Parkinson’s disease
the prodromal phase and consequences with respect to working life

Helena Nyström
To my parents, my siblings, and my dear husband Mattias
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Abstract

Parkinson’s disease (PD) is a common, progressive neurodegenerative disorder, recognized by the motor symptoms of bradykinesia, tremor, rigidity, and postural impairment. At clinical onset, extensive amounts of dopaminergic neurons have already been lost. The duration of this prodromal phase is uncertain, and it is thought to include predominantly non-motor symptoms. The progressive nature and the symptoms of PD are disabling and reduces the quality of life. Among patients affected in working age, early cessation of employment is common, and such socioeconomic consequences of PD may contribute to an impaired quality of life.

In the present work, we used a postal survey to investigate the self-perceived life situation among working-aged individuals with PD compared to matched controls, with a specific attention to socioeconomic consequences of disease (paper I). In this cohort, 38% of the PD participants and 9% of the controls were dissatisfied with life as a whole, and the working situation was an independent risk factor for dissatisfaction with life. In total, 59% of the PD participants had reduced working hours or stopped working due to PD, and many PD participants (36% of those still working) struggled to cope with their work demands.

To investigate risk markers preceding the diagnosis of PD, we used data from nationwide registers. In patients with PD, we found a lower muscle strength (paper II), and an increased risk of depression (paper III) more than 2 decades before diagnosis of PD. Finally, based on the lower muscle strength found, we hypothesized that PD patients would be at increased risk of injurious falls and fractures before diagnosis of PD (paper IV). In a nationwide nested case-control cohort, we found that patients with PD were at increased risk of fall-related injuries in general and hip fractures in particular a decade or more before the PD diagnosis. The results of the present studies suggest that the prodromal phase of PD may last for more than 2 decades and include also motor symptoms. The consequences of PD include a reduced quality of life associated with the working situation.

I Sverige beräknas nästan 22 000 människor vara drabbade av Parkinsons sjukdom, och cirka 30 % av patienterna får sin diagnos före 65 års ålder. Det finns ännu ingen behandling som visat sig effektiv för att bota eller bromsa sjukdomsförloppet, som på sikt leder till handikapp och försämrande livskvalitet. Många av dem som drabbas av Parkinsons sjukdom i arbetsförålder slutar arbeta i förtid, och konsekvenser av att stå utanför arbetsmarknaden kan vara ett skäl till att tidigt debuterande Parkinsons sjukdom tycks ha en särskilt stor inverkan på livskvalitén.

Vi har med en enkätstudie (studie I) undersökt hur individer med Parkinsons sjukdom i arbetsförålder (18–67 år) upplever sin livssituation, i jämförelse med en ålders- och könsmatchad kontrollgrupp. Särskilt fokus lades på socioekonomiska konsekvenser av Parkinsons sjukdom. Fler av deltagarna med Parkinsons sjukdom (38 %) än kontrollerna (9 %) uppgav att de var uttömt och stärkande med livet som helhet, och arbetsställningen var en oberoende faktor starkt relaterad till detta. Totalt 59 % av deltagarna i parkinsonsgruppen hade minskat arbetstiden eller slutat arbeta på grund av sjukdomen, och många (36 %) av dem som fortfarande arbetade upplevde att kraven på arbetet låg över deras kapacitet. Knappt en fjärde av deltagarna som levde med Parkinsons sjukdom i minst tio år arbetade fortfarande, vilket är en betydligt större andel än tidigare studier från andra länder rapporterat.
Deltagare med Parkinsons sjukdom som upplevt stöd från sin arbetsgivare i rehabiliteringsfrågor hade en tre gånger högre sannolikhet att fortfarande arbeta, jämfört med dem som saknat stöd från sin arbetsgivare.

För att söka riskmarkörer för Parkinsons sjukdom under decennier före diagnos har vi använt rikstäckande register med data insamlat vid militärens mönstringstester samt inom sjukvården. Vi fann att låg muskelstyrka vid mönstring (studies II) och depression (studies III) var associerade med en ökad risk för Parkinsons sjukdom över uppföljningstider på mer än två decennier, och att parkinsonpatienter hade en ökad risk för fallskador i allmänhet och höftfrakturer i synnerhet redan tio år eller mer före parkinsondiagnosen (studies IV). För depression och fallskador var associationen tydligt tidsberoende, starkast närmast parkinsondiagnosen.

Fynden i studies II–IV kan vara tidiga tecken till en förlust av nervceller, och tyder i så fall på att prodromalfasen av Parkinsons sjukdom kan sträcka sig över flera decennier. Den ökade risken för fallskador innan parkinsondiagnosen indikerar att kliniskt relevant påverkan på balans kan förekomma tidigt i sjukdomsförloppet, utan att noteras i traditionella kliniska tester. Resultaten av studies I belyser att Parkinsons sjukdom har en stor inverkan på livskvalitén och att arbetslivsrelaterade frågor är tydligt kopplade till tillfredsställelsen med livet i allmänhet. Arbetsgivaren tycks ha en särskilt viktig roll i yrkesinriktade rehabiliteringsfrågor, för att öka möjligheterna att fortsätta arbeta.
Original papers

I. Parkinson's Disease: A Population-Based Investigation of Life Satisfaction and Employment.
Helena Gustafsson, Peter Nordström, Stefan Stråhle, Anna Nordström.

II. Low muscle strength in late adolescence and Parkinson disease later in life.
Helena Gustafsson, Jan Aasly, Stefan Stråhle, Anna Nordström, Peter Nordström.

III. Depression and subsequent risk of Parkinson disease: A nationwide cohort study.
Helena Gustafsson, Anna Nordström, Peter Nordström.

IV. Risk of Injurious Fall and Hip Fracture up to 26 y before the Diagnosis of Parkinson Disease: Nested Case–Control Studies in a Nationwide Cohort.
Helena Nyström, Anna Nordström, Peter Nordström.

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## Abbreviations

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<th>Description</th>
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<td>CBD</td>
<td>Corticobasal degeneration</td>
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<td>CDR</td>
<td>Cause-of-Death Register</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>COMTI</td>
<td>Catechol-O-methyltransferase inhibitor</td>
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<td>DAT</td>
<td>Dopamine transporter</td>
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<td>DBS</td>
<td>Deep brain stimulation</td>
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<td>DLB</td>
<td>Dementia with Lewy bodies</td>
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<td>DRT</td>
<td>Dopaminergic replacement therapy</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>HRQoL</td>
<td>Health-related quality of life</td>
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<td>HY</td>
<td>Hoehn and Yahr</td>
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<tr>
<td>ICD</td>
<td>International classification of diseases</td>
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<td>LB</td>
<td>Lewy body</td>
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<td>LiSat</td>
<td>Life Satisfaction Questionnaire</td>
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<td>MAOBI</td>
<td>Monoamine oxidase B inhibitor</td>
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<td>MDS</td>
<td>Movements Disorders Society</td>
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<td>MGR</td>
<td>Multi-Generation Register</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MSA</td>
<td>Multiple system atrophy</td>
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<td>MSCR</td>
<td>Military Service Conscription Register</td>
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<td>Nested case-control</td>
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<td>National Patient Register</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PH</td>
<td>Proportional hazards</td>
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<td>PIGD</td>
<td>Postural instability gait disorder</td>
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<td>PPV</td>
<td>Positive predictive value</td>
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<td>PSP</td>
<td>Progressive supranuclear palsy</td>
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<td>QoL</td>
<td>Quality of life</td>
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<td>RBD</td>
<td>REM sleep behavior disorder</td>
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<td>REM</td>
<td>Rapid eye movement</td>
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<td>RTP</td>
<td>Register of Total Population</td>
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<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
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<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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Introduction

Parkinson’s disease (PD) was first described by James Parkinson in 1817 under the term “the shaking palsy”,¹ and later named to his honor. This progressive neurodegenerative disorder is primarily recognized by the motor symptoms of bradykinesia, tremor, rigidity, and postural impairment. Beside these cardinal motor signs, several non-motor manifestations are common, such as sensory symptoms (pain, tingling), hyposmia, sleep disturbance, depression, and cognitive impairment (Panel 1).²-⁴ The pathological hallmarks of PD are a loss of dopaminergic neurons, most prominently in certain parts of the basal ganglia (e.g., substantia nigra, putamen), and the aggregation of proteins to so-called Lewy bodies (LBs) in remaining nerve cells. A main component of the Lewy bodies is α-synuclein protein, why PD [along with dementia with Lewy bodies (DLB) and multiple system atrophy (MSA)], is sometimes referred to as an α-synucleinopathy.⁵ The etiology of the neurodegeneration in PD remains largely unknown. The clinical onset of PD is preceded by an extensive loss of dopaminergic neurons,⁶,⁷ for which the timeline remains unclear.⁸,⁹

Current therapies have not proven effective to modify the disease progression in PD. Clinically, the disease course reflects a complex interplay between the continuing neurodegeneration and the effects and complications of therapy (Panel 1).¹⁰,¹¹ The progressive nature of PD is disabling and reduces the quality of life (QoL).¹² Among patients affected in working age, early cessation of employment is common,¹³-¹⁷ and the social consequences of standing outside the labor market may be an important reason why people with young onset PD have been found to perceive a worse QoL compared to individuals with later onset PD.¹⁸,¹⁹
Panel 1: Manifestations of PD 3, 4, 10, 93

**Cardinal motor symptoms**

**Bradykinesia**
Bradykinesia means slowness of movements. Beside a loss of speed and amplitude in activities such as walking or raising from a chair, bradykinesia may cause hypomimia (decreased facial expression), hypophonia (soft voice), and swallowing difficulties. In milder cases of PD, bradykinesia can be detected by clinical evaluations where the patient is asked to perform repetitive movements as quick and wide as possible.

**Tremor**
The characteristic parkinsonian tremor is a rhythmic involuntary movement with low to mid-range frequency (3–6 Hz), apparent at rest but vanishing with active movement. It may also reappear when holding a static position, e.g. with the arms outstretched, and is then referred to as “re-emergent tremor”. Rest tremor in PD is usually prominent in the distal part of an extremity and may also involve the face (lips, chin, and/or jaw).

**Rigidity**
Parkinsonian rigidity is caused by an increased muscle tone, involving both flexor and extensor muscles. In contrast to spasticity, parkinsonian rigidity does not increase with higher speed of movement, and a classical finding in clinical examination is the “cog wheel rigidity”, appearing when rest tremor coexists with rigidity.

**Postural and gait impairments**
In advanced stage of PD, patients typically adopt a stooped posture, with flexed neck and trunk, and a slow gait with short, shuffling steps. These impairments are due to rigidity and poor axial coordination and reflexes. One of the most disabling symptoms of PD is ‘freezing’; a sudden and transient inability to move. This phenomenon most often affects the legs, and is a common cause of falls in PD patients.

In clinical routines, the “pull test” (pushing the patient’s shoulders quickly backward or forward) is commonly used to evaluate the balance in PD patients. Clinically evident balance deficits are traditionally considered as late-stage symptoms of PD.
Panel 1: Manifestations of PD (continued)

Non-motor symptoms
Autonomic dysfunction
PD commonly causes constipation, orthostatic hypotension, urinary dysfunction, sexual dysfunction, excessive sweating, seborrhea, and sialorrhea.

Cognitive and neuropsychiatric features
Cognitive impairment is a common symptom of PD, and many patients eventually develop dementia. Other common psychiatric features are depression, anxiety, and apathy.

Sensory dysfunction
Hyposmia, visual impairments (decreased contrast/color discrimination and visual motor perception), paresthesia, pain.

Sleep disorders
Insomnia, restless legs syndrome, periodic limb movements in sleep, rapid eye movement (REM) sleep behavior disorder (RBD), excessive daytime sleepiness.

Fatigue
Fatigue in PD may be related to disordered sleep, but may also occur independent of sleep disturbances.

Complications of dopaminergic replacement therapy (DRT)
Motor fluctuations
Shifts between periods of good motor symptom control (‘on’ time) and insufficient motor symptom control (‘off’ time).

Dyskinesia
Involuntary dystonic or choreiform movements, most common at peak concentrations of levodopa.

Hallucinations
May occur both as complication of DRT and as a primary feature of advanced disease in PD.

Impulsive control disorders
Most common with dopamine agonists. May include binge eating, compulsive spending and gambling, and hypersexuality.
Epidemiology

With more than 4 million individuals affected worldwide, and almost 22,000 in Sweden, PD is the second most common neurodegenerative disease. Men are at about 50% higher risk than women. The incidence is strongly related to age, but approximately 30% of the patients are younger than 65 years of age at the time of diagnosis. The terms “early onset” or “young onset” are commonly used with a cut-off age at 40 or 50 years.

Heritability

Most cases of PD appear sporadic. However, about 10–30% of PD patients have at least one first-degree relative with parkinsonism, with the higher numbers found among patients with young onset PD. Familial aggregation studies have reported that first-degree relatives of PD patients are at about 2-fold to 5-fold risk increase for PD, but such patterns have traditionally been thought to mainly arise from shared environmental risk factors (please see below). Twin studies are of value to distinguish between genetic and environmental effects, given that monozygotic twins share the whole genome while dizygotic twins share on average half of it, and early twin studies reported low concordance rates that were similar for mono- and dizygotic twins, thus not supporting a genetic component. However, a recent longitudinal twin study indicated a modest heritable component, and molecular genetic research have in the last 2 decades identified several loci related to familial PD. Such mutations and genetic polymorphism have subsequently also been found in apparently sporadic cases of PD, indicating that epidemiological studies may have underestimated the genetic contribution to the overall risk of PD. This applies in particular to gene variants associated with late-onset PD; when disease penetrance is highly dependent on age, patterns of heredity may be blurred by mortality and morbidity of other cause at high age. Susceptibility factors for PD may also be involved in other conditions; an increased risk of depressive and anxiety disorders has, for example, been reported in first-degree relatives of PD patients.

Environment

Several environmental factors have been hypothesized to affect the risk of PD, but few have been found significant and consistent. In a 2007 consensus report, the strength of evidence, graded according to the Institute of Medicine (IMO) classification, was concluded to be: sufficient for a negative association to smoking; suggestive but limited for a negative association to physical activity and to the use of nonsteroidal anti-
inflammatory drugs (NSAIDs); suggestive but limited for a positive association to pesticide exposure, to farming and agricultural work, to intake of dairy products, and to traumatic brain injury. Moreover, a negative association between caffeine intake and PD was noted, though with sufficient evidence only among men.\textsuperscript{34} Subsequent publications in the field include an extensive review on epidemiology and etiology in PD, published in 2011,\textsuperscript{29} which summarized the evidence according to the same classification with similar conclusions, and a meta-analysis\textsuperscript{35} reporting results in consistence with the previous reviews regarding the factors mentioned above. Additionally, the meta-analysis included antihypertensive drugs; a positive association to the use of beta-blockers and a negative association to use of calcium channel blockers was found in relation to risk of PD. However, these results should be interpreted with caution, as a negative association between hypertension and PD was also found in the same meta-analysis, and beta-blockers may be used as symptomatic treatment for tremor in the pre-diagnostic phase of PD.\textsuperscript{35} As for potential preventive effects from drugs, 2 Cochrane reviews have been published in the last 5 years, assessing the use of NSAIDs and antihypertensive drugs in relation to the risk of PD; concluding that NSAIDs may reduce the risk of PD, while there is no evidence for NSAIDs as neuroprotective agent in established disease, and no support for the use of antihypertensive drugs in primary or secondary prevention of PD.\textsuperscript{36,37}

The attention to pesticide exposure as a potential risk factor for PD was raised in the 1980’s, after the discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a substance similar to the herbicide Paraquat, had caused irreversible parkinsonism in a number of patients.\textsuperscript{38} The syndrome caused by MPTP was, however, not clinically identical to PD,\textsuperscript{12} and MPTP exposure is specified as an exclusion criteria for PD in the UK Brain Bank Criteria (Panel 2).\textsuperscript{39}

As most knowledge on environmental factors associated with PD arise from observational studies, causal relationships have not been confirmed.\textsuperscript{29} Thus, there is an obvious possibility of confounding by unidentified factors. Moreover, the likelihood of reverse causality must be taken into account; a growing body of evidence indicates that the prodromal phase of PD may be long, and a reduced function of dopamine-mediated reward systems may for example affect lifestyle factors such as smoking, coffee drinking, and physical activity.\textsuperscript{40,41} Similarly, an association between head injury and later risk of PD may be explained by an increased risk of accidents due to prodromal deficits\textsuperscript{40}; a time variation has been found in the association to head injury, strongest close to the diagnosis of PD.\textsuperscript{42,43}
Panel 2: UK Brain Bank Criteria for PD\textsuperscript{10, 39}

**Step 1. Diagnosis of Parkinsonian syndrome**
- Bradykinesia
- At least one of the following:
  - Muscular rigidity
  - 4–6 Hz rest tremor
  - Postural instability not caused by primary visual, vestibular cerebellar, or proprioceptive dysfunction

**Step 2. Exclusion criteria for PD**
- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- Negative response to large doses of levodopa (if malabsorption excluded)
- Sustained remission
- Strictly unilateral features after 3 years
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Oculogyric crisis
- Supranuclear gaze palsy
- Babinski sign
- Cerebellar signs
- MPTP exposure
- Presence of a cerebral tumor or communicating hydrocephalus on CT scan or MRI
- More than one affected relative\(^*\)

**Step 3. Supportive prospective criteria for PD**
Three or more of the following features are required for diagnosis of definite Parkinson’s disease:
- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side on onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more
\(^*\) This criterion is generally no longer applied
Diagnostic definitions and staging scales

The cardinal motor symptoms of PD (Panel 1) form a clinical syndrome termed parkinsonism, for which PD is the most common cause. However, parkinsonism may also arise e.g. from drugs or vascular lesions. Other differential diagnoses to PD are DLB, MSA, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD); degenerative disorders that share the cardinal symptoms with PD but differ in aspects of clinical course, characteristics of symptoms, responsiveness to levodopa, and/or the presence of additional features, such as cerebellar signs or supranuclear gaze palsy.3,44

The golden standard for a definite diagnosis of PD relies on the typical clinical presentation combined with a post-mortem histopathologic confirmation of characteristic neuronal loss and presence of LBs.44,45 Functional brain imaging [e.g., dopamine transporter (DAT) imaging combined with single-photon emission computed tomography (SPECT)] cannot distinguish PD from other degenerative causes of parkinsonism (e.g., PSP, MSA, CBD, and DLB), but is of value to differentiate against, e.g., essential tremor, drug induced tremor, and psychogenic symptoms. Structural brain imaging methods, such as magnetic resonance imaging (MRI), are also of value to rule out some differential diagnoses, e.g. vascular parkinsonism. Still, due to the lack of specific biomarkers, PD is in practice a clinical diagnosis.3,10 According to the UK Brain Bank Criteria (Panel 2), the clinical diagnosis of PD relies on the presence of bradykinesia together with at least one more of the cardinal motor symptoms, and the exclusion of underlying causes of secondary parkinsonism.39

The recognition of non-motor symptoms as a primary part of disease is a more recent insight, and such symptoms are currently not included in the diagnostic criteria for PD.3 One feature that remains debated is impairment of muscle strength; when James Parkinson first described “the shaking palsy” he held it as a key feature of the disease,1 and self-perceived muscle weakness is a common complaint in PD patients.46 Yet, in modern time, this symptom has received little attention, and clinically apparent reduction of muscle strength has generally not been considered a primary symptom of PD.47,48 However, clinical assessment of muscle strength can only provide rough estimations. Quantitative data of muscle strength in PD patients were first reported in 1986 by Koller and Kase, who found a generally reduced isokinetic muscle force in PD patients compared to controls, independent of the distribution of other parkinsonian symptoms, and not detected by clinical assessments.47 Similarly, later studies have reported reduced isokinetic muscle strength in PD patients also in early stages of disease.48-50
Functional capacities reported to correlate with reduced muscle strength in PD include impaired ability to rise from a chair,\textsuperscript{51} and gait disturbance.\textsuperscript{52}

**Grading of disease severity**

To assess and describe the severity of PD, several clinical scales have been developed.\textsuperscript{4-53} The most traditional example is the Hoehn and Yahr (HY) scale,\textsuperscript{54} first introduced in the 1960’s and since then used worldwide in clinical research as the standard staging system for PD. The original version include 5 stages defined by hallmarks such as bilateral involvement (stage 2) and impaired postural reflexes (stage 3). A modified version has later been introduced, with the addition of intermediate stages between the original 5 (\textbf{Panel 3}).\textsuperscript{55} The HY scale was developed in the era before dopaminergic replacement therapy (DRT) was available, and is only descriptive; the authors did not presume a sequential stage-to-stage progress of disease. The setup of hallmarks categorizing each stage in the HY scale is somewhat ambiguous, as clinical signs and functional impairment may occur in combinations that diverge from the criteria of each stage. As for evaluation of disease progress and treatment effects, more detailed scales have later been developed, commonly validated with the HY scale as the reference.\textsuperscript{55}

Currently, the most widely used clinical rating scale is the Unified Parkinson’s Disease Rating Scale (UPDRS), which was designed in the 1980’s and later revised by the Movements Disorders Society (MDS); the new version is termed MDS-UPDRS. The UPDRS is multidimensional tool, including both questionnaire parts (I, II, and IV) and a clinical examination (part III); part I-II addressing experiences of daily living (non-motor and motor), part III addressing clinical motor signs, and part IV addressing therapy complications (dyskinesias and motor fluctuations). In the UPDRS, evolvement of symptoms and/or disabilities are reflected by declined scores.\textsuperscript{56}
### Panel 3: Original and modified Hoehn & Yahr scale

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<th>Hoehn &amp; Yahr scale</th>
<th>Modified Hoehn &amp; Yahr scale</th>
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<tbody>
<tr>
<td><strong>1.0:</strong> Unilateral involvement only, usually with minimal or no functional impairment.</td>
<td><strong>1.0:</strong> Unilateral involvement only</td>
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<tr>
<td><strong>1.5:</strong> Unilateral and axial involvement</td>
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<tr>
<td><strong>2.0:</strong> Bilateral or midline involvement, without impairment of balance.</td>
<td><strong>2.0:</strong> Bilateral involvement without impairment of balance</td>
</tr>
<tr>
<td><strong>2.5:</strong> Mild bilateral disease with recovery on pull test</td>
<td></td>
</tr>
<tr>
<td><strong>3.0:</strong> First sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyes closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending upon the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.</td>
<td><strong>3.0:</strong> Mild to moderate bilateral disease; some postural instability; physically independent</td>
</tr>
<tr>
<td><strong>4.0:</strong> Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.</td>
<td><strong>4.0:</strong> Severe disability; still able to walk or stand unassisted</td>
</tr>
<tr>
<td><strong>5.0:</strong> Confinement to bed or wheelchair unless aided.</td>
<td><strong>5.0:</strong> Wheelchair bound or bedridden unless aided</td>
</tr>
</tbody>
</table>
Course of disease

Due to the insidious nature of the neurodegeneration in PD, the actual ‘onset’ of disease has not been clearly defined. The cardinal motor symptoms may initially be subtle, and commonly preceded by less specific features. PD is also a heterogeneous disorder, in some cases causing severe disability within a few years from diagnosis, while remaining mild to moderate for decades in others.

The prodromal phase

At the time of diagnosis, about 40–60% of the dopaminergic neurons may already have been lost in certain parts of the basal ganglia. To define the timeline of this pre-diagnostic neurodegeneration remains a challenge. Backward extrapolation of longitudinal neuroimaging data from patients diagnosed with PD have been used to estimate rates of pre-diagnostic neuronal loss, and yielded various results; approximates of the time from onset of neurodegeneration to onset of cardinal motor symptoms range from 3–40 years, and most studies indicate an exponential decay.

Epidemiological studies provide further evidence for a prodromal phase; an increased incidence of several non-motor symptoms, including constipation, olfactory impairment, sleep disorders, and psychiatric manifestations (e.g., depression and anxiety) have been reported to precede the diagnosis with years or decades. Observational studies cannot accurately evaluate causality of such associations, but they are of high value to provide insight of clinical risk markers for PD. Such clinical signs may, together with genetic risk markers, enable the identification of individuals at risk of PD and provide possibilities to further investigate the prodromal phase in a prospective manner. However, while the cardinal motor symptoms are fairly specific for parkinsonism, most prodromal symptoms of PD are not; e.g., among patients with depression or constipation, only a small fraction will later develop PD. These signs are therefore difficult to use as primary markers in the search for high-risk populations for studies including resource demanding methods, such as DAT scan, limiting the number of participants. An exception with higher specificity is rapid eye movement (REM) sleep behavior disorder (RBD), a rare disorder strongly associated with α-synucleinopathies; about 50% of RBD patients eventually develop parkinsonism, and RBD may precede the onset of parkinsonism with up to half a century. Thus, RBD patients have been recruited as at-risk population in studies evaluating other potential prodromal signs of PD.
Another prodromal sign of particular interest as a risk marker for PD is hyposmia; a condition not necessarily noted by the individual, but useful for research purposes as it can be screened for by a simple, postal delivery test. A recent study reported associations between hyposmia and a number of other prodromal PD symptoms. Functional brain imaging was used to further evaluate whether dopaminergic deficits could explain these findings, revealing DAT deficits (which may indicate prodromal PD) to be 10 times more common in hyposmic compared with normosmic participants (11% vs 1%). In hyposmic participants, the prevalence of DAT deficits increased in the presence of additional symptoms attributable to prodromal PD, with the peak prevalence (43%) reported in hyposmic men with constipation.

The prodromal phase of PD has frequently been referred to as “pre-motor”, as the first prodromal signs reported in literature were of non-motor type. This view has later been challenged by studies focused on potential occurrence of motor deficits prior to the onset of cardinal motor signs. Quantitative assessments of motor performance in individuals at high risk of PD have found subtle deficits. For example, in a longitudinal study of 68 RBD patients who underwent annual evaluations including UPDRS and quantitative motor tests (timed up-and-go, Purdue pegboard, and alternate tap test), 22 patients developed parkinsonism (PD or DLB) during follow up; in those, both UPDRS scores and motor test results deviated from normal at 3–4 years before diagnosis of parkinsonism. Other studies have reported balance deficits in RBD patients and subjects with other risk markers for PD, which is of particular interest as balance impairment is considered a late-stage manifestation of PD. However, quantitative assessments of balance have reported abnormal patterns also in early PD. Recent epidemiological studies provide evidence for balance problems, diagnosed in primary health care, to precede the diagnosis of PD with up to 5 years, and an increased risk of accidental injuries in the last 3 years before the PD diagnosis. Taken together, these findings suggest that subtle motor deficits may occur early in the disease course, and pass unnoticed in clinical assessments. Still, few studies have included quantitative variables of motor performance, and follow-up times of more than a few years are rare.

**The clinical phase**

PD is associated with a somewhat reduced life expectancy compared to the general population, but those affected before 40 years of age are still presumed to live with the disease for about 4 decades, and a disease course of at least 10 years is one of the supportive criteria for a diagnosis of definite PD. Longitudinal studies of disease progress, commonly assessing annual deterioration according to UPDRS and/or to the HY scale, report a wide
variability with respect to manifestations and rate of progress. In the search to understand the variation and to identify prognostic factors, several subtype classifications systems have been proposed, but no standardized version has yet been implemented. Empirical driven classifications include age of onset, commonly with the cut-off for ‘early’ or ‘young’ onset at age 40 or 50 years, and motor phenotype (defined according to UPDRS scores), commonly distinguishing ‘tremor dominant PD’ from non-tremor dominant forms; ‘postural instability gait disorder’ (PIGD) and intermediate form, or akinetic-rigid and mixed form. Tremor dominant phenotype and young age at onset are associated with a slower rate of progress.

**Strategies and challenges of treatment**

Dopaminergic replacement therapy (DRT) – that is, levodopa and dopamine agonists – is the mainstay of pharmacologic treatment for PD. Typically, most motor symptoms of PD initially respond well to DRT but many patients are affected by complications, such as motor fluctuations or dyskinesia, already within 5 years. By this reason, and due to the lack of evidence for neuroprotective effects from current therapies, the optimal time to initiate pharmacologic treatment remains debated. However, the evidence for benefits of therapy delay is thin, and current guidelines suggest that treatment should not be withheld when symptoms cause disability and discomfort for the patient. Levodopa is the most effective drug for symptomatic treatment in PD, but dopamine agonists provide an alternative in early PD, in particular for younger patients as they are more prone to motor complications. This adverse effect is less common with dopamine agonists than with levodopa. On contrary, freezing, somnolence, edema, hallucinations, and impulse control disorders are less common with levodopa than with dopamine agonists; thus, levodopa may be more suitable for older patients. Initially, a monoamine oxidase B inhibitor (MAOBI) may be tried, with aim to delay the need of levodopa. A MAOBI or catechol-O-methyltransferase inhibitor (COMTI) may also be of value to combine with DRT, to reduce motor fluctuations at more advanced stages of disease; similarly, levodopa and dopamine agonists may be combined to reduce off-time. Beta-blockers and anti-cholinergic medications may be used to reduce tremor though, due to adverse effects, these drugs may be problematic in patients prone to confusion, hallucinations, and disturbed sleep.

Non-motor symptoms of PD are common and contribute substantially to impairment of QoL. For example, a systematic review reported an overall prevalence of 35% for clinically significant depressive symptoms and a prevalence of 17% for major depression, though the percentages varied
widely between the studies included,⁹⁷ and as noted above, depression may occur already prior to the manifestation of motor symptoms.⁷⁴⁻⁸⁰ Cognitive impairment is another common and significant non-motor manifestation of PD; the crude prevalence of dementia in PD patients seem to be about 40%, though percentages vary widely according to the population investigated.⁹⁸ Risk factors for dementia include old age at onset, long duration of disease, severe motor symptoms, and occurrence of other neuropsychiatric symptoms.⁹⁸ Non-motor symptoms and postural impairment are often not responsive to DRT. Therefore, such features present the main therapeutic challenge in many cases.⁹⁹⁻¹⁰¹ Evidence for best treatment options is limited for many non-motor manifestations. For PD-related depression, current evidence suggest that tricyclic antidepressants provide the best effect.⁹³⁻⁹⁵ For cognitive impairment, cholinesterase inhibitors could possibly be useful but the documentation for such drugs in PD is limited.⁹³⁻⁹⁵ For RBD, clonazepam or melatonin are proposed, though the knowledge about effects of such treatment in PD is sparse.⁹³⁻⁹⁵ Orthostatic hypotension occur both as a primary symptom of PD and an adverse effect of DRT, and may require pharmacologic treatment, e.g., fludrocortisone.⁹³⁻⁹⁵ For axial impairments, physical therapy remains the most effective treatment.¹⁰⁰ Such interventions are still not enough to overcome the high risk of falls and consequent injuries in advanced disease.¹⁰²

In many PD patients, invasive treatment methods may eventually be required to manage motor complications and other challenging features of the disease. Three different invasive options are currently available: continuous subcutaneous administration of apomorphine, continuous duodenal administration of levodopa carbidopa intestinal gel (LCIG), and deep brain stimulation (DBS). Among these, DBS has the highest level of evidence, though there is a lack of large studies directly comparing these options.⁹⁵

Apomorphine is a rapid acting dopamine agonist, effective to manage motor fluctuations and some non-motor features in advanced PD. Adverse events reported with continuous subcutaneous administration of this drug include local skin reactions at the infusion site and typical dopamine agonist side effects, such as neuropsychiatric reactions and nausea.⁹⁵,¹⁰³,¹⁰⁴

LCIG is a technique developed to avoid variations in levodopa concentration, and it has proven effective to reduce motor fluctuations. Most adverse events with this intervention are associated with the percutaneous gastrostomy tube used for administration of the gel.⁹⁵,¹⁰⁵
DBS is a functional neurosurgical technique, different from the other 2 invasive options in that it does not directly involve DRT – the aim of DBS is rather to diminish the need of drugs. Importantly, though, with current techniques and targets for DBS, also this therapy is mainly effective against levodopa responsive features of PD. The leading indications for DBS are motor fluctuations, dyskinesia, or tremor refractory to medication. There is an ongoing debate whether, and in which scenarios, DBS should be considered at earlier stage of PD – this may e.g. apply to patients who are still working, to keep the ability to work. However, evidence for potential benefits in such situations is still sparse. Concerns of early surgery include difficulties to properly identify which patients will benefit from DBS in a long term perspective, and to distinguish them from patients who might never need surgery; e.g. may dopaminergic therapy alone remain sufficient for decades in some patients with tremor dominant PD. The most common complication of DBS is infection, occurring in up to 15% of surgeries. Other adverse effects reported after DBS surgery include cognitive decline, impaired gait and speech, and psychiatric disturbance (e.g., mania, depression, behavioral disorders). Thus, cognitive impairment and ongoing severe psychiatric symptoms are contraindications for DBS surgery, though it is difficult to distinguish whether worsening of such features are adverse effects of DBS, or rather part of the disease progression.

**Consequences of PD**

Given that current therapies available for PD cannot cure or adequately suppress all the symptoms, particularly not in the long term, the disease will have consequences for the patient in the context of daily life. Several studies have investigated the impact of PD on QoL, mainly from a health related perspective, consistently reporting disability and overall disease severity (as measured by e.g. UPDRS or the HY scale) to be correlated with a poorer QoL. Among specific symptoms of PD, depression, gait impairments, and complications of therapy appear to have a particular impact on the health-related QoL (HRQoL). However, such disease specific factors do not alone explain the differences in QoL, and a stronger impact of PD on QoL has been reported in young compared to older patients, also after adjustment for disease severity. Other perspectives of life situation, such as social functioning, are less well investigated. Among patients with young onset PD, disability related unemployment and early retirement is common, and such socioeconomic consequences may contribute to an impaired QoL. Studies of working-aged patients have reported employment rates to be <15% at 10 years after diagnosis of PD, and a recent nationwide study in Denmark found a decreased employment rate already 8 years before diagnosis, possibly indicating prodromal symptoms severe enough to
interfere with the working capacity. Supportive attitudes from employer, and availability of adjustment in work tasks seem to prolong the duration of employment after disease onset.\textsuperscript{13,14} Still, only few studies have investigated this aspect, which can also be expected to vary between countries due to cultural and political differences, e.g. considering availability of rehabilitation interventions and vocational support. The situation in Sweden in this matter has not previously been investigated.
Objectives

Paper I: Consequences of PD in a working aged cohort

The aim of paper I was to investigate the life situation for people affected by PD in working age, compared to a matched control group. Our purpose was to identify factors of importance for QoL and working situation, as such information would be of value to optimize support in rehabilitation and working opportunities for people with PD.

Paper II–IV: Prodromal markers for PD

The aim of paper II–IV was to evaluate long-term associations between potential prodromal signs and the later development of PD, using nationwide materials with excellent statistical power and prospectively registered data for reliable evaluations of time perspectives. A better understanding of the prodromal phase of PD would be of value to guide further research for causal risk factors for PD. Moreover, improved possibilities for early identification of the disease may be of high importance if current or future research succeeds to develop neuroprotective therapies for PD.

Paper II and IV were focused on potential early motor signs; the specific objective of paper II was to evaluate muscle strength in young adulthood in relation to the later risk of PD, and the objective of paper IV was to investigate if patients with PD are at increased risk of injurious falls already prior to the PD diagnosis.

Paper III was focused on depression in the prodromal phase of PD. Our objectives were to evaluate time perspectives of the association between depression and later risk of PD in a long-term perspective, and to assess potential confounding by shared familial factors.
Materials and methods

All cohorts included in this thesis project were population based, drawn from nationwide registers. In Sweden, a unique personal identification number is assigned to every citizen, enabling record linkage between several registers and ensuring a high consistency of the data included. Statistics Sweden and the National Board of Health and Welfare were responsible for encoding and depersonalizing the data before delivery to the researchers. Information was obtained from the registers and databases listed below.

The National Patient Register (NPR)

The NPR, administrated by the National Board of Health and Welfare, keeps records of all public inpatient care since 1987, and of both inpatient and outpatient care since 2001. Diagnoses are coded according to the Swedish versions of the International Classification of Diseases (ICD-9 in 1987–1997, ICD-10 since 1998). Diagnoses recorded in the NPR do in general have a high validity, with positive predictive values of 85–97%. Diagnoses included in the present thesis project as outcomes, predictors/exposures, or confounders are listed in table 1.

The Register of Total Population (RTP)

The RTP is administered by Statistics Sweden and includes records of births, deaths, immigrations, and emigrations. For the purpose of the present studies, this register enables a population based inclusion of healthy controls and minimizes the loss to follow up in longitudinal studies.

The Cause-of-Death Register (CDR)

The CDR is administrated by the National Board of Health and Welfare, and keeps records of death certificates linked to the RTP since 1961. Since 1997, all deaths reported to the RTP are included, also if a death certificate is missing.

The Multi-Generation Register (MGR)

The MGR, based on the RTP and administrated by Statistics Sweden, includes persons who were born in 1932 or later and have been registered in Sweden at some time since 1961. This register enables data linkage between index persons and their parents and siblings, and specifies the forms of relationship (e.g., biological parent, full sibling, half sibling).
**The LISA database**

Statistics Sweden administers a longitudinal database for research on health insurance and labor market topics. This database, termed LISA, contains information from several registers and agencies.\(^{119}\) For the present thesis project, information on education level and income was obtained from this database.

**The Swedish Military Service Conscription Register (MSCR)**

Until 2007, military service conscription was mandatory for Swedish men, including 2 days of highly standardized physical and cognitive tests, and all conscripts were examined by a physician. The MSCR include data from these tests in digital format since 1969. Additional data from questionnaires, including lifestyle factors, were recorded mainly in 1969–1970.\(^{120}\)
Table 1. Diagnose codes from the NPR included in the thesis.

<table>
<thead>
<tr>
<th>Predictors/exposures and outcomes</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>332A</td>
<td>G20.9</td>
</tr>
<tr>
<td>Depression</td>
<td>311</td>
<td>F32–F33</td>
</tr>
<tr>
<td>Fall on same level</td>
<td>E885</td>
<td>W00–W01</td>
</tr>
<tr>
<td>Hip fracture*</td>
<td>820</td>
<td>S72.0–S72.2</td>
</tr>
<tr>
<td>Wrist fracture*</td>
<td>813</td>
<td>S52</td>
</tr>
<tr>
<td>Lower leg fracture*</td>
<td>824</td>
<td>S82</td>
</tr>
<tr>
<td>Humerus fracture*</td>
<td>812</td>
<td>S42.2–S42.4</td>
</tr>
<tr>
<td>Head injury*</td>
<td>800–804, 850–853</td>
<td>I62, S02, S06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confounders</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Traumatic brain injury</td>
<td>850–853</td>
<td>S06</td>
</tr>
<tr>
<td>Stroke</td>
<td>431, 434</td>
<td>I61–I64</td>
</tr>
<tr>
<td>Alcohol dependency or abuse</td>
<td>303, 305A</td>
<td>F10</td>
</tr>
<tr>
<td>Drug dependency or abuse</td>
<td>304, 305X</td>
<td>F11–F19</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>250</td>
<td>E10–E11</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>410</td>
<td>I21–I22</td>
</tr>
<tr>
<td>Dementia</td>
<td>290, 291, 294B</td>
<td>F00, F01, F03.9, G30, G31, E51.2</td>
</tr>
</tbody>
</table>

* Only diagnoses specified as caused by a fall were included.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Material</th>
<th>Design</th>
<th>Data collection</th>
<th>Main predictors</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD, vocational rehabilitation support</td>
<td>Working situation</td>
</tr>
<tr>
<td>II</td>
<td>Nationwide cohort of men (N=1,317,713)</td>
<td>Cohort, mean follow up ≈ 30 years</td>
<td>Register data, including military conscription tests at baseline</td>
<td>Muscle strength (physical fitness, parents’ PD)</td>
<td>PD during follow up</td>
</tr>
<tr>
<td>III</td>
<td>Nationwide cohort (N=3,329,400)</td>
<td>Nested case-control cohort, 26 years of follow up for medical diagnoses</td>
<td>Register data</td>
<td>Depression</td>
<td>PD during follow up</td>
</tr>
<tr>
<td>IV</td>
<td>Nationwide cohort (N=3,329,400)</td>
<td>Nested case-control cohort, 26 years of follow up for medical diagnoses</td>
<td>Register data</td>
<td>Injurious falls</td>
<td>Hip fractures</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Injurious fall</td>
</tr>
</tbody>
</table>
**Paper I**

A population based survey study, including 2002 patients with PD and 2002 controls. The NPR was used to identify persons with PD who met the age criterion (18–67 years), and the 2002 patients with the most recent health care contact were selected for inclusion. One control person per case of PD, matched by age and sex, was drawn from the RTP. Data were collected in 2012 using a questionnaire mailed to all selected participants. The survey design was adapted from a questionnaire used in a large, population-based health examination program in northern Sweden, and aimed to explore several perspectives of life situation: living conditions, family situation, vocational situation, leisure, self-experienced health, and life quality. Questions from 2 validated instruments were built in: the Life Satisfaction Questionnaire (LiSat) and Karasek’s Job Content Questionnaire. Additional questions were included to assess subjective experience of employment situation and support, and PD-specific concerns. The survey was divided into cross-sectional and retrospective parts; for the retrospective questions, participants with PD were requested to recall their situation the year before diagnosis of PD, and participants without PD were requested to recall their situation 10 years ago. Demographic data, such as sex, age, marital status, and income, were obtained from registers.

The main outcomes for paper I were likelihood of dissatisfaction with life, defined as any level of dissatisfaction (score ≤3) on the 6-graded LiSat scale, and the likelihood to be employed (full time or part time). Secondary analyses were focused on descriptive data for specific factors, such as subjective balance of work demands in relation to one’s capacity, and experience of vocational support from different sources (trade union, employer, public social insurance, public employment services, primary healthcare, PD-treatment-responsible doctor, and team-based rehabilitation unit).

**Paper II**

The study cohort comprised 1.3 million men who underwent conscription tests between 1969 and 1996, based on data from the MSCR. The tests included measurement of maximal isometric force in knee extension, elbow flexion, and hand grip. Physical fitness was measured by a bicycle ergometer test. Medical conditions were diagnosed by a physician at conscription. A questionnaire including lifestyle factors, such as smoking, was used mainly in 1969 and 1970. Information about subjects’ health and socioeconomic situation during follow up was obtained from the NPR and the LISA database, respectively. Information about PD diagnoses in the subjects’
parents were obtained from the NPR, via linkage of personal identification numbers through the MGR. PD diagnoses in the NPR in the participants were traced between January 1, 1987 and December 31, 2012, and included as the main outcome of this paper.

**Paper III**

From a cohort comprising all citizens of Sweden aged ≥50 years on December 31, 2005, we drew a nested case-control (NCC) cohort including 140,688 individuals with a diagnosis of depression (as defined in table 1) recorded in the NPR during 1987–2012, matched 1:3 by age and sex to controls with no such diagnosis. In the same material, data from the MGR was used to form a second cohort, comprising 540,811 sibling pairs, to assess potential familial aggregation between depression and PD.

As the main outcome, we analyzed the risk of PD during follow up for individuals with depression compared to controls in the NCC cohort. Follow-up time was calculated from index date to date of PD, date of death, or December 31, 2012. Among individuals with depression, we also investigated whether severity of depression (as defined by hospitalization compared to outpatient care only) or recurrent hospitalizations for this diagnosis were associated with the risk of PD.

To analyze potential co-aggregation of depression and PD in siblings, we assigned one individual from each pair as index person, and investigated whether sibling’s depression was associated with the risk of PD in the index person.

**Paper IV**

From the same cohort of Swedish citizens as in paper III, we compiled 2 new NCC cohorts: the first (cohort I) included 24,412 patients with a diagnosis of PD recorded in the NPR between 1988 and 2012, matched 1:10 by age and sex to controls with no diagnosis of PD; the second (cohort II) included 622,333 patients with a record of at least one injurious fall (as defined in table 1) with no preceding diagnosis of PD in the NPR during 1988–2012, and one matched control per case.

In cohort I, we assessed the risk of injurious falls before the PD diagnosis; study time was calculated retrospectively from index date back to January 1, 1987.
Cohort II was compiled with the aim to evaluate time perspectives from first registered fall to diagnosis of PD in a prospective manner. Follow-up time was calculated from index date to date of PD, date of death, or December 31, 2012.

Statistical analyses

The SPSS (version 21.0 for Windows; SPSS Inc.) and Stata (version 12 for Macintosh and version 13 for Windows; StataCorp) were used for statistical analyses, with p-values <0.05 considered significant. In univariate analyses, the significance of differences was assessed by chi-squared tests, t-tests, or Wilcoxon rank-sum tests.

For multivariate analyses of cross-sectional data, we used binary logistic regression models and linear regression models. For longitudinal data, we used log minus log plots and Cox proportional hazard models (Cox regression) with Schoenfeld residuals to assess the accuracy of the proportional hazards (PH) assumption. When no significant time variation was found, Cox regression models were used for further analyses. When the PH assumption was not fulfilled, we used flexible parametric Royston–Parmar models and conditional logistic regression; the latter was applied after splitting the study time into intervals. In a similar manner, conditional logistic regression models were used for the retrospective analyzes in paper IV.

Ethical considerations

The studies were permitted by the local ethics committee of Umeå University, and conform to the World Medical Association Declaration of Helsinki. The registers included are legally protected by strict secrecy acts, why the data requests were also judged by Statistics Sweden and the National Board of Health and Welfare to ensure that the delivery of linked, depersonalized data to Umeå University in this context would not violate the law or risk to harm the individuals included in the studies.

A specific ethical concern was the postal delivery of the survey study; some individuals could find it offensive to receive a letter pointing them out according to a diagnosis in the NPR. Therefore, the information and questionnaire was designed so that the same version was applicable for both PD participants and the control group. For paper II–IV, no contact was made with the participants.
Results

Paper I

The overall response rate in the questionnaire study was 64% (n = 2567; 1432 people with PD; 1135 control participants), and the median age of participants was 63 years. Among participants with PD, the median time from diagnosis was 6 years. A majority of the PD participants (59%) had reduced working hours or quit work due to PD. Among men, 20% of the participants with PD worked full time and 21% worked part time, while 51% of the male controls worked full time and 15% worked part time (p < 0.001). Only 11% of the women with PD worked full time, and 21% worked part time, while 39% of the female controls worked full time and 21% worked part time (p < 0.001). The mean income was about 12% lower among participants with PD compared to controls, among both men and women (p < 0.001). Among participants who had lived with PD for ≥10 years, 24% remained employed and 6% worked full time. Both motor and non-motor features were reported to highly interfere with work; among those who had reduced or quit work due to PD, the most common such issues were “stiffness and/or slowness of movement” (45%), “stress intolerance” (36%), “sleep disturbance/fatigue” (24%), and “tremor” (23%).

Most PD participants (60%) had received vocational support from their doctor, while 5% reported a lack of help from this source. Many PD participants had also received help from employer (34%) and/or a team-based rehabilitation unit (31%), though another substantial number of participants (14% and 15%, respectively) reported an unmet need of help from these sources. Adjusted for age, sex, education level, family situation, and comorbidities, the likelihood to be employed was considerably reduced for participants with PD compared to controls [odds ratio (OR), 0.30; 95% confidence interval (CI), 0.25–0.37]. Among individuals with PD, employer’s support was associated with an about 3-fold increased likelihood to work, compared to participants reporting a lack of support from employer (p < 0.001). Support from the PD-treatment-responsible doctor or from a team-based rehabilitation unit was not significantly associated with the likelihood to work.

More PD participants than controls were dissatisfied with life; the largest differences appeared in the domains of “life as a whole” (38% vs 9%) and “working situation” (38% vs 15%) (p < 0.001 for both). In a multivariate model adjusted for age, sex, family situation, education level, employment situation, income, and comorbid diseases, PD was associated with an
increased risk of dissatisfaction with life as a whole (OR, 5.4; 95% CI, 4.2–7.1). In a separate analysis among PD participants, the likelihood of dissatisfaction with life as a whole increase with longer disease duration [OR, 1.04 (95% CI, 1.02–1.07) per year increase]. Compared to controls, PD participants also more frequently marked that their work demands exceeded their capacity (36% vs 13%; \(p<0.001\)). This factor and unemployment were independently related to an about 3-fold risk increase for dissatisfaction with life, compared to employed participants with a work load in balance with their capacity (\(p<0.05\) for both).

Paper II

Among the 1.3 million participants, 977 (0.07%) were diagnosed with PD during follow up, at a mean age of 50±7 years. At conscription, PD participants had a significantly lower muscle strength in the upper extremity [handgrip: mean difference (MD), −9.8 Newton (N); 95% CI, −16.4 to −3.2; elbow flexion: MD, −7.4 N; 95% CI, −13.1 to −1.9] but not in the leg (MD, −5.9 N; 95% CI, −13.4 to 1.7), after adjustment for confounders including physical fitness.

A similar pattern was found for those with a family history of PD; men whose parents were diagnosed with PD had less handgrip [fathers: MD, −5.7 N (95% CI, −7.3 to −4.0); mothers: MD, −5.0 N (95% CI, −7.0 to −2.9)] and elbow flexion [fathers: MD, −4.3 N (95% CI, −5.7 to −2.9); mothers: MD, −3.9 N (95% CI, −5.7 to −2.2)] strength, but not knee extension strength [fathers: MD, −1.1 N (95% CI, −2.9 to 0.8); mothers: MD, −0.7 N (95% CI, −3.1 to 1.6)], than those with no such familial history. Physical fitness was not related to the risk of PD during follow up.

More of the PD participants had at least one parent with PD, compared to those who were not diagnosed with PD during follow up (6.9% vs 1.6%; \(p<0.001\)). The increased risk of PD for those with a parent with PD was significant also in the multivariate analyses [father with PD: hazard ratio (HR), 2.63 (95% CI, 1.88–3.69); mother with PD: HR, 3.62 (95% CI, 2.59–5.05)].
Paper III

In the NCC cohort (N = 562,631), 3,260 (0.5%) of the individuals were diagnosed with PD during follow up; 1,485 (1.1%) individuals with depression and 1,775 (0.4%) controls (p<0.001). Graphically assessed by a flexible parametric model, the association between depression and subsequent risk of PD appeared clearly time dependent: strongest in close relation to the diagnosis of depression, but remaining significant over the entire time of follow up (Figure 1). A conditional logistic regression model, adjusted for education level and comorbid diagnoses, confirmed the same pattern; OR for PD was 3.2 (95% CI, 2.5–4.1) at 3–12 months after index, and decreased to 1.5 (95% CI, 1.1–2.0) after 15–25 years for individuals with depression compared to controls.

Recurrent hospitalization for depression was associated with increased risk of PD [OR, 1.3 (95% CI, 1.1–1.4) for 2–4 hospitalizations; OR, 1.4 (95% CI, 1.1–1.9) for ≥5 hospitalizations, compared to a single care event]. Among individuals first diagnosed with depression after 2001 (n = 111,001), the risk of PD was higher in those who were hospitalized for depression than those who received outpatient care only [OR, 3.5 (95% CI, 2.9–4.1)].

In the sibling cohort, we found no evidence for co-aggregation between depression and PD; OR for PD was 1.1 (95% CI, 0.9–1.4) for index persons whose sibling was diagnosed with depression compared to those whose sibling was not, after adjusting for age, sex, sibling’s PD, and depression and other comorbidities in the index person. In the same model, familial aggregation of PD appeared, with an OR for PD of 1.9 (95% CI, 1.3–2.9) for individuals whose sibling was diagnosed with PD compared to those whose sibling was not.
Figure 1. Risk of PD according to depression, from 3 months to 25 years after enrollment in the nested case-control cohort, estimated by a flexible parametric Royston–Parmar model adjusted for age, sex, education level, and comorbid diagnoses. The gray area represent the 95% CI.

Paper IV

In the PD-matched cohort (cohort I), the median retrospective study time was 19.9 years. During this time, 4,388 (18.0%) of the individuals with PD and 28,018 (11.5%) of the controls had at least one injurious fall, and the cumulative incidence of hip fractures was 7.1% ($n=1,729$) in individuals with PD and 3.2% ($n=7,757$) in controls ($p<0.001$ for both). Estimated by a conditional logistic regression model adjusted for education level and comorbid diagnoses, the risk of injurious falls was increased up to 10 years before the diagnosis of PD [OR, 1.19 (95% CI, 1.08–1.31) in the interval 7–10 years], and the risk of hip fractures was increased already 15–26 years prior to first PD diagnosis [OR, 1.36 (95% CI, 1.10–1.69)]. The highest relative risk of injurious fall and hip fracture was seen in the last 3 months prior to index [injurious fall: OR, 5.83 (95% CI, 5.30–6.42); hip fracture: OR, 7.49 (95% CI, 6.52–8.61)].

In the fall-matched cohort (NCC cohort II), 7,501 (0.6%) individuals were diagnosed with PD [4,299 (0.7%) fallers, 3,202 (0.5%) controls; $p<0.001$] during a median follow-up period of 5.8 (range 0–25.0) years. Graphically assessed by the flexible parametric model, the risk of PD for individuals with a fall compared to controls was elevated during the first approximately 10 years after index, while a reverse association appeared at follow-up times >15 years (Figure 2a). Regression analyses confirmed these findings [OR, 1.98 (95% CI 1.70–2.32) at 3–12 months after index, gradually decreasing to 0.79 (95% CI 0.65–0.95) at 15–26 years after the first fall]. The sensitivity analyses indicated that the inverse relationships observed may be explained by competing risk of death; when excluding all matched pairs where any participant deceased during the study, no significant association between falling and PD was seen at follow-up times >10 years (Figure 2b).
**Figure 2.** Risk of Parkinson’s disease after first injurious fall, estimated by a flexible parametric Royston–Parmar model adjusted for sex, age at index, education level, and comorbid diagnoses: (a) in the entire fall-matched cohort; (b) in the fall-matched cohort after exclusion of all matched pairs where any participant deceased during the study. The gray area represent the 95% CI.

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Discussion

Many PD patients, especially those affected in early age, have to cope with the disorder for decades. Given the insidious onset of PD, non-specific features may bother the patient already years or even decades before the cardinal motor symptoms appear.

Life satisfaction and employment situation

More PD participants than their matched controls were dissatisfied with life as a whole. In the multivariate analyses, work situation was an independent factor for dissatisfaction with life. Compared to the controls, the PD participants were less likely to be employed, less likely to be satisfied with their employment situation, and had a lower mean income. Substantially fewer PD participants than controls were full-time employed; this difference was particularly large among women. The difference between PD participants and controls was less obvious for part-time employment: here, pure demographic data only revealed that male PD participants were more likely to work part time than their matched controls, whereas among women, part-time work was equally common among PD participants and controls. However, many PD participants reported that their work demands exceeded their capacity and many controls reported that work capacity exceeded their work demands.

It remains unclear whether reducing working hours improves the likelihood of staying active in the labor market as, to our knowledge, no prospective study has addressed this issue. Using general population registers, a UK study found that abrupt cessation of work appeared more common than a gradual reduction of work, because part-time work was equally common among PD patients and age-matched controls.\textsuperscript{15} For controls, however, that study only included quantitative statistics and the motives for reduced work hours could thus not be analyzed. We found that a large number of healthy controls (women in particular) chose to work part time. That is, if only quantitative data are analyzed and the motives for reducing working hours differ between PD participants and controls, effects of this adjustment on the possibilities to stay employed may be underestimated. In the present study, the differences observed between men and women in rates and extent of employment may reflect societal perspectives, but could also indicate dissimilarities in PD-specific consequences. The analyses included in the scope of this paper did not allow such distinctions.
Compared to previous reports, the proportion of participants still employed 10 years or more after diagnosis of PD was remarkably large in our study. This contrast may be explained by a difference in the study populations, as most previous studies have recruited patients through specialist clinics or patient organizations, where patients with less severe forms of disease may be underrepresented.\textsuperscript{13-16} Our material was population based, making such selection bias less likely. It should be noted, though, that PD patients with severe cognitive impairment may be less likely to respond to the questionnaire and therefore underrepresented in our study.

Participants who were satisfied with the support from their employer were considerably more likely to remain employed, compared to those who marked an unmet need of help from this source. Taken together, our findings suggest that support from the employer is important to improve the possibilities to stay employed, and that reducing work hours may be an adjustment of value. However, the high number of participants with PD perceiving their work demands to exceed their capacity indicates a need to further improve the support systems.

**The prodromal phase**

Low muscle strength and depression were associated with an increased risk of PD over follow-up times of more than 2 decades, and patients with PD were at increased risk of fall-related injuries, hip fractures in particular, a decade or more before the PD diagnosis. If these associations arise from early neurodegenerative deficits, they all support the hypothesis of a very long prodromal phase of PD. Symptoms previously reported to occur more than a decade before diagnosis of PD include constipation,\textsuperscript{66,67} RBD,\textsuperscript{81} depression,\textsuperscript{78} and anxiety,\textsuperscript{79} while potential motor deficits are less well investigated. Thus, the association between low muscle strength in young adulthood and later risk of PD is of particular interest, given the long time perspective and given that this factor, to our knowledge, has not previously been investigated prior to the diagnosis of PD. Reduced muscle strength has been reported in the early phase of PD, also in the clinically asymptomatic side.\textsuperscript{47} The strength deficits found in our study were small, but in the light of a previous study based on the MSCR, where low muscle strength was associated with an increased risk of low-energy fractures,\textsuperscript{125} these subtle deficits may still be of clinical importance in a long-term perspective – e.g. as a factor explaining the increased risk of injurious falls in paper IV.

Traditionally, the assessment of motor symptoms of PD relies on clinical evaluation, which may not be sensitive enough to e.g. detect subtle signs of balance impairment. A number of recent studies have indicated balance
deficits also in early and prodromal PD, but the clinical relevance of signs such as increased postural sway remains unclear. However, the study by Frandsen et al, reporting increased risk of accidental injuries in the last 3 years prior to diagnosis of PD may, similar to ours, indicate that such deficits also can translate to a clinically important risk of injuries. In this field, our study contributes with prospectively collected data over a longer time perspective, and may also be more specific for balance deficits; the previous report included various accidental injuries, while we only captured those coded to be due to fall on same level.

Previous studies investigating the association between depression and subsequent risk of PD have reported a significant, positive association within approximately a decade before the diagnosis of PD, but data covering longer times have been inconclusive. We had the opportunity to evaluate long-term perspectives of this association in a nationwide material with prospectively collected data and excellent statistical power, and found the relation to be significant over the entire follow-up time of more than 2 decades.

**Prodromal features, causal factors, or shared susceptibility?**

Given that most evidence for environmental “risk factors” and/or “prodromal markers” of PD originate from observational studies, definite conclusions about causality cannot be drawn. Several theories, more or less likely, could explain the findings of our studies. These theories could be categorized as “causal risk/protective factors”, “prodromal signs”, and “shared susceptibility/confounding”. The first category includes factors that could explain the underlying causes of “sporadic” PD: either triggering the neurodegeneration or protecting against it. Identification of such factors would also be of value to understand the reduced penetrance in some genetic forms of PD. The second category includes all markers supposed to be symptoms of early neurodegenerative changes: a direct relationship that, from a chronological perspective, could be considered as “reverse causality”. The third category comprises every explanation involving another underlying factor affecting both the investigated exposure/predictor and the risk of PD.

Given our methodological limitations, we cannot certainly tell that the observations of paper II–IV represent prodromal signs of PD. The time-dependent patterns between the markers (depression, injurious fall, and hip fracture) and the outcome of PD in paper III and IV suggest that the associations observed reflect direct relationships; the same reasoning applies to the “dose-response” patterns observed between severity and recurrence of depression in relation to the later risk of PD in paper III. Still, it may be that
depression itself or anti-depressive drugs trigger the neurodegeneration and, similarly, some factors associated with muscle strength and falls, respectively, could actually be causal risk factors or protective agents for PD. For example, there is some evidence for physical activity to decrease the risk of PD.\textsuperscript{29,34,126-128} However, in our study, physical fitness measured by a bicycle test was not associated with the later risk of PD, why it is unlikely that the association between muscle strength and PD is solely due to exercise habits. In the context of falls, head trauma is a potential risk factor for PD that has been evaluated in several studies, with inconsistent results.\textsuperscript{42,43} In our study, only a minority of the falls involved head injuries, why this hypothesis is unlikely to explain the associations found.

To evaluate potential explanations belonging to the third category, confounding, we included information available on comorbid disorders, and smoking habits when possible, in the analyses. Unfortunately, smoking data was only available for a small subgroup of the population in paper II, and not at all for the participants in paper III and IV. This limitation is important, as there is strong evidence for a negative association between smoking and subsequent risk of PD.\textsuperscript{29,34,35} Another factor representing the category of confounding is familial co-aggregation due to shared susceptibility factors. We assessed this possible confounding by including diagnoses of PD in participants’ parents and siblings, respectively, in paper II and III. In paper III, we found no evidence for shared familial susceptibility between depression and PD, though there was a subtle trend towards it; it is possible that despite a large material, the statistical power was not sufficient or that a more sensitive method to capture and grade the severity of depression would have rendered different results, given that participants with severe or recurrent depression were at particularly high risk of PD. In paper II, the association observed between participant’s muscle strength and parent’s PD suggest a hereditary component of the relationship between muscle strength and PD, and could be considered a form of familial co-aggregation, though more of the participants with a parent with PD may still develop PD later in life; despite a long follow-up time, the majority of the PD cases in this study could be considered as early onset.

**Relevance and future directions**

In the context of prodromal markers, it should be noted that for most associations the “effect size” was small in absolute numbers; only 1% or less of the participants with depression or injurious fall, respectively, were diagnosed with PD during follow up, and the differences in muscle strength were subtle. Thus, these features cannot be used as single markers to identify individuals at high risk of PD, but few previous studies have included
prospectively collected data over such long follow up. These long-term associations, especially the differences seen already at 18 years of age, highlights the need to recruit young populations to further evaluate potential risk factors for PD in future studies.

From a clinical point of view, it should be noted that the cumulative incidence of fall-related injuries was considerable also in absolute numbers; about 7% of the PD participants had suffered at least one hip fracture before the diagnosis of PD. Given the severity of that injury, this finding highlights that “non-specific” features of the prodromal phase do not necessary translate to “minor” or “subtle”; PD patients may suffer considerable health issues long before the cardinal motor symptoms become troublesome. Such non-specific, yet important, manifestations may contribute to the reduced employment rate seen already 8 years before PD diagnosis in a Danish study.17

Some findings of paper I are of direct clinical importance; e.g., the substantial proportion of participants still employed a decade or more after PD diagnosis may be encouraging information for PD patients who are worried about having to leave their profession. On the other hand, the large number of PD participants reporting difficulties to meet their work demands is a bothersome finding that warrants attention; the support for this group of individuals appear insufficient. A considerable number of PD participants reported an unmet need of vocational support from their employer. Given the strong association between patient-reported support from employer and likelihood to remain employed, it is advisable to involve the employer in the vocational rehabilitation process. We found no such association between support received from a team-based rehabilitation unit and the likelihood to work. However, this study included no information on when the help had been received. Thus, this lack of evidence should be interpreted with caution; it is possible that such interventions have not been provided with optimal timing. It would be interesting to prospectively investigate in which phase patients typically receive help from team-based rehabilitation units, and which forms of adjustments and support, provided by different sources, were most common and effective. For such a study, our findings suggest that it would be advisable to pay specific attention to support provided by the employer.
Methodological considerations

With data acquired from nationwide registers based on mandatory recording, and large numbers of subjects, the external validity of the papers of this thesis is expected to be high. The statistical power is another strength, enabling detection of subtle differences between groups. Paper II–IV share the strength of prospectively collected data, enabling reliable evaluation of time perspectives.

Some limitations, in addition to those previously discussed, should be mentioned. First and foremost, the diagnoses of PD were obtained from registers and not clinically confirmed for the studies. The accuracy of parkinsonian disorder diagnoses in the NPR has recently been evaluated; the positive predictive value (PPV) for parkinsonian disorders overall was 88%, and the PPV for PD was 71%. More than half of the cases that were misclassified as PD suffered from some other form of parkinsonism. In our study, such misclassification could introduce a bias particularly in the context of falls; the latency from diagnosis to first fall is typically longer in PD than in other degenerative parkinsonian disorders. However, in another Swedish study using a dual-investigator approach and a 12-months reevaluation of the diagnoses for all new cases of idiopathic parkinsonism referred to the regional neurology clinic, more than 80% of the cases were classified as probable or definite PD, while only 9% and 4%, respectively, were classified as possible or probable MSA or PSP, and no case of CBD was identified among the 138 patients. Thus, even if some cases of atypical parkinsonism are misclassified as PD, such cases would likely comprise only a minority of the total number of PD cases, and are therefore unlikely to substantially bias the results of our studies.

To evaluate the consistency of our material in relation to similar studies, the familial aggregation patterns of PD also provide data for a sensitivity analysis of interest. In paper II and III, we found an approximately 2–3 fold increased risk of PD in participants with a parent or sibling with that diagnosis, compared to participants whose relatives were not diagnosed with PD; this level of familial aggregation is similar to previous studies. Noteworthy is that according to the meta-analysis by Thacker et al., such associations tend to be stronger between siblings than between generations, while we found stronger associations between participants and their parents in paper II than between siblings in paper III. However, our estimates are not directly comparable between the different papers, as neither the methodology nor the study population were the same. Given that patients with recognized monogenetic forms of PD are commonly affected in younger age than patients with apparently sporadic PD, it is not surprising that the
patterns of familial aggregation were more accentuated in the younger cohort of paper II.

As the NPR only includes data from specialist healthcare, any PD patients treated only in primary care would not be included as cases of PD in these studies. Similarly, the date of PD diagnosis is defined by first consultation recorded in NPR, why this date would be delayed for any patients initially treated in primary healthcare. However, any missed or random incorrect diagnoses of PD would cause a regression dilution bias, attenuating the associations of any risk markers towards zero. In case of delayed diagnosis, the duration of the prodromal phase would be overestimated. However, any such delay would likely be small in relation to the long time perspectives observed for the associations. In paper III and IV, the distinct time-dependent associations between risk markers (depression, fall, and hip fracture) and PD supports the consistency in the timing of PD diagnosis; if any large proportion of PD patients were treated in primary healthcare for years before the diagnosis was captured in the NPR, such variation would attenuate the time dependency of the associations seen. Moreover, as a sensitivity analysis for time perspectives in paper IV, we also explored the risk of injurious falls after PD diagnosis, compared to matched controls. This analysis was not included in the final version of paper IV, but the association between PD and injurious falls reached a peak strength within 3 months after PD diagnosis, then gradually decreased. This pattern further supports that the timing of PD diagnosis captured in the NPR was consistent within the population studied.

Paper I rely mainly on participant reported data, which is both a strength and a limitation of the study. Advantages of this approach include the possibility to capture the PD participants’ own experiences of their situation, and the access of comparable data for the controls, whereas major disadvantages of this approach are the risk of recall bias and the lack of clinical data on disease severity and treatment. The nonresponse rate also introduces a risk of bias, as the responders may not be representative for the target population.
Conclusions

Despite advances in PD treatment, the disease is still incurable and causes progressive disability and QoL impairment. In our study, more PD participants than their matched controls were dissatisfied with life as a whole, and employment situation was an independent factor for life satisfaction in this working-aged cohort. A majority of the PD participants reported that the disease interfered with their working capacity, and many indicated that they struggled to cope with their work demands. Still, the percentages of PD participants employed a decade after diagnosis (24%) was high compared to previous studies, and the employer appeared to be a key source for successful vocational support.

Depression, reduced muscle strength, and fall-related injuries were associated with an increased risk of PD over follow-up times of decades. Plausibly reflecting early neurodegenerative changes, these associations contribute to a growing body of evidence for a long prodromal phase of PD. The observations of reduced muscle strength and increased risk of fall-related injuries are of particular interest as previous evidence for motor deficits in the prodromal phase is limited.
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