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PERSONALITY, STRESS AND RISK OF PARKINSON'S DISEASE

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**Karolinska
Institutet**

Stockholm 2020

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Published by Karolinska Institutet.

Printed by Eprint AB 2020

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ISBN 978-91-7831-804-9

Personality, stress and risk of Parkinson's disease
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Till Eyvind och Ivar, skoja bara! Ni ska få något roligare.

Till Mamma och Pappa

ABSTRACT

The objective of this thesis was to investigate the relationship of personality and stress with subsequent risk of Parkinson's disease (PD).

In **Study I**, we conducted a population-based cohort study using questionnaire data from the Swedish Twin Registry to explore whether the personality traits, neuroticism and introversion, were associated with later PD risk. We also explored the role of smoking as a mediator in the relationship between personality and PD. Both neuroticism and introversion were associated with an increased PD risk. Further, smoking was a significant mediator in the relationship between personality traits and PD that partly accounted for the effect of introversion, whereas it acted as a suppressor for the effect of neuroticism on PD risk.

In **Study II**, we wanted to further explore the main findings from study I, with the aim to examine whether the observed associations between neuroticism, smoking and PD may be causal. We conducted a two-sample Mendelian randomization study in a network framework, consisting of three main analyses: (I) causal effect of neuroticism on PD, (II) causal effect of neuroticism on smoking initiation, (III) causal effect of smoking initiation on PD. We found no support for a causal association between neuroticism and PD risk. On the other hand, the results indicated that the association between neuroticism and smoking initiation is causal and that there is a strong causal effect of smoking initiation on a reduced PD risk.

In **Study III**, we explored the association between occupational stress according to the job demands-control model and risk of PD. We conducted a population-based cohort study including individuals born in Sweden between 1920 and 1950 who had an occupation in 1980 or 1970. Levels of job demands and control were determined using a job-exposure matrix. High job demands was associated with increased PD risk in men, especially in men with high education, whereas high job control was associated with increased PD risk among low educated, more strongly in women. High-strain jobs (high demands and low control) were only associated with increased PD risk among men with high education, whereas active jobs (high demands and high control) were associated with increased PD risk among men with low education.

In **Study IV**, we conducted a population- and sibling-matched cohort study to investigate the association between stress-related disorders and neurodegenerative diseases. Stress-related disorders (i.e. post-traumatic stress disorder (PTSD), acute stress reaction, adjustment disorder, and other stress reactions) and neurodegenerative diseases (classified as primary and vascular neurodegenerative diseases, as well as Alzheimer's disease (AD), PD, and amyotrophic lateral sclerosis (ALS)) were identified through the national patient register. We found that stress-related disorders were associated with increased risk of neurodegenerative diseases in general. The association was stronger for vascular neurodegenerative diseases, which might indicate importance of a cerebrovascular pathway. A statistically significant association was found for AD alone, but not for PD or ALS, although the estimates pointed in the same direction.

LIST OF SCIENTIFIC PAPERS

- I. Sieurin J, Gustavsson P, Weibull CE, Feldman AL, Petzinger GM, Gatz M, Pedersen NL, Wirdefeldt K. Personality traits and the risk for Parkinson disease: a prospective study. *Eur J Epidemiol.* 2016;31(2):169-75.
- II. Sieurin J, Zhan Y, Pedersen NL, Wirdefeldt K, Neuroticism, smoking and the risk of Parkinson's disease: A network Mendelian randomization study
Manuscript
- III. Sieurin J, Andel R, Tillander A, Valdes EG, Pedersen NL, Wirdefeldt K. Occupational stress and risk for Parkinson's disease: A nationwide cohort study. *Mov Disord.* 2018;33(9):1456-64.
- IV. Song H*, Sieurin J*, Wirdefeldt K, Pedersen NL, Almqvist C, Larsson H, Valdimarsdóttir UA, Fang F. Association of Stress-Related Disorders With Subsequent Neurodegenerative Diseases. *JAMA Neurol.* 2020 Mar. PubMed PMID: 32150226. Epub 2020/03/09. eng.
*Equal contribution

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LIST OF ABBREVIATIONS

| | |
|-------|---|
| ACTH | Adrenocorticotrophic hormone |
| AD | Alzheimer's Disease |
| ALS | Amyotrophic lateral sclerosis |
| CDR | The Swedish Cause of Death Register |
| CI | Confidence interval |
| CRF | Corticotropin-releasing factor |
| FFM | Big five-factor model |
| GPC | Genetics of personality consortium |
| GWAS | Genome-wide association study |
| HPA | Hypothalamic-pituitary-adrenal |
| HR | Hazard Ratio |
| ICD | International classification of Diseases |
| IVW | Inverse variance weighted |
| LISA | The longitudinal integration database for health insurance and labor market studies |
| LPS | Lipopolysaccharide |
| MGR | The Muliti-Generation Register |
| MR | Mendelian Randomization |
| NPR | The Swedish National Patient Register |
| NSAID | Nonsteroidal anti-inflammatory drugs |
| OR | Odds ratio |
| PD | Parkinson's Disease |
| PTSD | Post-traumatic stress disorder |
| RBD | Rapid eye movement sleep behavior disorder |
| RCT | Randomized controlled trials |
| SALT | Screening Across the Lifespan Twin study |
| SD | Standard deviation |
| SNP | Single nucleotide polymorphism |
| STR | The Swedish Twin Register |
| TPR | The Total population Register |

1 INTRODUCTION – A HISTORICAL BACKGROUND

“It would seem that paralysis agitans affected mostly those persons whose lives had been devoted to hard work... The people who take their work to bed with them and who never come under the inhibiting influences of tobacco or alcohol are the kind that are most frequently affected. In this respect, the disease may be almost regarded as a badge of respectable endeavor.”¹

- C.D. Camp, 1913

Paralysis agitans, the disease mentioned in the quotation above, was first described by James Parkinson (1755-1824), a London surgeon, paleontologist, geologist and political activist. However, today he is most known for his work ‘An Essay on the Shaking Palsy’ from 1871 in which he provided detailed descriptions of cases suffering from a neurological syndrome defined by a combination of motor symptoms; ‘*Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured*’.²

Some decades later, Jean-Martin Charcot (1825-1893) continued Parkinson’s work, by providing more thorough and refined descriptions of the clinical aspects of the disease (for example he distinguished bradykinesia from weakness, and resting tremor from action tremor). He also suggested the disease should be renamed to Parkinson’s disease (PD).³ Charcot is generally considered to be one of the founders of modern neurology, but may be most remembered for his today controversial work on hysteria and hypnosis, which later influenced Sigmund Freud. At that time, the neuropathology of PD was not known, however, Charcot considered PD to be a “névrose” - at that time broadly defined as a disorder of the nervous system without a definitive lesion. He further hypothesized emotional stress as a precipitant to PD and described cases where PD was induced after exposure to traumatic events.⁴ The idea of emotional stress as a risk factor for PD was later supported by Pierre Janet (1859-1947), a contemporary of Freud, who described similar cases as Charcot where PD was induced after strong emotional reactions to traumatic events.⁵

The opening quotation above by Camp from 1913 is often referred to as the first mentioning of a common personality profile among people with PD.⁶⁻⁸ He further identified common features such as industriousness and morality among persons with PD.¹ A pre-morbid personality in PD, sometimes referred to as the parkinsonian personality, continued to be discussed during the first half of the 20th century. In these works, the parkinsonian personality was interpreted within a psychoanalytical framework and often described pejoratively as rigid, tense, neurotic, compulsive, conform, introspective and emotionally repressed.⁹⁻¹³ However, words like ambitious, hard-working, trustworthy, conscientious, thorough, altruistic, independent, law-abiding, responsible, honest and family-oriented also occurred.¹¹⁻¹³

The parkinsonian personality was believed to cause an inner imbalance or tension due to, on one side striving for independence and freedom, while on the other side having high moral standards, a will to follow social norms and being overly self-controlled. This was hypothesized to have a direct effect on PD pathogenesis through excessive inhibition of emotions, impulses and intrinsic drives leading to an ‘over-activation’ in the brain ultimately manifesting in motor symptoms.⁹⁻¹¹ Some authors also used the term ‘masked personality’ by which they meant people with PD hid hostile and aggressive impulses.^{10 11}

Similar ideas were expressed as late as until the 1970s.^{12 13} Persons with PD were described as rigid, inflexible and having a difficulty in coping with emotional stress.¹² Others considered persons with PD to share a common compulsive-neurotic character and a lack of self-assertiveness. Thus, being dependent on job-achievement to assert themselves and therefore as a group they tended to work hard also during spare time.¹³ It was concluded that emotional and behavioral patterns (e.g. inward aggression and inhibition of impulses) established during early childhood, as an important period for both emotional and motor system development, could lead to an increased susceptibility to PD.^{12 13} However, there were also early studies concluding that no pre-morbid parkinsonian personality exists.^{14 15} Although common personality features were identified among persons with PD, these were interpreted as an initial reaction to receiving the diagnosis¹⁵ or a consequence of living with the disease.¹⁴

The referred literature above represents the first notions of a potential association of personality and stress with PD risk and illustrates how this idea was formed and continued to be discussed for many decades. Much of this work was based on anecdotal observations and often interpreted within a theoretical framework that lacks scientific relevance in today’s view. The parkinsonian personality was also often described in stigmatizing ways, in which motor symptoms such as rigidity or hypomimia (reduced facial expression) were seen as physical representations of a rigid mind, a lack of affect and emotional inhibition. These pieces of work could easily be criticized for being speculative. However, this literature is interesting from a historical perspective. Despite the insufficient and defective scientific value of these early studies, the idea of an association between personality, stress and PD risk is still being discussed. More recently, controlled studies, using standardized measures have been performed but epidemiological evidence is still scarce.

With this introduction, I wanted to set the historical context of the overall theme of this thesis. To conclude, the hypothesis of an association between personality, stress and risk of PD has been smoldering for a very long time, but as epidemiology many times has taught us: where there is smoke, there may not always be a fire.

2 BACKGROUND

2.1 PARKINSON'S DISEASE

PD is the second most common neurodegenerative disorder and the most common movement disorder, estimated to affect about six million people worldwide (in 2016).¹⁶ In Sweden, about 22,000 individuals are affected.¹⁷ PD is an age-related disorder, with a median age of onset of 60-65 years. The prevalence is estimated at 0.3% in the general population of industrialized countries, 1% in those older than 60 years, rising to 3% in those older than 80 years.¹⁸ Apart from age, male sex is an important risk factor. Men are at about 50% higher risk than women.¹⁹ PD is a multifactorial and heterogeneous disease, with a long preclinical period and the underlying mechanisms causing the disease remain unclear.

2.1.1 Symptoms and diagnosis

Parkinson's disease is a movement disorder with three cardinal motor symptoms; 1) resting tremor (involuntary shaking (4-6 Hz) of a limb or other body part when at rest), 2) rigidity (stiffness of muscles and joints due to hypertonia, i.e. too much muscle tone), and 3) bradykinesia (slowness of voluntary movements). Postural instability is also common but does not always count as a cardinal symptom and usually occurs late in the disease course.

Diagnosis of PD is based on clinical criteria as there are no reliable biomarkers or specific neuroimaging techniques available for the clinical diagnosis of PD. Several sets of clinical diagnostic criteria for PD have been proposed.²⁰⁻²² Essentially, they are all based on the presence of cardinal motor symptoms and signs of PD, but differ slightly in which combination is required to fulfill the diagnosis criteria of PD. They also contain different exclusion and supportive criteria. Examples of exclusion criteria are secondary parkinsonism induced by identified causes (e.g. vascular- or drug-induced) or alternative diagnoses of atypical parkinsonism. In PD there is normally an asymmetrical onset of motor symptoms, which appear slowly and gradually progress. Further, response to antiparkinsonian drugs is usually included as a supportive criterion.

Although PD is primarily a movement disorder, non-motor symptoms are also common and may occur in both clinical and preclinical stages of PD. Non-motor symptoms common in PD include hyposmia, constipation, rapid eye movement sleep behavior disorder (RBD), excessive daytime sleepiness and psychiatric symptoms such as depression and anxiety, as shown in a recent meta-analysis.²³ This is an important aspect of the disease, as these symptoms significantly contribute to disability independent of the severity of motor symptoms²⁴ and adversely affect the quality of life.²⁵ Non-motor symptoms that arise in the preclinical stage of PD are commonly referred to as prodromal or pre-motor symptoms.

2.1.2 Pathology

Neuropathologically, PD is characterized by a selective degeneration of dopaminergic neurons in the substantia nigra pars compacta causing a dopamine deficiency in the striatum

which results in the typical motor symptoms. PD is also characterized by the presence of Lewy pathology (Lewy bodies and Lewy neurites), which are intraneuronal inclusions consisting of a large number of proteins in which ubiquitin and α -synuclein are main components.^{26 27} α -synuclein is a small soluble protein mainly located in the presynaptic nerve terminals with a propensity to mis-fold and self-aggregate, become insoluble and eventually leading to Lewy pathology. Although Lewy bodies are related to neuronal degeneration, their role in neurodegeneration is not well understood. Whereas there are indications that the intermediates in the aggregation process (e.g. oligomeric and proto-fibrillar forms of α -synuclein) are cytotoxic, Lewy body formation may represent a neuroprotective mechanism.^{27 28} Increasing evidence suggests that misfolded α -synuclein might spread between neurons in a prion-like manner.²⁹ Further, according to autopsy studies, hypotheses have been suggested (known as Braak's or the dual-hit hypothesis) that PD may start with Lewy pathology in the peripheral enteric nervous system and the olfactory bulb which is supposed to be initiated by an unknown pathogen (potentially a virus) entering through the gut or nasal cavity. The Lewy pathology is then supposed to spread in a specific pattern via the vagus nerve and olfactory tract toward/within the central nervous system following six stages.^{30 31} However, this is still controversial. Although nigrostriatal dopamine deficiency is the major hallmark of PD, alterations in cholinergic, serotonergic and noradrenergic neurotransmission have all been observed in PD and are related to psychiatric and other non-motor symptoms of the disease.³²

PD is a slowly progressing disorder in which the neurodegeneration starts many years before the first symptoms appear. It has been estimated that motor signs first appear when about 30-70% of the dopaminergic neurons are already lost.³³ Based on extrapolation of nigrostriatal loss from autopsy studies and dopamine imaging techniques, the preclinical period has commonly been estimated at 5-6 years.³⁴ Epidemiological studies also suggest a longer preclinical period defined by the presence of pre-motor symptoms.²³ Further, some of these pre-motor symptoms may be present at least two decades before clinical PD diagnosis, and the timing of these symptoms (e.g. constipation, RBD, hyposmia) have been linked to the spread of α -synuclein pathology in the early preclinical Braak stages.³⁴⁻³⁶

2.1.3 Etiology

The etiology of PD is largely unknown, but most likely multifactorial involving both genetic and environmental factors.^{37 38} The vast majority of PD cases appear sporadic, although there are rare monogenic forms of PD in which mutations in specific genes can be directly implicated and have been linked to autosomal dominant or recessive forms of PD.

Monogenic (mostly familial) forms of PD account for less than 5% of the overall number of PD cases.³⁹ However, genetic factors are important also for sporadic PD. A meta-analysis reported that individuals having a first-degree or any relative with PD have a more than three times higher risk of PD, although this may indicate importance of both genetics and shared environment.⁴⁰ In twin studies it is possible to distinguish between genetic and environmental effects, given that monozygotic twins share the whole genome while dizygotic twins share on

average half of the segregating genes. In a Swedish longitudinal twin study the (narrow-sense) heritability of PD was estimated at 34%.⁴¹ Furthermore, a recent genome-wide association study (GWAS) meta-analysis identified 90 independent single nucleotide polymorphisms (SNPs) across 78 genomic loci and reported a SNP-based heritability of 22%.⁴²

Still, environmental factors are believed to be most important for sporadic PD. However, much remains to be explored regarding identifying which these factors are and quantifying their effects. A previous report on consensus opinions by experts⁴³ and an extensive literature review⁴⁴ on the topic have been published, both of which evaluated the strength of evidence according to the terminology of the Institute of Medicine. Environmental factors associated with PD at an at least limited evidence level according to these papers are listed in Table 1. These conclusions are consistent with results from a more recent meta-analysis on various environmental exposures and PD risk.⁴⁰ In general, the evidence is limited and/or inconclusive for many environmental factors related to PD. In contrast, the negative association between smoking and PD is well established.^{40 45-49}

Table 1. Environmental factors associated with PD risk and evaluated levels of evidence according to a previous literature review⁴⁴ and a report based on expert consensus opinions.⁴³

| Evidence | Increased risk | Reduced risk |
|-----------------|--------------------------------------|---------------------------------------|
| Sufficient | | Smoking ^{43 44} |
| | | Coffee ^{43 44} |
| Limited | Pesticides ^{43 44} | Physical activity ^{43 44} |
| | Farming/agriculture ⁴³ | Dietary antioxidants ⁴⁴ |
| | Traumatic brain injury ⁴³ | High blood urate levels ⁴³ |
| | Dairy products ^{43 44} | NSAIDs* ⁴³ |
| | | Alcohol ⁴⁴ |

* Nonsteroidal anti-inflammatory drugs (NSAIDs)

Environmental factors associated with increased or decreased PD risk are (for simplicity) commonly referred to as risk or protective factors. However, it is important to keep in mind that most results are derived from observational studies and that association, therefore, does not infer causality. Observational studies are always subjected to confounding to some degree. Moreover, given that PD has a late onset and a long prodromal phase, one must consider the possibility of reverse causality. Differentiating pre-motor symptoms from risk or protective factors is not straightforward. There are for example hypotheses that the inverse association between smoking and PD represents prodromal changes in PD, e.g. a reduced response to nicotine making it easier to quit smoking in prodromal phases of PD.⁵⁰

Personality traits and stress have also been related to subsequent PD, which will be discussed further in the following sections of the introduction.

2.2 PERSONALITY TRAITS

Personality is what makes us unique and the reason why we can say we ‘know’ someone – there is something stable and predictable in how people tend to react and behave in a given situation. Personality has historically often been described in terms of fixed categories, i.e. personality types. Personality states, on the other hand, represent temporary behaviors or feelings, and state theories usually emphasize environmental influences on fluctuations in behavior. However, the dominating approach to study differences in personality is using traits. Personality traits can generally be described as ‘relatively enduring patterns of thoughts, feelings, and behaviors that distinguish individuals from one another’.⁵¹ As most trait models rely on factor analysis, the derived dimensions are also referred to as factors. Two of the most used factor models of personality in research are Eysenck’s two-factor model and the big five-factor model (FFM).^{52 53}

Eysenck assumed that differences in personality have a biological basis and favored the use of few uncorrelated factors. Based on factor analysis he derived two broad dimensions of personality - neuroticism and extraversion/introversion.⁵⁴ Later he added a third factor (psychoticism) which, however, was shown to be correlated with other factors. By linking results from experimental psychology to personality he aimed to identify the biological basis of personality. He related extraversion/introversion to cortical excitation and inhibition, hypothesizing that introverts react more quickly and generate stronger excitation at a given stimulus compared to extroverts, whereas inhibition in introverts is weaker and generated more slowly compared to extroverts. Neuroticism was related to the autonomic nervous system due to its relationship with emotional reactions.^{52 54} Although the theory behind this model has been criticized, the identified dimensions neuroticism and extraversion/introversion seem to emerge in most personality inventories.^{52 53}

In contrast, the FFM is not supposed to represent any specific underlying theory of personality. It is derived from analyses of natural-language words used to describe self and others (mostly adjectives), under the assumption that language would encode all traits that are of importance. The FFM was developed to represent as much of the variability in individuals’ personalities as possible by using few uncorrelated factors (or dimensions) and is the result of decades of work by different research groups. Although different models including different number of factors have been proposed over the years, many researchers now seem to agree on the FFM consisting of the five broad dimensions; neuroticism, extraversion, openness, agreeableness and conscientiousness.^{53 55-57} Further, this model seems to be universal as the same factor structure emerges in studies performed in different languages and cultures.⁵⁸

2.2.1 Neuroticism and Introversion

As mentioned, neuroticism and introversion (i.e. the inverse of extraversion) are two main dimensions of personality that emerge in most models of personality, including Eysenck’s and the FFM. Neuroticism (also referred to as emotional stability/instability) is defined by a proneness to experience negative emotions and thoughts such as anxiety, sadness and fear,

whereas introversion is defined by low levels of activity, assertiveness, excitement-seeking, sociability and positive emotions.

Studies have shown that these traits are relatively stable through adulthood and have a moderate genetic component.⁵⁹⁻⁶² In a meta-analysis, the heritability for both neuroticism and introversion was estimated at about 40%.⁶⁰ A large GWAS meta-analysis of neuroticism recently identified 136 independent loci indicating that neuroticism is highly polygenic.⁶¹

2.2.2 The ‘parkinsonian personality’?

As outlined in the introduction, the term ‘parkinsonian personality’ has repeatedly occurred in the literature. However, a distinct ‘parkinsonian personality’ type has never been clearly defined, mainly due to a lack of standardized measures of personality and methodological limitations in older studies.

More recently the hypothesis of an association between personality and PD has gained further support.⁶³⁻⁶⁵ Several observational studies have examined the association between personality traits and PD in a more standardized and controlled manner. Most studies have used personality assessment tools based on Cloninger’s temperament model including the three dimensions novelty-seeking, harm-avoidance and reward dependence.⁶⁶ Overall, PD has been associated with lower levels of novelty-seeking and higher levels of harm-avoidance.⁶³⁻⁶⁵ However, studies based on Cloninger’s model were all case-control studies and most of them did not intend to measure premorbid personality, and those who did assessed premorbid personality retrospectively. Harm-avoidance is highly correlated with both neuroticism and introversion, whereas novelty-seeking is inversely correlated with introversion.⁶⁷ However, few studies have examined these traits in relation to PD. Nevertheless, in two longitudinal studies with up to four decades of follow-up, it was shown that neuroticism, but not introversion, was associated with risk of PD.^{68 69}

Altogether, despite the varying models and measures of personality that have been studied in relation to PD, there seems to be some convergence between the traits associated with PD. Whether these traits are present before PD onset is less clear, as most studies were retrospective case-control studies and subjected to recall bias. Therefore, more prospective studies with long follow-up periods are needed. Still, given the long prodromal period of PD, reverse causation is difficult to rule out. Personality changes could represent pre-motor aspects of PD, rather than being a risk factor.

2.2.3 Neuroticism, health and PD

Neuroticism is the personality trait that most consistently has been associated with poorer health and three main general hypotheses have been proposed to explain this association.⁷⁰⁻⁷² The first hypothesis implies that neuroticism causes adverse health outcomes potentially through mediation by unhealthy behaviors such as smoking, high alcohol consumption and substance abuse. There is, for example, a well-documented positive association between neuroticism and smoking.^{73 74} However, there is also a well-documented association between

smoking and reduced PD risk.⁴⁵ Thus, what factors that would mediate the potential association between neuroticism and PD is less clear.

The second hypothesis is reverse causation, meaning that illness and poor health causes individuals to display more neuroticism.⁷² In the context of PD, which has a long prodromal period, premorbid personality changes could represent pre-motor aspects of PD, rather than being a risk factor. Interestingly, it has also been suggested that reverse causation explains the inverse association between smoking and PD, due to prodromal changes that may lead to an ease of quitting smoking or less likelihood to start smoking (e.g. less reward from nicotine stimulation).⁵⁰

Third, individuals with high neuroticism levels may perceive and report symptoms to a greater extent without having the actual disease to a greater extent.⁷² Although it is unlikely that neuroticism will be misclassified as PD, high neuroticism levels could potentially lead to an earlier diagnosis.

Alternatively, associations between neuroticism and various health outcomes could be explained by genetic confounding. High neuroticism has particularly been associated with mental health problems and psychiatric disorders such as depressive symptoms, lower subjective well-being, major depressive disorder, anxiety-disorders and schizophrenia, which in part is due to genetic correlation.⁶² There is no evidence for a genetic correlation between neuroticism and PD.⁷⁵

Within the definition of neuroticism lies a vulnerability to stress as an increased tendency to react with negative emotions to stressful events. Neuroticism has also been associated with an increased risk of experiencing stressful events and with passive and ineffective ways to cope with stress.^{71 76} Stress has been associated with various adverse health outcomes, and could potentially be a mediator between neuroticism and PD. However, the association between stress and PD remains to be elucidated.

2.3 STRESS

Stress is a frequently used term in mass media and everyday language which could have several different meanings; both positive and negative. Stress is a very broad concept that incorporates both the external stimuli or exposure, a so called “stressor” and the resultant “stress response” that may be both psychological (emotional, behavioral, cognitive) and physiological (e.g. changes in stress hormones and neurotransmitters). Further, multiple individual factors influence how stressors are perceived and coped with, such as early life experience, sex, personality, social support, prior psychiatric history and various sociodemographic variables.⁷⁷ Therefore, there are several models and definitions in use that emphasize different aspects of stress. Lazarus and Folkman (1984) provided a transactional model of stress integrating individual and environmental factors and defined psychological stress as follows: “Psychological stress is a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being”.⁷⁸

Another influential theory of stress is the “allostatic load theory” which explains how the stress response may have either beneficial or damaging effects on the body by using the concepts of “allostasis” and “allostatic load”.⁷⁹ It is vital for humans to maintain a stable internal environment (homeostasis) to function and survive. “Allostasis” refers to the adaptive biological processes that serve to maintain homeostasis when the external or internal environment is changing. It is believed that allostasis has evolved to increase the body’s ability to cope efficiently with any threats and challenges we are exposed to. On the other hand, “allostatic load” refers to situations where allostatic systems are overstimulated, usually as a consequence of repeated or prolonged stress (i.e. chronic stress) or dysregulated (failure to shut off or respond adequately), which could have damaging effects on many physiological systems.^{79 80}

The main physiological stress response involves activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis resulting in release of the stress hormones catecholamines (mainly adrenaline and noradrenaline) and corticoids (mainly cortisol), respectively. The sympathetic nervous system reacts rapidly in response to acute stress and regulates a range of essential functions including cardiovascular, respiratory, and endocrine function seen in the fight-or-flight response.⁸¹ The HPA axis response is characterized by hypothalamic release of corticotropin-releasing factor (CRF) and arginine vasopressin into blood vessels connecting the paraventricular nucleus of hypothalamus with the anterior pituitary gland, where it stimulates the secretion of adrenocorticotrophic hormone (ACTH). ACTH then binds to receptors in the adrenal cortex to stimulate the release of large quantities of cortisol, which exerts its effects on multiple tissues and involves multiple physiological processes (e.g. metabolic, immune and cardiovascular).⁸¹ During acute stress, these pathways stimulate target systems leading to e.g. increased oxygenation and nutrition in the brain, heart, and skeletal muscles, which may be beneficial to cope with potentially dangerous or threatening situations. However, chronic and repeated stress may lead to dysregulation of the

HPA axis and altered cortisol levels, which is associated with many adverse health effects, including mood disorders, cardiovascular, metabolic, and inflammatory disorders.⁸²

2.3.1 Measures of stress

There are many definitions of stress and consequently many different ways to measure stress. Perceived stress is perhaps most commonly used and is usually assessed by different rating scales. However, measures of stress can also be related to exposure to a stressor, or to symptoms or disorders related to the stress response. In this project two different indicators of stress were used, occupational stress defined by the job-control-demand model measured by a job-exposure matrix, and a diagnosis of a stress-related disorder. As outlined in the introduction of this thesis, stress was actually one of the first suggested risk factors for PD. Intriguingly, this early work also touched upon specific aspects of stress related to this thesis. A severe response to trauma exposure was actually one of the earliest suggested risk factors for PD and people with PD were often described as hard-working, with a generally unhealthy attitude towards performance and job-achievement.

2.3.2 Occupational stress

Work-related stress might be an important indicator of the overall exposure to stress during adulthood as most adults spend much of their time at work. Work stress may refer to the conditions that induce some kind of stress response, or the actual stress-response in itself.⁸³ Work conditions that may induce stress include both physical (workload, working hours), psychosocial (conflicts, bullying, harassment) and organizational factors (job insecurity, work-family conflict).

The job demand-control model^{84 85} is one of the most influential models of work stress, aiming to explain how work conditions may lead to stress response and adverse health consequences. The job-demand dimension reflects workload and time pressure, whereas the job-control dimension measures skill discretion and decision authority and reflects to what extent the worker can influence its own social work environment, task content, pace and schedule. According to the model, low control, high demands and especially the combination of these are hypothesized to cause job strain (a stress response) and predict adverse health outcomes.⁸⁶ According to this model, jobs can be classified as high strain jobs (high demands and low control), low strain jobs (low demands and high control), active jobs (high control and high demands), or passive jobs (low demands and low control). High strain jobs are supposed to entail the highest health risk whereas low strain jobs are supposed to be associated with the lowest risk. This model has shown to predict various health outcomes including cardiovascular disease, psychiatric disorders, and musculoskeletal problems,⁸⁷⁻⁹⁰ but has previously not been studied in relation to PD.

In the work of this thesis, we used a job-exposure matrix to assess levels of job demands and job control. Thus, occupational stress in this thesis refers to stress-levels applied to an individual based on his or her specific job title (i.e. where work stress levels in one individual

is measured by how individuals having the same specific job title on average scored job demands and control).

2.3.3 Stress-related disorders

Stress-related disorders are defined not only by their symptoms but also by the presence of at least one causative stressor. These diagnoses can be used as a measure of a severe stress response. A stressful life-event and the resultant psychological distress might lead to a diagnosis of adjustment disorder whereas a threatening traumatic event might lead to an immediate and transient acute stress reaction or chronic post-traumatic stress disorder (PTSD).⁹¹ These disorders are supposed to arise as a *direct* consequence of an acute and severe or chronic or repeated stressor, in contrast to situations where stress events may contribute to the presentation of a disorder but the etiological importance is less clear.

Stress-related disorders are common psychiatric disorders⁹² and have been associated with several long-term physiological health consequences, predominantly cardiovascular diseases.⁹²⁻⁹⁴ Regarding the association between stress-related disorders and neurodegenerative diseases, studies of male veterans⁹⁵⁻⁹⁸, as well as two recent cohort studies of the general population^{99 100}, have demonstrated that PTSD is associated with an increased risk of dementia. Recently, evidence was also provided for an association between all stress-related disorders and risk of dementia.¹⁰¹ However, less is known about the relationship between stress-related disorders and other neurodegenerative diseases. However, PTSD^{102 103} and adjustment disorder¹⁰⁴ were shown to be associated with an increased PD risk, whereas stress-related disorders were not found to be associated with ALS risk,¹⁰⁵ but this is clearly under explored.

2.3.4 Stress and Parkinson's disease

Chronic stress and a dysregulated stress response have been suggested in experimental studies to influence the pathogenesis of neurodegenerative diseases¹⁰⁶⁻¹⁰⁸ and have been suggested as a potential risk factor for PD.¹⁰⁹⁻¹¹¹

The hypothesis of stress as a risk factor for PD has received some support from experimental animal studies. For example, it has been found that exposure to chronic unpredictable stress in addition to 6-hydroxydopamine (6-OHDA) in a rat model of PD caused greater loss of dopamine neurons and greater motor deficits.¹¹² Another study on the 6-OHDA rat model of PD found that chronic restraint stress and corticosterone treatment could impair motor function and accelerate nigral neuronal loss independent of each other.¹¹³ Further, pre-treatment with corticosterone at doses chosen to mimic physiological stress caused an enhanced neuroinflammatory response to methamphetamine and increased dopaminergic neurotoxicity in mice.¹¹⁴ A study using the lipopolysaccharide (LPS) model of PD showed that exposure to chronic stress prior to LPS treatment resulted in a higher inflammatory response, associated with more severe degeneration of dopaminergic neurons and more characteristic features of PD.¹¹⁵ Further, pre-exposure of chronic restraint isolation to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice caused more severe motor

deficits, and a reduced ability to acquire normal motor function correlated with severe depletion of dopaminergic neurons in the SN.¹¹⁶

However, there are few epidemiological studies on stress and risk of PD, and the results have so far been inconclusive.^{104 117-119} For example, studies on the effect of major life events on PD risk have shown both negative,¹¹⁷ positive¹¹⁸ and no¹¹⁹ association with PD. ‘Vital exhaustion’¹¹⁹ (a state of excessive fatigue and irritability often attributed to stress) has been associated with increased PD risk. Further, as already mentioned, a few studies have associated stress-related disorders (adjustment disorder and PTSD) with increased PD risk.¹⁰²⁻¹⁰⁴ Chronic stress is related to psychiatric disorders, including depression and anxiety, which are common in PD.^{120 121} Depression has been shown to precede clinical PD diagnosis,^{122 123} whereas the relationship between anxiety and PD is less explored.

3 AIMS

The overall aim of this project is to explore the relationships between personality, stress and risk of PD. Within this framework the following specific objectives will be addressed:

- I. To explore the association of the personality traits neuroticism and introversion with subsequent risk of PD using cohort data from the Swedish twin registry (STR).
- II. To examine the causal association between neuroticism and PD and the role of smoking as a potential mediator in this relationship using a Mendelian randomization approach and genome-wide association (GWAS) summary statistics.
- III. To explore the association between occupational stress according to the job-demand-control model and risk of PD using population-based cohort data.
- IV. To investigate stress-related psychiatric disorders as a measure of a severe stress response in relation to subsequent risk of PD and other neurodegenerative disorders using population-based cohort data.

4 DATA SOURCES AND MEASUREMENTS

4.1 REGISTER BASED STUDIES

Study I, III, and IV were conducted based on record linkage of multiple Swedish national health and population registers, national censuses and the Swedish twin registry (STR). This was enabled through the unique personal identity number, which has been assigned to all Swedish residents since 1947.¹²⁴

4.1.1 National Register data

The national patient register (NPR) held by the National Board of Health and Welfare was started in 1964 and initially covered 6 of 26 counties in Sweden. The register gradually expanded and in 1976 it covered more than 50% of the in-patient care. Since 1987 it has complete nationwide coverage and contains information about discharge records from all hospitals in Sweden. Since 2001, the NPR also includes all outpatient specialist care, from both public and private caregivers. Information in the NPR includes one primary diagnosis and up to eight secondary diagnoses coded according to the International Classification of Diseases (ICD) and date of admission/visit and discharge.¹²⁵

The cause of death register (CDR) held by the National Board of Health and Welfare contains information from death records, including date and place of death, underlying cause of death and contributory causes coded according to the ICD. The CDR became digitalized in 1961 and is annually updated since then, but records between 1952 and 1960 were compiled retrospectively and the coverage of CDR is virtually complete since 1952.¹²⁶

The total population register (TPR) maintained by Statistics Sweden contains data on life events including birth, death, place of death, civil status, migration within Sweden, emigration and immigration with almost complete coverage of the Swedish population.¹²⁷ The TPR constitutes the basis of the nation-wide cohort studies Study III & IV.

The Swedish multi-generation register (MGR) is part of the TPR and holds information on (biological and adoptive) parents for index persons who are defined as those born 1932 and later and lived in Sweden at any point since 1961.¹²⁸ The MGR contains almost all Swedish residents and can therefore be used to represent the Swedish general population and constitutes the basis of the nation-wide sibling cohort in Study IV.

The longitudinal integration database for health insurance and labor market studies (LISA) held by Statistics Sweden is a register-based longitudinal database which includes socioeconomic data about the adult Swedish population (aged ≥ 16 years) from 1990 and onwards (since 2010 individuals aged ≥ 15 years). Among others, it includes information on education, income, occupation, and employment status.¹²⁹

4.1.2 Censuses

The population and housing censuses were performed between 1960 and 1990 by Statistics Sweden. Each decade census questionnaires were sent to all Swedish residents older than 16 years at the time of the census. Responding to these questionnaires was mandatory, thus the response rate was very high (>99% in 1970 and 1980).^{130 131} The questionnaires included detailed information on housing, civil status, occupation, education, income, and social class.

4.1.3 The Swedish Twin Registry

The Swedish Twin Registry (STR) was initiated in the 1950's with the aim to study adverse health effects of smoking. It is one of the largest and oldest population-based twin registries in the world and contains a collection of different birth cohorts. *Study I* was based on a birth cohort of same-sexed twins born 1926-1958 from the STR. These twins were contacted by mailed questionnaires in 1973 collecting data on demographics, medical history, lifestyle factors and personality among other things.^{132 133} In study I, we also used data from the Screening Across the Lifespan Twin study (SALT), including follow-up data on smoking for twins born 1886-1958 who were interviewed in 1998-2002.¹³³

4.1.4 Exposures

4.1.4.1 Neuroticism and introversion

In study I, information on personality was collected as part of the questionnaire sent out in 1973, when the respondents were between 15 and 48 years old. This questionnaire included a short form of the Eysenck Personality Inventory, comprising 18 items 9 each from the neuroticism and introversion scales (see appendix). To be included in the study, individuals had to respond to at least 6 items on either trait. For respondents with 1–3 items missing on a trait, a score (0–9) was imputed based on the distribution of the provided responses.

4.1.4.2 Occupational stress

Indicators of occupational stress were derived from a job exposure matrix (JEM), which was developed based on a random sample of 12,084 employed Swedish citizens aged 25 to 74 years who answered the Swedish Survey of Living Conditions collected by Statistics Sweden in 1977 and 1979. The response rate was 81% in 1977 and 89% in 1979. The JEM was developed by aggregating survey responses of individuals to arrive at occupationally representative scores of job control and job demands for 261 occupational categories. As work conditions differed markedly between men and women within the same occupation, two different JEMs were developed—one for each sex. The job-control scale was based on 12 items and measured job authority and skill discretion. The job-demand scale was based on two items on hectic time schedule and psychological demands. Both scales were multiplicatively transformed into continuous scales that could possibly range from 0 to 10.

The appropriate JEM was then used to assign scores to each individual in the study population based on their sex and the occupation reported in the 1980 or 1970 census. Occupations were coded according to the Nordic version of the 3-digit International Standard Classification of Occupation manual. Information was primarily taken from the 1980 census, but for those not having an occupation registered in the 1980 census, information about occupation was retrieved from the 1970 census (8% of the cohort).

4.1.4.3 Stress-related disorders

We defined stress-related disorders as any first outpatient or inpatient hospital visit with the main diagnosis of a stress-related disorder according to the Swedish revisions of the ICD-9 codes 308 and 309, or ICD-10 code F43 as recorded in the NPR.

We then divided stress-related disorders into PTSD, acute stress reaction, and adjustment disorder and other stress reactions. ICD used to identify PTSD, acute stress reaction, and adjustment disorder are shown in Table 2 which also provides an overview of how these are defined in ICD-10. Other stress reactions (ICD-9: 309X; ICD-10: F43.8 and F43.9) include unspecified reactions to stress and exhaustion disorder which is only present in the Swedish version of ICD-10. These were classified together with adjustment disorder in the analyses.

As PTSD may initially be preceded by other stress-related disorders, we considered all exposed individuals who received a PTSD diagnosis within 1 year after their first stress-related disorder diagnosis as individuals with PTSD.

4.1.4.4 Covariates

In the statistical analyses of study I, III and IV we adjusted for several covariates to control for confounding and tested for potential mediation and interaction effects. **In Study I**, we adjusted for sex, smoking status (ever vs. never smoker), education (mandatory vs. higher education) and total number of hospital visits. **In Study II**, we adjusted for sex, education (elementary schooling, upper secondary schooling or university/college) and lifetime chronic obstructive pulmonary disease (as a proxy for smoking). **In Study IV**, we adjusted for educational level (<9, 9-12, >12 years, or unknown), family income (top 20%, middle, lowest 20%, or unknown), marital status (single, married/cohabiting, or divorced/widow), history of psychiatric disorders (yes or no), and family history of neurodegenerative diseases (yes or no).

Table 2. Brief overview of stress-related disorders.

| | Acute stress reaction | PTSD | Adjustment disorder |
|-----------------------|--|---|--|
| ICD-10 | F43.0 | F43.1 | F43.2 |
| ICD-9 | 308, 309A | 309B | |
| Trigger | Exceptional physical or mental stress | Exceptionally threatening or catastrophic event, likely to cause distress in almost anyone | One or many identifiable stressors (e.g. life events) |
| Time aspect | Immediate and Transient | Delayed or protracted, chronic | Symptoms arise within 1 month. Do not persist more than 6 months after termination of the stressor or its consequences |
| Symptoms/signs | Confusion, disorientation, narrowing of attention, flight-reaction, signs of panic anxiety (tachycardia, sweating, flushing) | “Flashbacks” (repeated reliving of the trauma), nightmares, a sense of "numbness" and emotional blunting, detachment from other people, unresponsiveness to surroundings, anhedonia, avoidance of activities and situations reminiscent of the trauma | Significant distress, impairment in social functioning, a feeling of inability to cope, plan ahead, or continue in the present situation. Some degree of disability in the performance of daily routine. Emotional symptoms (depressed mood, anxiety and/or worry) |

4.1.5 Outcome ascertainment

4.1.5.1 Parkinson's disease

In study I and III, incident cases of PD were defined as having a primary diagnosis of PD in the NPR or PD as the underlying cause of death in the CDR. ICD codes for PD were the following: 342.00 (ICD-8), 332.A (ICD-9), G20 (ICD-10). The date of ascertainment was defined as the first date of any PD diagnosis in the NPR or date of death in the CDR for those cases only identified at death.

4.1.5.2 Neurodegenerative diseases

In study IV, we defined incident neurodegenerative diseases as the first outpatient or inpatient hospital visit with a diagnosis of a neurodegenerative disease with corresponding ICD-9 or ICD-10 codes, as recorded in the NPR (Table 3). We categorized neurodegenerative diseases according to their potential origin, including primary neurodegenerative diseases and neurodegenerative diseases with a primary vascular cause. We also separately studied AD, PD, and ALS. Individuals who received two neurodegenerative disease diagnoses during the follow-up contributed to the analyses of both outcomes.

Table 3 ICD codes used to identify neurodegenerative diseases

| Neurodegenerative diseases | | ICD-10 codes | ICD-9 codes |
|--------------------------------------|----------|--|--|
| Any neurodegenerative diseases | Primary | F00, F02.0, F02.3, G12.2, G20, G23.1, G23.2, G23.8, G23.9, G25.9, G30, G31.0, G31.1, G31.8A, G31.9 | 209A, 209B, 331A, 331B, 331C, 331X, 332A, 333A, 335C |
| | Vascular | F01, G21.4 | 290E |
| | Other | F03, F05.1 | 290W, 290X |
| Selected neurodegenerative diseases: | | | |
| Amyotrophic lateral sclerosis | | G12.2 | 355C |
| Alzheimer's disease | | F00, G30 | 290A*, 290B*, 331A |
| Parkinson's disease | | G20 | 332A |

* If found as the primary diagnosis

4.2 GWAS DATA AND MEASUREMENTS

For Study II we used summary-level data from published genome-wide association studies (GWAS) meta-analyses. GWAS are observational studies investigating the association between a set of genetic variants, usually single nucleotide polymorphisms (SNPs), and specific traits (e.g. neuroticism, smoking initiation and PD).

4.2.1 Neuroticism GWAS

We extracted summary statistics for genetic variants influencing neuroticism levels identified from a recent GWAS meta-analysis on neuroticism.⁸ This study reported 136 independent genome-wide significant loci ($p < 5 \times 10^{-8}$) in a sample of 449,484 individuals of European descent, comprised of data from the UK Biobank (UKB) (n=372,903),²² 23andMe, Inc. (n=59,206),²³ and Genetics of personality consortium (GPC) (n=17,375).²⁴ In the current study, we used summary statistics based on analyses excluding 23andMe data, as these summary statistics were publicly available and have no sample overlap in the two-sample MR analyses.

Information on neuroticism was obtained through digital questionnaires in all samples: 12 yes/no items of the Eysenck Personality Questionnaire-Revised Short form (EPQ-RS) for

UKB and 12 five-point Likert-scale items from the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI) for GPC.

4.2.2 Smoking GWAS

We used publicly available summary statistics from a recent GWAS meta-analysis of smoking behaviors to extract summary statistics of genetic variants influencing smoking initiation. This is a binary phenotype defined as having ever been a regular smoker or not. The study reported 378 independent genome-wide significant loci ($p < 5 \times 10^{-8}$) in a sample of 1,232,091 individuals of European descent.²⁵

4.2.3 PD GWAS

We extracted summary statistics of associations between identified SNPs and PD from a large GWAS meta-analysis. Datasets included in this meta-analysis were the same as in a large recent PD GWAS meta-analysis¹⁰ excluding proxy PD-case data from the UK Biobank (UKB) and a smaller sample from the System Genomics of Parkinson's Disease (SGPD) whose data were not shared publicly. The data included 23andMe PD case-control summary statistics, which were provided by 23andMe under an agreement with 23andMe that protects the privacy of the 23andMe participants. This resulted in GWAS summary statistics data for 36,752 PD cases and 929,806 controls of European ancestry.

PD was either defined by self-report or by clinical diagnosis. The study included 9,157 self-reported PD cases and 822, 855 controls from 23andMe and 27, 595 clinical diagnosis PD cases and 106, 951 controls from all other datasets included in the meta-analysis.

5 STUDY DESIGNS AND STATISTICAL METHODS

5.1 COHORT STUDIES

Cohort studies follow a group of people over a certain amount of time to compare the incidence, rate or time to event. It is a longitudinal design, in which exposed and unexposed are followed prospectively for the occurrence of an outcome, and each member of the cohort contributes with individual person-time during the follow-up period. Cohort members are censored when they no longer contribute to person-time at risk for the outcome. Using PD as an outcome, which is chronic, members are censored when they receive their first PD diagnosis, die from other causes or are lost to follow-up. Due to the prospective design, cohort studies are generally less prone to bias, specifically recall bias, compared to, for example, case-control studies.

5.1.1 Personality and PD – Twin cohort

In study I, we used a traditional cohort design to explore whether neuroticism and introversion were related to the risk of PD. The study population was comprised of a birth cohort of same-sexed twins from the STR, born in Sweden between 1926 and 1958, who responded to a mailed questionnaire in 1973 covering demographic, medical and lifestyle factors, as well as personality. Twins who were residing in Sweden and not previously diagnosed with PD (according to records from the NPR) at the start of follow-up (January 1st, 1974) were eligible to enter the study cohort (n = 36,409). In total, 436 persons were excluded due to migration during follow-up or because it was not possible to link their data. Among the remaining population, 6,121 twins did not provide sufficient questionnaire data on the personality assessment and were excluded. This resulted in a study population of 29,852 individuals.

Associations with PD were analyzed using time-to-event methods with attained age as the underlying time scale. Risk time, expressed in terms of person-years, was accumulated from the date of study entry (January 1st, 1974) until first recorded PD diagnosis, death or when follow-up ended (December 31st, 2010), whichever came first.

Neuroticism and introversion were treated both as continuous variables and as categorical variables divided into quartiles based on the distribution of the data. The quartile of lowest scores was used as the reference group. We also tested for a linear trend across quartiles.

5.1.2 Occupational stress and PD – Population-based cohort

In study II, we also used a traditional cohort design to explore associations between occupational stress and risk of PD. Study II included all individuals born in Sweden between 1920 and 1950, who had an occupation linkable to a job exposure matrix reported in the Population and Housing Census in 1980 or 1970 and were living in Sweden at the start of follow-up on January 1st 1987 (n = 2,578,971). Individuals with a recorded PD diagnosis

from the NPR (n = 1,089) and individuals who were not continuously living in Sweden prior to the start of follow-up (n = 33,134) were excluded. This resulted in a final study cohort of 2,544,748 individuals.

All study participants were followed from baseline, (January 1st, 1987) until a diagnosis of PD or censoring (date of death, emigration or end of follow-up on December 31, 2010), whichever came first. Associations with PD were analyzed using time-to-event methods with attained age as the underlying time scale.

Control and demands were analyzed as categorical variables divided into tertiles with the lowest tertile used as the reference group. The combination of demands and control was further analyzed as a categorical variable by combining high and low (median split) levels of demands and control into four job-strain groups; low-strain jobs (low demands, high control), passive jobs (low demands, low control), active jobs (high demands, high control), and high-strain jobs (high demands, low control).

5.1.3 Stress-related disorders and PD – Matched cohort design

In study IV, we examined the association between stress-related disorders and PD risk by performing a population-matched cohort study to compare the risk of neurodegenerative diseases between individuals with and without a diagnosis of a stress-related disorder. Matching by confounding variables is an efficient way to adjust for confounding by design. Matching can also occur naturally, such as in full-siblings who share on average 50% of their co-segregating alleles and many environmental factors, especially factors related to upbringing. Matching is therefore a way to make use of family-clustered data to control for all confounding variables that are shared between the family members. Thus, to assess the role of unknown and unmeasured confounders, we also analyzed a sibling cohort to compare the risk of neurodegenerative diseases between individuals with stress-related disorders and their unaffected full siblings.

We identified an exposed group of all Swedish-born individuals who received their first diagnosis of a stress-related disorder between January 1st, 1987, and December 31st, 2008 (n = 99,714). We defined stress-related disorders as any first outpatient or inpatient hospital visit with a main diagnosis of a stress-related disorder. We then divided stress-related disorders into PTSD, acute stress reaction, and adjustment disorder and other stress reactions (see section 4.1.4.3). Exposed persons with a history of neurodegenerative diseases (n = 199) or with conflicting (n = 13) or missing (n = 15) information were excluded from the analysis. To ensure a complete familial link from the MGR, we excluded individuals who were born before 1932 (n = 6,311). Because the incidence rates of neurodegenerative diseases were low among individuals aged 40 years or younger, we also excluded individuals who were too young at index date to reach age 40 during the follow-up period (n = 27,072), leaving 66,017 eligible individuals in the exposed group.

Population-Matched Cohort: Individuals with stress-related disorders were compared with the general population in a matched cohort design. For each exposed person, 10 individuals

free of stress-related disorders and neurodegenerative diseases at the diagnosis date of the index person were randomly selected from the TPR using the method of incidence density sampling (n = 660,170). Exposed and unexposed individuals were individually matched by birth year, sex, and county of birth.

Sibling Cohort: Individuals with stress-related disorders were also compared to their full-siblings in a sibling cohort. Through the MGR, we identified all clusters of full siblings that were discordant for stress-related disorders, including a total of 92,643 full siblings of the 47,591 individuals with stress-related disorders who were free of stress-related disorders and neurodegenerative diseases at the diagnosis date of the affected sibling.

The date of stress-related disorder diagnosis was used as the index date for the exposed individuals and their matched unexposed counterparts and unaffected full siblings. Because the incidence rates of the neurodegenerative diseases were low among individuals aged 40 years or younger and diagnostic delays were common for these diseases, we started the follow-up of the study participants from age 40 years or 5 years after the index date, whichever came later, until the first diagnosis of a neurodegenerative disease, death, emigration, or the end of follow-up (December 31st, 2013), whichever occurred first. This method also rendered a better control for potential surveillance bias, assuming a greater than expected surveillance of neurodegenerative diseases and other diseases compared with the diagnostic workup and treatment for stress-related disorders. For the matched unexposed individuals and unaffected full siblings, the follow-up was additionally censored at their first diagnosis of a stress-related disorder, if any, during the follow-up.

5.1.4 Cox proportional hazard regression

Cox proportional hazards regression, yielding hazard ratios (HR) with 95% confidence intervals (CI) was used to evaluate possible associations between exposures and outcome in Study I, III and IV. Cox regression estimates the hazards (i.e. incidence) across an underlying time scale, and the HR are ratios of event rates between different exposure groups. In study I and III, attained age was used as the underlying time scale, thus the HR were automatically adjusted for age. HRs were interpreted as measures of relative risk.

In study I, we also used a conditional Cox regression model to test for confounding by familial factors shared within twin pairs. Twin pair id was used as the stratum variable, thereby fixing an individual baseline hazard within each pair of twins while at the same time allowing it to vary between twin pairs.¹³⁴ An attenuation of any observed effect would suggest that familial factors contribute to the association, while persistence of the effect would suggest an independent effect of personality on PD incidence. Only complete twin pairs discordant for personality and PD diagnosis contributed to the within twin pair analyses.

In study IV, we used conditional Cox regression models, using time after the start of follow-up as the underlying time scale, stratifying analyses by matching identifiers (age, sex, and county of birth). In the sibling cohort of study IV, we used Cox regression models stratified

by family identifiers. (In study IV, age was controlled for by matching (population matched) or by adjusting for birth year (sibling cohort)).

One key assumption of Cox regression is that the HR are assumed to be constant over the follow-up time. The assumption of proportional hazards was assessed using the Therneau and Grambsch test of the Schoenfeld residuals.¹³⁵ No evidence of non-proportionality was found. A robust sandwich estimator of the standard errors was used to account for the dependence between observations in the twin data (for Study I).

5.1.5 Mediation analysis

In study I, we investigated the role of smoking as a mediator in the relationship between personality trait and PD by performing a mediation analysis according to the approach suggested by Lange et al.¹³⁶ This analysis decomposes the total effect of an exposure into estimates of the so-called natural direct and indirect effects using nested counterfactuals. The natural direct and indirect (i.e. mediated through smoking) effects were calculated adjusting for sex as a baseline confounder and using attained age as the underlying time scale. The 95% CIs were calculated using a bootstrap method with 1,000 replications.

5.2 MENDELIAN RANDOMIZATION DESIGN

Observational epidemiological studies inevitably suffer from potential biases, such as confounding and reverse causation, which limit the ability to determine causality. Randomized controlled trials (RCT) are considered the gold standard for causal inference. Randomizing exposures is however not always ethically (or economically) motivated or even practically feasible. Mendelian randomization (MR) design is an application of instrumental variable analysis used to infer causality from observational studies. In MR, the association between an exposure and outcome (e.g. neuroticism and PD) is estimated by using a third variable (e.g. SNPs) as an instrument for the exposure that is independent of the confounders between the exposure and outcome. The MR design makes use of the principle that genotypes are not generally susceptible to reverse causation and confounding due to their fixed nature. Further it makes use of Mendel's laws of segregation and independent assortment of alleles as a sort of natural randomized experiment.

The essential assumptions for MR inference are: (i) The genetic variant (e.g. SNP) has a causal effect on the exposure (e.g. neuroticism). (ii) The genetic variant (e.g. SNP) affects the outcome (e.g. PD) only through the potential effect on the exposure (e.g. neuroticism) (iii) The genetic variant and the outcome do not have common causes.

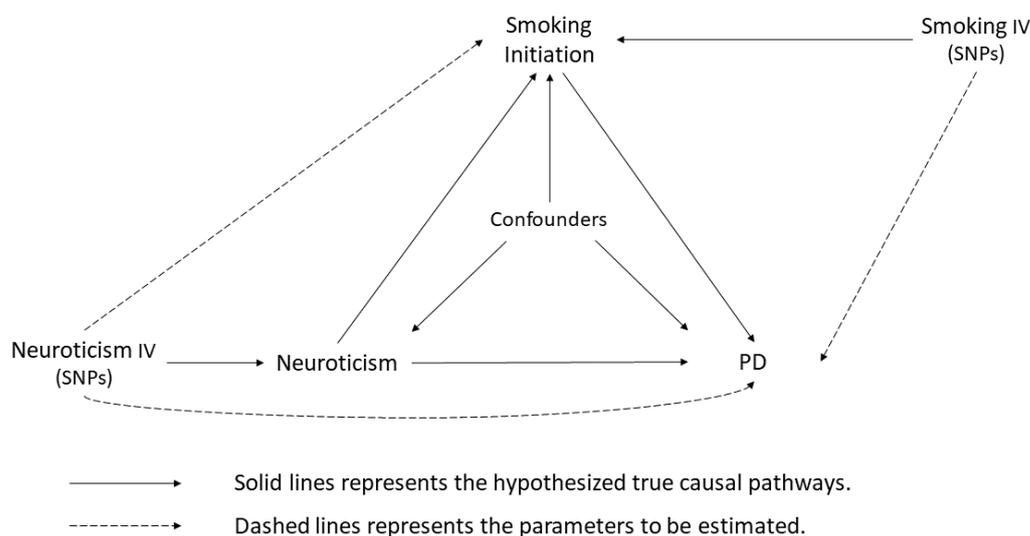
Given that the underlying assumptions hold, inference about causality can be made.

5.2.1 Two-sample MR

MR studies generally require very large sample sizes as the genetic variants usually explain a very small proportion of the variance in the exposure. Two-sample MR methods use data on gene-exposure and gene-outcome associations from different samples.¹³⁷ Thus, previously published genome-wide association studies (GWAS) of exposure and outcome can be combined to increase sample size and power.

In study II, we aimed to explore the causal association between neuroticism and PD and the role of smoking as a potential mediator in this relationship using a two-sample MR approach and GWAS summary statistics. Analyses were performed in a network framework consisting of three main analyses: (i) causal effect of neuroticism on PD using SNPs associated with neuroticism, (ii) causal effect of neuroticism on smoking initiation using SNPs associated with neuroticism, (iii) causal effect of smoking initiation on PD using SNPs associated with smoking initiation (Figure 5-1).

Figure 5-1 Network Mendelian randomization



IV = Instrumental Variable

5.2.2 Statistical methods

The main statistical method in Study II was the inverse variance weighted (IVW) method.¹³⁷ The IVW estimate of the causal effect ($\hat{\beta}_{IVW}$) combines the ratio estimate from multiple variants (SNPs) and can be seen as a weighted average of ratio estimates Y_k/X_k for each SNP.

$$\hat{\beta}_{IVW} = \frac{\sum_{k=1}^K X_k Y_k \sigma_{Yk}^{-2}}{\sum_{k=1}^K X_k^2 \sigma_{Yk}^{-2}} \quad se(\hat{\beta}_{IVW}) = \sqrt{\frac{1}{\sum_{k=1}^K x_k^2 \sigma_{Yk}^{-2}}}$$

| | |
|---------------|--|
| K | Number of SNPs |
| X_k | Effect of k^{th} SNP on X (neuroticism) |
| Y_k | Effect of k^{th} SNP on Y (PD) |
| σ_{Yk} | Standard error corresponding to Y_k |

6 MAIN RESULTS AND STUDY SUMMARIES

6.1 STUDY I – NEUROTICISM, INTROVERSION AND RISK OF PD

6.1.1 Objectives

In study I, we explored the effects of neuroticism and introversion on later risk of PD. Additionally, we investigated the mediating effect of smoking. Lastly, we explored the potential confounding effect of familial factors shared by twins.

6.1.2 Method

A population-based cohort study was conducted using questionnaire data from the Swedish Twin Registry for twins born 1926-1958 ($n = 29,852$). Personality traits were assessed in 1973 by a short form of Eysenck's Personality Inventory. The cohort was followed from 1974 to 2012 through the NPR and CDR for PD ascertainment. Cox proportional hazards regression with attained age as underlying timescale was used to estimate HRs for PD. Models were further adjusted for sex, smoking, education, and number of hospital visits. A mediation analysis was performed to further explore the role of smoking in the relationship between personality traits and PD. Confounding by familial factors was explored using a within twin pair analysis.

6.1.3 Main results

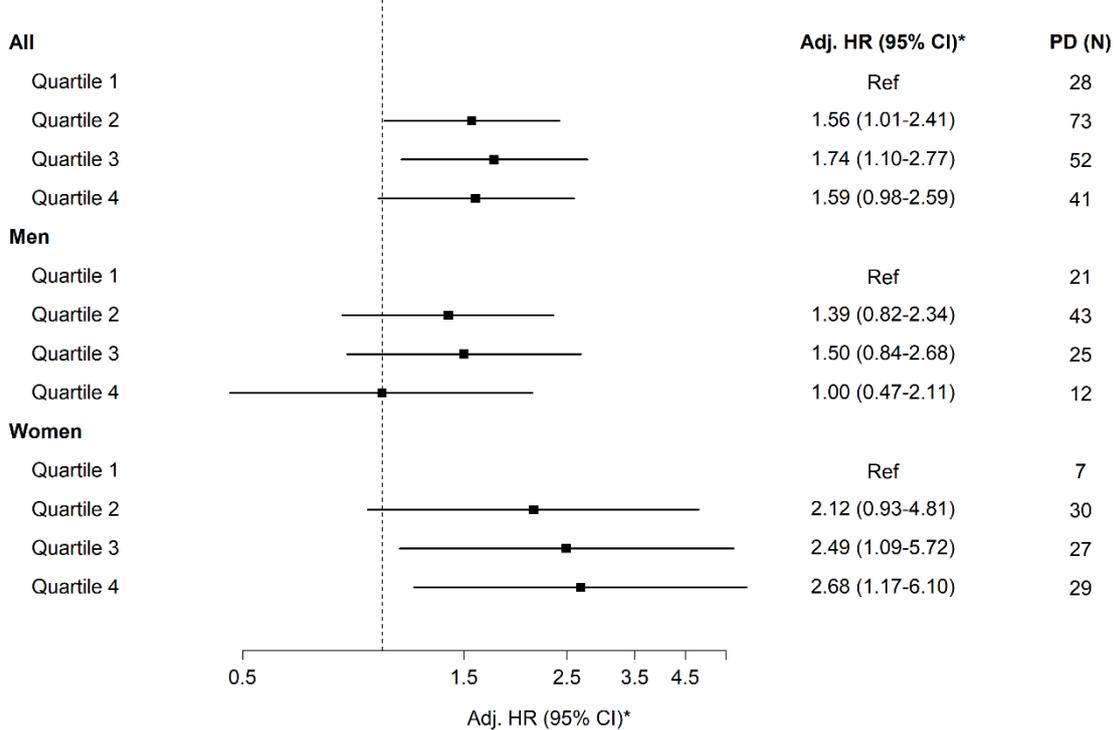
During a mean follow-up time of 36.8 years ($SD = 6.1$) we identified 197 incident PD cases. Mean age at personality assessment was 30.2 years ($SD = 9.2$) and mean age at PD ascertainment was 67.6 years ($SD = 8.9$).

Neuroticism was associated with an increased risk of PD. The relationship between neuroticism and PD seemed to be more pronounced in women, although the interaction term between sex and neuroticism was not significant (Figure 6-1). In women, there was also a significant linear relationship (HR: 1.09, 95%CI: 1.01-1.18).

There was a significant linear relationship between introversion and PD risk (HR: 1.07, 95%CI: 1.01-1.14) and a significant trend across quartiles ($p=0.04$) in the overall population. The HRs were higher in women than in men, but none were significant, including the interaction term ($p = 0.67$) (Figure 6-2).

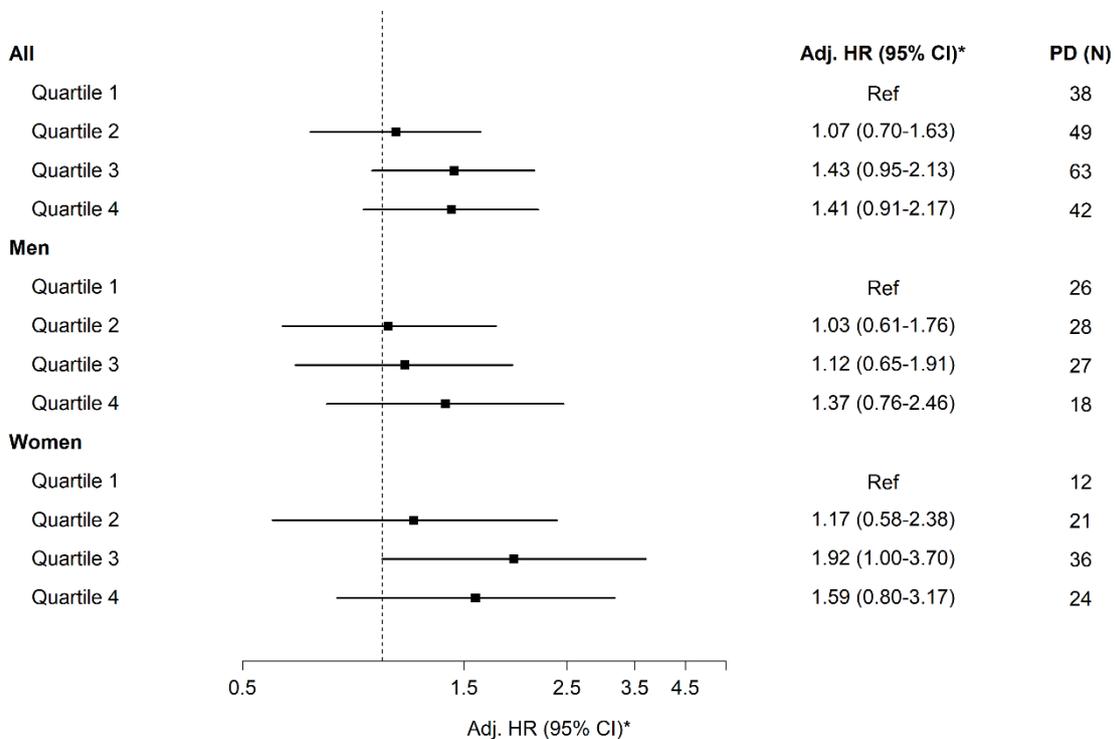
Results from the mediation analysis indicated that the indirect effect of neuroticism through smoking was protective for PD. Therefore, the direct effect of neuroticism was stronger than the total effect. Lastly, the HRs in the within twin pair analyses dropped compared to the main analyses, both for neuroticism and introversion, although the confidence intervals overlapped.

Figure 6-1 Hazard ratios and 95% confidence intervals for PD in relation to neuroticism.



* Attained age was used as the underlying timescale and models were further adjusted for sex and smoking status. Education and number of hospital visits (for all causes) were not statistical confounders and were not included in the final models.

Figure 6-2 Hazard ratios and 95% confidence intervals for PD in relation to introversion.



* Attained age was used as the underlying timescale and models were further adjusted for sex and smoking status. Education and number of hospital visits (for all causes) were not statistical confounders and were not included in the final models.

6.2 STUDY II – NEUROTICISM, SMOKING AND RISK OF PD

6.2.1 Objectives

In study II, we wanted to explore whether associations between neuroticism, smoking and PD risk are causal.

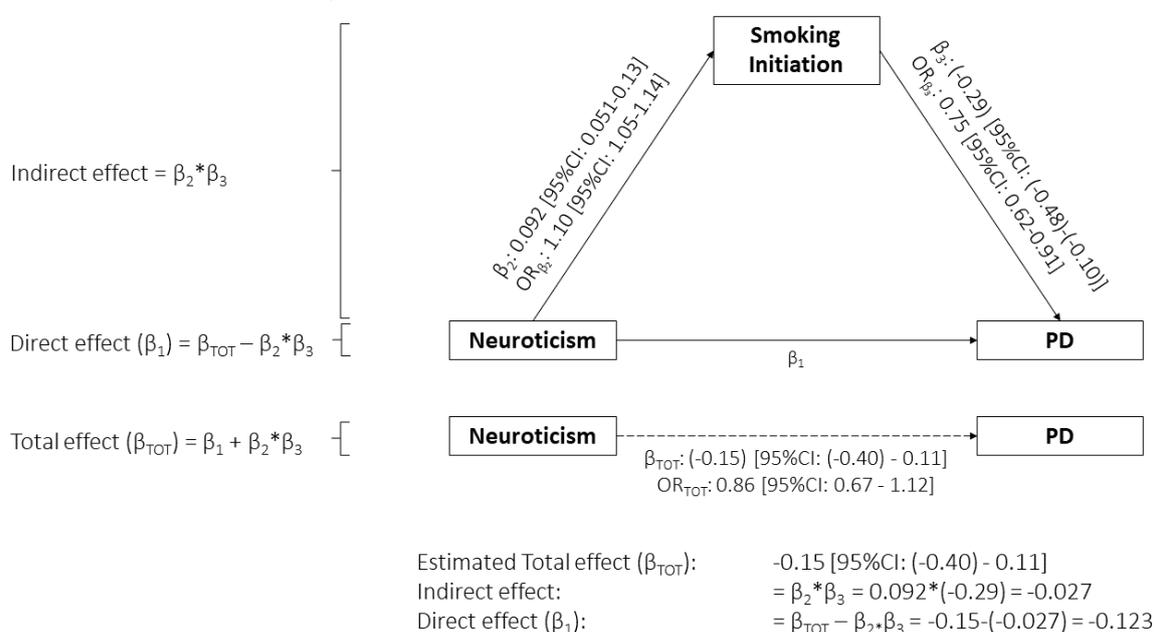
6.2.2 Method

Based on summary statistics from GWAS meta-analyses on large cohorts of European ancestry we applied a two-sample MR design in a network framework, consisting of three main analyses: (I) causal effect of neuroticism on PD, (II) causal effect of neuroticism on smoking initiation, (III) causal effect of smoking initiation on PD. The inverse variance weighting method was used as the main method to estimate the causal effects.

6.2.3 Main results

The main results of this study are presented in Figure 6-3. We found no evidence for a causal effect of neuroticism on PD risk. However, we found a significant effect of neuroticism on smoking initiation (OR: 1.10, 95% CI: 1.05 to 1.14). Further, our results provided evidence for a protective effect of smoking initiation on PD risk (OR: 0.75, 95% CI: 0.62 to 0.91). As there were significant associations between both neuroticism and increased smoking initiation and between smoking initiation and reduced PD risk, the total effect of neuroticism on PD risk may be an underestimation of the direct effect. However, since the observed total effect of neuroticism on PD was negative (non-significant), and the indirect effect was also weakly negative, the direct causal effect of neuroticism on PD risk may be even closer to unity.

Figure 6-3 Estimates of the total effect of neuroticism on PD risk and the mediating paths between neuroticism and smoking initiation and between smoking initiation and PD risk based on analyses using the IVW method. Based on estimated beta values, the indirect effect and direct effect of neuroticism on PD risk was calculated.



While we did not find a significant association between neuroticism and PD, one SNP, rs58879558 (located in *MAPT* region), was associated with both neuroticism and PD. This SNP was not included in the final analysis as it may violate the MR assumptions. However, it indicates presence of shared genetics between neuroticism and PD.

6.3 STUDY III – OCCUPATIONAL STRESS AND RISK OF PD

6.3.1 Objectives

In study III, we explored the association between occupational stress according to the job demands-control model and risk of PD.

6.3.2 Method

We conducted a population-based cohort study with 2,544,748 Swedes born 1920-1950 who had an occupation reported in the Population and Housing Censuses in 1980 or, if missing, in 1970. Job demands and control were measured using a job-exposure matrix. Incident PD cases were identified through Swedish national health registers between 1987 and 2010. Data were analyzed with Cox regression with age as the underlying time scale, adjusting for sex, education and chronic obstructive pulmonary disease as a proxy for smoking.

6.3.3 Main results

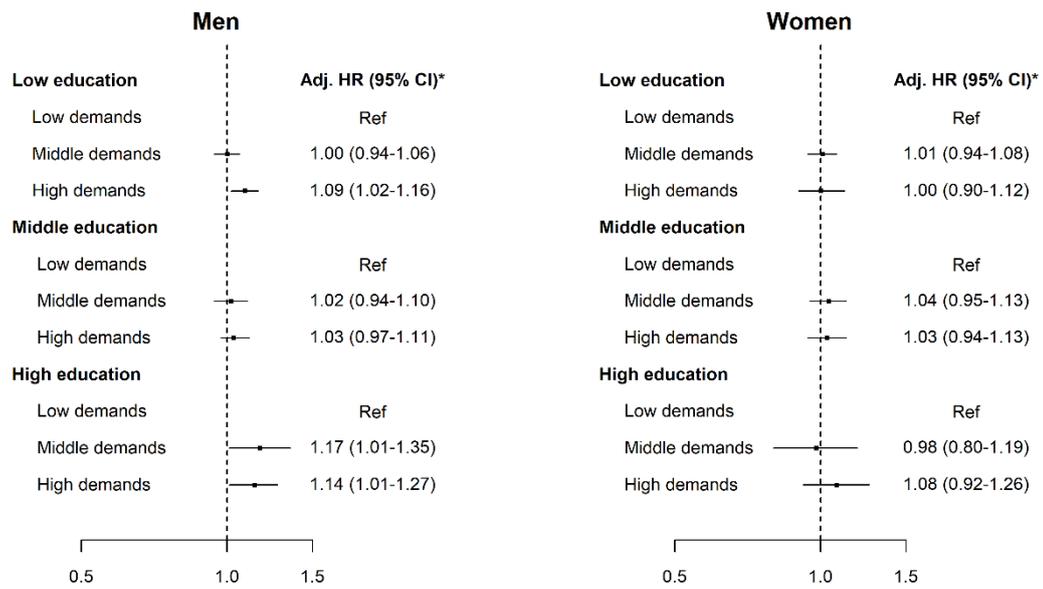
The study population consisted of 2,544,748 persons, who were followed on average for 21.3 years (SD 5.5). During follow-up 21,544 incident PD cases were identified. High levels of job demands and job control were associated with an increased risk of PD in the overall sample (Table 4).

Table 4. Hazard ratios and 95% confidence intervals for PD by job demands and job control in the overall population, adjusted for chronic obstructive pulmonary disease.

| Demands | HR | (95% CI) | Control | HR | (95% CI) |
|----------------|-------------|-----------------|----------------|-------------|-----------------|
| <i>Low</i> | <i>1.00</i> | <i>Ref.</i> | <i>Low</i> | <i>1.00</i> | <i>Ref.</i> |
| <i>Middle</i> | 0.97 | (0.94 - 1.01) | <i>Middle</i> | 0.98 | (0.95 - 1.02) |
| <i>High</i> | 1.19 | (1.15 - 1.23) | <i>High</i> | 1.29 | (1.25 - 1.33) |

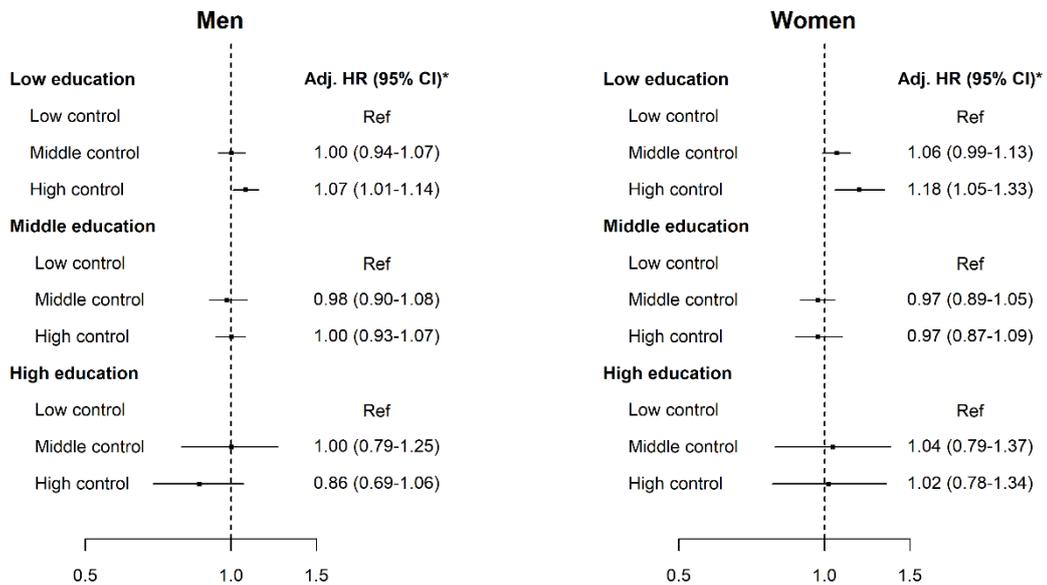
However, we found significant interactions with both sex and education. Results from models including three-way interaction terms with sex and education indicated that high demands are only associated with PD risk among men, especially men with high education, whereas there is no significant effect of job demands on PD risk among women (Figure 6-4). In contrast, high control was only associated with increased PD risk among the low educated, more pronounced in women than men (Figure 6-5).

Figure 6-4 Hazard ratios and 95% confidence intervals for PD by job demands



* Attained age was used as the underlying timescale, the model was further adjusted for chronic obstructive pulmonary disease and an interaction term with sex and education.

Figure 6-5 Hazard ratios and 95% confidence intervals for PD by job control



* Attained age was used as the underlying timescale, the model was further adjusted for chronic obstructive pulmonary disease and an interaction term with sex and education.

High strain jobs (combination of high demands and low control) were associated with PD risk in highly educated men only (HR: 1.25, 95%CI: 1.04-1.51), whereas active jobs (combinations of high demands and high control) were associated with increased PD risk in men with low education (HR: 1.20, 95%CI: 1.09-1.32). There were no associations between job strain groups and PD among women.

6.4 STUDY IV – STRESS-RELATED DISORDERS AND RISK OF NEURODEGENERATIVE DISEASES

6.4.1 Objectives

In study IV, we explored whether stress-related psychiatric disorders (PTSD, acute stress reaction, adjustment disorder, and other stress reactions) are associated with subsequent risk of neurodegenerative disorders, including PD.

6.4.2 Method

We conducted a population- and sibling-matched cohort study using data from nationwide health registers. Individuals who received their first diagnosis of a stress-related disorder between 1987 and 2008 were identified through the NPR. Individuals who had a history of neurodegenerative diseases, conflicting/missing information, no data on family links, or were younger than 40 at the end of follow-up were excluded. Neurodegenerative diseases were identified through the NPR and classified as primary or vascular. Alzheimer disease (AD), PD, and amyotrophic lateral sclerosis (ALS) were evaluated separately.

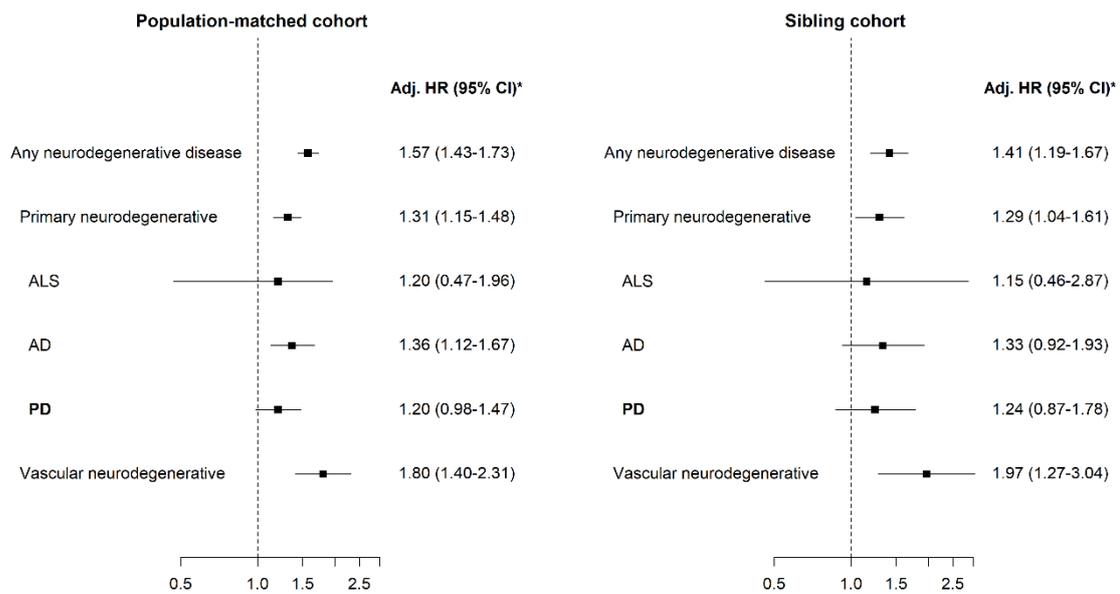
Individuals with stress-related disorders were compared with the general population in a matched cohort design. They were also compared with their siblings (if having any) in a sibling cohort design. Follow-up started from the age of 40 or 5 years after the diagnosis of stress-related disorders, whichever occurred later. End of follow up was defined as the first diagnosis of a neurodegenerative disease, death, emigration, or December 31st, 2013, whichever occurred first. Cox proportional hazards regression models were used to estimate hazard ratios with 95% confidence intervals after controlling for multiple confounders.

6.4.3 Main results

In total, 61,748 exposed individuals and 595,335 matched unexposed individuals were included in the analysis of the population-matched cohort, whereas 44,839 exposed individuals and their 78,482 unaffected full siblings were included in the analysis of the sibling cohort. The median age at the start of follow-up was 47 years (interquartile range: 41-56) and 39% of the exposed individuals were male. The median follow-up was 4.7 years (interquartile range: 2.1-9.8).

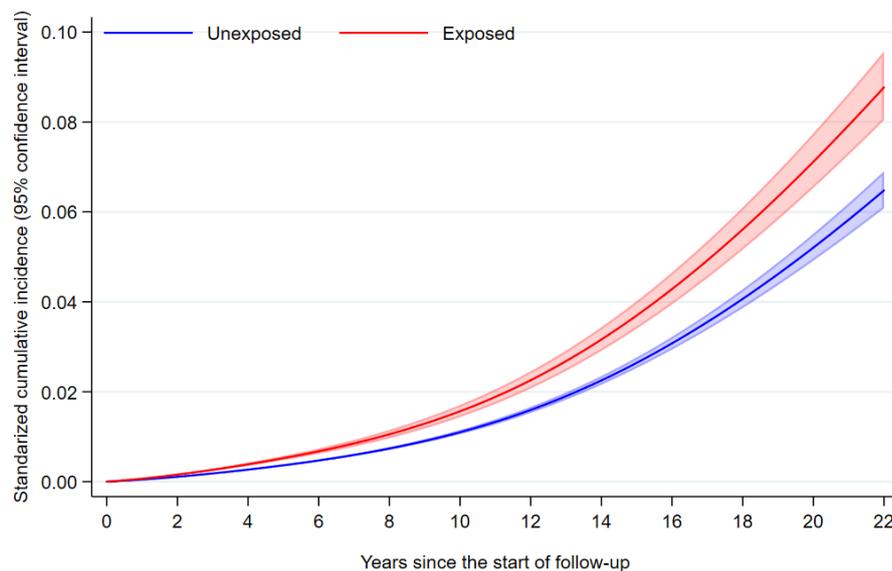
Compared to unexposed individuals, individuals with a stress-related disorder were at an increased risk of neurodegenerative diseases. The risk increase was greater for vascular neurodegenerative diseases than primary neurodegenerative diseases. A statistically significant association was found for AD, but not PD or ALS. Results from the sibling cohort corroborated results from the population cohort (Figure 6-6). The cumulative incidence plot shows the temporal pattern of neurodegenerative diseases among exposed individuals and their matched unexposed counterparts (Figure 6-7). These curves indicate that the increased incidence of neurodegenerative disease was observed right after the beginning of follow-up and appeared to be constant throughout the entire follow-up period.

Figure 6-6 Hazard ratios with 95% CIs for neurodegenerative diseases among individuals with stress-related disorders vs matched unexposed counterparts or unaffected full siblings



*HRs and 95% CIs were derived from Cox proportional hazards regression models, stratified by matching identifier (birth year, sex, and county of birth for population-matched cohort) and family identifier (for sibling cohort) and further adjusted for educational level, family income, marital status, history of psychiatric disorders, and family history of neurodegenerative diseases. Family history of neurodegenerative diseases was controlled for by design in the sibling cohort and not as a covariate. Time since start of follow-up was used as the underlying time scale.

Figure 6-7 Standardized cumulative incidence of neurodegenerative diseases among individuals with stress-related disorders (exposed) and their matched unexposed individuals (unexposed)



*Standardized cumulative incidence was estimated for the exposed and unexposed individuals using regression standardization over covariates' distributions, after fitting flexible parametric models and adjustment for birth year, sex, county of birth, educational level, family income, marital status, history of psychiatric disorders, and family history of neurodegenerative diseases. Time '0' represents at least five years after the diagnosis of stress-related disorders.

7 DISCUSSION

7.1 PERSONALITY AND PD

In study I, we investigated whether neuroticism and introversion measured in early adulthood to early middle age are associated with higher risk of PD in the following four decades. We found a relatively strong effect of neuroticism on PD risk, especially among women, whereas the effect of introversion was weaker. Our results for neuroticism are in line with a previous longitudinal study with over four decades of follow-up reporting a higher risk of PD related to neuroticism,⁶⁸ whereas a similar longitudinal study found no effect of introversion on PD risk.⁶⁹

It has been suggested that a part of the association between neuroticism and health in general partly could be explained by the fact that neurotic individuals perceive and report symptoms differently which would represent some sort of nuisance factor.^{138 139} Although it is unlikely that neurotic people will be misclassified as PD cases, neuroticism could influence the proneness to seek medical care which would influence the probability of being ascertained with the disease. We addressed this issue by counting and adjusting for the total number of hospital visits for causes other than PD during follow up. Indeed, neuroticism was associated with increased number of hospital visits. However, it did not influence the association with PD.

Another potential mechanism is mediation by health-related behaviors. However, given what is known about health-related behaviors related to neuroticism and known risk factors for PD, it is not clear what kind of factor that would mediate this association, as most of them would lead to a decreased PD risk. In fact, adjusting for smoking strengthened the association between neuroticism and PD risk and smoking was a significant mediator (suppressor) in this relationship. Education, which predicts various health behaviors and outcomes and may be used as an indicator of socioeconomic status, did not confound the association between personality and PD. Another hypothesis that we were not able to address in study I is mediation by stress, as neurotic individuals are more prone to stress and stress is a suggested risk factor for PD.¹⁰⁶⁻¹⁰⁸

Another potential explanation for the observed association between personality and the risk of PD is confounding by familial factors, such as shared genes or familial environment. Therefore, we performed a within twin pair analysis. Unfortunately, the sample size was markedly reduced in the within pair analyses limiting firm conclusions. However, we found that the estimates tended to drop compared to the initial cohort analyses which would indicate that the results may partly be explained by familial factors. This finding needs to be confirmed.

Finally, the observed associations between personality traits and PD could be explained by reverse causation. Since the personality traits were measured relatively early in life and we

had a long follow-up, the possibility of reverse causation is less likely compared to many other studies. However, since the personality trait was only measured once and the prodromal period of PD is very long, the possibility of personality changes as a prodrome could not be ruled out.

Therefore, in study II we wanted to examine whether the observed associations between neuroticism, smoking and PD risk from study I were causal using a network MR design to estimate the total effect of neuroticism on PD risk, as well as to assess the direct effect and indirect effect through smoking.

We found no evidence in support of a causal effect of neuroticism on PD risk. However, one SNP, rs58879558 (located in *MAPT* region), was associated with both neuroticism and PD. When excluding this variant in the MR analysis, the magnitude of the association was considerably attenuated, implying that genetics play an important role in the observed associations in conventional epidemiological studies and the variant may exhibit pleiotropic effects in MR analysis. Previous studies using bivariate linkage disequilibrium (LD) score regression reported no genetic correlation between neuroticism and PD⁴² whereas gene-set analysis revealed enrichment of genes associated with neuroticism in sets of genes that have previously been implicated in PD.⁶¹ It is therefore crucial to take genetic confounding into account when examining the role of neuroticism in PD.

In Study II, we also found significant associations between neuroticism and smoking initiation, and between smoking initiation and PD risk, which is in line with the results from study I of an indirect path between neuroticism and PD risk through smoking.

Our results are supported by several observational cohort studies associating neuroticism with increased smoking behaviours.¹⁴⁰ A previous MR study using ten SNPs as instrumental variables for neuroticism reported that neuroticism was associated with increased odds ratio for smoking initiation although the results were not statistically significant.⁷⁴ Study II, empowered with more SNPs as instrumental variables and a larger sample size for smoking initiation, updates previous findings and provides additional evidence for the causal association between them.

Our finding that smoking initiation was associated with a reduced risk of PD is also supported by previous MR studies reporting a reduced risk of PD for ever smokers¹⁴¹ and for smoking initiation.⁴² Further, numerous observational studies have consistently showed a reduced risk of PD in relation to smoking.⁴⁵ Several explanations have been suggested for this association, including residual confounding and reverse causation such that individuals with prodromal PD are less likely to start smoking or more likely to quit.⁵⁰ However, some findings from observational studies support a causal effect of smoking on PD. For example, smoking intensity and duration are both related to PD risk reduction,⁴⁶ and passive smoking among never smokers has also been associated with reduced PD risk.⁴⁹ Further, smoking has also been associated with reduced PD risk in co-twin control studies, reducing confounding due to genetic and familial environmental factors.¹⁴² Taken together, these findings support the

theory that smoking actually has a protective effect on PD risk. One should never over-interpret the results of one single study. Likewise, one should not over-interpret the results from many studies using the same methodological approach. Each approach makes different assumptions and has its own keys sources of bias. Therefore, when it comes to causal questions, integrating results from different studies using different approaches to answer the same research question is the best option.¹⁴³

To summarize, neuroticism is associated with an increased risk of PD but this association is not likely to be causal. In study I, importance of familial factors in this association was indicated, although limited power precluded firm conclusions. However, in study II additional evidence for shared genetics between neuroticism and PD was provided. Further, we found evidence that genetic liability to neuroticism is associated with an increased tendency to start smoking regularly. Finally, our study provided evidence that genetic liability to smoking initiation is associated with a reduced risk of PD.

7.2 STRESS AND PD

7.2.1 Occupational stress

In study III, we found that both high job demands and (somewhat unexpected) high job control were associated with increased PD risk in the overall sample. However, we also found significant interaction effects with both sex and education. After taking this into consideration, high job demands was only associated with PD risk among men, especially men with high education. In contrast, high control was only associated with increased PD risk among people with low education, especially among women. Accordingly, high strain jobs were only associated with increased PD risk among highly educated men, whereas active jobs were associated with increased PD risk among men with low education.

Thus, the results for job control are contrary to the hypothesis and are not easily interpreted. This could of course mean that occupational stress defined by low control could have beneficial effects on PD risk. Alternatively, high control and especially the aspect of job authority may lead to more interpersonal conflicts and more work-to-home interference which would induce more stress.¹⁴⁴ Thus, the effect of job control may vary depending on various organizational, individual or social factors. In line with this hypothesis, studies have also shown that high control or active jobs were associated with negative health outcomes in women, for example depressive symptoms,¹⁴⁵ coronary heart disease¹⁴⁶ and increased mortality.¹⁴⁷ Due to inequalities in the labor market, it is possible that women did not derive the same benefits of positions of authority as men,¹⁴⁸ which would explain why the positive effect of high control on PD risk was stronger in women compared to men, and stronger in those with low education compared to higher education. Further, the job demand-control model has been criticized for being more valid for men, with generally larger effect sizes or effects only present in men.^{87 89} Thus, this could explain why we only found associations between high strain jobs and PD risk in men.

Another potential explanation is confounding by traits that predispose both to seeking specific types of jobs and to increased PD risk, such as personality. However, a study using choice of occupation as a proxy for personality found no evidence for an association between occupation-derived personality traits and PD.¹⁴⁹

To summarize, our findings suggest that occupational stress is related to PD risk; high demands with increased risk and low control with decreased risk. The effects were dependent on sex and education. Thus, this highlights the importance of considering interaction effects between sex, education or other indicators of socioeconomic position with occupational stress in future studies and not only consider them as confounders as often have been done. The results from study III are intriguing, and one can only speculate about potential explanations for the observed associations. As this study is the first to explore the association between occupational stress and risk of PD, we cannot compare our results with others which is required to draw firm conclusions. To better understand the relationship between occupational stress and PD risk, more studies are motivated and future studies may consider other models of occupational stress in order to elucidate whether occupational stress only is a risk factor for PD or if there are also aspects of stress that may be protective.

7.2.2 Stress-related disorders

In study IV, we found that stress-related disorders were associated with an increased subsequent risk of neurodegenerative diseases. This association was robust and remained after adjustment for potential confounders, including demographic, health-related and familial factors. The stronger association observed for neurodegenerative diseases with a vascular component compared to primary neurodegenerative diseases suggested a considerable role of a possible cerebrovascular pathway.

Our finding that individuals with a stress-related disorder were at an increased risk of developing a neurodegenerative disease gains support from previous studies.^{95-102 104} However, most of the previous research has focused solely on PTSD^{95-100 102} and dementia,⁹⁶⁻¹⁰¹ and were often derived from studies of male veterans, who differ significantly from the general population and in terms of trauma exposure.⁹⁵⁻⁹⁸

For specific neurodegenerative diseases, we found a statistically significant association for AD but not for PD or ALS. Although the estimates for PD, as well as for ALS, implied an increased risk in relation to stress-related disorders, the associations were not statistically significant. This might be partly attributable to the relatively young cohort and the low incidence of PD and ALS at early age. Although our results for PD should be interpreted with caution, taken together with previous findings of an increased PD risk in relation to adjustment disorder and PTSD, this question deserves further attention.

Stress-related disorders are a major public health problem in itself, which leads to suffering for the affected individual and costs for the society. Thus, preventing and treating stress-related disorders is important to reduce suffering from the stress in itself. Potentially, this

could also have an effect on other health outcomes as well, such as reduced numbers of neurodegenerative disorders.

7.3 METHODOLOGICAL CONSIDERATIONS

7.3.1 Misclassifications

The quality of the data is the most important factor to consider as no study design or statistical method can fix the problem of poor data. Measurement errors may lead to misclassification bias. If misclassifications are independent of other variables, it is called non-differential misclassification and generally biases results towards the null. If misclassifications are related to other variables (e.g. exposures) it is referred to as differential misclassification, which is a more severe concern as it can bias the results in both directions.

In study I and III, the outcome measures were derived from the NPR and CDR. A previous validation study concluded that the NPR and CDR are valid data sources in epidemiological studies of PD with generally good accuracy and sensitivity.¹⁵⁰ The positive predictive value (PPV) of an inpatient PD diagnosis (primary or secondary) was 70.8% compared to the gold-standard clinical work-up, and the PPV increased to 80.3% when restricted to primary inpatient diagnoses. The sensitivity of PD diagnoses in the NPR and CDR combined was 83.1%.¹⁵⁰ Although misclassification of PD diagnoses in registers occur, for Study I and III they are most likely non-differential and would bias our results towards the null.¹⁵¹

In study IV, both exposures and outcomes were derived from the NPR. Diagnoses of stress-related disorders have not been validated. Although validation studies have shown satisfactory to excellent positive predictive values for neurodegenerative diseases identified through the NPR, the sensitivity of these diagnoses, especially dementia (i.e., 50% for dementia diagnosis based on inpatient care records¹⁵²) is low. This misclassification would, however, most likely bias the studied associations towards the null.¹⁵¹ Further, the register-based definitions of stress-related disorders and neurodegenerative diseases might have included patients with more severe stress-related disorders or neurodegenerative diseases compared to all patients with these diseases. This might be especially relevant for the period of 1987-2000 when these diseases were only ascertained through inpatient hospital visits. Therefore, the association of stress-related disorders with milder forms of neurodegenerative diseases, as well as the generalizability of our findings to individuals with milder stress-related disorders, need further investigation. As both exposures and outcomes were derived from the NPR in Study IV, it is possible that having the first diagnosis increases the likelihood of the receiving the other. To deal with potential surveillance bias, we started the follow-up of the study participants at the earliest 5 years after the index date.

Study I, III and IV are not subjected to recall bias given the prospective design and use of registry data.

7.3.2 Validity and generalizability

External validity refers to the extent to which the results from one study can be generalized to other populations, situations, and times. External validity is strengthened if the findings can be reproduced in other settings. The results from Study I, that neuroticism and similar traits are associated with PD risk, have been found in other populations as well, which strengthens the validity of these results. It has been questioned whether results from twin cohorts (as in Study I) could be generalized to the general population. However, a large Swedish study reported no differences in morbidity and mortality when twins were compared with singletons, indicating that findings from twins could be generalized to the general population.¹⁵³ The findings of study IV are also supported by similar findings from other studies on other populations. The finding of study III is novel and we do not know whether these results would replicate in other populations or times. It is for example possible that structural differences between countries and changes on the labor market over time would interfere with our results.

Results from MR studies should not be over-interpreted in practice. It is important to keep in mind that MR studies estimate the effects of the *genetic liability of a trait* on an outcome. That does not have to be the same as the effect of the actual trait. However, in Study I and II we were able to replicate findings of an associations between neuroticism and smoking and between smoking and PD using different methodological approaches which increases the validity of our conclusions.

7.3.3 MR assumptions

The validity of Study II mainly concerns the general assumptions of MR analysis. The first assumption, that the SNPs used as instrumental variables must be associated with the exposure, is the only testable assumption. We only used SNPs that were associated with the exposures at genome-wide significance, which makes this assumption more likely to hold. The second assumption is that the SNPs should not be associated with any confounding factors between neuroticism, smoking initiation and PD. MR studies are less vulnerable to confounding compared to observational studies given the random assortment of alleles. However, violation of this assumption is possible and cannot be ruled out. One important potential cause of violation to this assumption is population stratification. However, we only included data based on participants of European ancestry thus reducing this potential bias. The third assumption is that the SNPs should only affect the outcome through the exposure, i.e. there should be no pleiotropy. To address this issue, we used additional MR models that allow for different types of genetic pleiotropy and make different assumptions regarding instrument validity. As these different models produced similar causal effect estimates, our findings seem to be robust.

7.4 ETHICAL CONSIDERATIONS

Ethical considerations in medical research must always be taken seriously. In epidemiological research using sensitive personal data the main concern is ensuring the personal integrity of participants. All studies using sensitive personal data (Study I, III, IV) needed an approval from the Regional Ethics Committee. Summary statistics data, which were used in Study IV are not covered by the general data protection regulation (GDPR) or the ethical review act. Nevertheless, all studies in this thesis were approved by the Regional Ethics Review Board in Stockholm.

For Study I, based on questionnaire data from the STR, informed consent was obtained from all participants. Further, twins in the STR have the right to opt out from the register at any time. For Study III and IV, which are registry-based studies, informed consent is not required according to Swedish law and obtaining consents from participants in a nationwide cohort study would not be feasible. Individuals included in Swedish national registers have no possibility to opt out, and might not even know that they are included in these registers and thus included in research projects. The potential harm and benefit should always be carefully weighed in all studies. As register-based research has an important value for society, and the risk of physical harm or discomfort for the individual is minimal, the benefits often outweigh the potential harm. However, it is crucial to ensure that data are handled safely and respectfully to make sure that the study participants' personal integrity is not violated. That would have devastating consequences for the individual but also for the trust and belief in scientific research. There are strict regulations on how personal data are allowed to be handled. Data available to researchers are de-identified (personal identification numbers, names, addresses and other personal identifiers are removed) and reverse identification is prohibited by law. Access to data is restricted to only those involved in the project.

8 CONCLUSIONS

- I. Neuroticism and introversion measured in early adulthood to early middle age are associated with higher risks of PD in the following three decades.
Smoking is a significant mediator in these relationships – acting as a suppressor for the effect of neuroticism on PD risk, whereas partly accounting for the association between introversion and PD risk.
The observed effects of these personality traits on PD risk may partly be explained by familial factors shared by twins, although more data would be required to confirm or disprove this conclusion.
- II. Neuroticism does not seem to have a causal effect on PD risk.
Neuroticism seems to be causally related to an increased tendency to start smoking.
This study supports the hypothesis that smoking has a protective effect on PD, rather than that the association is explained by residual confounding.
- III. High job demands appear to increase PD risk in men, especially in men with high education.
High job control increases PD risk among low educated, more strongly in women.
High strain jobs (the combination of high demands and low control) is associated with increased PD risk in men with high education.
Active jobs (combinations of high demands and high control) is associated with increased PD risk in men with low education.
- IV. Stress-related disorders were associated with increased risks of neurodegenerative diseases. The relative strength of the association for vascular neurodegenerative diseases might indicate the importance of a cerebrovascular pathway.

9 ACKNOWLEDGEMENTS

I would like to express my gratitude to people who have contributed to the work of this thesis.

To **Karin Wirdefeldt**, my main supervisor and **Nancy Pedersen**, my co-supervisor throughout my whole PhD period, thanks you for providing me the opportunity to do a PhD at MEB. Thanks for sharing your knowledge and ideas related to this project and for your support and invaluable comments to my texts throughout the years.

To **Petter Gustavsson**, my co-supervisor for the former part of my PhD period, thanks for valuable input and comments on Study I.

Yiqiang Zhan, you were my co-supervisor only for a short time during the last part of my PhD period but without your support would not have finished this PhD journey, thanks for sharing your knowledge, expertise, and not the least, kindness.

To my co-authors, **Petter Gustavsson, Caroline Weibull, Adina Feldman, Giselle Petzinger, Margaret Gatz, Ross Andel, Elise Valdes, Annika Tillander, Catarina Almqvist, Henrik Larsson, Unnur Valdimarsdóttir**, thanks for your comments and contributions to the studies involved in this thesis. Especially thanks to **Fang Fang** and **Huan Song**. I'm so grateful you let me do Study IV together with you after finding out we were working on similar ideas.

Past and present members of Sara's and Nancy's group and other MEB colleagues also deserves gratitude. **Adina Feldman**, my 'fadder' who introduced me to MEB, thanks for showing so great enthusiasm and for your help and support when I started my PhD. To **Bojing Liu**, thanks for your generosity, thoughtfulness and for your moral support. To **Xiaoying Kang**, for participating in my pre-dissertation committee. And a special thank you to **Juulia Jylhävä**, for serving as the chairperson of my defense.

Till **Mamma** och **Pappa**, tack för all villkorslös kärlek ni har gett mig och som ni nu också ger till mina barn. Till mina syskon **Elin, Henrik** och **Åsa** och era familjer, tack för att ni är som ni är. Jag är så glad över att ha en familj som jag umgås med för att jag verkligen tycker om att spendera tid med er. Och tack **Elsa** för att du har hjälpt till att passa barn när det har krisat.

Alexander, gu va vi har vart me om, tänk att allt ska hända oss! Jag är så glad att jag har dig vid min sida. Tack för all kärlek och för att du alltid uppmuntrat och trott på mig. Mina oändligt älskade barn, **Eyvind** och **Ivar**, tack för att just ni kom till mig och för att ni förgyller mitt liv.

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11 APPENDIX

QUESTIONS RELATING TO YOUR CHARACTER, FEELINGS AND ACTIONS

Decide whether “yes” or “no” best corresponds to your character, feelings and actions. Do not spend too much time on each question. We are trying to determine your immediate reactions.

| | YES | NO |
|--|--------------------------|--------------------------|
| 1 Do you like having a lot of things going on around you? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2 Are you often uneasy, feeling that there is something you want without knowing it? | <input type="checkbox"/> | <input type="checkbox"/> |
| 3 Do you almost always have an answer ready when spoken to? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4 Are you sometimes happy and sometimes sad without any special reason? | <input type="checkbox"/> | <input type="checkbox"/> |
| 5 Do you prefer to keep to the background in the company of other people? | <input type="checkbox"/> | <input type="checkbox"/> |
| 6 Do you regard yourself as happy and carefree? | <input type="checkbox"/> | <input type="checkbox"/> |
| 7 Do you often reach decision too late? | <input type="checkbox"/> | <input type="checkbox"/> |
| 8 Do you often feel tired and listless without any special reason? | <input type="checkbox"/> | <input type="checkbox"/> |
| 9 Do you have a lively manner? | <input type="checkbox"/> | <input type="checkbox"/> |
| 10 Can you quickly describe your thoughts in words? | <input type="checkbox"/> | <input type="checkbox"/> |
| 11 Are you often lost in your thoughts? | <input type="checkbox"/> | <input type="checkbox"/> |
| 12 Do you have anything against selling things or asking people for money for some charitable purpose? | <input type="checkbox"/> | <input type="checkbox"/> |
| 13 Are you extremely sensitive in any respects? | <input type="checkbox"/> | <input type="checkbox"/> |
| 14 Are you ever too restless to sit still? | <input type="checkbox"/> | <input type="checkbox"/> |
| 15 Do you keep things to yourself except with good friends? | <input type="checkbox"/> | <input type="checkbox"/> |
| 16 Do you have any nervous problems? | <input type="checkbox"/> | <input type="checkbox"/> |
| 17 Do you like to crack jokes and tell funny stories to your friends? | <input type="checkbox"/> | <input type="checkbox"/> |
| 18 Do you usually worry a long time after a distressing incident? | <input type="checkbox"/> | <input type="checkbox"/> |

Scoring

Neuroticism: Rated by summing the numbers of “yes” in the questions 2, 4, 7, 8, 11, 13, 14, 16 and 18. A high total score implies neuroticism.

Introversion: Rated by giving one score for answering “no” in question 1, 3, 6, 9, 10, 17 and “yes” in question 5, 12, 15 and then adding up the total number of scores. A high total score implies introversion.