Multi-MeMo

Shorter- and longer-term mechanisms of multimodal interventions to prevent dementia (Multi-MeMo)

Preventing dementia and Alzheimer disease (AD) is a global priority. Dementia pathogenesis is complex and multifactorial, with abnormalities in multiple cellular and molecular pathways that result from multifaceted interactions between several (non)modifiable risk factors. Currently available single-mode-of-action interventions are little effective to trigger a sustained clinically relevant benefit. However, this can be improved via combinations of interventions (i.e. multimodal approach) applied early in the disease process to address more targets simultaneously and trigger a stronger response from individual targets. Given the progressive nature of AD/dementia, some targets may be more effectively addressed in different stages of the disease continuum therefore timing and sustainability is another key mechanistic factor to be analysed.

Multi-MeMo aligns experimental molecular, cellular, and animal models with a very strong array of unique multi-national multimodal human trials which have already demonstrated multi-year cognitive and functional benefits across the entire continuum from at-risk to prodromal disease stages. This will allow comprehensive in-depth analysis of multiple relevant molecular and cellular mechanisms that cannot be clarified from human trials alone, as well as to rapidly validate the identified mechanisms for clinical relevance using successful long-term (up to 11 years) human trial data and samples. We hypothesise that multimodal interventions may exert their effects via a combination of synergistic mechanisms, possibly amyloid/Ab and tau-related, but likely also unrelated or only indirectly related to classical AD mechanisms (e.g. synaptic plasticity, inflammatory-immune responses, glucose/lipid homeostasis and bioenergetic metabolism, promotion of neurotrophic factors and insulin signalling, vascular function, stress hormone level alteration, and oxidative stress). Key questions we will address are e.g. if lifestyle intervention actually modifies the AD pathological process itself; or if responsiveness to intervention depends on baseline biomarker status and psychosocial factors, once AD has already started. We aim to identify individual targets and pathways, and their complex interaction. This will be done either for a given intervention or combination of interventions.

Specific aims are to: (1) Identify the mechanistic basis for multimodal preventive interventions with experimental molecular, cellular and animal models, including 2 species and 3 different neurodegeneration models, mirroring the human non-pharmacological trial design and interventions; (2) Validate the mechanistic basis for multimodal preventive interventions with our unique set of human randomised controlled trials (samples and clinical data); (3) Based on the mechanistic findings, to investigate the effectiveness window for targets addressed by the interventions studied, and (4) identify personalized predictors (markers) of short-term (<2 years) and sustainable (long-term, up to 11 years) intervention response. Moreover, (5) Investigate patient-centred psychological and social mechanisms in shorter- and longer-term multimodal preventive interventions, including patient and public involvement (PPI) activities throughout the project; and (6) Develop an enhanced, mechanistically driven multimodal intervention model, compatible for combinations of pharmacological and non-pharmacological modalities that enhance each other's effects. Project results will ultimately lead to timely, personalised interventions to effectively prevent or delay dementia onset.

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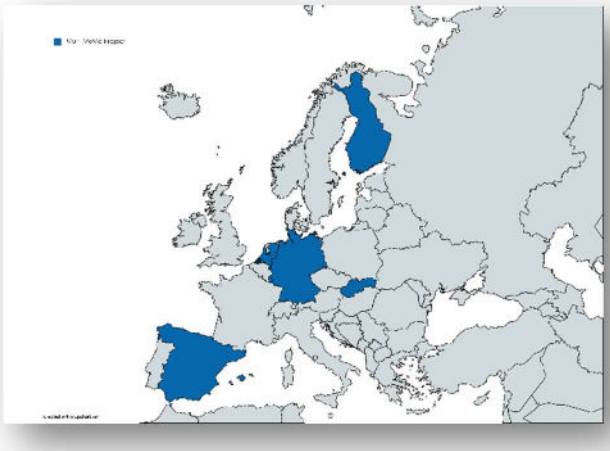

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