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OCCUPATIONAL PREDISPOSITION IN ASYMPTOMATIC STROKES

ABSTRACT

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The dissertation is presented on 122 pages and contains 21 figures and 17 tables.
The bibliography covers a total of 507 literary sources, of which 10 are in Cyrillic and 497 are in Latin.

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All studies included in the dissertation are conducted in Second Clinic of Neurology with ICU and Stroke Unit, St. Marina University Hospital, Varna

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ABBREVIATIONS

aICVD	**Asymptomatic ischemic cerebrovascular disorders**
aCVD	**Asymptomatic cerebrovascular disease**
CVD	**Cerebrovalcular disease**
DM	**Diabetes melitus**
Hol	**Holesterol**
IHD	**Ischemic heart disease**
RF	**Risk fakrors**
TG	**Triglicerides**
TIA	**Transient ischemic attack**

CONTENTS

1. INTRODUCTION

Cerebrovascular diseases are among the first places as a cause of disability and mortality. This makes them a socially significant disease that worsens the quality of life, including among the working population. Globally, stroke is the second leading cause of death (6.6 million people) and disability (143 million life years lost due to disability - DALYs). Over the past 3 decades, morbidity has increased by 70%, its prevalence by 80%, and mortality by 32%, with the greatest increase observed in countries with low and middle income, including Bulgaria. Also, the average age of stroke is 15 years lower than in high-income countries, leading to a marked negative impact on socio-economic development, as people are most affected at the peak of their working lives.

In Bulgaria, about 82,000 cases of cerebrovascular disease (CVD) are registered annually, of which about 40,000 are strokes. Of these, 8,000 patients end up dead, and around 28,600 with varying degrees of disability. About half of patients are left with a permanent neurological deficit, which requires care from family and society and seriously impairs their quality of life.

Asymptomatic cerebrovascular disease (aCVD) is defined as the stage of cerebrovascular disease in individuals with vascular risk factors who do not have clinically established neurological and retinal symptoms of cerebrovascular disease. Given the significantly higher frequency of asymptomatic, "silent" cerebrovascular disease compared to the frequency of stroke, its great importance as a threat to the health of the population should be taken into account. According to the American Heart Association and the American Stroke Association, there are three cardinal manifestations of "silent" CVD: "silent" cerebral infarcts, magnetic resonance (MRI) imaging of white matter hyperintensities of presumed vascular origin, and microhemorrhages. The described changes are associated with an increased frequency of symptomatic strokes, dementia and death.

Asymptomatic ischemic cerebrovascular disorders affect patients at a young, working age, and the work process is an invariable part of a person's daily life. Therefore, the study of work factors and hazards and their impact on workers' health is important.

2. OBJECTIVES AND TASKS

2.1 Objectives

To study the role of occupational factors in the development of asymptomatic ischemic cerebrovascular disorders in patients of working age.

2.2 Tasks

1. To study the influence of demographic factors - gender and age - on the frequency of asymptomatic cerebrovascular disease;

2. To study the frequency of measurable risk factors (hypertension, diabetes mellitus, atrial fibrillation and flutter, heart failure) in patients with evidence of asymptomatic disorders and Risk Assessment;

3. To study the influence of professional factors (work experience, position, working regime, length of the working day, type of work, location of the work process, work posture, movements and norm) on the risk of asymptomatic lesions;

4. To determine the relationship between work factors and accompanying risk factors for cerebrovascular disease, in patients with MRI lesions;

5. To study the influence of occupational stress levels on the risk of asymptomatic MRI lesions;

6. To evaluate the impact of asymptomatic lesions on the cognition of patients;

3. MATERIAL AND METHODS

3.1 Material

The object of the study is a total of 151 patients, divided into two groups. The first group is represent by 41 patients, with vascular risk factors, without anamnestic and clinical evidence of stroke or transient ischemic attack (TIA), with the presence of magnetic resonance changes described as white matter hyperintensities of presumed vascular origin, lacunar infarcts, cerebral microhemorrhages or brain atrophy. The second group includes 110 patients, with vascular risk factors, without anamnestic and clinical data of stroke or TIA, without magnetic resonance changes.

The studied patients are hospitalized in Second Clinic of Neurology with ICU and Stroke Unit, St. Marina University Hospital, Varna in the period February 2019 - May 2022.

Inclusion criteria-patients with aICVD:

• Age between 18 and 64 years;
• Working at the time of the study;
• Presence of at least one vascular risk factor;
• Without anamnestic and clinical data of stroke or TIA;
• Conducted neuroimaging study - MRI of the brain, with data on white matter hyperintensities of presumed vascular origin, lacunar infarctions, brain microhemorrhages or brain atrophy;
• Patients with signed informed consent;

Inclusive criteria-controls:

• Age between 18 and 64 years;
• Working at the time of the study;
• Presence of at least one vascular risk factor;
• Without anamnestic and clinical data of stroke or TIA;
• Conducted neuroimaging study - MRI of the brain, without neuroimaging criteria for pathology of the nervous system;
• Patients with signed informed consent;

Exclusion criteria:

• Patients under the age of 18 and over 64;
• Unemployed at the time of the survey;
• Absence of vascular risk factors;
• Presence of anamnestic and clinical data on brain stroke or TIA;

• Presence of changes from an MRI examination, characteristic of other diseases of the nervous system;
• Lack of signed informed consent;

3.2 Methods

3.2.1 Clinical study

The patients from both groups meeting the inclusion criteria were:

• collected complete anamnestic data, in relation to their current and past complaints, their occupational history and accompanying diseases. Information was collected personally from patients and from available medical records;
• detailed somatic and neurological status taken;

3.2.2 Vascular risk factors

Data were collected on the vascular risk profile of the participants. A questionnaire completed by the patient and accompanying medical records were used as sources of information.

• Modifiable risk factors (RF) - age and gender;
• Non-modifiable risk factors (documented and newly discovered)
o Vascular RF - hypertension, diabetes mellitus, rhythm-conduction disorders, chronic heart failure, ischemic heart disease, other heart diseases, dyslipidemia;
o Behavioral RF - smoking and alcohol abuse;

3.2.3 Occupational factors

Information related to occupational hazards is collected through a survey method and a scale assessing the level of occupational stress.

Researched occupational factors:

• Professional route - years of work experience, position held;
• Factors of the labor process - heaviness, tension, work posture, work movements, work and rest regime;
• Factors of the working environment - microclimate, mechanical fluctuations, dust, presence of chemical hazards;
• Professional stress - levels and specifics of the work process causing it;

3.2.4 Laboratory studies

The laboratory tests are carried out in the clinical laboratory of the UMBAL "St. Marina"-Varna, by means of automatic biochemical analysis, by means of a consolidating system ADVIA 1800 ++.

Dyslipidemia is considered in patients receiving lipid-lowering medication prior to hospitalization or in those with elevated levels of serum lipids during the hospital stay.

3.2.5 Neuroimaging studies

The magnetic resonance examinations are carried out with a Siemens Magnetom 3T device in the Department of Imaging Diagnostics at the "St. Marina" - Varna.

Patients participating in the study are divided into two groups, depending on the presence of MRI changes:

• With neuroimaging data for aICVD;

• No neuroimaging data for aICVD;

In the first group, the presence of the different types of changes are assessed as:

• Whitte matter hyperintensities with a presumed vascular origin - a modified Fazekas scale is applied. The scale assesses the number and distribution of hyperintensities and includes 4 grades (Appendix 1);

• Lacunar infarcts;

• Microhemorrhages;

• Brain atrophy;

3.2.6 Rating scales

3.2.6.1 The Workplace Stress Scale (WSS) - (Appendix 2)

The Workplace Stress Scale was developed by the Marlin Company, North Haven, CT, USA, and the American Institute of Stress, Yonkers, NY, USA (2001). The WSS consists of eight items including certain statements about the emotional state of research at work. The scale is in a five-point response format, ranging from never (scored 1) to very often (scored 5). Points numbered 6, 7 and 8 are scored backwards. High scores are indicative of higher levels of workplace stress. The general results of the researched are interpreted as follows:

• <=15 p.- relatively calm;

• 16–20 p. - low levels of professional stress;

• 21–25 p.- moderate levels;

• 26–30 p. - high levels;
• 31–40 p. - potentially dangerous level of occupational stress.

3.2.6.2 Montreal Cognitive Assessment Test (MoCA) - (Appendix 3)

The MoCA test is used as a screening for initial cognitive impairment in various neurological diseases. It contains 30 questions, in sections, assessing different areas of cognitive functioning and thinking activity (executive functions, naming, memory, attention, language, generalization, orientation). It is evaluated in points from 0 to 30 points, with a lower score indicating a more severe cognitive impairment:

• ≥26 p.. norm
• 18-25 p. - minimal damage
• 10-17 p. - moderate damage
• <10 p. severe injury

3.2.6.3 Patient Health Questionnaire-9 (PHQ-9) - (Appendix 4)

The PHQ-9 is used as a questionnaire for screening, monitoring and measuring the severity of depression. It consists of 9 questions related to depressive symptoms in the last 2 weeks before the study. Answers are evaluated from 0 points. (never) up to 3p. (almost every day), depending on the size of the time window in which the statement was valid for the patient. Scores for individual responses are summed, and a higher score indicates the presence of more severe depressive symptoms.

• 0-4 p.- without depressive symptoms
• 5-9 p. - minimal symptoms
• 10-14 p. - moderately pronounced depression
• 15-19 p.- moderate-severe depression
• 20-27 p.- severe depression

3.2.6.4 Questionnaire

For the purpose of the study, the participants filled out a questionnaire developed by the researcher. The form contains 5 sections - general data, accompanying diseases, harmful habits, free time, professional route, current workplace, clinical picture.

3.2.7. Statistical methods for data processing

The statistical processing of the data is performed with a computer program SPSS v25 and Jamovi 2.2.0. Data are graphically presented using Jamovi 2.2.0 and Microsoft Excel, Windows 10.

The present work included various descriptive and analytical methods based on parametric and non-parametric tests addressing the research objectives:

1. Descriptive methods

Descriptive analysis is used to describe the main characteristics of the sample and the indicators included in the study. Central tendency measures such as arithmetic mean, standard deviation, minimum-maximum values in rank and non-parametric tests such as Chi-square test and crosstabulation (Chi-square test and crosstabulation) are used for the analysis in search of significant differences in frequency representation of categorical values. Statistical significance in non-parametric tests is accepted at $p \leq 0.05$.

2. Analytical methods

o Independent T-test is used to compare the average values of various indicators between the two groups of patients - with and without changes after MR examination. The differences between the groups are statistically significant at $p \leq 0.05$.;

o Spearman's correlation analysis (rho) is used to examine the relationships between different indicators to establish the strength of their mutual impact. The degree of association between variables is defined as significant at $r > 0.5 < r = 0.7$; large at $0.7 < r = 0.9$ and extremely large at $r > 0.9$ at $p \leq 0.05$;

o Logistic regression is used to establish the relative risk (Odds ratio = OR) in the patient group. Values above 1 are defined as risky. Statistically significant are those results with $p > 0.05$;

4. RESULTS

4.1 Study population

The object of the study is a total of 151 participants, divided into 2 groups:

• 41 patients with data of aCVD (presence of white matter hyperintensities, asymptomatic infarctions, microhemorrhages and/or brain atrophy from MRI examination);

• 110 patients without data on asymptomatic cerebrovascular disease, with the presence of risk factors for CVD (controls);

4.2 Comparative statistics

4.2.1 Demographic characteristics and general data

The average age of patients with aMSB data was 54.61 ± 6.719, and in controls it is lower - 48.5818 ± 7.91165, with a statistically significant difference observed between the two groups (p=0.0001) (Fig. 1).

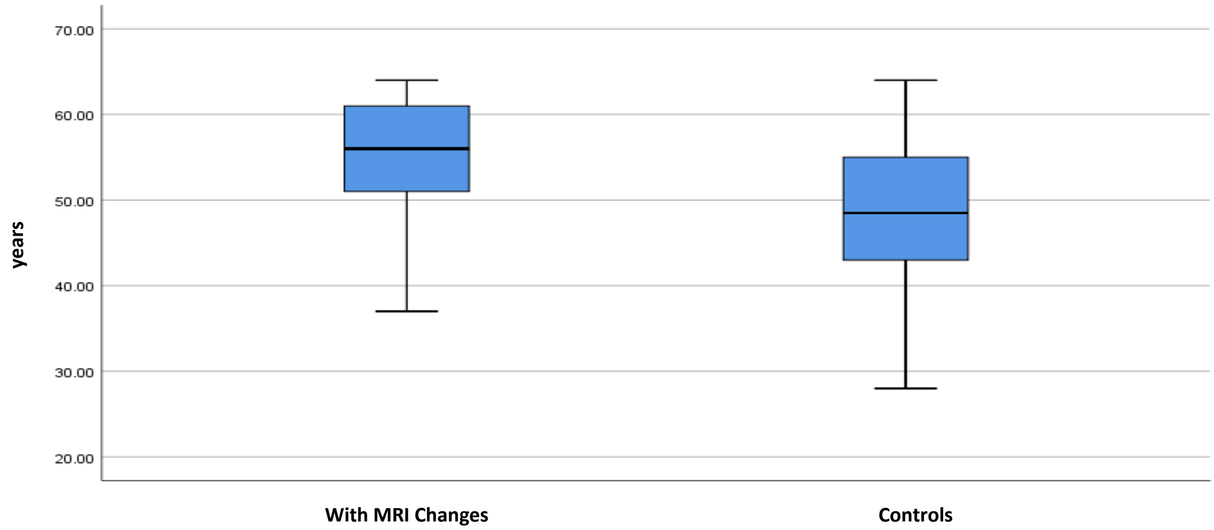

Fig. 1 Distribution of patients according to age

A relatively equal gender distribution is observed in both groups, with a predominance of women among patients, both in the group with evidence of MRI changes - 28 (68.3%) and in the control group 75 (68, 2%) (Fig. 2).

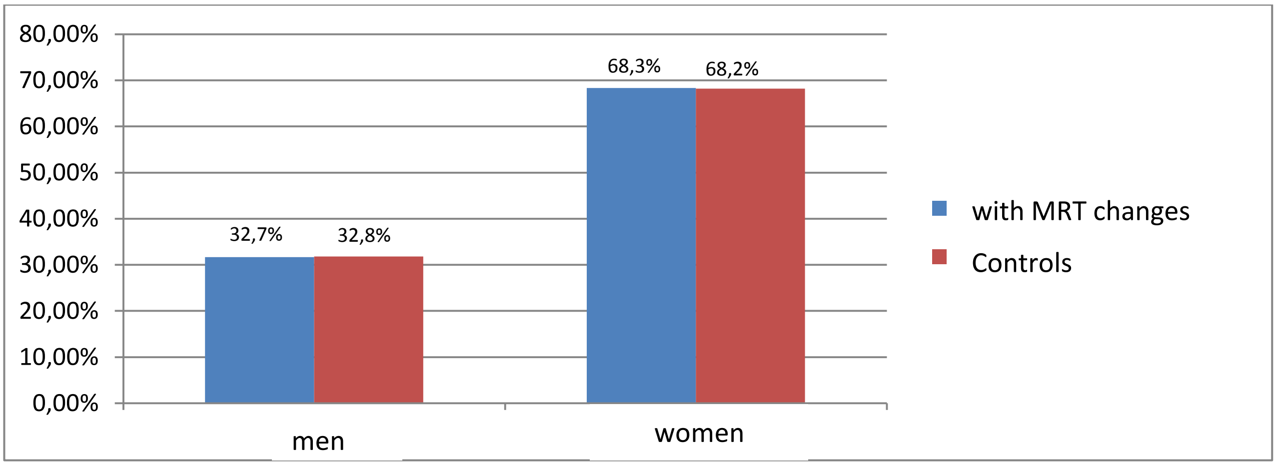

Fig. 2 Distribution of patients by gender

The statistical data show a higher frequency of leisure activities related to more physical activity (sport- 43.9%, walking 59.1%, housework- 59.1%), among the control patients.

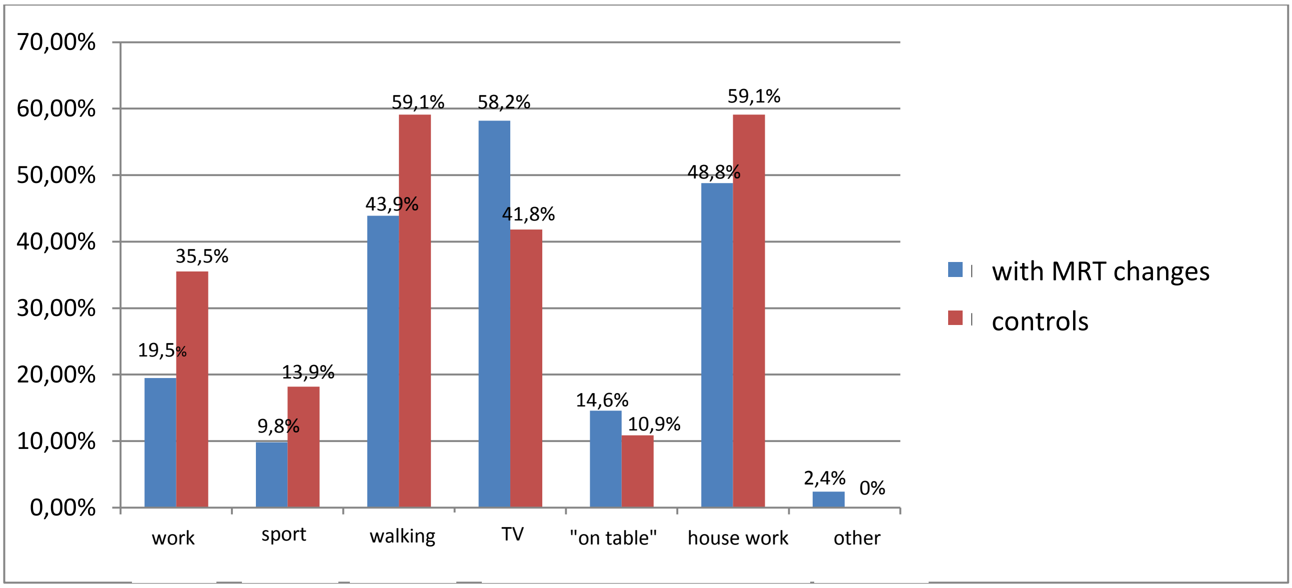

Fig. 3 Distribution of patients according to leisure activities

4.2.2 Risk Profile

4.2.2.1 Behavioral risk factors

Smoking is a common risk factor, with a relatively equal frequency among the studied groups. There is a slight preponderance of smokers in the group, with a prevalence of MRI changes - "current smokers" - 21 (51.2%), "former smokers" - 11 (26.8%), and in the controls respectively 48 (43.6 %) "current smokers" and 23 (20.9%) "former smokers" (p=0.279) (Fig.4).

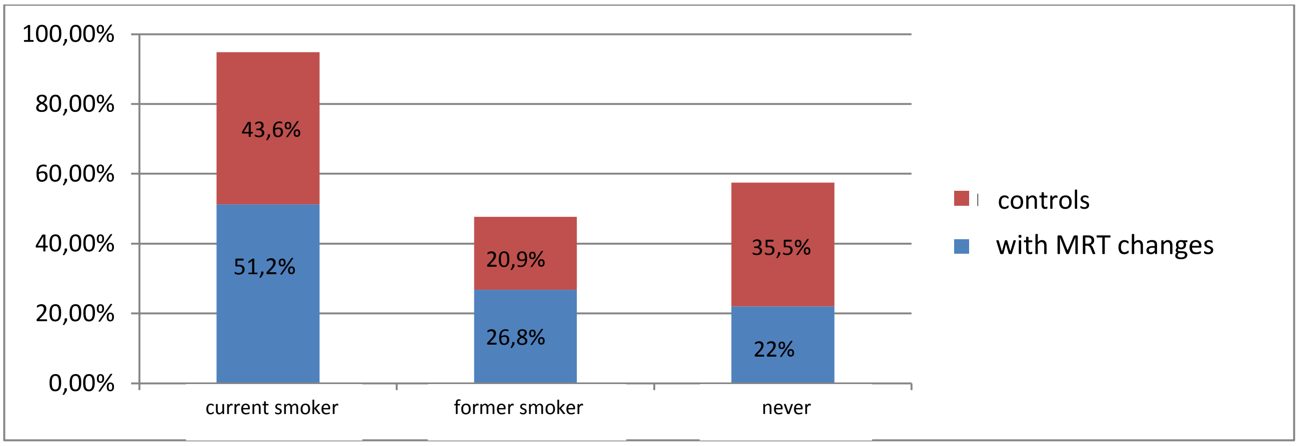

Fig. 4 Distribution of patients according to smoking

In the patients, with the presence of changes, a higher frequency of intake of "hard" alcohol is observed (p=0.017), and with regard to "light" the distribution was relatively the same among the studied groups (Fig. 8). Regarding the degree of alcohol consumption, the largest proportion of patients from both groups reported "low-risk consumption" (p=0.370) (Fig. 5).

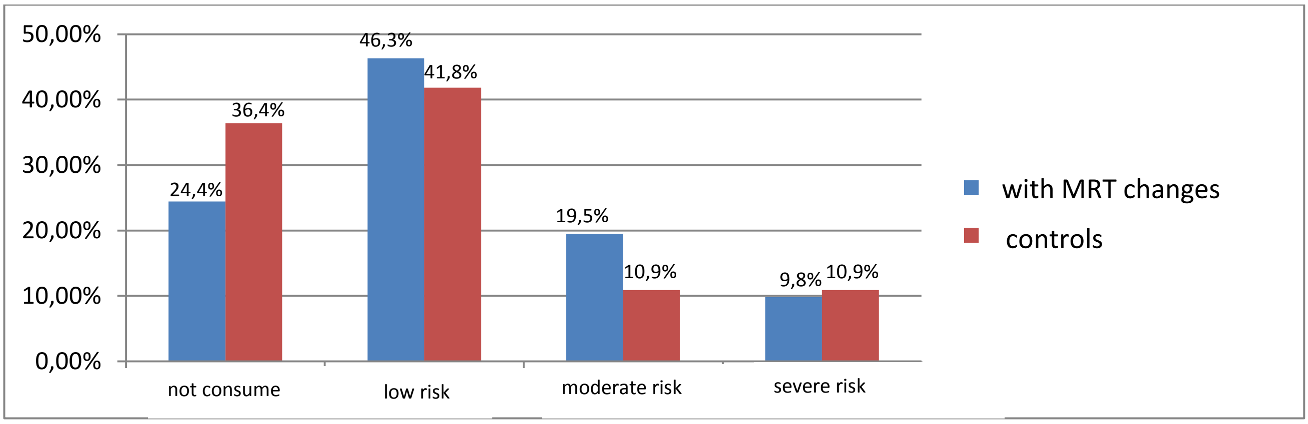

Fig. 5 Distribution of patients according to alcohol consumption

4.2.2.2 Main modifiable risk factors

Dyslipidemia is the most common modifiable risk factor for IBD in the study population. Elevated total cholesterol was found in 70.7% of patients with MRI changes and in 62.7% of the control group (p=0.359). Elevated LDL in 78% and 82.9% respectively (p=0.511), and hypertriglyceridemia in 46.3% of those examined with evidence of changes and 36.4% in those with normal MRI (p=0.264).

Hypertensive disease is the second most frequent risk factor (diagnosed in the past or newly diagnosed in the clinic). It occurs in 31 (75.7%) of patients with available changes and 38.3% of controls, with a significant difference (p=0.004).

In third place is diabetes mellitus, present as a disease in 17.1% of the group with changes and 4.5% of the controls (p=0.011). Ischemic heart disease and heart failure also showed a statistically significant higher incidence in the group with MRI changes (CHD p=<0.001; HF p=0.016). Among the modifiable risk factors studied, atrial fibrillation/flutter has the smallest share, but again with a higher percentage in patients, with change data - 4.9% and 0.9% in controls (p=0.120) (tab. 1).

Risk factors	With MRT changes	Controls	p- value
Hypertension	75,7%	38,3%	***0,004***
Diabetes melitus	17,1%	4,5%	***0,011***
Atrial fibrillation/flutter	4,9%	0,9%	0,120
Heart failure	7,3%	0%	***0,016***
Ischemic heart disease	17,1%	1,8%	***<0,001***
↑ **Total cholesterol**	70,7%	62,7%	0,359
↑ **LDL**	78%	82,7%	0,511
↑ **Triglycerides**	46,3%	36,4%	0,264

Tab. 1 Distribution of patients according to modifiable risk factors

4.2.2.3 Occupational factors

According to our study, the largest share of patients with available MRI changes have a work experience between 31-40 years (34.1%), while the controls reported a shorter work experience - 21-30 years. (40.4%). From the graph, it can be seen that with longer work experience, the share of patients prevails, with MRI changes, and vice versa, for controls, shorter work experience prevails - under 30 years. (p=0.032) (Fig. 6).

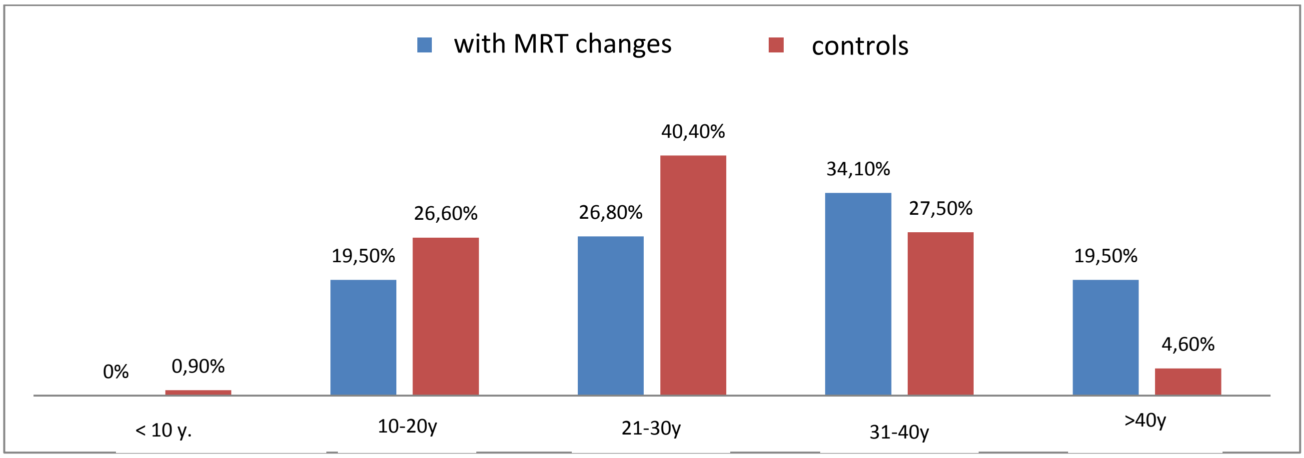

Fig. 6 Distribution of patients according to work experience

The largest part of the participants from both groups define their position as "worker" - 70.7% of patients with MRI changes and 67.3% of those without changes, 29.3% of participants define themselves as "manager" with changes and 18.2% with a normal MRI examination (p=0.052). The graph shows a more noticeable difference between the patients who defined their job as "self-employed" - 0% of the experimental group and 14.5% of the control group (Fig. 7).

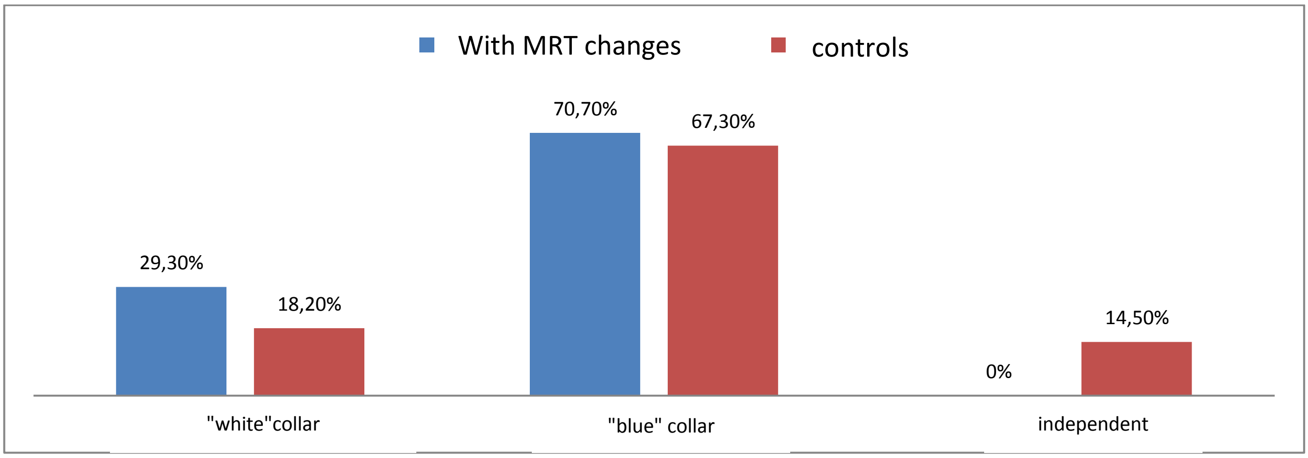

Fig. 7 Distribution of patients according to possition

Regarding the mode of work, patients show a relatively equal distribution (p= 0.472). It can be seen from the graph that the shares of participants, with MRT changes, doing night work are higher (only night shifts - 17.1% and day/night shifts - 29.3%) (Fig. 8).

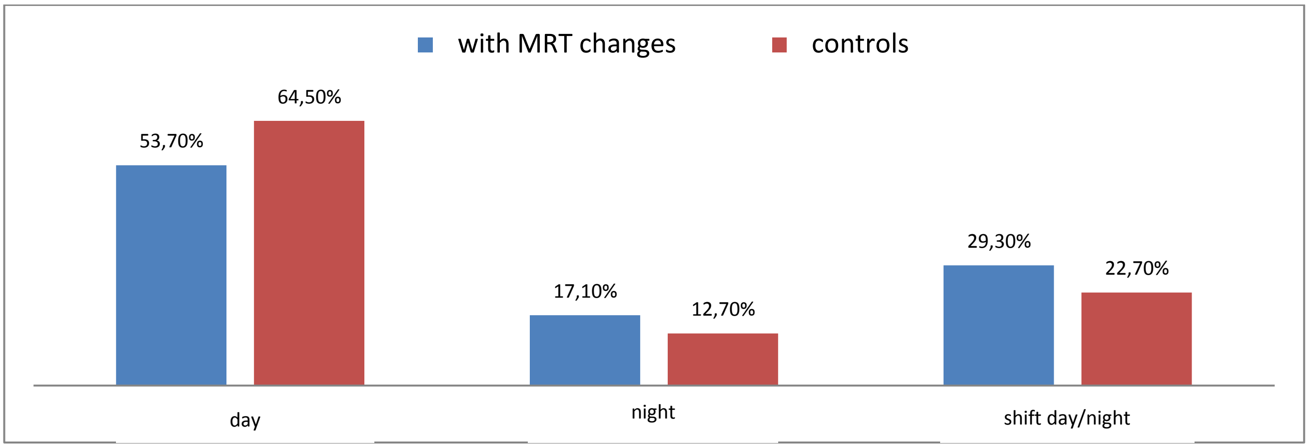

Fig. 8 Distribution of patients according to work regime

Our results show differences regarding the type of work in the two groups, although without statistical significance (p=0.077). A greater part of the patients, with data on MRI changes, indicate that they perform "mostly physical work" - 56.1%, while in controls - 38.2%. Regarding the severity of the physical work, in the experimental group the participants performing "medium" (26.8%) and heavy (19.5%) physical work predominated (p=0.007). (fig. 9).

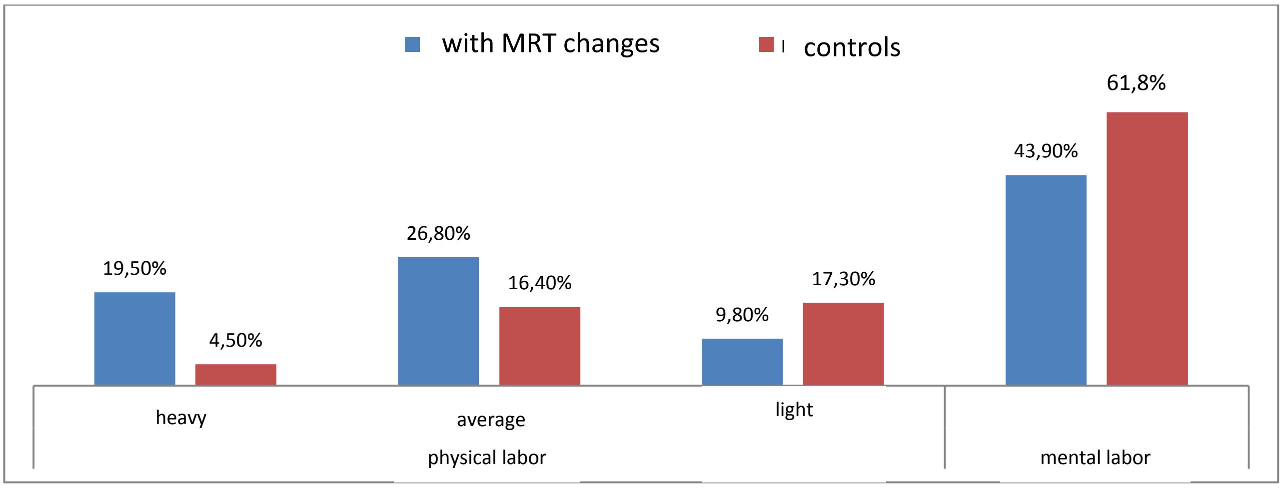

Fig. 9 Distribution of patients according to type of work

In patients with the presence of MRI changes, a higher average number of working hours/week was calculated - 48.41±6.26, compared to 44.45±3.85 hours in the control group. A significant difference was found between the two groups regarding this indicator (p<0.001) (Fig. 10).

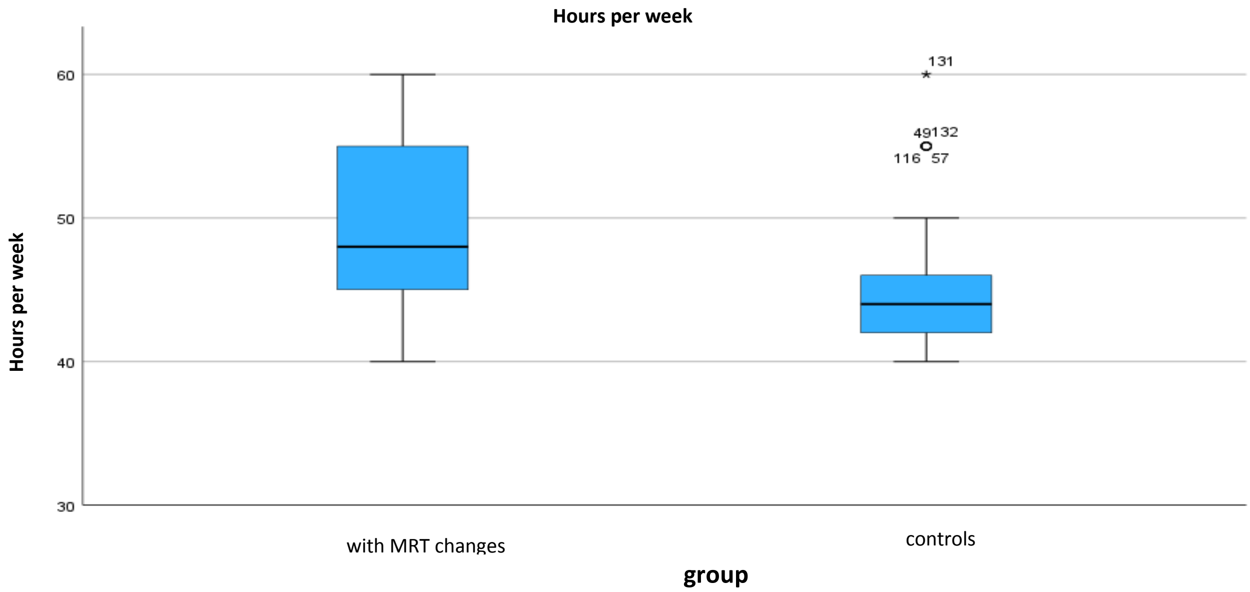

Fig. 10 Average number of hours/week

The characteristics of the labor process of the participants from both groups are also studied. According to the location of the work process, the patients showed a statistically significant difference (p=0.046), 14.6% of the patients, with evidence of MRI changes, worked outdoors and only 4.5% of the controls.

Regarding the working posture, patients from both groups who work "sitting" or "standing" have relatively equal shares. A significantly greater percentage of participants with MRI changes reported a 'forced' work posture (19.5%), while controls had a higher proportion of 'varied' posture (28.2%) (p<0.001).

The vast majority of both groups reported "diverse" work movements. However, a statistically significant greater proportion of patients with MRI changes performing "uniform" movements (39.0%) was calculated, compared to 21.8% for those without changes (p=0.033).

The participants did not show significant differences regarding the presence of a "working norm" for performance (p=0.476) (tab. 2).

Occupational factors		**With MRT changes**	**controls**	**P-value**
Location	outdoor	14,6%	4,5%	***0,046***
	indoor	85,4%	95,5%	
Working posture	sitting	43,9%	40,9%	***<0,001***
	upright	34,1%	27,3%	
	forced	19,5%	3,6%	
	diverse	2,4%	28,2%	
Work movements	monotonous	39,0%	21,8%	***0,033***
	diverse	61,0%	78,2%	
Norm	yes	9,8%	6,4%	*0,476*
	no	90,2%	93,6%	

Tab. 2 Distribution of patients according to labor process factors

The object of our research are also the most frequent harmful physical and chemical factors of the working environment. The most common harmful factor is the work environment and in both groups it is dust, with 24.4% of the patients with MRI changes and 15.5% of the control group under its influence (p=0.203). The results showed statistically significant differences between the two groups regarding the impact of: organic solvents (p=0.025), gases (p=0.005), noise (p=0.030) and vibration (p=0.048) (tab. 4).

Occupational factors	**With MRT changes**	**Controls**	**P-value**
Heavy Metals	2,4%	2,7%	0,92
Organic solvents	17,1%	5,5%	***0,025***
Gases	17,1%	3,6%	***0,005***
Plastic	2,4%	1,8%	0,808
Pesticides	4,95%	0,9%	0,250
Dust	24,4%	15,5%	0,203
Noise	19,5%	7,3%	***0,030***
Vibrations	12,2%	3,6%	***0,048***
Others	2,4%	2,7%	0,681

Tab. 4 Distribution of patients according to harmful factors of the working environment

4.2.3 The Workplace Stress Scale (WSS)

The two studied groups are compared according to the total number of points that were calculated and their distribution by categories of The Workplace Stress Scale. The mean score in the group with MRI changes was 21.34±5.47 points, and in the control group it was 19.08±4.29 points, and this difference showed statistical significance (p=0.009) (Fig. 12).

Fig. 12 Average value- The Workplace stress scale

4.2.4 Montreal Cognitive Assessment Test (MoCA)

No significant difference was observed between the patients regarding the mean MoCA values - 27.02±2.44 points in the experimental group and 27.78±2.18 points in the controls (p=0.068) (Fig. 14).

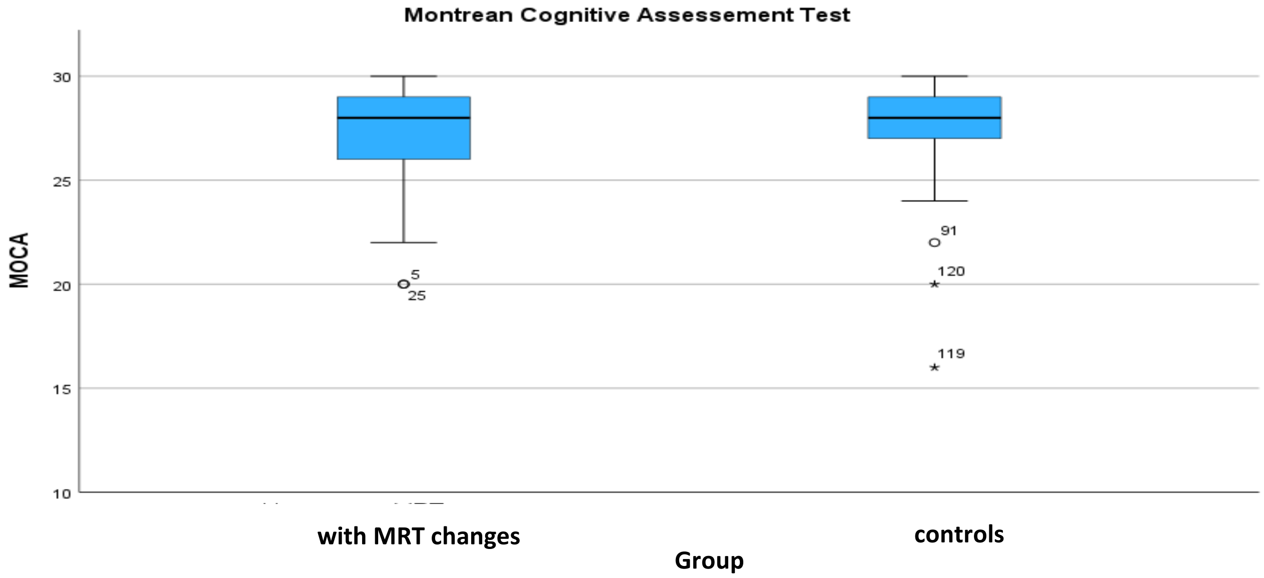

Fig. 14 Average value of MoCA

5.3 Correlation dependencies

5.3.1 Risk Factors

5.3.1.1 Modifiable vascular risk factors

There is a weak, statistically significant correlation between any of the modifiable vascular risk factors and the presence of MRI changes. A positive correlation is calculated for hypertension (rho=0.263, p=0.001), diabetes mellitus (rho=0.206, p=0.011), heart failure (rho=0.233, p=0.004), ischemic heart disease (rho=0.287, p<0.001) and other heart diseases (rho=0.412, p<0.001). Contrary to these results, an inversely proportional correlation dependence is established regarding hypercholesterolemia and hypertriglyceridemia and the presence of MRI changes, without reaching statistical significance (p>0.05) (tab. 5).

	Hypertonia	Diabetes melitus	Atrial fluter	Heart failure	ICD	Other car.	Holesterol	LDL	TG
rho	***0,263***	***0,206***	0,126	***0,233***	***0,287***	***0,412***	-0,075	0,054	-0,91
p-value	***0,001***	***0,011***	0,122	***0,004***	***<0,001***	***<0,001***	0,363	0,514	0,267

Tab. 5 Correlations between modifiable risk factors and presence of MRI changes

5.3.1.2 Professional factors

Some of the studied occupational risk factors showed a statistically significant association with the presence of MRI changes. The most significant directly proportional dependence is found with the greater number of working hours/week (rho=0.298, p<0.001), higher levels of work stress (survey) (rho=0.290, p<0.001), longer working hours seniority (rho=0.203, p=0.013). The interpretation of the results shows that the type of job also shows a statistically significant relationship (rho=-0.201, p=0.013) with MRI changes, and it is more pronounced for the worker job. Another such occupational factor is the location of the work process (rho=-0.175, p=0.032), and the probability of changes is greater for "outdoor" workers. Work movements also showed a correlation (rho=-0.173,p=0.033), as work with "uniform" movements increased the probability of asymptomatic MRI changes (table 6).

In the next step, we examine the correlations between occupational factors and modifiable, vascular risk factors. The most statistically significant relationships are found between pro-factors and hypertensive disease. The relationship between HB and longer work experience (rho=0.308, p<0.001) and the greater number of working hours per week (rho=0.187, p=0.022) is directly proportional. The results show that those working in physical labor are more likely to have CKD (rho=0.277, p<0.001), and as the burden of physical labor increases, the dependence becomes stronger (rho=0.225, p=0.006). The type of work posture also show a relationship with the presence of HB in the studied patients (rho=-0.161, p=0.048).

A greater number of hours/week (rho=0.209, p=0.10) and a longer working day (rho=182, p=0.025) are associated with the presence of heart failure in patients. The location of the underlying process also correlates with the presence of CH, with outdoor work increasing the likelihood. (rho=0.330, p<0.001).

A proportional relationship is found between longer work experience (rho=0.163, p=0.046) and the presence of coronary artery disease in the participants, with the correlation being stronger in patients performing mental work (rho=-0.169, p=0.38).

No statistically significant correlations are calculated between diabetes mellitus, atrial fibrillation/flutter, other heart diseases, lipid profile changes and occupational factors (tab. 7).

	Work experience	Position	Regime	Duration	Hours/weak	Type	Location	Posture	Movement	Norm	Stres
Rho	***0,203***	***-0,201***	0,096	0,115	***0,298***	-0,114	***-0,175***	0,108	***-0,173***	0,058	***0,290***
p	***0,013***	***0,013***	0,243	0,161	***<0,001***	0,078	***0,032***	0,186	***0,033***	0,479	***<0,001***

Таб.10 Correlations between occupational factors and presence of MRI changes

	Hypertonia		**DM**		**Atrial flutter**		**Heart failure**		**IHD**		**Other**		**Hol.**		**LDL**		**TG**	
	rho	**p**	**rho**	**p**	**rho**	**p**	**rho**	**p**	**rho**	**p**	**rho**	**p**	**rho**	**p**	**rho**	**p**	**rho**	**p**
Work experience	***,308***	***<,001***	,088	,284	-,029	,726	,025	,765	***,163***	***,046***	-,020	,811	000	,998	,038	,645	,002	,981
Position	-,140	,087	,055	,504	,032	,698	,032	,698	,103	,208	,102	,212	-,018	,826	-,039	638	,084	,304
Regime	-,042	,611	,71	,384	,070	,390	,003	,974	,082	,315	,118	,021	-,207	,011	-,134	,101	,043	,599
Hours/week	***,187***	***,022***	,117	,152	-,031	,704	***,209***	***,010***	-,056	,494	,034	,677	-,132	,107	-,163	,054	,076	,352
Duration	,117	,153	,062	,452	,111	,174	***,182***	***,025***	,135	,098	,030	,715	,044	,593	,115	,159	,082	,230
Work type	***,277***	***<,001***	-,083	,313	-,064	,436	-,159	,051	***-,169***	***,038***	-,113	,167	,014	,860	,054	,510	,159	,051
Workload	***,225***	***,006***	,042	,612	,084	,303	,113	,166	,151	,164	,082	,317	,051	,533	,030	,716	1	...
Location	,051	,531	,012	,879	,144	,078	***,330***	***<,001***	,146	,073	,038	,645	-,152	,062	-,134	,102	,087	,287
Posture	***-,161***	***,048***	-050	,543	,003	,966	-,098	,232	-,061	,453	-,041	,619	,076	,354	,043	,596	,102	,214
Movement	-,078	,342	-,010	,904	-,085	,297	,021	,801	,039	,639	,039	,634	-,096	,243	-,016	,844	,165	,054
Norm	0	1	,082	,315	,040	,627	,040	,627	,071	,389	-,037	,651	-,061	,458	-,063	,442	,089	,278
Stress	,087	,288	-,146	,074	,103	,206	,030	,711	,106	,197	,028	,731	,060	,461	,011	,889	,093	,257

Таб.11 Correlations between occupational factors and modifiable risk factors

4.3.2 The Workplace stress scale

Higher levels of stress measured by WSS are associated with the presence of MRI changes (rho=213, p=0.009) (Fig. 16).

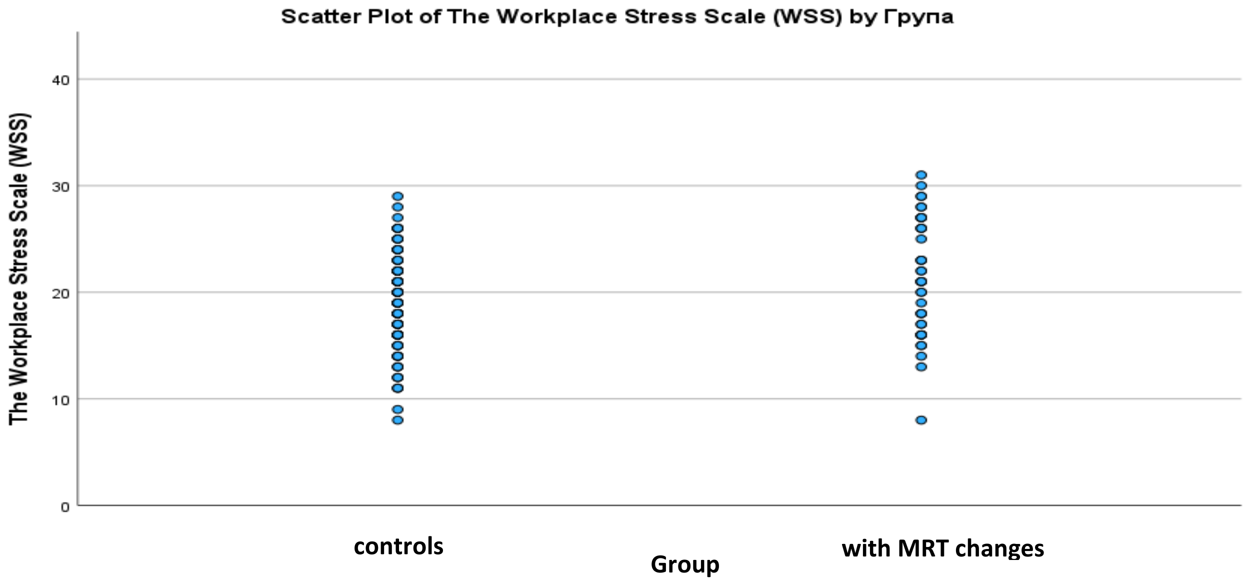

Fig. 16 Correlation analysis between WSS scores and the presence of MRI changes

The analysis performed shows a statistically significant relationship between hypertensive disease and higher levels of occupational stress in the studied groups. A minimal and statistically insignificant correlation is calculated for the remaining modifiable risk factors (tab. 8).

	Hypertonia	DM	Atrial flutter	Heart failure	IHD	Others	Hol	LDL	TG
rho	***0,212***	0,013	0,083	0,039	0,058	0,005	0,060	0,082	0,023
p-стойност	***0,009***	0,875	0,311	0,632	0,483	0,980	0,462	0,316	0,780

Tab. 8 Correlations between WSS scores and modifiable risk factors

Longer work experience (rho=0.172, p=0.036) and longer working week (rho=0.244, p=0.003) are associated with higher levels of occupational stress. The shift mode of work (rho=0.209, p=0.010) and the localization of the working process of "closed" (rho=0.177, p=0.030) show a stronger relationship with higher levels of stress in our patients (tab. 9).

	Working experience	Position	Regime	Hours/ week	Duration	Work type	Location	Postire	Movement	Norm
rho	***0,172***	0,154	***0,209***	***0,244***	0,061	0,034	***0,177***	0,038	0,099	0,128
p-стойност	***0,036***	0,507	***0,010***	***0,003***	0,457	0,678	***0,030***	0,643	0,226	0,070

Tab. 9 Correlations between occupational factors and WSS scores

4.3 Relative Risk

Of the modifiable risk factors studied, Ischemic heart disease is associated with the highest risk of MRI changes - 3.334 (95% confidence interval 1.485; 7.488). Statistically significant differences are also found for hypertension and diabetes. HB increases the risk by 1.910 times (95% confidence interval 1.275; 2.860), and diabetes mellitus by 2.079 times (95% confidence interval 1.135; 3.810).

Of the professional factors, work experience "between 30 and 40 years" increases the risk of changes the most - 6.4 times (95% confidence interval 1.748; 23.438), followed by work experience "between 20 and 30 years - 5.8 times (95% CI 1.482;22.694). A statically significant higher risk is also calculated for the factor "position" - 2.372 (95% confidence interval 1.202; 4.678), and the risk for different positions cannot be presented because the results for all types of position are insignificant and are zero . When considering the risk with a longer working week, a significantly higher risk is found with more working hours/week, and it is highest when working > 55 hours/week. The study also shows a 2.610 times (95% confidence interval 1.478; 4.611) greater risk of changes in the "stress" factor, with a statistically significant difference observed in "stress during more than 50% of the working day. The results of calculations using the results of the stress scale also show an increased risk at higher values (tab. 10).

Fartors	**OR**	**95% интервал на доверие**	**Р-стойност**
Hypertonia	***1,910***	***[1,275; 2,860]***	***<0,001***
Diabetes melitus	***2,079***	***[1,135; 3,810]***	***0,018***
Heart failure	20,309	[0,001; 6,293]	0,999
Ischemic heart disease	***3,334***	***[1,485; 7,488]***	***0,004***
Holesterol	1,436	[0,661; 3,120]	0,361
LDL	1,347	[0,553; 3,279]	0,512
Triglicerides	1,511	[0,553; 3,279]	0,265
Smoke	1,331	[0,870; 2,036]	0,870
Alcohol	1,162	[0,801; 1,686]	0,430

Work expirience Between 20-30y. between 30-40y. > 40 y.	***0,578*** ***5,800*** ***6,400*** 3,429	***[0,393; 0,877]*** ***[1,482;22,694]*** ***[1,748;23,438]*** [0,949;12,392]	***0,009*** ***0,012*** ***0,005*** 0,060
Posture	***2,372***	***[1,202; 4,678]***	***0,013***
Regime Day Night	1,154 0,759 0,514	[0,718; 1,854] 0,311; 2,034] -	0,554 0,633 0,999
Duration	0,977	[0,739; 1,290]	0,867
Hours/week 40-49 h 50-55 h >55 h	***2,470*** 2,470 2,712 ***5,835***	***[1,309; 4,663]*** [1,309; 4,663] [0,299; 24,629] ***[2,810; 12,119]***	***0,005*** 0,131 0,651 ***<0,001***
Work type	1,048	[0,545; 2,016]	0,888
Location outdoor indoor	1,723 0,286 0,607	[0,981; 3,029] [0,545; 2,016] [0,280; 1,317]	0,058 0,095 0,207
Posture sitting stand diverse	1,365 ***0,081*** ***0,069*** ***0,016***	[0,973; 1,916] ***[0,010; 0,636]*** ***[0,009; 0,559]*** ***[0,002; 0,165]***	0,072 ***0,017*** ***0,012*** ***0,001***
Movement	0,670	[0,317; 1,415]	0,294
Stress	***1,734***	***[0,492; 1,093]***	***0,041***

Tab. 10 Risk assessment for modifiable risk factors and occupational factors

5. DISSCUSION

Our results showed a higher mean age (54.61 ± 6.719) in the patients with evidence of MRI changes, compared to 48.5818 ± 7.91165 years, in the controls. This is consistent with data from studies that indicate age as a significant risk factor for asymptomatic myocardial infarctions (AMI), hyperintense brain white matter lesions, and cerebral atrophy, and also confirms the opinion of Moura A. et al., who demonstrate a sharp increase in white matter hyperintensities (WMH) in the 5th and 6th decades [Fukuda K. et al., 2014; Smith E. et al. 2015; Zhuang F. et al., 2018; Moura A. et al., 2019].

Regarding asymptomatic strokes, the data on the role of gender are contradictory [Vermeer S. et al., 2002; Prabhakaran S. et al., 2008], but in WMH, the female gender is defined as being at risk for a larger volume and faster progression of changes [Farzan F. et al., 2018]. In our study, a higher frequency of female participants was reported in both groups, without a statistically significant difference, which may be explained by the fact that female participants seek medical help more often and earlier, compared to the male gender [Thompson A. et al., 2016].

According to the results of our study, there was no statistical difference between the two groups in terms of smoking and the average number of cigarettes/day. This corresponds to the contradictory conclusions of a number of authors about the role of smoking in the development of asymptomatic strokes and microhemorrhages [Fukuda K. et al., 2014; Howard G. et al., 1998; Yoo J. et al., 2020]. Large studies such as Rotterdam and Framingham establish a definite link between cigarette smoking and WMH, as Gray J. et al. point out the higher frequency in "ex-smokers", and Power M. et al. in "current smokers" [Gray J. et al., 2020; Power M. et al., 2015]. In our patients, a higher proportion of "former" and "current" smokers was observed in the group with MRI appointments compared to controls. The fact that the number of smokers predominates in both studied groups can be explained by the fact that Bulgaria ranks first in the European Union in terms of smoking, according to the European Commission. The National Statistical Institute (NSI) reports the highest percentage of working-age smokers, an age range that also corresponds to our study.

Data in the literature showing the influence of alcohol intake on asymptomatic ischemic disorders are scarce. Lee et al. confirm the protective role of low alcohol consumption [Lee S. et al., 2000], while regarding high consumption the results are mixed [Mukamal K. et al., 2001; Fukuda K. et al., 2014]. Our study did not find an increased risk for asymptomatic disorders OR: 1.162 (95% CI: 0.801;1.686) with higher consumption, in contrast to Fukuda K. et al., who calculated OR: 4.1 (95% CI: 1.7 ,10) [Fukuda K. et al., 2009]. Our results contradict large studies such as the "Cardiovascular Health Study" [Mukamal K. et al., 2001] and "the Rotterdam study" [den Heijer T. et al., 2004], probably due to the fact that they cover an older population (over 60 years of age). At the same time, they confirm the null results of "the ARIC" (average age 57 years) [Ding J. et al., 2004] and "PATH Through Life" (60-64 years) [Anstey K. et al., 2006.] conducted among younger subjects.

Analysis of our data determined a high percentage of patients with dyslipidemia in both groups, with no statistically significant difference ($p>0.05$). Not establishing a correlation between this factor and the presence of MRI data of changes, as well as an increased relative risk in our patients. Our calculated 78% in the group, with changes and 82.7% in the controls, patients with elevated LDL, are close to the data of the EUROASPIRE IV study, which found an 86% frequency in the population, with an increased cardiovascular risk [Kotseva K. and editor, 2016]. Our values are higher than those found in other studies in Bulgaria and Europe [Borissova M., 2015; Rostohar B. et al., 2018], which can be explained by local factors, some harmful habits and unhealthy diet. The literature data on the role of elevated serum lipids in the pathogenesis of asymptomatic disorders are also inconclusive. Only a few studies associate them with a higher frequency of AMI, HBV and microhemorrhages [Feng X. et al., 2021; Nam K. et al., 2019].

Hypertensive disease was the second most frequent modifiable risk factor in our patients, with a proportion of 75.7% in the group with MRI lesions. Multiple studies have linked hypertension to the incidence of "silent" CVD such as define as the main risk factor [Lee S. et al., 2000.]. This is also confirmed by data on an increase in the frequency of asymptomatic infarcts and the volume of WMH at a higher average value of BP [Zhao Y. et al., 2019]. We also found a correlation between hypertension and the presence of MRI changes (rho=0.263, p=0.001). From the present literature review, it is clear that asymptomatic ischemic disorders are associated with an increased incidence of symptomatic stroke. Our results overlap with the data on the frequency of hypertension in stroke patients in most European countries - Great Britain, Greece, Croatia, etc. [CleryA. et al., 2020; Tsivgoulis G. et al., 2018; Rostohar B. et al., 2018]. We calculated an almost two-fold higher risk of asymptomatic lesions in patient with hypertension, which approximated the risk calculated by Vermeer S. et al. in their study [Vermeer S. et al., 2002].

Diabetes mellitus occurred in 17.4% of our patients with MRI changes, which showed a statistically significant difference with the control group. Diabetes mellitus also showed a correlation with the presence of MRI changes (rho=0.206, p=0.011), and increased the risk almost twice in the studied population. These results are consistent with scientific reports of a higher incidence of lacunar infarcts, WMH in patients with diabetes mellitus. [Zafar A. et al., 2017; Grosu S. et al., 2021]. The results of studies on the frequency of DM in stroke patients in Europe and Bulgaria are significantly higher than those of the present study [Rostohar B. et al., 2018; Tsivgoulis G. et al., 2018; Tsalta-Mladenov M., 2021]. This can probably be explained by the lower average age of the patients studied by us, since the incidence of DM increases with age [Scheen A. et al., 2014]. It should also be taken into account the established greater frequency of changes when

DM is combined with other factors: hypertension, diabetic nephropathy, metabolic syndrome [Bell D. et al., 2020], which was not observed in our patients.

In the studied literature, there are definite data on an increased frequency of diagnosed heart failure in patients with asymptomaticstrokes and WMH - between 10 and 24% in different sources [Scherbakov N. et al., 2015. ; Alosco M. et al., 2013]. We calculated - 7.3%, which is a lower result than expected, probably due to the lower average age of the subjects and the low comorbidity. Despite the low rate, it was significantly higher than the control group and correlated with the presence of asymptomatic MRI changes.

Rhythm-conduction disorders, as a risk factor, have a relatively low frequency in our population - 4.9% of patients, with data on changes. Consistent with other studies, in younger patients and in ours, no correlation was found between AF and asymptomatic lesions, as well as an increased risk of their occurrence. At the same time, our data contradict studies in older patients [Ryden L. et al., 2021], incl. and the Framingham study, which determined a significant role of AF in the development of „silent“ infarcts.

It is clear from the literature review that there is a connection between the manifestations of the atherosclerotic process with different localization, incl. and relationship between coronary atherosclerosis, asimptomatic strokes and WMH volume. Increased cardiovascular risk and the presence of cardiovascular risk factors increase the risk of asymptomatic CVD. 17.1% of our patients with asymptomatic lesions reported ischemic heart disease, which was a statistically significant higher proportion compared to the control group. In our study, the presence of IHD, as a clinical manifestation of coronary atherosclerosis, increased the risk of lesions slightly more than three times OR: 3.334 (95% CI 1.485;7.488).

Longer working experience and long working hours (> 41 hours/week) are associated with longer exposure to harmful factors such as: occupational stress, night work, physical and chemical hazards, etc. With an increase in work experience, there is also an increase in age-related risk factors: hypertension, diabetes, dyslipidemia, etc. Fadel et al. found a significant association between exposure to overtime work, with work experience over 10 years, and the incidence of stroke [Fadel M. et al., 2019]. Our results show an increase in the proportion of patients with evidence of MRI changes with work experience over 30 years. We also found a 6 times higher risk for MRI lesions with work experience between 20-30 years. and 31 and 40 years, compared to patients with 10-20 years of work experience. In the group with changes, we found a higher average number of working hours compared to the control group, as well as a correlation between a greater number of hours/week and the presence of MRI lesions. Virtanen M. et al. [Virtanen M. et al., 2018]. found an increased risk of stroke in a workday lasting >55 hours, which our study also confirms. Data on the association of working lonh hour with vascular risk factors for CVD are conflicting. We found a statistically significant association between long working hours, hypertension and heart failure.

A higher percentage of our patients with MRI lesions defined themselves as "workers" (70.7%) and their work as "mostly physical" (56.1%), without statistical difference. This puts them in the „blue-collar“ group according to English literature. In this type of workers, a higher risk of stroke is reported due to a number of factors [Perez-Martinez P. et al., 2017]. The risk increases in patients subjected to heavy physical work, compared to those performing light work [Holtermann A. et al., 2018]. In our patients, the proportion of those performing "medium" and "heavy" physical work also prevailed with MRI lesions. According to the authors, one of the mechanisms that increases the risk is a low level of activity during leisure time. A greater proportion of our patients with available MRI changes report more static activities ("at the table" - 14.6%, "in front of the TV" - 58.2%) during their free time. Regarding the influence of the type of work on the risk factors for stroke, the data from the literature are mixed here as well. In our research, a relationship was established between the type of work and hypertensive disease, as it is more pronounced for physical work (rho=0.277, p<0.001), and with an increase in the severity of physical work, the dependence becomes stronger (rho=0.225, p =0.006). A study in China proved that moderate exercise reduced the risk of hypertension in both sexes, while high exercise increased the risk among female workers [Li Q. et al., 2021].

In our results, no influence of the working mode (day, night, shift) on the appearance of MRI lesions and vascular risk factors was found. Only a higher number of patients working at night was found among those with MRI changes. The authors conclusively prove the greater frequency of cerebrovascular diseases with a shift schedule, especially in those working night shifts > for 5 years [Akerstedt T. et al., 2020]. It is likely that the difference in results is due to the small number of patients included in our study (N= 151) compared to those reported in the literature.

A greater proportion of our patients from both groups work indoors. The percentage of patients with MRI lesions (14.6%) who work "outdoors" is statistically significantly higher compared to controls (4.5%). Workers who spend the main part of the working day in open spaces are significantly more exposed to atmospheric pollutants [Vega-Calderón L. et al., 2021]. In the literature, exposure to atmospheric pollutants is associated with an increased risk of cerebrovascular events, incl. and lacunar infarcts [Corea F. et al., 2012]. We do not calculate an increased risk, but we establish an association between "outdoor" work and the presence of MRI lesions. Population studies positively associate atmospheric pollution with vascular risk factors, such as hypertension, type 2 diabetes, atrial fibrillation, carotid atherosclerosis. We found such an association only with heart failure. It is likely that the lack of positive results is due to the smaller number of patients included in the present study.

Different work postures and work movements do not show a correlation with MRI lesions and no increased risk of their development is calculated. In both groups, they have a relatively equal distribution - there is a predominance of participants working in a mostly "sitting" position. Rempel D. et al. did not establish an increased risk of cerebrovascular diseases in sitting working positions [Rempel D. et al., 2018]. Hall C. et al. reported a greater incidence of CVD in an "upright" working posture, a result that our study could not confirm [Hall C. et al., 2019]. Our descriptive data, however, report a higher percentage of workers in a "forced posture" (19.5%) and performing "uniform" movements (35%), in the group with MRI changes. This type of work is associated with lower control over work, insufficient time for recovery and rest, more pronounced fatigue in free time, which limits free physical activity. These factors are associated with an increased risk of stroke [Kang M. et al., 2012; Lee D. et al., 2016].

We investigated the levels of occupational stress by two methods - as a percentage of working time in which patients are stressed and by filling in a scale assessing workplace stress. Both methods showed that higher levels of stress (over 50% of working time or a higher number of points on the stress scale) were associated with the presence of ischemic lesions on MRI. Patients with higher stress scale scores are at higher risk for MRI changes OR:1.734 [0.492;1.093]. As we did not find studies linking occupational stress to asymptomatic ischemic disorders, we compared our results with literature data on its association with stroke. Different studies use different scales and questionnaires to assess stress levels, but most find a higher risk of stroke with exposure to high levels of occupational stress [Tsutsumi A. et al., 2009; Toivanen S. et al., 2012]. Job strain is considered to be the most stressful work factor and includes two components: psychological demands (short deadlines, mental load and responsibilities) and job control (skills and decision-making powers). With high demands and low control, stress levels are high and vice versa [Toivanen S. et al., 2012]. In the group with the presence of MRI lesions, a higher frequency of some factors leading to stress is reported: 1. Associated with high work stress (high workload, too much information) 2. Associated with low work control (lack of control, discrepancy between requirements and capabilities, impossibility of independent decisions). Longer work experience is associated with higher scores on the stress scale. This can be explained by the negative influence of age on work ability, especially when performing physical work [Imarinen J. et al., 2001], this reduces control over the work process and leads to an increase in occupational stress [Toivanen S. et al. ., 2012]. In the studies, higher stress levels were measured in participants with a changed work regime [Ma C. et al., 2015] and long working hours (>55h/week) [Kivimäki M. et al., 2015], this is also confirmed by our research.

The pathophysiological and biochemical changes to which stress leads negatively affect the occurrence and control of measurable risk factors for CVD. We found a statistically significant association only between high levels of stress and hypertension. The lack of data on the association with the other factors may be due to the smaller volume of patients studied, as well as the lack of longitudinal follow-up.

With specialized neuropsychological tests, such as the Montreal cognitive test (MoCA), in patients with asymptomatic disorders, discrete changes in different domains of cognitive functioning can be detected. The burden of lacunar infarcts, white matter hyperintensities, and microhemorrhages is associated with worse cognitive functioning and accordingly lower MoCA test scores [Akoudad S. et al., 2016; Warren M. et al., 2015]. Studies that strongly demonstrate decline in cognition and lower scores on specialized tests have been conducted in older patients, for example the mean age in "The Northern Manhattan Study" was 70.4 years Warren M. et al. confirm the negative role of lacunar infarcts in cognitive performance, but do not confirm the role of hyperintensities in a relatively younger population. Our results showed no statistical difference in MoCA test scores between the two groups. This may be explained by the lower average age of our patients, as well as by the fact that 82.9% of patients had only hyperintensities on MRI.

Depressive symptoms can negatively affect the results of cognitive tests, including the MoCA [Blair M. et al., 2016]. For this reason, our patients are screened for depression by filling out a short questionnaire (Patient Health Questionnaire-9). All study participants had no evidence of depressive symptoms and these should not be taken into account when interpreting the results.

6. CONCLUSIONS

1. The risk of ischemic cerebrovascular disorders increases statistically reliably with increasing age of the patients in the study group and is not affected by gender;
2. Hypertensive disease, followed by diabetes mellitus and ischemic heart disease increase statistically significantly the risk of asymptomatic ischemic disorders;
3. Harmful habits (smoking and alcohol intake) are not associated with a statistically significant increased risk for "silent" cerebrovascular disease;
4. Longer working experience (>20 years), long working hours (>55 hours/week) and work related to mostly physical labor increase the risk of asymptomatic lesions with statistical significance;
5. Hypertension is in a statistically significant relationship with longer working experience, longer working week (>55 hours/week) and heavy physical work, heart failure shows a statistical relationship with longer working week and longer working day;
6. Higher levels of workplace stress determine a statistically significant, increased risk for asymptomatic lesions and show a relationship with hypertensive disease in the studied patients;
7. High levels of professional stress show a statistically reliable relationship with longer work experience, longer working week and shift work;
8. No statistical relationship is found between the asymptomatic changes and the memory disorders of the examined workers;

7. CONTRIBUTIONS

Contributions of original character

1. For the first time in our country, a study was conducted on the influence of occupational factors on asymptomatic ischemic cerebrovascular disorders in patients of working age;
2. The relationship between levels of occupational stress and asymptomatic cerebrovascular disease was analyzed;
3. For the first time in Bulgaria, the dependence between vascular risk factors and work factors was investigated;
4. The relationship between asymptomatic MRI lesions and memory disorders in patients of working age was studied;

Contributions of a confirmatory nature

1. The role of vascular risk factors such as age, hypertension, type 2 diabetes in increasing the risk of asymptomatic cerebrovascular disease is confirmed;
2. The increased risk of cerebrovascular diseases with longer work experience and a longer working week (>55 hours/week) was confirmed;
3. The negative impact of high levels of occupational stress on the risk of cerebrovascular disease is confirmed;
4. The positive relationship between long work experience, long working week, hard physical work and hypertensive disease was confirmed.

8. PUBLICATIONS AND SCIENTIFIC EVENTS RELATED TO THE DISSERTATION WORK

1. Vladina Dimitrova-Kirilova, Alexandra Yankova, Dimitrinka Rosenova, Michael Tzalta-Mladenov, Veselinka Nestorova, Influence of the work regime on the risk factors for cerebrovascular disease-review; Varna Medical Forum, Vol 11, No 2 (2022)
2. Vladina Dimitrova-Kirilova, Alexandra Yankova, Dimitrinka Rosenova, Michael Tzalta-Mladenov, Veselinka Nestorova, Asymptomatic ischemic cerebrovascular disorders and cognition, Varna medical forum, Vol 12, No 1 (2023)
3. Mihael Tzalta-Mladenov, Vladina Dimitrova-Kirilova, Darina Georgieva-Hristova, Silva Andonova, Study of the risk profile of patients with acute cerebral stroke hospitalized in the Second Neurological Clinic, UMBAL "St. Marina", Varna Medical Forum, item 8, issue 1, Varna 2019.

9. APPLICATIONS

Periventricular white matter (PVWM)

- 0 = absent
- 1 = “caps” or pencil-thin lining
- 2 = smooth “halo”
- 3 = irregular periventricular signal extending into the deep white matter

Deep white matter (DWM)

- 0 = absent
- 1 = punctate foci
- 2 = beginning confluence
- 3 = large confluent areas

App. 1 Fazekas Scale

The Workplace Stress Scale™

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Directions: Thinking about your current job, how often does each of the following statements describe how you feel?

	Never	Rarely	Sometimes	Often	Very Often
A. Conditions at work are unpleasant or sometimes even unsafe.	1	2	3	4	5
B. I feel that my job is negatively affecting my physical or emotional well being.	1	2	3	4	5
C. I have too much work to do and/or too many unreasonable deadlines.	1	2	3	4	5
D. I find it difficult to express my opinions or feelings about my job conditions to my superiors.	1	2	3	4	5
E. I feel that job pressures interfere with my family or personal life.	1	2	3	4	5
F. I have adequate control or input over my work duties.	5	4	3	2	1
G. I receive appropriate recognition or rewards for good performance.	5	4	3	2	1
H. I am able to utilize my skills and talents to the fullest extent at work.	5	4	3	2	1

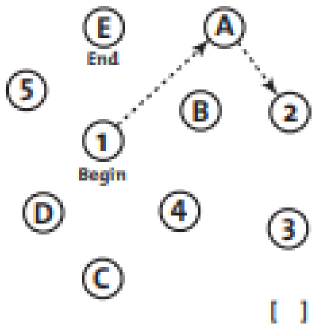
To get your score, add the numbers you answered to all of the eight questions and see how you compare.

App. 2 The WorkPlace stress Scale

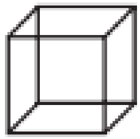
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



[ ]



Copy cube

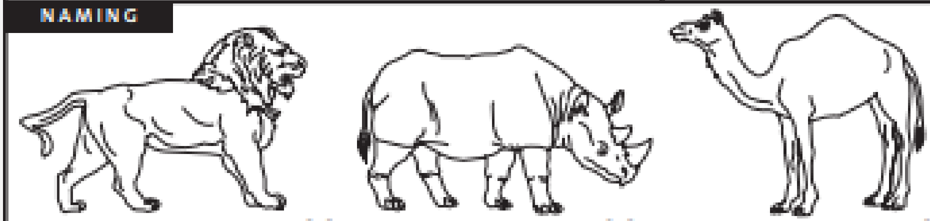
[ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING



[ ] [ ] [ ] ___/3

MEMORY	Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
		1st trial						
		2nd trial						

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) ___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only	___/5
		[ ]	[ ]	[ ]	[ ]	[ ]		
Optional	Category cue							
	Multiple choice cue							

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

Normal ≥ 26 / 30 TOTAL ___/30
Add 1 point if ≤ 12 yr edu

App. 3 MoCA

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

ID #: ______________________ DATE: ____________

Over the last *2 weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite —being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns		+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	
	Not difficult at all ______
	Somewhat difficult ______
	Very difficult ______
	Extremely difficult ______

App. 4 Patient health questionaire PHQ-9