PhD Candidate	Vasiliki – Amaryllis Skyfa
PhD Thesis Title	"Integrating Multi-Biomarker Panels, Lifestyle Factors and Conventional Risk Factors to Develop Predictive Models for Cognitive Decline"
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Abstract	**Introduction:** Cognitive decline (CI) and dementia are critical public health issues that, in addition to affecting the health and well-being of older adults, also impact their family members and friends who serve as caregivers. Currently, there are no known effective methods for preventing or curing dementia, and the available approaches can only slow the progression of the disease and the escalation of its symptoms. Identifying biomarkers of CI that precede dementia may provide insights into the mechanisms of disease progression and reveal potential targets for developing predictive models and effective treatments. Since the metabolic and neurodegenerative changes that ultimately lead to dementia occur at least 10–20 years before the onset of clinical symptoms, research primarily focuses on the preclinical and prodromal stages. **Aim:** The aim of this study is to investigate whether lifestyle factors modify the associations between metabolic disorders and cognitive function in order to clarify the underlying biological processes and identify opportunities for effective strategies against cognitive decline. We also plan to develop a predictive tool for cognitive decline by combining cerebrospinal fluid (CSF) proteins and metabolites with lifestyle data and conventional risk factors, as well as to use artificial intelligence algorithms for improved risk assessment. **Methodology and Sample:** To achieve this study's objectives, we will take advantage of two existing Greek cohorts. The first one, named HELIAD, is a population-based, multidisciplinary, collaborative study, which is designed to estimate the prevalence and incidence of dementia, AD and MCI in 1.960 older adults (≥65 years

	old) selected through random sampling from the record of two Greek municipalities; Larisa and Marousi, and to investigate associations between lifestyle and cognitive dysfunction/age-related neuropsychiatric diseases. The second cohort, named ALBION, is a longitudinal ongoing study that aims to address several research questions concerning the preclinical and prodromal stage of AD and explore potential markers for early detection, prediction and primary prevention of dementia. The study's sample consists of 180 individuals aged 40 years or older who are even minimally concerned about their current cognitive status or are solely concerned about their future cognitive performance. **Thesis Contribution:** Through this research, we aim to identify novel combinations of metabolic and proteomic biomarkers of cognitive decline and impairment, whose detection will enable earlier and more accurate diagnosis of the disease and prediction of its progression. Additionally, we will examine the associations between the identified omics signatures and well-established biomarkers of Alzheimer's disease (AD), such as Aβ42, T-tau, and P-tau, enhancing our understanding of the biological mechanisms underlying the disease's pathological changes. The findings are also expected to shed light on how lifestyle and metabolism interact to influence cognitive decline, providing insights into the disease's pathogenesis and supporting personalized healthcare strategies. Finally, by leveraging advanced artificial intelligence techniques, we will develop a non-invasive predictive tool to assist healthcare professionals and patients in making informed decisions.
Keywords	Mild Cognitive Impairment, Dementia, Alzheimer's Disease, Biomarkers, Proteomics, Metabolomics, Lifestyle