Göteborg, 2021

Risk factors for dementia

Lifestyle, hormones, neurochemistry, and genetics

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3 (Akademicum), Göteborg, den 11 juni, klockan 13:00

av Jenna Najar

Fakultetsopponent: Dr. Mirjam Geerlings,
UMC Utrecht, Utrecht, Netherlands

Avhandlingen baseras på följande delarbeten

I. Najar J, Aakre A.J, Vassilaki M, Wetterberg H, Rydén L, Zettergren A, Skoog I, Jack C.R, Knopman D.S, Petersen R.C, Kern S, Mielke M.M. Sex differences in the relation between marital status and dementia risk in two population-based cohorts. *(submitted manuscript)*

II. Najar J, Östling S, Gudmundsson P, Sundh V, Johansson L, Kern S, Guo X, Hällström T, Skoog I. Cognitive and physical activity and dementia: A 44-year longitudinal population study of women. *Neurology.* 2019; 92(12): e1322–e1330.

III. Najar J, Östling S, Waern M, Zettergren A, Kern S, Wetterberg H, Hällström T, Skoog I. Reproductive period and dementia: A 44-year longitudinal population study of Swedish women. *Alzheimer's Dement*. 2020; 16(8): 1153–1163.

IV. Najar J, Hällström T, Zettergren A, Johansson L, Joas E, Mellqvist Fässberg M, Zetterberg H, Blennow K, Kern S, Skoog I. Reproductive period and preclinical cerebrospinal fluid markers for Alzheimer's disease. *(Accepted for publication in Menopause)*

V. Najar J, van der Lee S.J, Joas E, Wetterberg H, Hardy J, Guerreiro R, Bras J, Waern M, Kern S, Zetterberg H, Blennow K, Skoog I, Zettergren A. Polygenic risk scores for Alzheimer's disease are related to dementia risk in APOE ε4 negatives. *Alzheimer's Dement: Diagnosis, Assessment & Disease Monitoring.* 2021; 13(1): e12142.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Abstract

Objective: The aim of this thesis was to expand the understanding about the effects of lifestyle factors, indicators of endogenous estrogens, and genetic factors on the risk of dementia and cerebrospinal fluid (CSF) markers for Alzheimer's disease (AD).
Method: We used population-based samples from the Gothenburg H70 Birth Cohort Studies (H70-studies), the Prospective Population Study of Women (PPSW), and the Mayo Clinic Study of Aging (MCSA 70+ study). Information on exposures (marital status [married vs not married], cognitive and physical activity [active vs inactive], indicators of endogenous estrogen [age at menarche and menopause, reproductive period, number of pregnancies, and months of breastfeeding], and genetic factors [polygenic risk scores for AD (AD-PRSs), and APOE genotype]) was obtained through interviews and examinations performed by experienced health personnel. Dementia was diagnosed according to established criteria based on information from the examinations. CSF levels of Aβ42, Aβ40, P-tau, and T-tau were measured with immunochemical methods.
Results: In ***Project I*** (the H70-studies, n=913; the MCSA 70+ study, n=3,471), we found that married men had a reduced risk of dementia compared to unmarried men, while no association was observed in women. In ***Project II*** (PPSW and the H70-studies, n=784), we found that midlife cognitive and physical activity were independently associated with reduced risk of late-life dementia disorders. In ***Project III*** (PPSW and the H70-studies, n=1,364), we found that longer reproductive period and later age at menopause were associated with increased risk of dementia and AD. In ***Project IV*** (PPSW and the H70-studies, n=75), we found that longer reproductive period was associated with CSF biomarkers for AD (lower levels of Aβ42, lower ratio of Aβ42/Aβ40, and higher levels of P-tau). In ***Project V*** (the H70-studies, n=2,052), we found that AD-PRSs (including 39 and 57 genetic variants) and *APOE* genotype were associated with risk of dementia up to very old ages.
Conclusion: The results from this thesis add knowledge about risk factors for dementia, and add further knowledge on the protective effects of cognitive and physical activity on risk of dementia disorders.

Keywords: Dementia, Alzheimer's disease, marital status, leisure time activity, menopause, polygenic risk scores, *APOE* genotype.

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