

RISK FACTORS OF COGNITIVE DECLINE IN ELDERLY POPULATION

PhD Thesis Booklet

Zsolt Huszár MD

Translational Medicine Program

Mental Health Sciences Division Doctoral School

SEMMELWEIS UNIVERSITY



Supervisor: Gábor Csukly, MD, PhD

Official reviewers: Zsolt Datki, MSc, PhD, Tamás Kiss, MD, PhD

Head of the Complex Examination Committee: Professor

Gábor Varga, MD, DSc

Members of the Complex Examination Committee: Kinga

Farkas, MD, PhD, Professor Mitja Lainscak, MD, PhD,

Professor Tamás Tényi, MD, DSc, Péter Fehérvári, MSc, PhD

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1. INTRODUCTION

1.1. What is the topic?

Our research aims to contribute to the understanding of early identification of individuals at risk of developing dementia. To this end, we are investigating the association between changes in Alzheimer's-related proteins (amyloid-beta ($A\beta$) and phosphorylated tau (p-tau)) and dementia progression. It also examines known modifiable dementia risk factors (namely obesity, hypertension, hyperlipidaemia, smoking and depression) in relation to changes in $A\beta$ and p-tau biomarkers.

1.2. What is the problem to solve?

Although $A\beta$ and p-tau play a central role in the development of Alzheimer's disease (AD), and pathological $A\beta$ changes are highly prevalent in all cases of dementia, the specificity of abnormal $A\beta$ levels for AD and their central role in its pathomechanism have been questioned. Their use as a preventive screening target is still under debate. The extent to which the presence of these protein changes accelerates cognitive decline is still uncertain. In addition, the role of modifiable dementia risk factors in the context of these existing biomarker pathologies remains to be clarified.

1.3. What is the importance of the topic?

Dementia is a leading cause of years lived with disability and represents a significant long-term economic challenge to society. As the population ages, the consequences of dementia are anticipated to become even more severe. Given the current therapeutic limitations, early identification of at-risk individuals and the development of preventive strategies are crucial in dementia care.

1.4. What would be the impact of our research results?

By examining the correlation between A β and p-tau pathology and the rate of dementia progression, it may be possible to identify the population most susceptible to developing dementia even before cognitive symptoms appear. Furthermore, if the role of modifiable dementia risk factors is estimated according to A β and p-tau status, the development of prevention strategies can be further advanced.

2. OBJECTIVES

2.1. Study I - Risk of conversion to mild cognitive impairment or dementia among subjects with amyloid and tau pathology: a systematic review and meta-analysis

Pathological changes in A β and tau proteins associated with Alzheimer's disease (AD) can emerge decades before cognitive symptoms, but their impact on accelerating cognitive decline remains unclear. Predictive estimates for individuals with abnormal protein levels who are cognitively unimpaired (CU) or have mild cognitive impairment (MCI) vary widely. Meanwhile, in CU individuals over the age of 50, A β positivity ranges from 10% to 44%, and in MCI, from 27% to 71%. This study aims to evaluate the effect of A β alone and in combination with p-tau on the progression to MCI or dementia through a systematic review and meta-analysis. Understanding the prognostic value of these biomarkers could highlight their clinical potential, particularly given the current limitations of therapies for slowing disease progression. Therefore, early prevention, even before symptoms appear, is critical for effective disease management.

2.2. Study II - Association of modifiable risk factors with progression to dementia in relation to amyloid and tau pathology

Lifestyle and healthcare-related factors, such as hypertension, obesity, hyperlipidaemia, depression, and smoking, are known dementia risk factors. However, their role in clinical progression within biomarker-specific cognitive profiles is less understood. Our study examines the impact of the Cardiovascular Risk Factors, Aging, and

Incidence of Dementia (CAIDE) score, depression, and smoking on the progression to MCI or dementia among biomarker-homogeneous CU and MCI subgroups. Progression rates were analyzed based on participants' biomarker status ($A\beta$ and p-tau) and the presence of these risk factors, providing insight into their combined effects on cognitive decline.

3. METHODS

3.1. Study I.

Our systematic review and meta-analysis was registered in the PROSPERO database and adhered to the PRISMA 2020 guideline and the Cochrane Handbook. We included longitudinal studies using the NIA-AA 2018 recommended measurement techniques for $A\beta$ and p-tau to examine progression from CU and MCI to dementia. Data were extracted systematically from screened studies.

In the synthesis of the data, when overlapping studies used the same cohort, the largest data set was selected for data synthesis. Odds ratios (OR) and hazard ratios (HR) were calculated to assess progression to dementia. To evaluate the effects of age on progression meta-regression analyses were used. The risk of bias was assessed using the QUIPS tool, with two investigators independently evaluating study quality and a third resolving the disagreements. While publication bias was analyzed using Peter's regression test and adjusted funnel plots. Subgroup

analyses were adjusted for differences in biomarker measurements.

Statistical analyses, including forest plots and heterogeneity measures (I^2 , τ^2), were performed using R, with sensitivity testing to assess outliers and ensure robust results.

3.2. Study II

The data from a follow-up study of 1,045 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were analysed. Of these participants, 434 were CU and 611 were diagnosed with MCI. And a total of four years of follow-up were conducted. The age range of the participants was 55–90 years, individuals with severe disorders affecting cognition were excluded. Study participants were classified according to the criteria set out in the Clinical Dementia Rating (CDR) scale and cognitive assessment tests. The potential risk factors, including depression, smoking, hypertension, obesity, and hyperlipidaemia, were analysed as dichotomous variables. Hypertension, obesity, and hyperlipidaemia were combined into a CAIDE score, calculated using age, sex, education, and clinical metrics (obesity, hypertension, and hyperlipidemia), with a high-risk cut-off of six points. Depression was evaluated using medical records and the Neuropsychiatric Inventory. Smoking status was determined based on medical records. A β status was

quantified via PET or CSF ($A\beta$ 42/40 ratio, or $A\beta$ 42) assays, and p-tau by CSF p-tau181 levels or tau PET data. Standardised cut-off values were used.

A statistical analysis divided the CU and MCI groups into $A\beta$ and p-tau biomarker subgroups, designated as A+/A-, T+/T-, A+T+/A-T-. The potential associations between the CAIDE score, depression and smoking with the progression to MCI or dementia were investigated using Cox proportional hazard models, with adjustments made for age, sex, education, baseline MMSE score, baseline hippocampal volume and ApoE4 carrier status. The results were validated through the use of Kaplan-Meier survival analyses. Sensitivity analyses were conducted to test CAIDE as a continuous variable and alternative cut-offs, thereby ensuring the robustness of the findings.

4. RESULTS

4.1. Study I.

The systematic search identified 18,162 records, of which 12,605 were included after the removal of duplicates. 55 studies met the eligibility criteria, 40 unique studies were analysed due to overlapping study populations. Cohen's kappa was 0.91 for title-abstract selection and 0.86 for full-text selection. studies varied in exposure ($A\beta$ alone or with p-tau), detection techniques (PET-CT or CSF) and populations (CU, MCI or mixed

(CU and MCI analysed together)). As the mixed studies were all large studies ($n > 180$), we decided that their joint analysis with MCI was more valuable, as we could obtain results for a larger sample size. To test this decision, we performed subgroup analyses of the A β -positive MCI and mixed population studies. Both the MCI (OR 5.83 [3.80; 8.93]) and mixed (OR 4.64 [95% CI 1.16; 18.61]) subgroups showed significantly different ORs compared with the unexposed group, with no significant difference between the two subgroups ($p=0.55$).

Progression from CU to MCI or Dementia

Based on meta-analysis of data from a total of 4,217 subjects, the OR for progression to MCI or dementia among A β -positive (A+) CU subjects compared with A β -negative (A-) subjects was 5.79 [95% CI 2.88; 11.64], with high heterogeneity between studies ($I^2 = 73\%$ [55%; 84%]). Meta-regression analysis examining the relationship between mean age and OR values showed no significant association.

The combined effect of A β and p-tau was analysed in 2,228 CU subjects. Compared to A-T- cases, the OR was 13.46 [95% CI 3.69; 49.11] for A+T+ and 2.04 [95% CI 0.70; 5.97] for A+T-, showing an increase at trend level ($t=2.1$, $P=0.12$). Subgroup analysis showed a significantly higher OR for A+T+ compared to A+T- ($p < 0.01$). A-T+ was not analysed due to small sample size.

The HR analysis pooled data from 2,700 subjects, showed a 2.33 [95% CI 1.88; 2.88] HR for progression to MCI or dementia for the A+ group compared with the A-group.

Progression from MCI to Dementia

Meta-analysis of 3,576 subjects showed that the A+ group had a significantly increased risk of progression to dementia (OR 5.18 [95% CI 3.93; 6.81]). Meta-regression analysis of the pooled studies showed that the ORs decreased with increasing age ($p = 0.036$).

The combined association of p-tau and A β with dementia progression was analysed in 1,327 subjects, comparing A+T+, A+T- and A-T+ exposures with A-T-. The OR for A+T+ was 11.60 [95% CI 7.96; 16.91], significantly higher ($p < 0.001$) than A+T- (2.73 [95% CI 1.65; 4.52]), while A-T+ showed no significant association (OR: 1.47 [0.55; 3.92]).

Subgroup analysis comparing A β measurement techniques showed no significant difference between groups ($p = 0.88$). The ORs were 5.87 [2.83; 12.19] for CSF A β 42, 5.00 [3.31; 7.55] for CSF A β 42/40 ratio and 5.32 [2.53; 11.18] for amyloid PET. Furthermore, meta-regression analysis showed no association between different follow-up times and OR values.

HR analysis of 1,888 subjects indicated a progression HR of 3.16 [95% CI 2.07; 4.83] for A+ compare to A-.

The risk of bias was assessed separately for each of the analyses discussed. Most studies had low or moderate bias; three high-risk studies (n=197) were excluded.

4.2. Study II

Baseline characteristics of 434 CU and 611 MCI ADNI participants were analysed for associations between CAIDE score, smoking, depression and A β /p-tau status with progression to MCI or dementia. Significant differences were found in age, ApoE4 status, MMSE, hippocampal volume, and progression rates between the biomarker-positive and -negative groups.

In the CU group, no significant association was found between progression to MCI or dementia and higher CAIDE scores or depression in any of the biomarker subgroups (A β , or p-tau). The effect of smoking was not examined due to the small number of cases.

In the MCI group, higher CAIDE scores significantly increased the risk of progression in the A-, T+, A-T- and A+T+ subgroups, with trend-level associations in A+ and T-. Sensitivity analysis using CAIDE as a continuous variable confirmed the increased risk with higher scores in the A-, T+, A-T- and A+T+ subgroups.

Smokers in the MCI A+ subgroup had a significantly increased risk of progression and a trend-level association in T+. No association was observed in the A- or T- subgroups.

Depression significantly increased the risk of progression in the MCI T+ subgroup and showed a trend-level association in A+T+. No significant association was found in the A-, A+, T-, A-T- subgroups. The association between modifiable risk factors and dementia progression in the MCI biomarker subgroups is shown in **Table 1**.

Table 1 The effect of modifiable risk factors on progression from MCI to dementia

	MCI			
		aHR (95% CI)		aHR (95% CI)
Higher CAIDE score	A-	3.1 (1.43; 6.53)	A+	1.3 (0.98; 1.75)
	T-	1.6 (0.94; 2.83)	T+	1.7 (1.20; 2.27)
	A-T-	2.6 (1.06; 6.59)	A+T+	1.6 (1.15; 2.22)
Smoking	A-	1.3 (0.39; 4.23)	A+	1.6 (1.07; 2.34)
	T-	1.8 (0.89; 3.78)	T+	1.5 (0.99; 2.31)
	A-T-	n.e.	A+T+	n.e.
Depression	A-	1.0 (0.48; 2.19)	A+	1.2 (0.86; 1.57)
	T-	0.6 (0.30; 1.05)	T+	1.5 (1.06; 2.02)
	A-T-	0.6 (0.22; 1.49)	A+T+	1.3 (0.94; 1.84)

Bold numbers indicate a significant change

A- beta-amyloid negative, **A+** beta-amyloid positive, **aHR** adjusted Hazard Ratio, **CI** Confidence Interval, **MCI** Mild Cognitive Impairment, **n.e.** not estimated (due to small number of cases), **T-** phosphorylated tau negative, **T+** phosphorylated tau positive.

5. CONCLUSIONS

The systematic review of the literature indicates that measuring A β and p-tau levels enables the identification of individuals at markedly increased risk of cognitive decline, even before the onset of clinical symptoms. Similarly, in mild cognitive impairment, abnormal levels of these proteins are strong predictors of further progression. In particular, A β is a key indicator of progression, although its predictive value appears to decline slightly with age. Importantly, this prognostic advantage of A β measurement is consistently observed across techniques, including amyloid PET, CSF A β 42/40 ratio, and CSF A β 42 measurement.

As in other diseases, both primary and secondary prevention are key priorities in dementia care. The impact of potentially modifiable risk factors on the development of dementia is well established; extending this evidence, our cohort analysis indicates that cardiovascular risk factors, depression, and smoking continue to play a significant role in disease progression even in the presence of abnormal A β and p-tau levels. Consequently, efforts

should be directed towards reducing the harmful effects of these factors in at-risk populations. For clinical practice our findings highlight the potential for integrating biomarker-based risk stratification with assessment of modifiable risk factors. By identifying individuals according to A β and p-tau status, clinicians can better identify those at higher risk of dementia progression. Combining this approach with an assessment of modifiable risk factors could allow for a more personalised preventive care plan. This combined assessment could inform early interventions, particularly those targeting modifiable factors, to potentially delay or reduce cognitive decline in at-risk populations.

Further research into the interaction between AD biomarkers and modifiable risk factors is needed to refine preventive strategies. The different progression rates between biomarker-positive and biomarker-negative groups highlight the importance of considering biomarker status in dementia research. Our study, probably due to limited statistical power, did not find significant associations between modifiable risk factors and AD pathology in the CU population. Larger, long-term studies are needed to clarify these associations and to determine the temporal relationship between risk factor management and dementia progression. Inclusion of diverse populations with varying baseline health status in future research would improve generalisability and support tailored prevention strategies. Investigating how lifestyle

factors influence biomarker changes and progression could further elucidate modifiable pathways in dementia.

Prioritising early risk detection through biomarker screening and lifestyle assessment could have a significant impact on public health. While routine biomarker screening for individuals with CU remains uncertain, the development of anti-amyloid therapies is a key factor in this context. For people with MCI, routine biomarker screening already appears valuable. Policymakers could explore initiatives to improve access to biomarker testing for those at risk and to promote preventive interventions targeting vascular health, physical activity and mental well-being. Collaboration between healthcare systems, public health agencies and community organisations could promote community-based dementia prevention strategies that focus on improving quality of life and reducing future health care burdens to meet the growing challenges of an ageing population.

Future perspectives highlight the potential of combining biomarker-based interventions with lifestyle strategies to optimize dementia prevention. Advances in anti-amyloid and tau-targeted therapies may further enhance the relevance of biomarker screening, providing a holistic framework to reduce healthcare burdens and improve quality of life for at-risk populations.

6. BIBLIOGRAPHY

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