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SUPERVISOR'S REVIEW

of 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 dissertation by Aiym Kaiyrlykyzy is a comprehensive, methodologically rigorous, and conceptually innovative study that identifies risk factors and emerging biomarkers of Alzheimer's disease at the population level. The work fully aligns with the current priorities of modern epidemiology of non-communicable diseases. In the context of rapid demographic aging and the steadily increasing burden of dementia worldwide, this research is of outstanding scientific and public health importance, particularly for the Republic of Kazakhstan and the broader Central Asian region.

The study is based on a well-designed analytical epidemiological case-control framework and is distinguished by its truly integrative, multidomain approach. The author successfully bridges multiple levels of analysis, from socio-demographic and behavioral determinants to clinical, metabolic, microbiome, and molecular-genetic factors. Such a comprehensive design reflects a deep understanding of contemporary paradigms, including life-course epidemiology, systems epidemiology, and precision public health. Notably, the candidate demonstrates an exceptional ability to synthesize complex, multidimensional datasets into coherent and meaningful conclusions.

The scientific novelty of the dissertation is substantial. For the first time, robust population-specific evidence on the structure and hierarchy of Alzheimer's disease risk factors has been generated for Kazakhstan. This region has long remained underrepresented in global epidemiological research. Particularly noteworthy is the identification of functional illiteracy as a powerful and consistent predictor of disease risk. This finding not only has profound implications for public health policy but also significantly extends existing theoretical frameworks regarding cognitive reserve, highlighting the importance of functional, rather than merely formal, education.

The work provides compelling evidence on the role of psychosocial determinants, including depression and social isolation, as independent and modifiable risk factors. The candidate's ability to incorporate these variables into advanced multivariate models and to demonstrate their substantial contribution to disease risk reflects a high level of analytical sophistication. These findings underscore the critical importance of integrating mental health into national dementia prevention strategies and represent a meaningful contribution to the field.

The genetic component of the study is executed at a high scientific level. The confirmation of the significant effect of the APOE ε4 allele, accompanied by clear demonstration of sex-specific and regional heterogeneity, provides important insights into gene–environment interactions. The pilot genome-wide association study (GWAS) conducted as part of this work deserves special recognition as one of the first efforts to establish a foundation for the genetic epidemiology of Alzheimer's disease in Central Asia. The candidate's competence in handling genetic data and interpreting complex interaction effects is particularly impressive.

A substantial contribution to nutritional epidemiology is the demonstrated limited applicability of Western dietary indices and the identification of alternative, population-relevant

dietary patterns associated with disease risk. This highlights the need to adapt dietary assessment tools to local cultures in epidemiological studies.

The study also convincingly demonstrates the role of metabolic disturbances, systemic inflammation, and microbiome alterations as potential components in the pathogenesis of Alzheimer's disease. The integration of these data into a unified analytical framework reflects the modern concept of the disease's multifactorial etiology.

Particular attention should be given to the identified regional (Astana and Almaty) and gender heterogeneity of risk factors, which is of fundamental importance for the development of targeted prevention programs and aligns with approaches of stratified and personalized prevention in epidemiology.

The practical significance of the work lies in establishing an evidence-based foundation for the development of national dementia prevention strategies tailored to specific risk groups, taking into account social, behavioral, and biological factors. The results can be utilized in public health program planning, as well as in the development of screening and preventive interventions.

It is important to emphasize the candidate's outstanding academic and research competencies. Aiym Kaiyrlykyzy has demonstrated exceptional independence, critical thinking, and scientific maturity. She possesses advanced skills in epidemiological analysis, including the construction and interpretation of complex multivariate models, assessment of interaction effects, and integration of heterogeneous datasets. Her ability to formulate scientifically meaningful hypotheses, apply appropriate methodological approaches, and present results in a clear and logically structured manner is exemplary.

The dissertation is written at a high academic standard, characterized by clarity, coherence, and internal consistency. The objectives, research questions, methodology, results, and conclusions are fully aligned, and the arguments are convincingly substantiated. The work reflects not only technical proficiency but also a deep conceptual understanding of the field.

In my professional opinion, Aiym Kaiyrlykyzy has demonstrated herself to be a highly talented, motivated, and promising researcher with significant potential for future scientific leadership. The level of this work clearly exceeds the standard expectations for a PhD dissertation and makes a meaningful contribution to international epidemiological science.

Overall, the dissertation constitutes a complete, original, and highly significant scientific contribution that fully meets the requirements for the award of the Doctor of Philosophy (PhD) degree in Public Health.

I strongly recommend that Aiym Kaiyrlykyzy be awarded the degree of Doctor of Philosophy (PhD) in Public Health.

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