Karolinska Institutet

**Department of Medical Epidemiology and Biostatistics**

# IF I ONLY HAD A BRAIN
# - Epidemiological Studies of Parkinson's Disease

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i hörsal Andreas Vesalius, Berzelius väg 3

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av

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# ABSTRACT

Parkinson's disease (PD) is an aging-related movement disorder caused by selective degeneration of dopaminergic neurons in the substantia nigra in the midbrain. Onset of PD symptoms, which include tremor, bradykinesia and rigidity (together referred to as parkinsonism), is most common after age 65. As the disease progresses, PD cases are at a substantially increased risk of cognitive impairment and dementia. There are two hypotheses that could explain comorbidity of parkinsonism and dementia; 1) PD-related pathological protein aggregation of α-synuclein and its downstream effects cause dementia-related pathology and subsequent cognitive symptoms, and 2) there is overlap in environmental and/or genetic risk factors for PD and dementia. One way to study if such an overlap of risk factors for two diseases exists is by investigating if the diseases coaggregate in families.

The overall aim of this thesis was to increase the understanding of the etiology of PD and of the causes of comorbidity of parkinsonism and dementia.

Study I evaluated the validity of the Swedish National Patient (NPR) and Cause of Death (CDR) registers as sources of PD diagnoses in epidemiological studies (such as study II and IV). As the gold standard against which register-based PD diagnoses were compared we used data from a population-based screening and subsequent clinical work-up of suspected PD cases among over 35,000 twins in 1998-2002. The best validity was achieved by using primary NPR diagnoses to define PD status with a positive predictive value and sensitivity of 83.0% and 50.0%, respectively.

Study II investigated the association between PD risk and 14 occupational exposures in a Swedish population-based sample of over 14,000 male twins who participated in questionnaires in the 1960's and 1970's and were then followed-up for PD in NPR and CDR for up to 43 years. The results showed an association between PD risk and inorganic dust exposure; hazard ratio (HR) 1.63 (95% confidence interval (CI): 1.09-2.44). There was no association with any other exposure, including occupational exposure to pesticides.

Study III investigated familial coaggregation of PD and dementia in a systematic review and meta-analysis that synthesized the results from 16 previously published studies of dementia risk associated with first-degree family history of PD, or PD risk associated with first-degree family history of dementia. Study IV investigated the same associations in a study population of over 2 million Swedish residents born 1932-1960 for whom PD and dementia status was ascertained using NPR and CDR. Results from both studies were similar and indicated increased risk of dementia associated with family history of PD: HR 1.18 (95% CI: 1.00-1.39) for all first-degree relatives (Study III), and HR 1.20 (95% CI: 1.02-1.41) for siblings (Study IV). However, the magnitude of the association was modest and thus overlap in familial risk factors (*i.e.*, hypothesis 2 above) likely does not fully explain the comorbidity of parkinsonism and dementia.