REVIEW OF THE SCIENTIFIC CONSULTANT

on the doctoral dissertation by Aiym Kaiyrlykyzy
entitled "Risk Factors Associated with Alzheimer's Disease in Kazakhstan"
submitted for the degree of Doctor of Philosophy (PhD) in Public Health (8D10101).

The doctoral dissertation of Aiym Kaiyrlykyzy addresses an important and highly relevant public health problem—the identification and characterization of risk factors associated with Alzheimer's disease (AD) in the population of Kazakhstan. Given the rapid demographic aging observed both globally and nationally, the increasing burden of dementia represents a major challenge for healthcare systems, social services, patients, and their families. In this context, the presented work is timely, scientifically justified, and of considerable practical significance.

The dissertation is based on a multicenter case-control study conducted in two major regions of Kazakhstan and represents one of the most comprehensive investigations of Alzheimer's disease risk factors performed in the country to date. The study integrates epidemiological, clinical, genetic, biochemical, lifestyle, and psychosocial data, providing a broad and multidimensional assessment of factors potentially associated with AD development.

The author demonstrates a strong understanding of contemporary concepts in dementia epidemiology and successfully applies modern methodological approaches to investigate the complex interplay of biological, environmental, and social determinants of Alzheimer's disease. The literature review is comprehensive and reflects a thorough analysis of current international evidence regarding modifiable and non-modifiable risk factors for dementia.

A major strength of the dissertation is the establishment of a well-characterized cohort of patients with clinically diagnosed Alzheimer's disease and cognitively healthy controls. The study employs standardized diagnostic criteria, validated cognitive assessment tools, and harmonized procedures for data collection across study sites. The inclusion of genetic analyses, particularly assessment of APOE ε4 status, alongside evaluation of social, educational, and metabolic factors, significantly enhances the scientific value of the work.

The results obtained are of substantial scientific interest. The dissertation demonstrates that early-life factors, particularly illiteracy and rural birthplace, are strongly associated with Alzheimer's disease in the studied population. Furthermore, social isolation, depression, physical inactivity, and APOE ε4 carriage emerged as important correlates of disease status. The findings contribute valuable evidence supporting the cognitive reserve hypothesis and highlight the potential importance of lifelong educational opportunities and social engagement in healthy cognitive aging.

Particularly noteworthy is the author's identification of several findings that differ from conventional expectations, including the higher prevalence of certain cardiovascular conditions among controls than among AD cases. Rather than overlooking these observations, the candidate critically discusses possible explanations, including selection bias, survival bias, reverse causation, and healthcare utilization patterns. Such balanced interpretation demonstrates scientific maturity and an appropriate understanding of the strengths and limitations of observational epidemiological research.

The statistical analyses were conducted using appropriate methods. Both crude and multivariable logistic regression models were developed, allowing assessment of the independent contribution

of various risk factors. The hierarchical modeling strategy provides additional insight into the relative influence of demographic, genetic, metabolic, lifestyle, and psychosocial factors. The presentation of results is clear, logical, and generally well supported by the data.

The dissertation has several notable strengths:

• It represents one of the first comprehensive investigations of Alzheimer's disease risk factors conducted in Kazakhstan.

• It combines epidemiological, clinical, genetic, and psychosocial approaches within a single analytical framework.

• It provides region-specific evidence that may support future dementia prevention strategies and public health planning.

• It contributes novel data regarding literacy, social isolation, and early-life determinants of cognitive health in Central Asia.

At the same time, as with any observational case-control study, certain limitations should be acknowledged. The possibility of selection bias related to control recruitment, recall bias in the assessment of historical exposures, and reverse causation for some lifestyle and psychosocial variables cannot be entirely excluded. In addition, the cross-sectional nature of exposure assessment limits causal inference. However, these limitations are appropriately recognized by the author and do not diminish the overall scientific value of the work.

The dissertation is characterized by a clear structure, sound methodology, appropriate statistical analysis, and thoughtful interpretation of results. The conclusions are generally supported by the presented data and are consistent with the stated aims and objectives of the study.

The research findings have both scientific and practical significance and may contribute to the development of future strategies aimed at dementia prevention, early detection, and promotion of healthy aging in Kazakhstan.

In my opinion, the doctoral dissertation "Risk Factors Associated with Alzheimer's Disease in Kazakhstan" represents an independent and completed scientific work that meets the requirements established for doctoral dissertations in the field of Public Health. The author has demonstrated the ability to formulate relevant scientific questions, apply appropriate research methodology, analyze complex datasets, and draw scientifically justified conclusions.

Based on the above, I believe that Aiym Kaiyrlykyzy deserves to be awarded the degree of Doctor of Philosophy (PhD) in Public Health (8D10101).

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