ABSTRACT

of the dissertation for the degree of Doctor of Philosophy (PhD)
in the educational program 8D10101 – Public Health
by **Kaiyrykyzy Aiym**
on the topic **"Risk factors associated with Alzheimer's disease in Kazakhstan"**

General characteristics of the work. This dissertation conducts a comprehensive, multi-domain investigation of risk factors and emerging biomarkers of Alzheimer's disease (AD) in the Kazakhstani population. The study employs a case-control design with 177 patients with clinically diagnosed AD and 241 age-matched cognitively healthy controls from Astana and Almaty, the two largest cities in Kazakhstan. The research integrates sociodemographic, lifestyle, genetic, biochemical, epigenetic, immune/inflammatory, dietary, and microbiome approaches to characterize, for the first time, the multifactorial risk architecture of AD in a Central Asian population.

Relevance of the research topic. Alzheimer's disease is the leading cause of dementia worldwide, accounting for 60–70% of all dementia cases. According to the Global Burden of Disease Study 2021, the number of individuals living with dementia reached 57.4 million globally and is projected to exceed 152 million by 2050, with the most rapid increases expected in low- and middle-income countries. Kazakhstan, with a population of over 20 million and a steadily increasing life expectancy over the past two decades, faces an accelerating demographic transition. The proportion of the population aged 65 years and older is growing, yet the country lacks systematic epidemiological data on AD and its determinants.

The 2024 Lancet Commission on dementia prevention, intervention, and care identified 14 potentially modifiable risk factors that collectively account for approximately 45% of global dementia cases. However, these estimates are derived predominantly from populations in North America, Western Europe, and East Asia. Central Asian populations, which are characterized by admixed genetic ancestry, traditional meat- and dairy-heavy diets, distinctive patterns of education and literacy shaped by Soviet and post-Soviet transitions, and unique environmental exposures, have been virtually absent from the global dementia epidemiology literature. The few existing studies from the region are limited to small-scale cognitive screening surveys and do not address the full spectrum of genetic, metabolic, dietary, and microbiome-related risk factors.

Understanding the population-specific determinants of AD in Kazakhstan is essential for several reasons: first, to determine whether established risk factors from Western populations apply in a local context or whether novel, region-specific factors predominate; second, to provide an evidence base for national dementia prevention policy; and third, to contribute to the still-limited global evidence on AD risk factors in ethnically and geographically diverse populations. This dissertation addresses these needs by providing the first comprehensive, multi-domain characterization of AD risk factors in a Central Asian population.

The purpose and objectives of the study. The purpose of this study was to investigate risk factors and emerging biomarkers of Alzheimer's disease in the Kazakhstani population through a comprehensive, multi-domain case-control approach.

To achieve this goal, the following objectives were set:

1. To compare sociodemographic, psychosocial, clinical, and lifestyle factors of AD and healthy controls and to identify independent predictors of AD using hierarchical multivariable logistic regression modeling

2. To assess genetic factors associated with Alzheimer's disease in the Kazakh population, including apolipoprotein E genotype distribution and a pilot genome-wide association study.
3. To assess biochemical biomarkers and metabolic profiles associated with AD, including glucose metabolism, lipid profiles, and liver function parameters.
4. To evaluate blood cytokine profiles in patients with Alzheimer's disease and cognitively healthy controls.
5. To investigate adiponectin levels, promoter methylation of the adiponectin gene, and adiponectin receptor expression in relation to AD.
6. To evaluate dietary patterns and nutritional risk factors associated with Alzheimer's disease based on data from a food frequency questionnaire.
7. To characterize gut and oral microbiome composition in AD patients and controls and identify microbial taxa and metabolic pathways associated with cognitive status.

Object of study. Individuals aged 55 years and older with clinically diagnosed Alzheimer's disease and age-matched cognitively healthy controls residing in Astana and Almaty, Republic of Kazakhstan.

Subject of study. Sociodemographic, psychosocial, lifestyle, genetic, metabolic, immune/inflammatory, dietary, and microbiome-related risk factors as well as emerging molecular and biochemical biomarkers associated with Alzheimer's disease in the Kazakhstani population

Research methods: The study employed a case-control design with comprehensive multi-domain data collection. Cognitive assessment was performed using the Mini-Mental State Examination (MMSE) and the Clock Drawing Test (CDT). Sociodemographic and lifestyle data were collected via a structured questionnaire, with social integration assessed using the Berkman–Syme Social Network Index. Dietary intake was evaluated using a validated Food Frequency Questionnaire processed through the FETA nutrient analysis tool; dietary patterns were assessed using the MIND diet score and principal component analysis. PCR-based methods were used for APOE genotyping; a pilot genome-wide genotyping study was conducted on Illumina SNP arrays, with bioinformatic analysis using PLINK and BCFtools. Biochemical profiling included fasting glucose, insulin, lipid panel, liver function markers (ALT, AST, bilirubin), C-reactive protein, and adiponectin (ELISA). ADIPOQ promoter methylation was assessed by methylation-specific PCR. Adiponectin receptor (AdipoR1, AdipoR2) expression in peripheral blood mononuclear cells was measured by ELISA. Plasma concentrations of 41 cytokines, chemokines, and growth factors were quantified using a multiplex magnetic-bead immunoassay (Milliplex MAP Human Cytokine/Chemokine panel). Gut and oral microbiome composition was characterized by 16S rRNA gene sequencing with bioinformatic analysis using QIIME2, DESeq2, and LEfSe. Statistical analyses included descriptive statistics, Mann–Whitney U tests, chi-square tests, hierarchical multivariable logistic regression, principal component analysis with varimax rotation, and Spearman correlation analyses.

Scientific novelty of the dissertation. This dissertation provides several novel contributions to the field:

For the first time in Central Asia, a comprehensive multi-domain case-control study was conducted, simultaneously analyzing sociodemographic, psychosocial, genetic, biochemical, epigenetic, dietary, and microbiome risk factors for AD within a single cohort. Functional illiteracy, rather than formal educational attainment, was identified as the strongest independent predictor of AD, a finding that reframes how educational variables should be operationalized in

dementia research across low- and middle-income countries. Pronounced regional (Astana vs. Almaty) and sex-specific heterogeneity in the APOE ε4–AD association was demonstrated for the first time in a Central Asian population, with the ε4 allele conferring significant risk among women but not men, and in Astana but not Almaty. The first pilot genome-wide association study in Central Asia was conducted, identifying suggestive signals in biologically plausible candidate genes (ADARB2, MAST4, ADAM23, LINC01122). PCA-derived culturally specific dietary patterns substantially outperformed the Western-derived MIND diet score in discriminating AD cases from controls, underscoring the need for culturally adapted dietary assessment tools. Elevated serum adiponectin was identified as the most powerful biochemical discriminator of AD, and a novel association between increased ADIPOQ promoter methylation at CpG −74 nt and AD was described. A predominantly pro-inflammatory systemic cytokine signature was characterized for the first time in this population, with IL-1α and IL-17A remaining significantly elevated in AD after correction for multiple comparisons. The first characterization of both gut and oral microbiome composition in AD patients from Central Asia was performed, revealing population-specific microbial signatures and regional variation within the same ethnic group.

Theoretical and practical significance of the work. From a theoretical perspective, this dissertation advances understanding of the architecture of AD risk factors in a previously unstudied Central Asian population. The finding that functional illiteracy surpasses formal education as a predictor of AD contributes to refining the cognitive reserve hypothesis and has implications for how educational variables are conceptualized in global dementia epidemiology. The demonstration of region- and sex-specific heterogeneity in genetic associations highlights the importance of context-sensitive approaches to genetic epidemiology. The superiority of locally derived dietary patterns over Western indices underscores the limitations of applying culturally non-adapted assessment tools across diverse populations.

From a practical perspective, the findings provide a population-specific evidence base for the development of targeted dementia prevention strategies in Kazakhstan. The identification of illiteracy, depression, social isolation, physical inactivity, and dietary patterns as the leading modifiable risk factors directly informs the design of multi-domain intervention programs. The metabolic biomarker profile (adiponectin, glucose, ALT, and triglycerides) provides candidate markers for early risk stratification in clinical settings. The microbiome findings open new avenues for prevention through dietary modification and probiotic interventions. The results are directly relevant to the implementation of Kazakhstan's national health policy and to the WHO Global Action Plan on Dementia 2017–2025.

Key points of the dissertation to be defended:

1. Hierarchical logistic regression identified functional illiteracy, depression, social isolation, and rural birthplace as independent predictors of AD. Functional illiteracy was the strongest predictor, with an effect size substantially exceeding that reported for low formal education in Western cohorts, confirming that socio-educational disadvantage accumulated over the life course represents the dominant modifiable risk burden in this population.
2. APOE ε4 was confirmed as a significant genetic risk factor for AD, with a pronounced dose effect among ε4/ε4 homozygotes. The association showed marked regional and sex-specific heterogeneity, being significant in Astana and among women but absent in Almaty and among men, indicating that the population-level impact of this genetic variant is shaped by environmental and

demographic context. A pilot genome-wide association study identified suggestive novel loci, contributing some of the first genome-wide data from a Central Asian population and establishing a foundation for future genetic epidemiology work in the region.

3. A distinctive metabolic profile was identified in AD patients, characterized by hepatic and lipid metabolic dysregulation that diverges from the cardiovascular-predominant patterns typical of Western cohorts. The independence of these biochemical alterations from APOE ε4 genotype suggests that metabolic dysfunction represents a pathophysiological axis of public health relevance that operates separately from genetic predisposition and may be amenable to population-level intervention through cardiometabolic risk management programs.
4. Serum adiponectin emerged as the strongest single biochemical discriminator of AD status in this cohort. Epigenetic and transcriptional dysregulation of the adiponectin signalling pathway was observed alongside a positive correlation between adiponectin levels and cognitive performance within the AD group, suggesting a compensatory neuroprotective response. These findings position adiponectin as a candidate population biomarker for AD risk stratification, though longitudinal evidence is needed to establish its predictive utility in public health screening contexts.
5. Multiplex cytokine profiling identified a predominantly pro-inflammatory systemic immune signature in AD patients, with IL-1α and IL-17A retaining significance after correction for multiple comparisons. The pattern of innate and adaptive immune co-activation, mechanistically coherent with the observed adiponectin dysregulation, supports chronic low-grade systemic inflammation as a measurable and potentially modifiable feature of AD in this population. From a public health perspective, inflammatory burden may serve as a biological mediator linking known upstream risk exposures such as poor diet, physical inactivity, and social isolation to downstream neurodegeneration.
6. Dietary analysis using three complementary approaches demonstrated broad nutritional compromise in AD patients, with deficits concentrated in neuroprotective nutrients and beneficial fatty acids. The uniform failure of the MIND diet score to discriminate between groups across the entire cohort reflects a fundamental mismatch between Western-derived dietary assessment tools and the Central Asian food environment, with direct methodological implications for nutritional epidemiology in the region. PCA-derived dietary patterns were more contextually appropriate and more discriminative, identifying low vegetable intake and high red meat consumption as independently significant risk exposures that persisted after genetic adjustment.
7. Significant compositional alterations were identified in both the gut and oral microbiome compartments of AD patients, including depletion of beneficial commensal taxa and enrichment of pro-inflammatory organisms. Preliminary correlations between microbial metabolic pathways and clinical parameters suggest mechanistic links between dysbiosis and cognitive impairment. Taken together with the dietary findings, these results highlight the gut-brain axis as an

emerging and underexplored area for dementia prevention research in Central Asia, warranting dedicated prospective investigation.

Connection of work with research programs. The dissertation work was completed within the framework of grant funding from the Ministry of Science and Higher Education (AP14871338, AP09259730) and as part of the Nazarbayev University Collaborative Research Program grant (No. 091019CRP2112).

Approval of work. The main results of the dissertation were presented and discussed at the following international conferences: Alzheimer's Association International Conference (AAIC) 2020 (online), AAIC 2021 (online), AAIC 2022 (online), AAIC 2023 (Amsterdam, Netherlands), International Brain Research Organization World Congress (Granada, Spain), 36th Global Conference of Alzheimer's Disease International 2024 (Krakow, Poland), and AAIC 2025 (Toronto, Canada).

Publications. The main findings of the research on the dissertation topic were published in 16 scientific papers. It includes five articles in an international peer-reviewed journal listed in the Scopus and Web of Science databases, which have an impact factor; ten abstracts in journals that appear in the proceedings of international conferences; and one article in a journal recommended by the Committee for Control in the Sphere of Education and Science of the Ministry of Higher Education of the Republic of Kazakhstan.

Volume and structure of the dissertation. The dissertation is presented on 125 pages of typewritten text. It consists of a list of notations and abbreviations, an introduction, a literature review, materials and methods, results and discussion, conclusions, and a list of references comprising 244 entries. The work contains 21 tables and 21 figures.