, adjusted means between two adjacent categories were compared using Tukey's multiple comparison procedures to control for the family-wise error rate. Then, the «effect sizes» between adjacent categories were calculated using Cohen's *d* coefficients, based on the differences between the adjusted means of the two categories standardized by the (pooled) standard deviation of all neuropsychological test scores. We assed Multicollinearity using the variance inflation factor which had a maximum value of 1.7 after removing the variable "center of inclusion" which was collinear with the variable "neuropsychologist" because there was only one or two neuropsychologist in many centers.

Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina) with $\alpha = 0.05$ (two-tailed tests).

Results

Among the 14,162 subjects (45 to 75-year-old) included in the cohort up to May 2014, 11,711 (83%) had complete socio-demographic, lifestyle, cardiovascular and psychological data and were retained for this study. The scores of one or more neuropsychological tests were missing for 5.7%-6.9% of participants. The participants' characteristics are detailed in *Table 1*.

The «effect sizes» for the different socio-demographic, lifestyle, cardiovascular and psychological variables are shown in *Table 2* and in *Figure 1*. Overall, these variables explained from R^2=10% (semantic fluency) to R^2=26% (DSST) of the total variance of the neuropsychological test scores. Socio-demographic variable accounted for the greatest part of the explained variance in all tests.

The «effect size» of gender was important for the two FCSRT scores (Free Recall: ω^2=5.2% and Delayed Free Recall: ω^2=4.4%), moderate for the DSST (ω^2=2.2%) and phonemic fluency task (ω^2=0.8%) scores, and negligible or null for the semantic fluency task and TMT (A and B) scores.

Age explained independently a large part of the total variance of the DSST (ω^2=7.5%), TMT (part A: ω^2=7.3 and part B: ω^2=5.9) and FCSRT (Free Recall: ω^2=4.4% and Delayed Free Recall: ω^2=3.1%) scores. Conversely, only a small part of the total variance of the semantic and phonemic fluency tasks was explained by age (ω^2=0.5% and ω^2=0.8%, respectively). Pairwise comparison of the «effect size» of successive age categories (*Figure 2* and *Table 3*) showed that, for the DSST and the TMT-A and -B scores, the association was quite linear across all age categories. For the two FCSRT scores, the «effect sizes» increased with age. Conversely, for the phonemic and semantic fluency tasks, the association appeared only after the age of 60.

The education level was strongly correlated with all neuropsychological scores, with a large «effect size» for the DSST (ω^2=7.2%), TMT-B (ω^2=6.9%) and the two verbal fluency task scores (semantic fluency: ω^2=5.8%, and phonemic fluency: ω^2=8.9%). The «effect size» was less important for the FCSRT scores (Free Recall: ω^2=4.7%, and Delayed Free Recall: ω^2=2.8%) and low for the TMT-A score (ω^2=1.4%). Pairwise comparison of the «effect size» of consecutive education levels (*Figure 3* and *Table 3*) highlighted larger correlations for categories below senior high school), but with very little difference between subjects with 5 to 8 years and those with 9 to 11 years of education, for all neuropsychological tests. «Effect sizes» were smaller above 12-13 years of education, particularly for the DSST and the TMT scores.

A significant effect of the inclusion center was observed only for the phonemic fluency score, but with a small «effect size» (ω^2=0.1%, p=0.03) and was thus removed from the final model to avoid collinearity with the "neuropsychologist" variable. The «effect size» of this last variable ranged from ω^2=2.9% (TMT-A score) to ω^2=1.2% (FCSRT Free Recall score).

The «effect sizes» of lifestyle variables were much less important than those of the socio-demographic variables (*Table 2* and *3*). The DSST score was higher in the non-smoker group (never or former smokers) than in the smoker group. Former smokers had higher TMT-A and B scores and non-smokers had poorer results in the semantic fluency test. For all these associations, the «effect sizes» were small (respectively, ω^2=0.18%, ω^2=0.13%, ω^2=0.21% and ω^2=0.14%). Occasional alcohol consumption or abstinence was significantly associated with lower phonemic and semantic fluency task scores (ω^2=0.28% and ω^2=0.06%), with a possible dose effect. Finally, a high level of physical activity was associated with a better phonemic fluency task score, but with a very small «effect size» (ω^2=0.06%).

Depressive symptomatology (CES-D score) was negatively correlated with all neuropsychological scores, but with a moderate «effect size» (from ω^2=0.09% for the phonemic fluency task score to ω^2=0.8% for the TMT-B).

Finally, cardiovascular variables also were associated with the cognitive performance, but with very modest «effect sizes». Systolic blood pressure between 120 and 140 mmHg was associated with better TMT-A scores (ω^2=0.05%) and diastolic blood pressure between 70 and 80 mmHg with better FCSRT Free Recall (ω2=0.05%) and DSST scores (ω^2=0.04%). Diabetes was associated with poorer DSST scores (ω^2=0.03%).

Several interactions between socio-demographic variables were tested, but were not included in the final model presented above. The interaction between age and gender was generally not significant. Only the FCSRT Free Recall and TMT-A scores showed a weaker association of age among women than men, but with a very little «effect size» (respectively, ω^2=0.06% and ω^2=0.11%). Interactions between age and education were not significant, except for semantic fluency (ω^2=0.13%), but without a clear direction. The interaction between gender and education was significant for the DSST and TMT-A and -B scores with a weaker association of education among women than men, but with small «effect sizes» (respectively, ω^2=0.24%, ω^2=0.17% and ω^2=0.19%).

Discussion

Our analysis based on data from a large population-based study provides reliable estimates of the «effect size» of the main cognitive function determinants. Overall, these variables explained from R^2=10% (semantic fluency) to R^2=26% (DSST) of the total score variance. Specifically, the socio-demographic characteristics (age, sex and education) are the main variables associated with cognitive performance variations. Conversely, lifestyle, cardiovascular variables and depressive symptoms display little association with cognitive performances ofsubjects aged 45-75 years.

The «effect size» of age was large for nearly all the tests used in the present study. The cognitive test scores decreased with age, from 50 years for most tests, but only after 60 years for phonemic fluency and 60-65 years for semantic fluency. These findings are consistent with previous cross-sectional studies that demonstrated the existence of early and significant associations of age with working memory, episodic memory and processing speed (7, 43). This relationship was delayed for verbal abilities (7), and more pronounced for phonemic than for semantic fluency (44). However, our cross-sectional study did not allow us to distinguish cognitive ageing from intergenerational differences, also called “cohort effect”. Some authors (6) have reported that cross-sectional analysis of cognitive decline with age overestimates such decline compared to longitudinal analyses. This overestimation occurred only in women because of a large difference in educational attainment between age cohorts. In this publication (6), adjustment for education partially corrected this bias. In our study, women’s educational attainment was comparable in all age groups and we adjusted our model for education, thus minimizing the risk of bias.

Gender was also associated with performance in most of the cognitive tests used in our study. This result is consistent with publications showing that women outperform men in tests

involving verbal episodic memory (9, 10) and phonemic, but not semantic fluency (8). Our study highlights that the size of the observed association is important, with a Cohen's d value of about 0.5 for the FCSRT score, which represents a larger difference than the one observed between the 60-64 and 70-75 age groups. Gender also influenced the DSST score, consistently with previous publications (45).

Education was strongly associated with all neuropsychological performances, which is consistent with current knowledge. (11-13). In accordance with other studies, this association was more important for verbal fluency and smaller for processing speed (TMT-A)(14). This association was observed in all education categories, thus stressing the importance of taking into account the maximum of information when adjusting for this variable in epidemiological studies. The association between education and cognitive performances can be explained by brain development and lifelong experiences, such as lifestyle choices, health behaviors, social interactions and type of occupation (12, 46).

Our study also shows that the «effect sizes» of lifestyle variables are much smaller than those of socio-demographic characteristics. Alcohol consumption was positively correlated with phonemic and semantic fluency and with the DSST, consistently with previous works (16-18). Some authors reported a larger association for alcohol in women (17, 47), not found in our study (no significant interaction between sex and alcohol consumption). Physical activity was associated with phonemic but not with semantic fluency, as previously reported (19). However, these [19] and other authors (20) also found associations with memory that we did not find in the present study, possibly because of differences in the methods used to measure physical activity intensity. Finally, tobacco consumption was associated with the performance in several cognitive tests; however, the inconstant direction of the interaction, as previously reported (15), makes difficult the interpretation of these results.

The «effect sizes» of cardiovascular variables were also very small. Previous publications reported a negative linear trend between blood pressure and cognitive performance (25, 48, 49). We did not find such a trend for any of the used neuropsychological tests, possibly because we analyzed mainly middle-aged subjects and we cannot exclude a more important effect in older people. However, our results are consistent with other works showing negative or positive associations with diastolic blood pressure, according to the studied cognitive function (24), or non-linear correlations between blood pressure and cognitive function (26). In all these studies the «effect sizes» were very small and comparable with our estimations. We also observed an association of diabetes mellitus with the DSST score and potentially with the FCSRT Free Recall score (statistical tendency). These results are consistent with studies showing the association of diabetes with global fluid intelligence (22) and with attention and immediate verbal memory (21, 23).

The small effect size observed for lifestyle and cardiovascular variables could be partly explained by measurement errors or by the selection of particularly healthy subjects in our study. In addition, our analyses were focused mainly on a middle-aged population (from 45 to 75 years). Therefore, the small «effect size» of the cardiovascular variables, including diabetes, should not be interpreted as an absence of or a limited effect of these variables on the risk of dementia or cognitive decline in a population of older subjects.

Depressive symptomatology (CES-D score) was negatively correlated with the performance in all neuropsychological tests. This association was quite homogeneous in all tests and was not explained only by the difference in cognitive functioning between depressed and non-depressed participants. Indeed, no threshold effect (i.e., CES-D score higher than 17 for “possible” depression and 23 for “probable” depression (37)) was observed in the association between the CES-D score and the neuropsychological test performance. This association was more pronounced for tests involving executive functions (particularly the

TMT-B test). This is consistent with many studies showing the association of depressive symptoms with executive functioning (29, 30). The «effect sizes» were smaller than those reported in recent meta-analyses (29, 30), possibly because these meta-analyses included mainly case/control studies where people with major depressive disorders were compared with healthy volunteers. Conversely, cohort-based studies on the evaluation of the effect of depressive symptomatology reported «effect sizes» similar to ours (27, 28).

An original finding of our study is the large proportion of variance explained by the "neuropsychologist" variable, despite the high level of standardization. Its "effect size" was considerably higher than that of lifestyle, cardiovascular or psychological variables. This result emphasizes the importance of taking into account a "neuropsychologist effect" by appropriate adjustments in the analyses and/or by stratification in the study design when assessing cognition.

Our results are particularly original because we used the best adapted statistics for quantifying effect size. Indeed many studies report inadequate parameters to quantify effect sizes. Odds ratios are dependent on the threshold chosen for defining a "low cognitive level" and beta coefficients are highly dependent on the scale and the dispersion of the neuropsychological test(31). Here, we choose omega square rather than eta square coefficient because eta square measures the variance explained of the sample, not the population, and thus always overestimates the effect size (50). Further, omega square coefficient was chosen rather than partial omega square coefficient because its denominator (the total variance of the neuropsychological test) remains the same no matter which variable is being examined(31). This makes this coefficient very interpretable for the visual representation of the level of association of these different variables.

We chose to analyze the factors which were directly and easily available, and we did not take into account some factors such as APOE4 or dietary habits. It is possible that the consideration of these factors could have change the amount of variability explained by the model (R^2 coefficient). However, it is unlikely that this would have changed estimation of effect sizes of factors already in the model."

Our study has many strengths, including its population-based design and the very large sample size that gives a high power to study variables with expected modest «effect sizes». This analysis was possible because the CONSTANCES study simultaneously collected data on many variables and on cognitive performances.

Participants of our study were selected from a data base containing over 80% of the French population. However, subjects with a low level of education (<12 years of education), smoker or diabetics were under-represented in our study compared to general statistics from France. This could be due, as in most epidemiological study, to a higher rate of participation of subject with a higher education and/or a better health. This is a limitation to the external validity of our study which can slightly affect our estimates, but with a limited impact on our interpretations and conclusions. In a general way, these "effect sizes" cannot be extrapolated to other populations in which the total variability of neuropsychological tests would be strongly different (for example older populations, with memory complaints, or with different structures of age, gender or education).

Our findings have significant clinical implications as they provide arguments to justify what categories should be used to construct norms for each of neuropsychological tests. Different norms for men and women should for example be used for FCRST, DDST and phonemic fluency. Regarding education, groups "5 to 11 years" and "11 to 12" years could be merged for all tests. Other levels of study could also be grouped depending on the test. It is

essential to take into account age when constructing norms, although our results indicate, for example, that age groups between 45 and 60 could be merged for verbal fluencies tasks.

Conclusion

Socio-demographic variables (age, gender and education) are the main variables associated with cognitive performance variations in the general 45 to 75-y-o population in France. Conversely, lifestyle, cardiovascular and psychological variables are only slightly or not associated with these performances.

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Figure 1: Percentage of variance in the neuropsychological testing scores explained by socio-demographic, behavioral, cardiovascular and psychological variables

Figure 2: Adjusted means of the neuropsychological scores according to the age categories (means with the same letter are not significantly different).

Figure 3: Adjusted means of the neuropsychological scores according to the years of education (means with the same letter are not significantly different).

Table 1. Characteristics of the participants

	n	Mean (±SD) or %
Age (years)	11711	58.2 (7.2)
Age category		
45-49	2056	17.6%
50-54	2184	18.6%
55-59	2354	20.1%
60-64	2527	21.6%
65-69	2138	18.3%
70-75	452	3.9%
Gender		
men	5551	47.4 %
Years of education		
17 years or more	1844	15.7%
16 years	1042	8.9 %
14 to 15 years	2558	21.8%
12 to 13 years	2203	18.8%
11 to 12 years	2499	21.3%
5 to 11 years	1225	10.5%
less than 5 years	342	2.9%
Smoking		
Never	5200	44.4 %
Former	4977	42.5 %
Current	1534	13.1 %
Alcohol drinking		
Abstinent	4796	41.0 %
Occasional	2563	21.9 %
Moderate	3175	27.1 %
Heavy	1177	10.0 %
Physical Activity		
Very low	2131	18.2 %
Low	3962	33.8 %
Moderate	2052	17.5 %
High	3566	30.5%
Depressive Symptomatology		
CES-D 0-4	3351	28.6%
CES-D 5-10	3867	33.0%
CES-D 11-16	2369	20.2%

CES-D 17-22	986	8.4%
CES-D 23-28	528	4.5%
CES-D 29-60	610	5.2%
Systolic Blood Pressure		
<120 mmHg	2738	23.4%
120-140 mmHg	5331	45.5%
140-160 mmHg	2835	24.2%
>160 mmHg	807	6.9%
Diastolic Blood Pressure		
<70 mmHg	2082	17.8%
70-80 mmHg	4594	39.2%
80-90 mmHg	3615	30.9%
>90 mmHg	1420	12.1%
Diabetes		
Yes	647	5.5%
Neuropsychological tests		
FCSRT Free recall	11048	32.7 (5.4)
FCSRT Delayed free recall	11043	12.9 (2.1)
DDST	11080	65.8 (15.1)
Semantic Fluency	11054	23.5 (5.9)
Phonemic Fluency	11052	15.5 (4.8)
TMT-A	10916	7.7 (2.5)
TMT-B	10916	4.0 (1.5)

Table 2: Adjusted means (±sem) of the neuropsychological testing scores and effect size (semi-partial *ω2* coefficient) of socio-demographical, behavioral, cardiovascular factors and depressive symptomatology

	FCSRT Free recall		FCSRT Delayed free recall		DSST		Semantic Fluency		Phonemic Fluency		TMT-A		TMT-B	
	Adjusted mean[†]	*ω2*	*Adjusted means*[†]	*ω2*	*Adjusted means*[†]	*ω2*	*Adjusted means*[†]	*ω2*	*Adjusted means*[†]	*ω2*	*Adjusted means*[†]	*ω2*	*Adjusted means*[†]	*ω2*
Age category														
45-49 years	33.5(0.21)	4.36%**	13.2(0.08)	3.07%**	69.2(0.55)	7.49%**	23.3(0.24)	0.48%**	15.4(0.19)	0.81%**	8.57(0.09)	7.28%**	4.41(0.05)	5.86%**
50-54 years	33.2(0.20)		13.0(0.08)		66.4(0.54)		23.4(0.23)		15.4(0.18)		8.00(0.09)		4.08(0.05)	
55-59 years	32.5(0.20)		12.9(0.08)		63.7(0.53)		23.3(0.23)		15.3(0.18)		7.57(0.09)		3.89(0.05)	
60-64 years	31.4(0.19)		12.5(0.08)		59.9(0.51)		22.8(0.22)		14.8(0.17)		6.96(0.09)		3.55(0.05)	
65-69 years	30.4(0.20)		12.2(0.08)		56.9(0.53)		22.3(0.23)		14.3(0.18)		6.59(0.09)		3.36(0.05)	
70-75 years	29.1(0.29)		11.8(0.12)		53.9(0.77)		21.8(0.33)		13.8(0.26)		5.99(0.13)		3.00(0.08)	
Gender														
women	33.1(0.18)	5.24%**	13.1(0.07)	4.38%**	64.2(0.49)	2.23%**	23.0(0.21)	0.05%*	15.3(0.17)	0.80%**	7.34(0.08)	0.03%*	3.78(0.05)	0.13%**
men	30.2(0.18)		12.1(0.07)		59.1(0.49)		22.6(0.21)		14.3(0.16)		7.22(0.08)		3.65(0.05)	
Years of education														
17 years or more	33.6(0.20)	4.68%**	13.2(0.08)	2.83%**	67.8(0.54)	7.24%**	24.8(0.23)	5.82%**	17.0(0.18)	8.89%**	7.72(0.09)	1.41%**	4.35(0.05)	6.93%**
16 years	33.4(0.23)		13.1(0.09)		66.2(0.60)		24.4(0.26)		16.5(0.20)		7.52(0.10)		4.11(0.06)	
14 to 15 years	32.5(0.19)		12.8(0.08)		65.3(0.51)		24.2(0.22)		16.2(0.17)		7.60(0.09)		4.06(0.05)	
12 to 13 years	31.9(0.20)		12.6(0.08)		64.2(0.53)		22.9(0.23)		15.3(0.18)		7.46(0.09)		3.88(0.05)	
11 to 12 years	30.5(0.19)		12.2(0.08)		58.3(0.51)		21.3(0.22)		13.4(0.17)		7.02(0.09)		3.33(0.05)	

5 to 11 years	30.7(0.21)		12.3(0.09)		58.4(0.57)		21.4(0.25)		13.6(0.19)		7.01(0.10)		3.36(0.06)	
less than 5 years	28.8(0.33)		11.8(0.13)		49.1(0.86)		19.6(0.37)		11.3(0.29)		6.39(0.16)		2.79(0.09)	
Smoking														
Never	31.7(0.19)	0.01%	12.6(0.07)	0.01%	62.1(0.49)	0.18%**	22.5(0.21)	0.14%**	14.7(0.17)	0.07%**	7.23(0.08)	0.13%**	3.68(0.05)	0.21%**
Former	31.7(0.18)		12.6(0.07)		62.5(0.48)		22.9(0.21)		15.0(0.16)		7.41(0.08)		3.82(0.05)	
Current	31.6(0.21)		12.6(0.09)		60.4(0.56)		23.0(0.24)		14.9(0.19)		7.20(0.10)		3.66(0.05)	
Alcohol drinking														
Abstinent	31.5(0.18)	0.00%	12.5(0.07)	0.01%	61.1(0.49)	0.04%*	22.5(0.21)	0.06%*	14.5(0.16)	0.28%**	7.28(0.08)	0.00%	3.71(0.05)	0.02%
Occasional	31.6(0.20)		12.6(0.08)		62.0(0.53)		22.7(0.23)		14.7(0.18)		7.29(0.09)		3.73(0.05)	
Moderate	31.7(0.19)		12.7(0.08)		61.9(0.51)		22.9(0.22)		15.0(0.17)		7.34(0.09)		3.73(0.05)	
Heavy	31.8(0.22)		12.6(0.09)		61.6(0.59)		23.1(0.25)		15.2(0.20)		7.21(0.10)		3.70(0.06)	
Physical Activity														
Very low	31.5(0.20)	0.00%	12.6(0.08)	0.02%	61.7(0.53)	0.00%	22.6(0.23)	0.01%	14.6(0.18)	0.06%*	7.27(0.09)	0.01%	3.74(0.05)	0.00%
Low	31.7(0.19)		12.6(0.08)		61.3(0.50)		22.8(0.21)		14.8(0.17)		7.29(0.08)		3.73(0.05)	
Moderate	31.7(0.20)		12.6(0.08)		61.8(0.54)		22.9(0.23)		14.9(0.18)		7.23(0.09)		3.70(0.05)	
High	31.7(0.19)		12.6(0.08)		61.9(0.51)		22.9(0.22)		15.0(0.17)		7.33(0.09)		3.69(0.05)	
Depressive Symptomatology														
CES-D 0-4	32.1(0.18)	0.15%**	12.8(0.07)	0.13%**	63.9(0.49)	0.63%**	23.4(0.21)	0.23%**	15.1(0.17)	0.09%**	7.67(0.08)	0.62%**	3.98(0.05)	0.79%**
CES-D 5-10	31.8(0.19)		12.7(0.08)		63.0(0.50)		23.0(0.21)		15.0(0.17)		7..40(0.08)		3.78(0.05)	
CES-D 11-16	31.6(0.19)		12.6(0.08)		62.0(0.52)		22.8(0.22)		14.8(0.17)		7.38(0.09)		3.73(0.05)	
CES-D 17-22	31.5(0.23)		12.5(0.09)		61.4(0.61)		22.8(0.26)		14.8(0.21)		7.22(0.11)		3.65(0.06)	

CES-D 23-28	31.8(0.27)		12.5(0.11)		60.9(0.74)		22.8(0.31)		14.9(0.25)		7.12(0.13)		3.64(0.07)	
CES-D 29-60	31.3(0.26)		12.5(0.11)		58.9(0.70)		22.1(0.30)		14.4(0.24)		6.92(0.12)		3.54(0.07)	
Systolic Blood Pressure														
<120 mmHg	31.7(0.21)	0.01%	12.6(0.09)	0.00%	61.3(0.56)	0.00%	22.9(0.24)	0.02%	15.0(0.19)	0.01%	7.27(0.10)	0.05%*	3.75(0.05)	0.01%
120-140 mmHg	31.7(0.19)		12.6(0.08)		61.9(0.50)		22.8(0.21)		14.9(0.17)		7.39(0.08)		3.74(0.05)	
140-160 mmHg	31.6(0.20)		12.5(0.08)		61.6(0.52)		22.7(0.22)		14.8(0.18)		7.23(0.09)		3.67(0.05)	
>160 mmHg	31.6(0.25)		12.6(0.10)		61.8(0.68)		22.8(0.29)		14.7(0.23)		7.23(0.12)		3.71(0.07)	
Diastolic Blood Pressure														
<70 mmHg	31.4(0.22)	0.05%*	12.5(0.09)	0.02%	61.8(0.58)	0.04%*	22.9(0.25)	0.01%	14.7(0.20)	0.03%	7.26(0.10)	0.02%	3.67(0.06)	0.00%
70-80 mmHg	31.8(0.19)		12.6(0.08)		62.1(0.51)		22.9(0.22)		15.0(0.17)		7.29(0.09)		3.74(0.05)	
80-90 mmHg	31.6(0.19)		12.6(0.08)		62.1(0.51)		22.8(0.22)		14.8(0.17)		7.27(0.09)		3.73(0.05)	
>90 mmHg	31.8(0.22)		12.6(0.09)		60.8(0.59)		22.7(0.25)		14.8(0.20)		7.30(0.10)		3.72(0.06)	
Diabetes														
No	31.9(0.15)	0.02%	12.6(0.06)	0.00%	62.3(0.40)	0.03%*	22.9(0.17)	0.00%	14.9(0.14)	0.01%	7.29(0.07)	0.01%	3.74(0.04)	0.00%
Yes	31.5(0.25)		12.5(0.10)		61.0(0.66)		22.7(0.28)		14.8(0.22)		7.27(0.11)		3.69(0.07)	
Neuropsychologist														
		1.16%**		1.81%**		2.69%**		1.41%**		2.40%**		2.87%**		2.37%**
Total variance explained (R^2)														
		20%		15%		26%		10%		16%		15%		21%

[†]Adjusted mean (±Standard Error of the Mean): Adjusted for all covariates shown in the table and for the inclusion center.

*$p<0.05$ and **$p<0.01$ for the pairwise comparisons using Tukey's multiple comparison procedures to control for the family-wise error rate.

Table 3: Effect Size using the Cohen's *d:* difference between the adjusted means divided (standardized) by the pooled standard deviation of the neuropsychological test scores

		FCSRT Free recall	*FCSRT Delayed free recall*	*DDST*	*Semantic Fluency*	*Phonemic Fluency*	*TMT-A*	*TMT*
Age								
50-54	*45-49*	-0.08	-0.11**	-0.19**	0.01	-0.01	-0.22**	-0
55-59	*50-54*	-0.13**	-0.08	-0.19**	-0.02	-0.01	-0.18**	-0
60-64	*55-59*	-0.21**	-0.19**	-0.27**	-0.08	-0.12**	-0.27**	-0
65-69	*60-64*	-0.18**	-0.13**	-0.22**	-0.09*	-0.09**	-0.18**	-0
70-75	*65-69*	-0.24**	-0.17**	-0.22**	-0.08	-0.12	-0.30**	-0
Gender								
men	*women*	-0.54**	-0.49**	-0.35**	-0.05**	-0.21**	-0.05*	-0
Years of education								
16 years	*17 years or more*	-0.04	-0.03	-0.11*	-0.07	-0.12*	-0.08	-0
14 to 15 years	*16 years*	-0.17**	-0.13**	-0.06	-0.03	-0.08	0.03	-0
12 to 13 years	*14 to 15 years*	-0.12**	-0.11**	-0.08	-0.23**	-0.18**	-0.06	-0
11 to 12 years	*12 to 13 years*	-0.26**	-0.18**	-0.42**	-0.29**	-0.44**	-0.18**	-0
5 to 11 years	*11 to 12 years*	0.03	0.01	0.01	0.01	0.03	-0.01	0
less than 5 years	*5 to 11 years*	-0.33**	-0.21**	-0.67**	-0.31**	-0.49**	-0.27**	-0
Smoking								
Never	*Current*	0.02	-0.00	0.12**	-0.10*	-0.05	0.01	0
Former	*Current*	0.01	-0.01	0.14**	-0.02	0.01	0.09	0.
Alcohol drinking								
Abstinent	*Moderate*	-0.04	-0.05	-0.05	-0.06	-0.12**	-0.02	-
Occasional	*Moderate*	-0.03	-0.03	0.01	-0.03	-0.08**	-0.02	0
Heavy	*Moderate*	0.01	-0.02	-0.02	0.03	0.03	-0.06	-0
Physical Activity								
Very low	*High*	-0.04	-0.02	-0.02	-0.05	-0.08**	-0.02	0
Low	*High*	0.01	0.00	-0.04	-0.01	-0.05	-0.02	0
Moderate	*High*	0.00	-0.01	-0.01	0.00	-0.04	-0.04	0

Depressive Symptomatology								
CES-D 5-10	*CES-D 0-4*	-0.05	-0.04	-0.06*	-0.05	-0.02	-0.11**	-0
CES-D 11-16	*CES-D 5-10*	-0.04	-0.04	-0.07*	-0.05	-0.04	0.01	-0
CES-D 17-22	*CES-D 11-16*	-0.01	-0.02	-0.03	0.00	0.01	-0.06	-0
CES-D 23-28	*CES-D 17-22*	0.05	-0.00	-0.04	0.01	0.01	-0.04	-0
CES-D 29-60	*CES-D 23-28*	-0.10	-0.04	-0.12	-0.14	-0.12	-0.08	-0
Systolic Blood Pressure								
<120 mmHg	*120-140 mmHg*	0.00	-0.00	-0.04	0.00	0.03	-0.05	0
140-160 mmHg	*120-140 mmHg*	-0.03	-0.04	-0.02	-0.02	-0.02	-0.06*	-0
>160 mmHg	*120-140 mmHg*	-0.01	-0.01	-0.01	-0.01	-0.03	-0.06	-0
Diastolic Blood Pressure								
<70 mmHg	*70-80 mmHg*	-0.07*	-0.06	-0.02	-0.00	-0.06	-0.01	-0
80-90 mmHg	*70-80 mmHg*	-0.04	-0.03	0.00	-0.02	-0.04	-0.01	-0
>90 mmHg	*70-80 mmHg*	-0.01	0.01	-0.09*	-0.04	-0.05	0.00	-0
Diabetes								
Yes	*No*	-0.07*	-0.05	-0.08*	-0.04	-0.02	-0.01	-0

*p<0.05 and **p<0.01 for the pairwise comparisons using Tukey's multiple comparison procedures to control for the family-wise error rate.