

# Cognitive functions and serum cortisol concentration in perimenopausal and postmenopausal women working non-manually

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## Abstract

**OBJECTIVES:** To assess a possible relationship between serum cortisol concentration and cognitive function in peri- and postmenopausal women engaging in non-manual work.

**METHODS:** The Montreal Cognitive Assessment (MoCA) was used to screen women for the study and the Computerized Neurocognitive-assessment Software (CNS) Vital Signs to diagnose cognitive functions.

**RESULTS:** Cognitive functions and serum cortisol concentration did not differ between women in early and late perimenopause and postmenopause. The women in the study obtained lower reaction time compared to other cognitive functions studied. Cognitive functions correlated negatively with age and educational level, but not BMI. Serum cortisol concentration correlated negatively to NCI, motor speed, psychomotor speed and reaction time in postmenopausal women, but positively to complex memory in early perimenopausal women and to processing speed in early and late perimenopausal women.

**CONCLUSION:** Higher serum cortisol concentration may negatively affect cognitive functions in women post menopause.

## INTRODUCTION

Cortisol, a glucocorticoid known as the “stress hormone” may be potentially linked to various cognitive deficits. It is primarily regulated through the hypothalamic-pituitary-adrenal (HPA) axis. The dysregulation of the HPA axis seems to be a significant risk factor in cognitive impairment and Alzheimer's disease (Lucassen *et al.* 2014; Libro *et*

*al.* 2017). The main role in the acute elevation of glucocorticoids is to engage the human body in the fight-flight response to stress. The action of glucocorticoids may occur with or without modulation of gene expression (slow or rapid action, respectively) (Joëls *et al.* 2011). The study of Reul & de Kloet (1985) on rat brains demonstrated that in the regions of the brain supporting core executive functions, glucocorticoids receptors are especially

concentrated. According to the authors, the septohippocampal complex is the main target of cortisol action (Reul & de Kloet 1985). Stress was found to have impact on behavior and hippocampal neurogenesis in rat dams (Belovicova *et al.* 2017).

Numerous studies analyzed the relationship between cortisol level and one or more cognitive functions (Popp *et al.* 2009; Umegaki *et al.* 2000; Johansson *et al.* 2011; Kuehl *et al.* 2017; Hansson *et al.* 2015). However, the data gave conflicting results. In some studies, correlations between increased levels of cortisol and mild dementia were observed (Umegaki *et al.* 2000), while others showed that the association between cortisol level and dementia may be gender specific (Johansson *et al.* 2011). On the other hand, there are studies demonstrating no relation between cortisol and cognitive impairments (Popp *et al.* 2009; Kuehl *et al.* 2017; Hanson *et al.* 2015). In fact, it is still not fully understood whether the cortisol level is a cause or the effect of cognitive deficits. Previous meta-analysis of available data on the topic demonstrated that acute elevation of cortisol influenced the impairment of working memory (Shields *et al.* 2015).

The aim of the present study was to analyze the relationship between serum cortisol concentration and cognitive function in peri- and postmenopausal women engaging in non-manual work.

## MATERIAL AND METHODS

### The study group

The study was conducted at the Institute of Rural Health in Lublin and included 300 women aged 44–66 years working in non-manual jobs (e.g. office work). The exclusion criteria were: educational level lower than secondary, chronic diseases, addictions, or diagnosed mental disease. The examined women were divided into 3 subgroups according to their reproductive status: 1) 100 women in the early perimenopausal period: menstruating, with FSH below 20 mlU/ml; 2) 43 women in the late perimenopausal period: menstruating, with FSH 20 mlU/ml and over; and 3) 157 women in the postmenopausal period: not menstruating for at least 12 months.

Body weight and height were measured in the studied women to calculate body mass index (BMI). The studied women were asked about the date of their last menstruation, age and educational level.

### Montreal Cognitive Assessment (MoCA)

At the preliminary stage of the study, the MoCA test was applied (Magierska *et al.* 2012) in order to enrol the women who did not show symptoms of dementia. The maximum number of scores in this test is 30 and a score of 26 or more is considered as normal. The examined women who were included for further stages of the study had to obtain a score of 26 or more on the MoCA test.

### Computerized Neurocognitive-assessment Software (CNS) Vital Signs

Assessment of cognitive functions (Gualiteri & Johnson 2006) was performed using the diagnostic equipment CNS Vital Signs (1829 East Franklin Street, Bldg 500, Chapel Hill NC 27514, 919-933-0932). The instrument is in the form of a battery of computer tests, is standardized, and was subjected to the full validation procedure. It has many cultural and language adaptations, including a version for Polish. Cognitive functions such as: Complex Memory, Verbal Memory, Visual Memory, Psychomotor Speed, Reaction Time, Complex Attention, Cognitive Flexibility, Processing Speed, Executive Function, Simple Attention, Motor Speed were assessed. The CNS VS test provides Neurocognitive Index based on five cognitive functions: memory, psychomotor speed, reaction time, attention, and cognitive flexibility. Standard scores of NCI and 11 cognitive functions were analysed and interpreted as: above average (>109), average (90–109), low average (80–89), (70–79), very low (<70), so higher values of standard scores indicate better cognitive functions.

### Laboratory tests

The blood samples were taken for laboratory tests: follicle stimulating hormone (FSH) and cortisol concentrations, collected in the morning between 7am and 8am, after at least half an hour rest. Blood samples were promptly delivered to an accredited laboratory. Laboratory standards for cortisol levels in the morning ranged from 4.30 to 22.40 µg/dL.

### Statistical methods

The data were statistically analyzed using STATISTICA software. We estimated mean values (M) with standard deviations (SD) for continuous variables, and absolute (n) and relative numbers (%) of occurrence of items for categorical variables.

The  $\chi^2$  test was used to compare the educational levels among 3 groups of women: in early and late perimenopausal and postmenopausal periods. We used F test analysis of variance to compare age, BMI, serum cortisol concentration and cognitive functions among the 3 groups of women mentioned above. We also used t test of differences between two means in independent samples to compare cognitive functions between women with secondary and tertiary educational levels. Pearson correlation coefficient (r) was used to correlate cognitive functions with age and BMI in the total group of women. It was also used to correlate cognitive functions with serum cortisol concentration first in the total group of women, then in 3 subgroups of the women examined. The value of  $p \leq 0.05$  was considered as a significant difference.

Informed consent for participation in the study was obtained from all women. The study was approved by the Ethics Committee of the Institute of Rural Medicine in Lublin, Poland.

## RESULTS

The women in postmenopausal period were significantly older and with lower education levels than those in early and late postmenopausal periods. The 3 subgroups of women examined did not significantly differ in terms of BMI and serum cortisol concentration (Table 1).

The women studied obtained poor results in reaction time – low average, whereas their NCI and other cognitive functions were assessed as average (Figure 1). Cognitive functions did not significantly differ between the 3 investigated periods of women's reproductive life ( $p>0.05$ ).

NCI and most cognitive functions such as verbal, visual and complex memories, motor, psychomotor and processing speeds, reaction time correlated negatively to age, i.e. the elder women the worse cognitive functions observed. No significant correlations between BMI and cognitive functions were found. NCI and most cognitive functions (apart from visual memory and simple attention) were significantly better in the women with tertiary educational level than those with a secondary one (Table 2).

Serum cortisol concentration correlated negatively to NCI and 3 cognitive functions: motor and psychomotor speeds as well as reaction time but only in postmenopausal women, i.e. the higher cortisol concentration,

**Tab. 1.** Characteristics of the women studied.

Characteristics	Total women (N=300)	Early peri-menopausal women (N=100)	Late peri-menopausal women (N=43)	Post-menopausal women (N=157)	Test	p-value
Age (years), M±SD	53.1±4.8	48.6±2.7	51.6±3.3	56.4±3.4	F	<0.001
44 - 49, n (%)	89 (29.66)	69 (69.00)	13 (30.24)	7 (4.46)	194.211	
50 - 54	86 (28.66)	26 (26.00)	23 (53.49)	37 (23.57)		
55 - 59	94 (31.33)	5 (5.00)	6 (13.95)	83 (52.87)		
60 - 66	31 (10.33)	0 (0.00)	1 (2.33)	30 (19.11)		
Educational level, n (%)					$\chi^2$	0.001
secondary	106 (35.33)	24 (24.00)	11 (25.58)	71 (45.22)	16.811	
tertiary	194 (64.66)	76 (76.00)	32 (74.42)	86 (54.78)		
BMI (kg/m <sup>2</sup> ), M±SD	26.24±4.62	26.39±5.14	25.47±4.27	26.36±4.36	F	0.493
underweight, n (%)	1 (0.33)	1 (1.00)	0 (0.00)	0 (0.00)	0.709	
normal, n (%)	131 (43.67)	44 (44.00)	22 (51.16)	65 (41.40)		
overweight, n (%)	118 (39.33)	41 (41.00)	13 (30.23)	64 (40.76)		
obesity, n (%)	50 (16.67)	14 (14.00)	8 (18.60)	28 (17.83)		
Cortisol (µg/dl), M±SD	12.31±4.79	12.54±4.64	11.18±3.79	12.46±5.10	F	0.250
normal, n (%)	287 (95.67)	95 (95.00)	42 (97.67)	150 (95.54)	1.394	
above normal, n (%)	12 (4.00)	5 (5.00)	1 (2.33)	6 (3.82)		

**Tab. 2.** Cognitive functions vs age, BMI and educational level for the total women studied.

Cognitive function	Age (years)		BMI (kg/m <sup>2</sup> )		Educational level		t	p-value
	r	p-value	r	p-value	tertiary	secondary		
					(cognitive function M±SD)			
NCI	-0.164	0.004	0.033	0.567	94.97±11.58	88.32±14.48	4.345	0.000
Complex memory	-0.124	0.031	0.071	0.221	97.15±14.58	93.42±16.21	2.032	0.043
Verbal memory	-0.151	0.050	0.080	0.167	98.21±14.26	94.33±15.62	2.178	0.030
Visual memory	-0.150	0.050	0.045	0.438	97.35±14.66	95.65±14.69	0.956	0.340
Psychomotor speed	-0.185	0.001	-0.036	0.538	95.47±14.29	87.91±13.98	4.416	0.000
Reaction time	-0.113	0.050	-0.014	0.808	90.98±15.25	84.59±19.32	3.151	0.002
Complex attention	-0.083	0.151	0.036	0.530	96.43±20.00	89.61±24.07	2.623	0.009
Cognitive flexibility	-0.112	0.050	0.030	0.605	95.30±19.44	86.73±21.82	3.494	0.001
Processing speed	-0.131	0.024	-0.061	0.290	94.15±13.59	86.86±14.83	4.301	0.000
Executive function	-0.089	0.124	0.021	0.724	95.86±19.20	87.55±21.47	3.436	0.001
Simple attention	-0.052	0.373	-0.031	0.591	101.19±11.17	99.97±12.95	0.850	0.396
Motor speed	-0.194	0.001	0.015	0.801	97.83±14.49	92.39±14.56	3.105	0.002

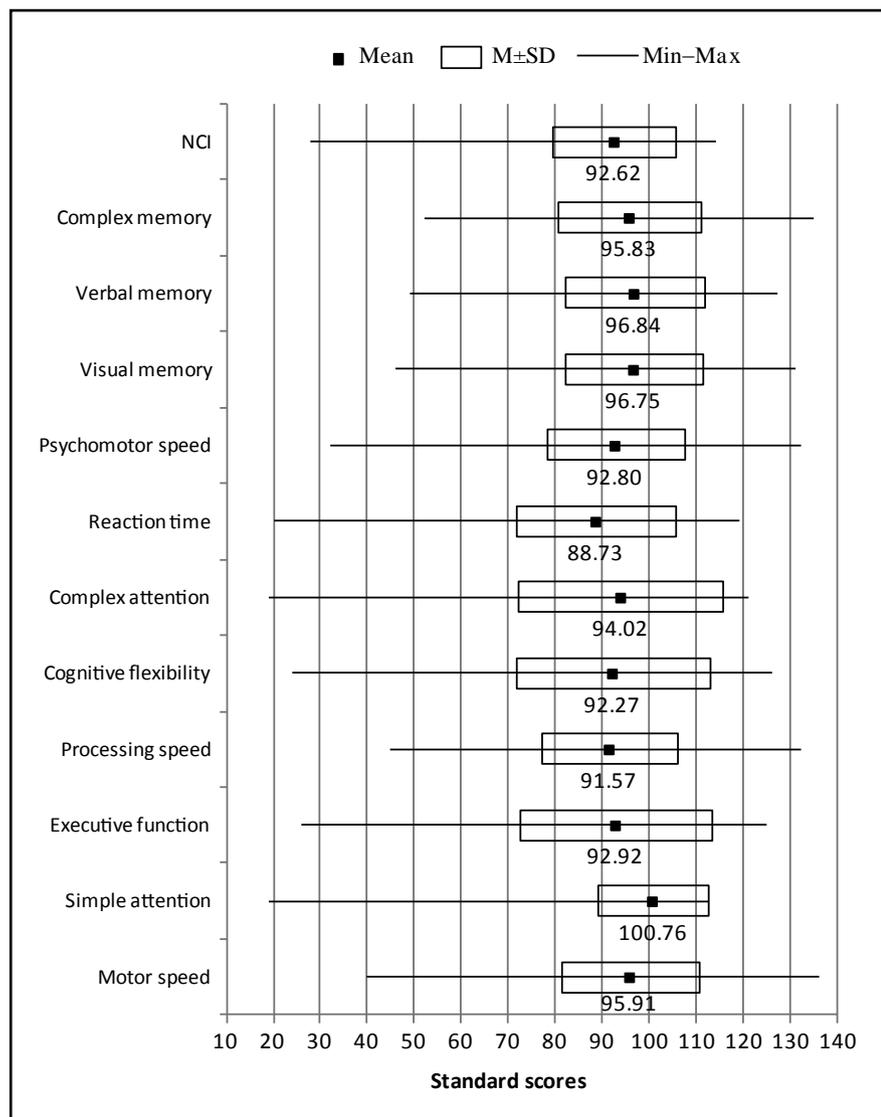


Fig. 1. Cognitive functions of the total women studied.

Tab. 3. Correlation coefficients between cognitive functions and serum cortisol concentration for the women studied

Cognitive function	Total women		Early peri-menopausal women		Late peri-menopausal women		Post-menopausal women	
	r	p-value	r	p-value	r	p-value	r	p-value
NCI	-0.075	0.198	0.089	0.381	0.162	0.299	-0.183	0.022
Complex memory	0.081	0.160	0.201	0.045	0.148	0.343	-0.002	0.984
Verbal memory	0.047	0.415	0.163	0.105	0.118	0.452	-0.028	0.731
Visual memory	0.079	0.170	0.168	0.094	0.101	0.518	0.018	0.826
Psychomotor speed	-0.066	0.257	0.101	0.320	-0.001	0.995	-0.183	0.022
Reaction time	-0.073	0.209	0.075	0.456	0.221	0.155	-0.174	0.030
Complex attention	-0.083	0.150	-0.019	0.853	0.027	0.863	-0.125	0.119
Cognitive flexibility	-0.071	0.218	0.001	0.999	0.089	0.568	-0.128	0.110
Processing speed	0.010	0.860	0.192	0.050	0.312	0.042	-0.120	0.133
Executive function	-0.077	0.185	-0.007	0.947	0.085	0.586	-0.135	0.092
Simple attention	0.012	0.831	0.135	0.182	0.003	0.984	-0.047	0.556
Motor speed	-0.103	0.074	0.032	0.753	-0.199	0.202	-0.169	0.035

the worse cognitive functions were observed. However, serum cortisol concentration correlated positively to complex memory in early perimenopausal women and to processing speed in early and late perimenopausal women, i.e. the higher cortisol concentration, the better the cognitive functions that were listed above (Table 3).

## DISCUSSION

Due to the fact that estrogens have significant neurophysiologic effects, their decreased concentration during the perimenopause period seems to be detrimental to cognition (McEwen 2002; Ycaza Herrera & Mather 2016). The most frequent symptom of menopause are hot flashes which were reported to be predictors of delayed verbal memory (Maki *et al.* 2008). One of the possible links of menopausal symptoms with cognitive deficits is elevated level of cortisol. Since chronic exposure to cortisol exhibits neurotoxic effects, high levels of cortisol may cause such neuroendocrine changes, along with age and affect the hippocam-

pus and in turn lead to cognitive deficits. The ACTH/cortisol ratio was found to be a negative biomarker of aging in females (Reece & Hulse 2016). Previous study in 99 postmenopausal women (treated with hormone replacement therapy vs controls) the cumulative effect of cortisol and oral estrogens on explicit memory was found (Hampson & Duff-Canning 2016). In the present study we aimed to analyze the possible impact of cortisol level on cognitive functions in a large group of 300 women in peri- as well as postmenopausal periods working non-manually. We observed both, positive and negative correlations between serum cortisol concentration and some of the cognitive functions in different subgroups of analyzed women. Cortisol was negatively correlated to NCI, motor and psychomotor speeds, as well as reaction time, only in postmenopausal women, whereas a positive correlation was found between cortisol concentration and complex memory in early perimenopausal women and between cortisol and processing speed in early and late perimenopausal women. In case of educational level cognitive functions were significantly better in women with a tertiary educational level than those with a secondary one.

Negative correlation between cortisol level and declarative memory was observed in the study performed on Chinese postmenopausal women (Peng *et al.* 2016). Almela *et al.* (2014) observed that in older people a poorer declarative and working memory performance resulted from low cortisol response to stress. In turn, better declarative and working memory capabilities characterized people with no increase in their cortisol levels or with the largest cortisol increase. A previous study performed with a group of women using oral contraceptives showed that cortisol levels were not related to memory performance (Mordecai *et al.* 2017). On the contrary, a correlation between high cortisol level and impaired declarative memory was observed in a group of older non-demented people (Li *et al.* 2006). What was interesting, the authors also noted that high salivary cortisol concentration can predict some impairments in declarative memory over the next 3 years (Li *et al.* 2006).

Cortisol concentrations exhibit daily fluctuations, with a peak in the morning and a decline in late hours. In a large group of Icelandic elderly, without dementia, the impact of cortisol on total brain volume was assessed (Geerlings *et al.* 2015). The authors found that higher evening cortisol was related to smaller total brain volume, especially in gray matter regions while its higher morning levels – to greater normal white matter volume. Elevated evening cortisol was associated with poorer cognitive performance whereas higher morning cortisol – with better processing speed and executive functioning (Geerlings *et al.* 2015). In contrast, poorer cognitive function was earlier related to higher morning cortisol levels (Beluche *et al.* 2010; Venero *et al.* 2013). Johar *et al.* (2015) observed that higher morning to evening ratios were related to reduced odds of cogni-

tive deficits and that male subjects had increased risk for cognitive impairment.

The main limitation of our study is the homogenous study group, because it comprised 44–66 year-old women who worked non-manually. It would be interesting to conduct such analyses in other groups: physically working women, lower educated women, and other age groups or men.

Our research confirms the important role of cortisol in order to maintain cognitive functions in women and indicates the need for further research in this area.

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