Risk factors and predictors of dementia and cognitive impairment

The greying of the world population has led to what was previously referred to as the “silent” epidemic of our century, namely dementia. The epidemic is primarily driven by an epidemiological transition, where prolonged longevity and declining fertility rates have led to increasing proportions of older people in the total population. Dementia and cognitive impairment are by far the leading causes of disability and in particularly the need for care among older people. Surprisingly there has been much less investment in dementia research, given its burden.

Consequently, Alzheimer’s disease, being the most prevalent dementia type, is the only cause of death among the top 10 killers in the United States that cannot be prevented, cured, or even delayed. The knowledge of risk and protective factors is therefore especially important for the development of prevention strategies, as prevention by risk factor intervention, is considered the key to a better control of the epidemic. Women outlive men on average, however they have poorer health status. Moreover, women have an elevated risk of dementia. This clearly justifies an increased focus on dementia specifically for women. In the development of new disease modifying interventions there has been a devastating low rate of success in the area of dementia. Resources have therefore been directed at identifying preclinical stages of dementia-related diseases as this is considered the optimal “window” for intervention. Identification of subjects with preclinical disease and subsequent high likelihood of progression are therefore an indisputable prerequisite for the success of future drugs. Here, biomarkers play a crucial role, as the pre-symptomatic diagnosis will rely on these. Hence, advances in biomarkers, especially non-invasive blood-based biomarkers, are required to ensure that the new drugs are tested on the right patients at the right time.

The aims of this thesis were: i) to identify risk factors for all cause and differential dementia diagnoses, ii) to identify risk factors associated with progression from normal cognition to dementia within the follow-up period and iii) to evaluate the possible utility of two novel serological biomarkers of truncated tau as predictors of incident dementia. This was investigated using data from the Prospective Epidemiological Risk Factor (PERF) study, a population-based prospective cohort study on 5,855 elderly Danish women initially enrolled between year 1999 and 2001 with a follow-up examination of 2,103 of the women in year 2013-2014.

We aimed at identifying risk factors for incident dementia and its subtypes in chapter 4. With special focus on a range of metabolic risk factors we investigated how these factors were related to cognitive dysfunction at the follow-up visit (chapter 5). These studies found that Body Mass Index (BMI) in the overweight range and physical activity were associated with lower risk of dementia (Chapter 4), while increasing age, history of depression, insulin resistance (using the homeostasis model assessment index) and elevated fasting plasma glucose increased the risk of dementia or cognitive dysfunction (chapter 4 or Chapter 5, respectively).

In chapter 6 we specifically aimed at assessing the risk of progression to dementia in subpopulation(s) of women with signs of mild cognitive deficits and further to investigate the cognitive courses from baseline to follow-up (reverse trajectory, stable, and progressive) including a risk-profile specifically associated with progression. We found that the degree of cognitive impairment at baseline (single versus multiple domains) was an important predictor of dementia and in subjects with subtle objective cognitive impairment physical inactivity, elevated total cholesterol and a history of depression were associated with progression to dementia or severe cognitive impairment.

In chapter 7, we evaluated the possible utility of two novel serological biomarkers of truncated tau as predictors of incident dementia in women. We found that high levels of Tau-A and Tau-C were associated with lower risk of dementia and Alzheimer’s disease. Tau-C gave a very modest increase in the area under the curve (AUC) in a 5-year prediction horizon compared to a reference model with age and education.

Finally, we summarised our results in a nomogram, a simple tool for prediction of dementia tailored for individual risk prediction. This illustrates the applicability of such findings for dementia risk screening (chapter 8). Overall, many of the identified risk factors are considered modifiable and therefore provide further evidence that prevention strategies could be a way to counteract the otherwise poor future prospects for dementias in the ageing population. Also, we show that the risk factors and blood-based tau biomarkers may be useful in screening and thereby early identification of individuals at-risk for dementia, one of the most persisting needs in dementia drug development.