

REVIEW

by Prof. Zlatka Borisova Stoyneva-Paskaleva, PhD,
Medical faculty (MF) - St. Cl. Ohridski Sofia university and MF – Medical university (MU) -
Plovdiv, member of the scientific jury according to Order No. R-109-37/25.01.2023 of the
Rector of the MU - Varna and on the basis of Protocol No. 1/26.01.2023 of the first meeting of
the scientific jury

REGARDING: Defense of the dissertation work of *Dr. Vladina Miroslavova Dimitrova-Kirilova*,
for awarding the educational and scientific degree "*doctor*" in the field of higher education 7.
"Health and sports", professional direction 7.1. "Medicine", scientific specialty " Occupational
Diseases" at the Prof. Dr. Paraskev Stoyanov Medical MU - Varna, on the *topic "Occupational
predisposition in asymptomatic strokes"* with scientific supervisor *Prof. Dr. Veselinka Dimitrova
Nestorova, MD*.

I. Defense procedure

The presented set of documents is in accordance with the Regulations for the acquisition
of the the educational and scientific degree "doctor" in the Medical University - Varna.
Dr. Vladina Miroslavova Dimitrova-Kirilova has gone through all the procedures provided
for in the Regulations for the development of the academic staff of the Medical University
- Varna. A copy of the Protocol No. 2/12.01.2023 of the Department council of the
Department of Optometry and Occupational Diseases at the MU - Varna was presented, at
which a decision was made to expel the full-time doctoral student Dr. Dimitrova-Kirilova
with the right to defense. By Order No. R-109-37/25.01.2023 of the Rector of the MU - Varna on
the basis of a report with Entry No. 102-123/16.01.2023 by Prof. Dr. Zornitsa Ivanova Zlatarova-
Angelova, MD - Head of the "Optometry and Occupational Diseases" department, with decision
under Protocol No. 199/18.01.2023 of the Faculty Council and Report with Entry No. 104-
49/19.01.2023 by Prof. Antonia Slavcheva Dimova-Yordanova, MD - Dean of the Faculty of Public
Health at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, on the basis of art. 24, para.
6 and art. 30, para. 3 of Regulations for the Implementation of the Law on the Development of the
Academic Staff in the Republic of Bulgaria (RILDASRB), art. 68, para. 1 of the Regulations for the
development of the academic staff at the MU - Varna is charged with the right to defense Dr. Vladina
Miroslavova Dimitrova-Kirilova - PhD student in full-time study in the doctoral program
"Occupational Diseases", professional direction 7.1 Medicine, enrolled with Order No. P-109-
60/01.02.2019.

Copies have been provided of the Protocol dated 12.04.2021 in implementation of Order No. R-109-
126/05.04.2021 of the Rector of the MU - Varna for a successfully passed exam to cover the doctoral
minimum in the specialty "Occupational diseases" and of the Minutes of 24.06.2021 in
implementation of Order No. R-100-30/19.01.2021, amended by Order No. R-100-296/18.05.2021,
for a successfully passed exam for a doctoral minimum in a foreign language.

Dr. Dimitrova-Kirilova has the mandatory registered profiles in ORCID with ORCID ID:
<https://orcid.org/0000-0002-9833-2702> and in Google Scholar at the Internet address:
<https://scholar.google.bg/citations?hl=bg&user=7jEnvIsAAAAJ>, and also in another scientific
database – Researchgate with internet address: [http://www.researchgate.net/profile/Vladina-
Dimitrova](http://www.researchgate.net/profile/Vladina-Dimitrova) .

Information maps of the National Center for Information and Documentation (NACID) have been
created in Bulgarian and English (on electronic media - flash memory) in Word.

The doctoral student has attached 3 publications and 5 participations in scientific forums in Bulgaria
related to the topic of her dissertation work.

II. Brief biographical data and career development

Dr. Vladina Miroslavova Dimitrova-Kirilova was born in 1988 in the city of Dobrich, where she graduated her secondary education in 2007. In 2013, she graduated with honors from the MU - Varna as a "master" in the specialty "Medicine" (Diploma for higher education, educational qualification degree "Master", Ministry of Education and Science No. 047077, Reg. No. 002378/06.11.2013), and in 2021 she acquired a specialty in "Nervous diseases" (Certificate of specialty No. 4517/considered from 01.01.2021).

Dr. Dimitrova's professional career began in October 2013 as a doctor at the Emergency Medical Center - Varna, Dolni Chiflik branch, where she worked until May 2015. In June 2015, she was appointed as a specialist doctor in Second neurological clinic of UMBAL "St. Marina" EAD - Varna. Her academic career began in 2017, when, after winning a competition, she became a full-time assistant at the Department of Occupational Diseases, and in 2018, after successfully passing an exam, she was enrolled as a full-time doctoral student in the doctoral program "Occupational Diseases" at the Learning center "Occupational diseases", Department of "Optometry and occupational diseases", MU-Varna, in professional direction 7.1 Medicine.

Dr. Dimitrova-Kirilova teaches "Occupational Diseases" to Bulgarian-speaking and English-speaking medical students at the University of Varna, as well as "Nerve Diseases" to Kinesitherapy and Speech Therapy students.

She has participated in qualifying thematic courses for postgraduate training: Legal basis regulating the training of doctoral students, Methodology of scientific research work, Ethics of scientific research, Statistical methods for data processing and presentation, Communication techniques and presentation skills, etc.

Her main professional and scientific interests are in the field of cerebrovascular diseases, deep brain stimulation, electroencephalography and occupational nerve disorders.

Dr. Dimitrova-Kirilova is fluent in written and spoken English.

She has theoretical and practical knowledge in the field of neurology and occupational diseases, which she applies daily in her practice as a doctor and in her teaching activities.

She has good teamwork, communication and organizational skills.

She is a member of the Bulgarian Medical Union, the Bulgarian Society of Neurology and the European Stroke Organization.

III. Publications and scientific activity

Dr. Vladina Dimitrova-Kirilova is the author of 3 full-text scientific publications in Bulgarian periodicals on the problem of her dissertation work. She is the lead author of 2 and second author of 1 of the publications, which testifies to her leading role in conducting the research, preparing the publications and presenting the scientific results in the scientific articles. The publications are in 2019, 2022 and 2023 and reflect the topicality of the subject.

Also attached are 5 dissertation-related active participations in scientific forums, 4 of which in national congresses with international participation and 1 in a jubilee scientific conference, in 2 of which she is the lead author, in 2 she is the second author and in 1 - consecutive 4th author.

IV. Structure of the dissertation

The dissertation presented for review is structured according to the accepted standards of a dissertation for obtaining the scientific degree "doctor". It is developed in a volume of 122 standard pages, contains 21 figures and 17 tables and includes: Table of contents (2 pages), Abbreviations (1 page), Introduction (1 page), logically structured Literature review (41 pages), Objective and tasks (1 p.), Working hypotheses (1/2 p.), Material and methods (2 p.), Own results (23 p.), Discussion (8 p.), Conclusions (1 p.), Contributions (1 p.), Bibliography (25 p.), Dissertation-related publications and participation in scientific forums (1 p.) and 5 appendices (7 p.).

The bibliographic reference contains 507 sources, of which 10 are in Cyrillic and 497 are in Latin, and about 60% of the cited sources are from the last decade.

V. Evaluation of the relevance of the dissertation work

The significance of the presented dissertation work is predetermined by the choice of the topic about asymptomatic strokes associated with occupational risk factors. Cerebrovascular diseases are socially significant, they are among the leading causes of disability and mortality, with increasing morbidity, prevalence and mortality worldwide and in our country. There is a 15-year reduction in the average age of stroke, which causes a negative impact on socio-economic development due to affecting people in their most active working age. Asymptomatic cerebrovascular disorders (aCVD) as initial manifestations of cerebrovascular disease (CVD) in individuals with existing vascular risk factors, but without clinically established neurological and retinal symptoms, have a significantly greater frequency than that of strokes. That is why studies on the role of not only generally accepted and proven vascular risk factors, but also on the impact of ecopathogenic and occupational hazards and factors of the working environment and the labour process are innovative, modern, up-to-date, important and necessary for successful prevention, early diagnosis and adequate control of asymptomatic cerebrovascular disorders as a significant problem in our country even now.

The significance and relevance of the problem developed in the dissertation work in scientific-theoretical and scientific-applied terms are indisputable.

VI. Literature review

The literature review impresses with the versatility and depth of the content analysis of the available literature from cited sources, mostly from the last decade. The presentation is characterized by logical consistency, thoroughness and sufficient concreteness in the presentation of the published foreign and Bulgarian experience on the problems of asymptomatic cerebrovascular disease (aCVD) and the associated risk and impaired quality of life of patients. A number of insufficiently clarified aspects and still controversial issues have been highlighted, mostly in terms of terminology; types of asymptomatic cerebrovascular disorders; etiological and contributing risk factors, including occupational hazards, stressors and factors of the work environment and labour process; pathogenetic mechanisms; the criteria for early diagnosis with modern methods for psychological, neurosonographic, imaging studies; the organization and prevention of occupational and work-related diseases. The factors of the labour process are comprehensively presented - professional stress, long working hours, working mode, physical and mental work, working posture; the factors of the working environment - chemical, atmospheric pollutants with dust particles, carbon monoxide gases, heavy metals, organic solvents, noise, vibrations, production microclimate.

The review presents the author as a well-informed, conscientious and thorough researcher with a critical mind. Dr. Dimitrova-Kirilova has managed to synthesize and summarize the vast amount of information, skilfully analyze the available specialized literary sources and present controversial and poorly clarified issues.

The literature review shows knowledge of the essence of the problem by the doctoral student, who creatively and critically evaluates the literature data. This allows her to formulate, in accordance with modern scientific research in this direction, a clear scientifically based goal of her work, namely: "To study the role of occupational factors in the development of asymptomatic ischemic disorders of cerebral circulation (aIDCC) in patients of working age" .

The tasks are comprehensive, thorough, specific and realistic, well defined and more than extensive, namely: to study the influence of demographic immutable factors - gender and age, on the frequency of aCVD; to investigate the frequency of modifiable risk factors (hypertension, diabetes mellitus, atrial fibrillation and flutter, heart failure) in patients with evidence of asymptomatic disorders and to make a risk assessment; to study the influence of occupational factors (work experience, position, working time regimes, length of the working day, type of work, location of the work process, work

posture, movements and norm) on the risk of asymptomatic lesions; to determine the relationship between occupational factors and concomitant risk factors for CVD in patients with evidence of magnetic resonance imaging (MRI) lesions; to investigate the influence of occupational stress levels on the risk of asymptomatic MRI lesions; to assess the impact of asymptomatic lesions on patients' cognitive abilities.

Five working hypotheses are substantiated and logically derived.

VII. Material and methods

The study included a sufficient number of patients - 151, divided into two groups according to precisely defined criteria: 41 patients with MRI data for aCVD and 110 patients without MRI data for aCVD, but with available risk factors for CVD - control group. All patients filled out a questionnaire containing accompanying diseases, harmful habits, free time, occupational route, current workplace, clinical picture. Their medical history, physical and neurological status were taken. Hematological and biochemical laboratory tests were performed. A head MRI was done, on the basis of which the contingent was divided into patients with and without neuroimaging evidence of aINMK. The following assessment scales are also applied: for stress - The Workplace Stress Scale (WSS); for cognitive impairment - Montreal Cognitive Assessment Test (MoCA); for severity of depression - Patient Health Questionnaire-9 (PHQ-9). Based on the received precisely selected comprehensive data, the following risk factors were derived and analyzed for all patients: immutable - age and gender; modifiable - hypertension, diabetes mellitus (DM), rhythm-conduction disorders, chronic heart failure (HF), ischemic heart disease (IHD), other heart diseases, dyslipidemia (DLP); behavioral - smoking and alcohol use; occupational - total length of service, position, weight, stress, working posture, work movements, work and rest regime, microclimate, mechanical fluctuations - vibrations and noise, dust, chemical hazards, stress.

The chosen research methodology exceeds the requirements for achieving the set goal and obtaining an adequate answer to the comprehensive tasks set in the dissertation work.

The statistical methods are adequate, up-to-date, chosen appropriately for a complete analysis and reliable evaluation of the data obtained.

VIII. Main results and contributions of the dissertation work

A lot of data have been obtained and successfully analyzed, which have been very well systematized and appropriately illustrated with sufficient tables, figures and appendices. The results correspond to the tasks set.

The investigated patients from both groups did not have depressive symptoms (PHQ-9).

The age of the patients from the control group was significantly lower than that of the patients with aCVD.

Among patients with aCVD, the percentage with primary education and practicing physical activity in their free time (sports, walks, housework) was significantly higher compared to controls.

Smokers and light alcohol drinkers were evenly distributed between the groups. The frequency of aCVD among those consuming hard alcohol was significantly higher.

No significant differences were found in serum lipid values between groups.

The frequency of aCVD was significantly higher in patients with hypertension ($p=0.004$), DM ($p<0.02$), CHD ($p<0.001$), HF ($p<0.02$) compared to the control group.

No significant differences were found between the groups regarding the occupation - manager, worker, self-employed, as well as regarding the work mode - night, day, shift, but there was a tendency for a greater frequency of aMSB among patients performing heavy and moderately heavy physical work ($p>0.05$), aCVD was significantly more common among those with more working hours/week ($p<0.001$), those working outdoors ($p<0.05$), with a forced work posture ($p<0.001$) and with uniform work movements ($p<0.05$).

The frequency of aCVD was significantly greater in patients with stress during more than 50% of the working day ($p=0.002$), especially pronounced at a high level of stress ($p<0.001$) according to WSS data. It was also greater in those exposed to organic solvents ($p=0.025$), gases ($p<0.005$), noise ($p<0.05$), vibrations ($p<0.05$) compared to the control group of patients without aCVD.

MRI data showed the highest percentage of patients with leukoaraiosis, significantly less with lacunar infarcts and atrophy of brain structures.

The degree of cognitive impairment on the Montreal Cognitive Assessment Test did not differ between groups.

Reliable correlations were established between the presence of MRI changes and hypertension ($p=0.001$), DM ($p=0.11$), HF ($p=0.004$), CHD ($p<0.001$), other heart diseases ($p<0.001$), as well as with a greater number of working hours per week ($r=0.298$, $p<0.001$), higher levels of work stress ($r=0.290$, $p<0.001$), longer work experience ($r=0.203$, $p=0.013$), occupation worker, not manager or freelancer ($r=0.201$, $p=0.013$), outdoor work ($r=0.175$, $p=0.032$), uniform work movements ($r=0.173$, $p=0.033$).

A proportional relationship was established between hypertension and: longer years of service ($r=0.308$, $p<0.001$); the greater number of working hours per week ($r=0.187$, $p=0.022$); working physical labour ($r=0.277$, $p<0.001$); those with forced work posture ($r=0.161$, $p=0.048$). Similar is the correlation between HF and: number of hours/week ($r=0.209$, $p=0.10$); the longer working day ($r=0.182$, $p=0.025$); outdoor work ($r=0.330$, $p<0.001$), as well as between CHD and patients with longer work experience ($r=0.163$, $p=0.046$).

A reliable weak ($r<0.3$) correlation was found between the presence of MRI changes and organic solvents, gases, noise and vibration ($p<0.05$).

Gas exposure was correlated with hypertension ($r=0.212$, $p=0.009$), DM ($r=0.294$, $p<0.001$), CF ($r=0.324$, $p<0.001$) and CHD ($r=0.252$, $p=0.002$). CF was also in reliable correlation with: organic solvents ($r=0.293$, $p<0.001$); pesticides ($r=0.284$, $p<0.001$); dust ($r=0.305$, $p<0.001$); vibrations ($r=0.162$, $p=0.047$).

For manifestation of MRI changes, the relative risk was highest and significant in: CHD carrier with OR=3.334 (CI 1.485, 7.488); hypertension with OR=1.910 (95% CI 1.275, 2.860); DM with OR=2.079 (CI 1.135, 3.810).

The relative risk for MRI manifestations was significantly greater in: work experience between 30 and 40 years with OR=6.4 (95% CI 1.748;23.438); followed by work experience between 20 and 30 years, OR=5.8 (95% CI 1.482;22.694); more working hours/week with the highest risk working more than 55 hours per week, OR=2.610 (95% CI 1.478, 4.611); stress for more than 50% of the working day, OR=0.456 (CI 1.478; 4.611).

In the discussion of the dissertation, Dr. Dimitrova-Kirilova compares her own results with those in contemporary specialized literary sources, emphasizing the novelties, differences and corroborating data established by the research in her dissertation.

In conclusion, the most important results of the study are summarized with an emphasis on the length of work experience in a worker position, outdoor work, exposure to organic solvents, gases, noise and vibration increasing the risk of asymptomatic cerebrovascular disorders, as well as reliable correlations between work factors (longer work experience, longer work week, hard physical work, flatulence) and hypertension. A long work experience, a working week exceeding 55 hours and a shift work regime are work factors that increase stress levels, and stress, in turn, causes an increased risk of asymptomatic MRI changes.

Nine clearly formulated conclusions have been synthesized, which accurately reflect the results of the conducted research and fully meet the set objective and tasks.

I accept the scientific-theoretical and scientific-practical contributions made by the doctoral student herself: for the first time in our country, an in-depth study was conducted on the influence of occupational factors on aIDCC in patients of working age; the relationship between levels of occupational stress and aCVD and the dependence between vascular risk factors and work factors

were thoroughly analyzed; the relationship between asymptomatic MRI lesions and memory disorders in patients of working age was studied.

Of a confirmatory nature are: the role of vascular risk factors such as age, hypertension, DM type 2 in increasing the risk of CVD; the increased risk of CVD with longer work experience and a longer working week (over 55 hours/week); the negative impact of high levels of occupational stress on the risk of MSDs; the positive relationship between long work experience, long working week, hard physical work and hypertension.

The dissertation student has clearly indicated the contributions of a scientific-theoretical and scientific-practical nature, which I accept. The working scientific hypotheses, defined tasks and summaries of the results obtained in the dissertation are original and authentic.

IX. The abstract is structured in accordance with the requirements, and its content fully corresponds to the dissertation work. It is illustrated with 10 tables, 16 figures and 5 appendices.

X. Recommendations

It is appropriate for Dr. Dimitrova-Kirilova to prepare parts of her multifaceted research for publication in international peer-reviewed scientific journals, referenced and indexed in world-renowned databases of scientific information.

XI. Conclusion


The dissertation work of Dr. Vladina Miroslavova Dimitrova-Kirilova is on the topic of association of asymptomatic cerebrovascular disorders with occupational hazards and factors of the work environment and the organization of work, which is relevant not only for our country, it is elaborated thoroughly and comprehensively and presents scientific and scientific applied results and conclusions with an original contribution to science and meets all the requirements of the Law on the Development of the Academic Staff of the Republic of Bulgaria (ZRASRB), the Regulations for the Implementation of ZRASRB and the Regulations of the University of Varna.

The dissertation shows that the doctoral student Dr. Vladina Miroslavova Dimitrova-Kirilova possesses in-depth theoretical knowledge and professional qualities and skills for independent conducting of scientific research.

All of this gives me sufficient reason to confidently give my **positive assessment** of the peer-reviewed dissertation work and to suggest to the respected members of the respected scientific jury to give their **positive vote** for awarding Dr. Vladina Miroslavova Dimitrova-Kirilova an educational and scientific degree, doctor. in the field of higher education 7. "Healthcare and sports", professional direction 7.1. "Medicine", scientific specialty "Occupational diseases" at Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

03/01/2023

Prepared the review:


Prof. Dr. Zlatka Stoineva-Paskaleva, MD,
member of the Scientific Jury